Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 31, 2014 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

I. CALL TO ORDER
- a. Roll Call & Introductions — T. Klein (Vice Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — T. Klein (Vice Chair)
- d. Department Update — D. Weston (OHA)

II. DUR ACTIVITIES
- a. Quarterly Utilization Reports — R. Citron (OSU)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Oregon State Drug Reviews — K. Sentena (OSU)
  1. 2nd Generation Antipsychotics: Are these Drugs effective in treating PTSD?
  2. New Cholesterol Guidelines: A Significant Shift in Cholesterol Management
- e. FDB Drug File Update — T. Williams (OSU)
  1. List of Drugs

III. DUR BUSINESS
- a. Hepatitis C Class Update — M. Herink (OSU)
  1. Class Update
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- b. Hepatitis C Readiness to Treat — M. Herink (OSU)
  1. Readiness to Treat Document
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA
- c. Botulinum Toxins Drug Use Evaluation — K. Ketchum (OSU)
  1. DUE
  2. Prior Authorization Criteria
  3. Public Comment
  4. Discussion of Clinical recommendations to OHA

IV. PREFERRED DRUG LIST NEW BUSINESS

a. Alcohol Dependence Class Review — B. Liang (OSU)
1. Class Review
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

b. Androgens Class Update — B. Liang (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

c. Pulmonary Arterial Hypertension — K. Sentena (OSU)
1. Class Update
2. Riociguat and Macitentan NDE
3. Public comment
4. Discussion of Clinical recommendations to OHA

d. Anticoagulant Class Update — K. Sentena (OSU)
1. Class Update
2. Public comment
3. Discussion of Clinical Recommendations to OHA

e. Antiplatelet Class Update — K. Ketchum (OSU)
1. Vorapaxar NDE
2. Class Update
3. Public comment
4. Discussion of Clinical Recommendations to OHA

f. Asthma/COPD Class Update — A. Meeker (OSU)
1. Class Update
2. Anoro™ Ellipta NDE
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

g. First Generation Antidepressants — B. Fouts (OSU)
1. Class Review
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

h. Insomnia Class Update — K. Ketchum (OSU)
1. Tasimelteon NDE
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

i. Drug Class Scans — M. Herink (OSU)
1. Insulins
2. Skeletal Muscle Relaxants
3. NSAIDs
4. Oral Hypoglycemics
5. Newer Antiemetics
6. Public Comment
7. Discussion of Clinical Recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS
VII. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 29, 2014 1:00-5:00 PM
Wilson Training Center
29353 SW Town Center
Wilsonville, OR 97070

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

Members Present: Tracy Klein, PhD, FNP; Cathy Zehrung, RPh; Phillip Levine, PhD; Zahia Esber, MD;

Members Present by Phone: Dave Pass, MD; James Slater, PharmD;

Staff Present: Kathy Ketchum, RPh, MPA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Trevor Douglass, DC, MPH; Shannon Jasper; Amanda Meeker, PharmD; Dee Weston; Linnea Saris;

Staff Present by Phone: Kathy Sentena, PharmD; Brandy Fouts, PharmD; Walter Shaffer, MD

Audience: Cheryl Fletcher (AbbVie); Michelle Bice (Gilead); Vantana Slater (Amgen)*; Mark Pledger (Novartis); Camille Kerr (Allergan); Chris Doyle (Allergen); Deirdre Monroe (Allergan)*; Venus Holder (Lilly); Paul Bonham (Novo Nordisk); Kimberly Blood (WVP Health Authority); Seth Adams (WVP Health Authority); Bob Snediker (J & J)*; Alyssa Tuttle; Phillip Do; Jeana Colabianchi, PharmD (Sunovion); Greg Broutman, PhD (Sunovion)*; Jamilyn Perez Aragon (Astellas); Cory Bradley (CareOregon); Shannon Betty (MedImmune); Paul Nielsen (Astra Zeneca); Mike Willett (Pfizer); Shane Hall (Purdue); Scott Larson (BMS); Amy Bauman (Giliead); Stuart O'Brochta (Gilead)*; Emily Van Woerden (AbbVie); Stephanie Kendall (J&J); Bill Struyk (J&J)*; Barry Benson (Merck); Jenny Morrison (BIPI); Michael Estes (Pfizer); Brad Peacock (Gilead); Ann Neilson (Amgen); Jim Davidson (Myers and Stauffer); Adrienne McCormick (Myers and Stauffer); Dean Haxby (OSU); David Barba (Forrest); Troy Larsen; Molly Meeker (Hyperion); Lorren Sandt (Caring Ambassadors Program)*; Brett Masett (Bristol Myers Squibb)*; Darlene Halverson (Novartis)

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:00 pm. Introductions of Committee members and staff.

b. Mr. Citron reported there are no new conflicts of interest to declare.

c. Approval of agenda and minutes presented by Tracy Klein (pages 3 - 9)

ACTION: Approved as is.

d. Department updates presented by Dr. Trevor Douglass.
Introduction of Linnea Saris to Pharmacy Policy.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 10-14)

b. ProDUR Report presented by Rich Holsapple, RPh (pages 15 - 17)

c. RetroDUR Report presented by Ted Williams, PharmD (pages 18 - 21)

d. Oregon State Drug Reviews presented by Kathy Sentena
   1. Strategies for Effective Monitoring and Management of Psychotropics in Children (pages 22 – 23)
   2. Evidence Based Review of Fish Oil: Going Beyond the Headlines (pages 24 – 25)

e. FDB Drug File Update presented by Ted Williams, PharmD (page 26)

Public Comment:

III. DUR OLD BUSINESS

a. Multivitamin PA Criteria (pages 27 – 28)
Dr. Herink presented the following proposal:

Approve PA criteria to cover multi-vitamins and antioxidants MVI combinations for documented nutritional deficiency or diagnosis associated with nutritional deficiency only.

ACTION: Motion, 2nd, All in Favor. Approved.

b. Hepatitis C "Readiness to Treat" (pages 29 - 42)
Dr. Herink presented the following information:

1. Develop a Hepatitis C readiness to treat assessment to supplement the drug prior authorization process, to help identify red flags that may affect treatment adherence and cure rates of hepatitis D virus.

2. Screen Hepatits C patients to ensure the follow:
   a. The patient is motivated to start treatment and understand the general goals of therapy.
   b. Identify any potential barriers to treatment
   c. The patient is not homeless or has a high-risk home status.
   d. The patient has not had alcohol or drug abuse in the past 6 – 12 months.
   e. The patient is getting adequate psychiatric support and treatment if applicable.

f. The patient has access to care and support system, including such things a s transportation to appointments.
g. The patient meets the criteria in the prior authorization criteria.

3. Presentation from Cory Bradley, PharmD of CareOregon presented the studies and research.
4. Clerical changes on document
   Point system identity risk factor, but not denying treatment
   Non-emergent medical assistance and transportation
   Non compliance contract between client and provider
   Risk of reinfection
   Medical coverage or loss of eligibility

Public Comment:
Stuart O'Brochta, RPh from Gilead provided comment regarding adherence and the readiness to treat document.

Bill Struyk from Johnson and Johnson just asked if document was for all products.

Lorren Sandt from Caring Ambassador's presented comment and provided data sheets regarding the epidemic of patients with Hepatitis C.

ACTION: Defer action to incorporate feedback and bring back to the July meeting a couple of proposals to be considered.

IV. DUR NEW BUSINESS

a. Botulinum Toxins (pages 43 - 67)
   Dr. Herink presented the following new guidelines:

   1. Manually review claim profiles for patients not associated with evidence-supported diagnosis to determine if BoNT was used appropriately.

   2. Consider implementing prior authorization criteria to limit use to evidence supported diagnosis.

Public Testimony:
Deirdre Monroe from Allergan, clarification of injection of botox for migraine.

ACTION: Defer action to conduct DUE with CCO utilization and bring back PA recommendations.

b. ADHD DUE (pages 68 – 82)
   Dr. Williams presented the following new guidelines:

   1. Create a safety edit for:
      Prescribing of ADHD medications by non-psychiatrists, psych mental health Nurse practioners, and pediatrician's with developmental specialty when the regimen is:
      1. Outside of the standard ages
      2. Outside of the standard doses
      3. Non-standard polypharmacy

   2. Develop retrospective program to survey providers and educational campaign.

3. Do a RetroDUR analysis to follow denials.

4. Bring back information on OPAL-K (Oregon Psychiatric Access Line for Kids) as it progresses.

ACTION: Motion, 2nd, All in Favor. Approved

V. PREFERRED DRUG LIST NEW BUSINESS

a. Cystic Fibrosis Abbreviated Update (pages 83 - 97)
Dr. Herink presented the following review:

1. Update Kalydeco PA criteria to include additional FDA approved CFTR mutations.

2. Evaluate comparative costs of tobramycin 300 mg/ 4 ml (Bethkis) in executive session for PDL (Y) placement.

3. *After executive session make Bethkis preferred.

***ACTION:** After Executive Session, all in favor.

b. Antidepressants Class Update (pages 98 - 128)
Dr. Meeker presented the following review:

1. Evidence does not support superiority of vortioxetine or levomilnacipran over other agents in this drug class. Recommend that both be listed as non-preferred agents.

2. Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

3. *After executive session. Make generic escitalopram oxalate tablets preferred.

4. *After executive session. Make imipramine pamoate and clomipramine HCL non-preferred on the voluntary PDL and when dispensed require brand name Anafranil (clomipramine).

***ACTION:** After Executive Session, all in favor.

c. Inflammatory Bowel Agents (pages 129 - 135)
Dr. Herink presented the following new class updates:

1. Continue to maintain topical and oral options as preferred on the PDL.

2. No further review of research needed at this time and review comparative costs in executive session.

3. *After executive session. No changes to PDL.

***ACTION:** After Executive Session, all in favor.

d. Phosphate Binders (pages 136 - 143) presented early

Ms. Fouts presented the following new drug evaluation:

1. Phosphate binders should be selected based on each patient's specific clinical needs.

2. Maintain a non-calcium based phosphate binder to the preferred class, based on cost.

3. Evaluate comparative costs in executive session.

4. *After executive session. Make calcium acetate generic tablets preferred.

***ACTION:** After Executive Session, all in favor.

e. Antiepileptic Class Update (pages 144 – 152)
Ms. Ketchum presented the following updates:

1. No further research required at this time. Evaluate comparative costs in executive session.

2. *After executive session. Maintain Aptiom as non-preferred.

Public Comment:
Greg Broutman from Sunovion regarding antiepileptic drugs.

***ACTION:** After Executive Session, all in favor.

f. Drug Class Scans

1. Bone Metabolism (pages 153 – 161)
Ms. Ketchum presented the following updates:

a. No further research or review needed at this time.

b. Evaluate comparative costs in executive session.

c. *After executive session. No changes to the PDL.

Public Comment:
Vandanna Slatter from Amgen gave public comment about the drug class review.

***ACTION:** After Executive Session, all in favor.

2. Erythropoiesis Stimulating Agents (pages 162 – 167)
Ms. Ketchum presented the following updates:

a. Peginesatide was removed from the market in February 2013 due to 19 reports of anaphylaxis following first dose (including 3 deaths) in patients receiving dialysis. It is recommended it be removed entirely from the PDL.

b. No further research or review is needed at this time. Evaluate comparative costs in executive session.

c. *After executive session. No changes to the PDL.

***ACTION:** After Executive Session, all in favor.

3. Hepatitis B Antivirals (pages 168 - 179)
   Dr. Herink presented the following updates:

   a. No further research or review is needed at this time. Update PA criteria to specify HBV undetectable levels and include a caveat for patients with decompensated cirrhosis.

   b. Update pediatric age restriction of entecavir on PA criteria.

   c. Evaluate comparative costs in executive session.

   d. *After executive session no changes to the PDL.

Public Comment:
Brett Marett from Bristol Myers Squibb gave public comment about updates.

***ACTION:** After Executive Session, all in favor.

4. BPH (pages 180 – 190)
   Dr. Herink presented the following updates:

   a. No further research or review needed at this time. Evaluate comparative costs in executive session.

   b. *After executive session. No changes to PDL.

***ACTION:** After Executive Session, all in favor.

5. Overactive Bladder (pages 191- 213)
   Dr. Herink presented the following updates:

   a. No further research or review needed at this time. Evaluate comparative costs in executive session.

   b. *After executive session. No changes to PDL.

***ACTION:** After Executive Session, all in favor.

6. Triptans (pages 214 – 239)
   Dr. Herink presented the following updates:

   a. No further research or review needed at this time. Evaluate comparative costs in executive session.

   b. *After executive session. Make Imitrex Brand only injectable preferred over its generic.

***ACTION:** After Executive Session, all in favor.

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

Mr. Citron confirmed the next P & T meeting will be held July 31, 2014.

VII. ADJOURN

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DHS - Division of Medical Assistance Programs
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Pharmacy Utilization Summary Report: January 2013 - December 2013

Eligibility	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Total Members (FFS & Encounter)	621,239	624,167	626,033	624,719	625,809	625,127	624,642	625,272	625,526	621,935	622,966	613,155	623,383
FFS Members	76,316	78,706	79,138	75,030	75,828	78,595	75,688	78,915	81,973	75,036	76,075	79,453	77,563
OHP Basic with Medicare	26,683	26,680	26,910	26,930	26,793	26,934	26,987	27,103	27,264	27,177	27,343	27,371	27,015
OHP Basic without Medicare	25,554	26,614	26,619	25,029	25,492	27,114	25,664	27,154	28,571	25,347	25,569	27,446	26,348
ACA	23,447	24,773	24,958	22,965	23,434	24,410	22,894	24,587	26,528	22,100	22,925	23,945	23,914
Encounter Members	544,923	545,461	546,895	549,689	549,981	546,532	548,954	546,357	543,553	546,899	546,891	533,702	545,820
OHP Basic with Medicare	36,571	36,560	36,680	36,739	37,009	37,143	37,207	37,215	37,313	37,420	37,665	37,741	37,105
OHP Basic without Medicare	233,209	233,851	234,061	234,763	235,023	232,840	234,071	233,053	230,913	230,687	228,678	222,953	232,009
ACA	274,397	274,313	275,415	277,465	277,341	275,957	277,082	275,479	274,742	278,211	279,977	272,459	276,070

Gross Cost Figures for Drugs	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	YTD Sum
Total Amount Paid (FFS & Encounter)	$34,583,082	$31,533,622	$32,646,569	$32,805,206	$33,575,135	$30,228,303	$33,915,001	$33,234,713	$32,592,899	$34,989,069	$33,786,664	$32,572,219	$396,462,480
Mental Health Carve-Out Drugs	$7,685,575	$7,122,208	$7,395,393	$7,710,456	$7,865,450	$7,177,134	$8,038,148	$7,887,685	$7,599,368	$8,228,070	$7,434,555	$7,908,255	$92,052,297
OHP Basic with Medicare	$87,077	$69,519	$64,464	$41,590	$41,635	$42,562	$44,148	$36,249	$37,419	$21,032	$13,060	$11,010	$509,764
OHP Basic without Medicare	$5,639,533	$5,253,372	$5,482,108	$5,743,232	$5,856,890	$5,358,529	$6,087,537	$5,977,943	$5,767,293	$6,207,813	$5,634,325	$5,987,747	$68,996,321
ACA	$1,905,539	$1,748,139	$1,797,444	$1,873,115	$1,910,538	$1,724,424	$1,848,276	$1,822,789	$1,738,026	$1,938,459	$1,737,438	$1,849,527	$21,893,713
FFS Physical Health Drugs	$2,865,846	$2,380,074	$2,486,317	$2,402,292	$2,400,561	$2,119,978	$2,337,104	$2,233,155	$2,226,880	$2,336,245	$2,205,473	$2,411,354	$28,405,278
OHP Basic with Medicare	$290,956	$273,580	$270,575	$277,790	$263,471	$250,798	$273,512	$269,956	$262,515	$275,323	$251,918	$272,014	$3,232,408
OHP Basic without Medicare	$1,863,122	$1,555,132	$1,626,852	$1,528,036	$1,566,947	$1,346,311	$1,533,939	$1,441,390	$1,465,746	$1,553,249	$1,457,756	$1,645,484	$18,583,964
ACA	$534,127	$430,622	$471,637	$435,904	$418,557	$402,738	$412,983	$410,100	$370,505	$392,983	$386,911	$377,623	$5,044,691
FFS Physician Administered Drugs	$1,429,669	$1,064,188	$1,222,820	$1,355,738	$1,414,525	$1,138,794	$1,296,751	$995,481	$1,095,988	$1,175,394	$1,025,838	$839,384	$14,054,569
OHP Basic with Medicare	$83,126	$84,594	$80,377	$138,688	$102,633	$88,809	$161,719	$136,071	$149,091	$160,967	$156,020	$126,724	$1,468,818
OHP Basic without Medicare	$704,118	$536,204	$629,334	$719,971	$657,507	$578,749	$636,538	$461,475	$607,512	$605,503	$421,141	$427,158	$6,985,210
ACA	$339,607	$209,743	$238,040	$114,040	$256,639	$199,414	$226,672	$175,597	$133,508	$123,621	$162,720	$64,444	$2,244,046
Encounter Physical Health Drugs	$18,463,521	$17,173,612	$17,840,448	$17,778,573	$17,555,067	$16,297,020	$17,893,352	$18,045,222	$17,539,084	$18,864,117	$19,144,092	$17,421,121	$214,015,229
OHP Basic with Medicare	$206,787	$177,649	$179,513	$176,968	$168,551	$167,607	$180,242	$195,525	$197,261	$230,974	$194,496	$243,784	$2,319,358
OHP Basic without Medicare	$11,732,676	$10,889,975	$11,456,786	$11,418,669	$11,324,652	$10,725,011	$11,874,744	$11,913,477	$11,492,182	$12,398,844	$12,485,718	$11,419,862	$139,132,597
ACA	$6,424,591	$6,011,387	$6,086,792	$6,050,825	$5,921,974	$5,284,347	$5,702,613	$5,790,799	$5,717,114	$6,074,397	$6,284,816	$5,627,659	$70,977,312
Encounter Physician Administered Drugs	$4,138,472	$3,793,540	$3,701,591	$3,558,147	$4,339,531	$3,495,377	$4,349,646	$4,073,170	$4,131,578	$4,385,244	$3,976,707	$3,992,106	$47,935,108
OHP Basic with Medicare	$116,588	$104,465	$103,968	$131,838	$137,932	$100,779	$109,851	$123,404	$91,586	$118,215	$85,537	$101,802	$1,325,966
OHP Basic without Medicare	$2,413,785	$2,256,622	$2,315,052	$2,171,633	$2,615,590	$2,158,034	$2,694,047	$2,470,192	$2,504,643	$2,596,096	$2,410,267	$2,386,240	$28,992,200
ACA	$930,295	$954,044	$811,673	$857,384	$915,275	$726,260	$852,016	$916,283	$884,917	$963,682	$853,257	$923,188	$10,588,275

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion

Last Updated: July 17, 2014

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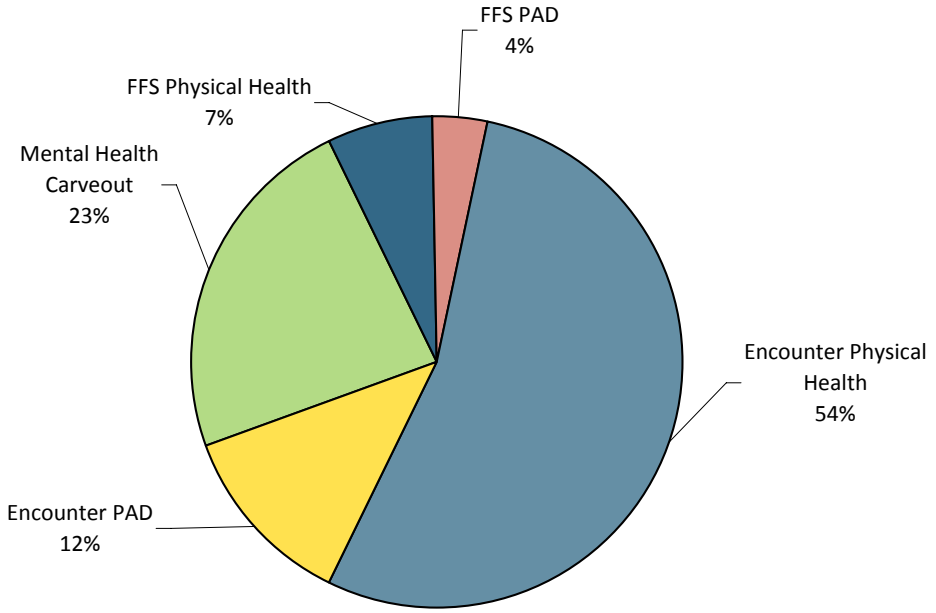
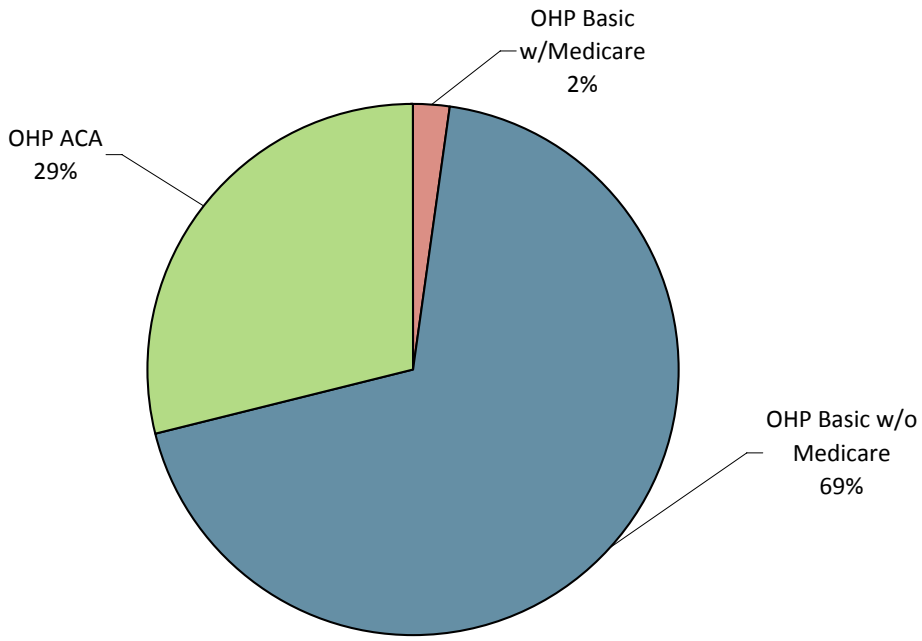
Pharmacy Utilization Summary Report: January 2013 - December 2013

YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs

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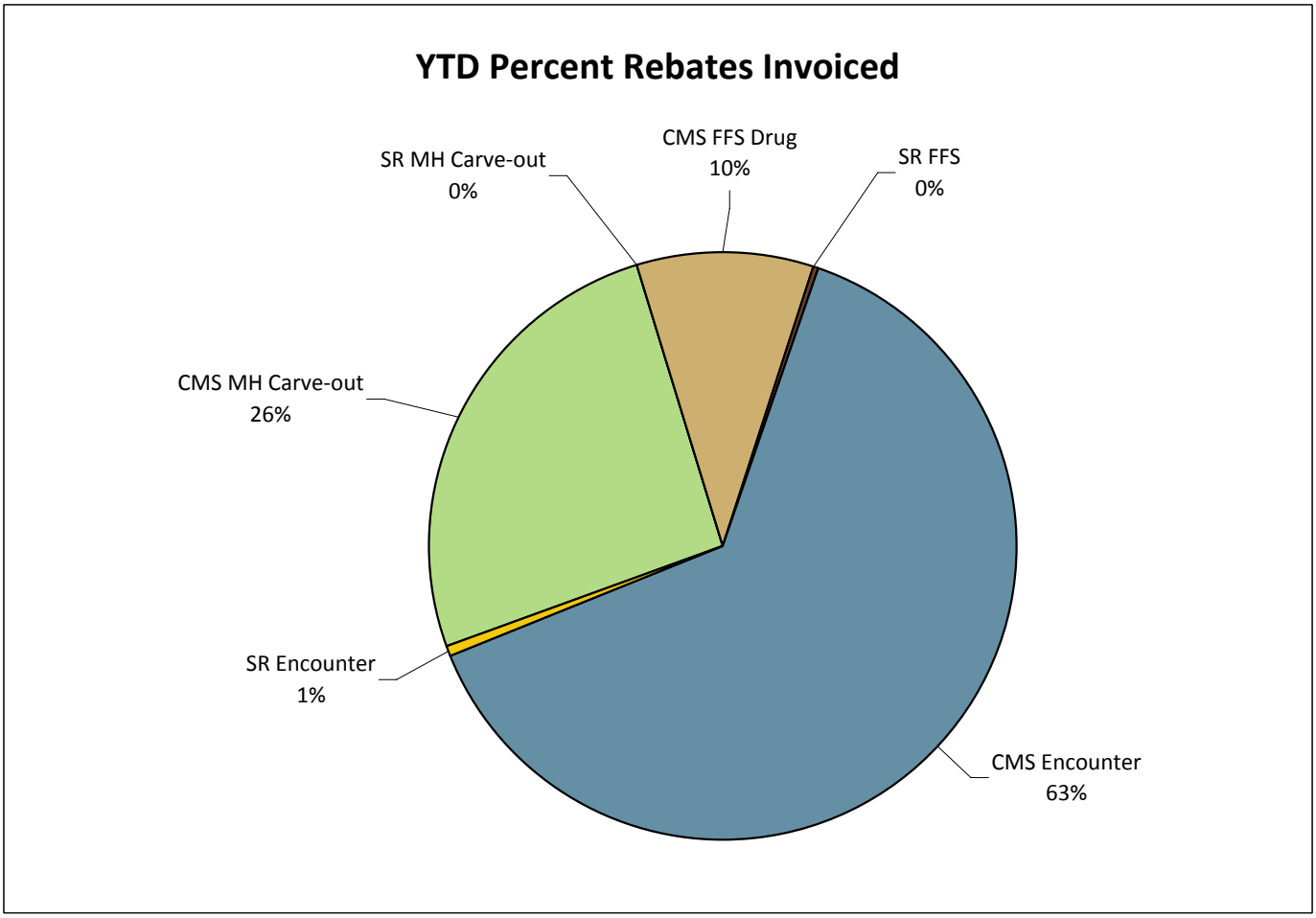
Pharmacy Utilization Summary Report: January 2013 - December 2013

Quarterly Rebates Invoiced	2013-Q1	2013-Q2	2013-Q3	2013-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$47,012,120	$50,576,074	$40,883,253	$40,974,375	$179,445,822
CMS MH Carve-out	$11,356,020	$11,511,668	$11,890,992	$11,801,015	$46,559,694
SR MH Carve-out					$0
CMS FFS Drug	$4,631,261	$4,250,177	$4,077,856	$4,206,159	$17,165,453
SR FFS	$196,493	$203,962	$169,833	$189,687	$759,974
CMS Encounter	$30,616,460	$34,249,026	$24,615,359	$24,496,481	$113,977,326
SR Encounter	$211,886	$361,242	$129,212	$281,034	$983,374

Quaterly Net Drug Costs	2013-Q1	2013-Q2	2013-Q3	2013-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$49,596,523	$49,166,538	$60,464,699	$64,217,880	$223,445,640
Mental Health Carve-Out Drugs	$11,397,020	$12,013,534	$11,679,888	$14,940,212	$50,030,653
FFS Phys Health + PAD	$6,004,134	$5,731,220	$5,745,998	$6,029,743	$23,511,095
Encounter Phys Health + PAD	$32,195,369	$31,421,784	$43,038,814	$43,247,925	$149,903,892



SR = Supplemental Rebate
CMS = Center for Medicaid Services
PAD = Physician-administered drugs
MH = Mental Health

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Pharmacy Utilization Summary Report: January 2013 - December 2013

PMPM Drug Costs (Excludes Rebate)	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$55.67	$50.52	$52.15	$52.51	$53.65	$48.36	$54.30	$53.15	$52.10	$56.26	$54.24	$53.12	$53.00
Mental Health Carve-Out Drugs	$12.37	$11.41	$11.81	$12.34	$12.57	$11.48	$12.87	$12.61	$12.15	$13.23	$11.93	$12.90	$12.31
FFS Physical Health Drugs	$37.55	$30.24	$31.42	$32.02	$31.66	$26.97	$30.88	$28.30	$27.17	$31.13	$28.99	$30.35	$30.56
FFS Physician Administered Drugs	$18.73	$13.52	$15.45	$18.07	$18.65	$14.49	$17.13	$12.61	$13.37	$15.66	$13.48	$10.56	$15.15
Encounter Physical Health Drugs	$33.88	$31.48	$32.62	$32.34	$31.92	$29.82	$32.60	$33.03	$32.27	$34.49	$35.01	$32.64	$32.68
Encounter Physician Administered Drugs	$7.59	$6.95	$6.77	$6.47	$7.89	$6.40	$7.92	$7.46	$7.60	$8.02	$7.27	$7.48	$7.32

Claim Counts	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Total Claim Count (FFS & Encounter)	672,980	601,720	620,371	619,047	612,722	565,041	611,656	603,021	589,198	674,493	617,750	591,560	614,963
Mental Health Carve-Out Drugs	102,676	92,076	96,617	97,933	98,333	89,459	97,153	94,388	90,828	97,399	89,093	93,661	94,968
FFS Physical Health Drugs	70,148	63,325	65,350	65,136	63,284	58,263	62,453	60,482	59,695	63,980	57,440	60,745	62,525
FFS Physician Administered Drugs	9,356	8,436	8,382	8,468	8,670	8,087	8,480	8,499	7,779	7,993	7,465	7,541	8,263
Encounter Physical Health Drugs	450,758	403,098	414,796	411,761	404,522	375,336	406,824	401,996	394,460	462,603	425,398	391,809	411,947
Encounter Physician Administered Drugs	40,042	34,785	35,226	35,749	37,913	33,896	36,746	37,656	36,436	42,518	38,354	37,804	37,260

Amount Paid per Claim (Excludes Rebate)	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$51.39	$52.41	$52.62	$52.99	$54.80	$53.50	$55.45	$55.11	$55.32	$51.87	$54.69	$55.06	$53.77
Mental Health Carve-Out Drugs	$74.85	$77.35	$76.54	$78.73	$79.99	$80.23	$82.74	$83.57	$83.67	$84.48	$83.45	$84.43	$80.84
FFS Physical Health Drugs	$40.85	$37.59	$38.05	$36.88	$37.93	$36.39	$37.42	$36.92	$37.30	$36.52	$38.40	$39.70	$37.83
FFS Physician Administered Drugs	$152.81	$126.15	$145.89	$160.10	$163.15	$140.82	$152.92	$117.13	$140.89	$147.05	$137.42	$111.31	$141.30
Encounter Physical Health Drugs	$40.96	$42.60	$43.01	$43.18	$43.40	$43.42	$43.98	$44.89	$44.46	$40.78	$45.00	$44.46	$43.35
Encounter Physician Administered Drugs	$103.35	$109.06	$105.08	$99.53	$114.46	$103.12	$118.37	$108.17	$113.39	$103.14	$103.68	$105.60	$107.25

Amount Paid per Claim - Multi Source Drugs (Excludes Rebate)	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.80	$23.21	$23.31	$23.45	$23.51	$23.15	$23.57	$24.01	$24.21	$22.76	$24.14	$23.69	$23.48
Mental Health Carve-Out Drugs	$35.26	$35.98	$35.80	$36.75	$36.74	$36.08	$39.10	$39.50	$39.94	$39.55	$39.28	$38.63	$37.72
FFS Physical Health Drugs	$21.00	$20.34	$20.98	$20.61	$21.28	$20.59	$21.11	$21.32	$21.03	$20.70	$20.92	$21.69	$20.96
Encounter Physical Health Drugs	$20.27	$20.80	$20.83	$20.82	$20.72	$20.55	$20.33	$20.87	$21.14	$19.60	$21.48	$20.52	$20.66

Amount Paid per Claim - Single Source Drugs (Excludes Rebate)	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$309.37	$326.33	$334.66	$342.40	$349.99	$352.31	$359.69	$360.58	$342.51	$314.94	$348.01	$358.16	$341.58
Mental Health Carve-Out Drugs	$461.73	$464.89	$461.03	$463.19	$476.79	$483.81	$486.01	$485.29	$482.88	$480.01	$480.56	$486.70	$476.07
FFS Physical Health Drugs	$251.27	$226.51	$226.64	$221.48	$226.40	$218.98	$220.11	$215.36	$221.75	$213.68	$241.05	$246.65	$227.49
Encounter Physical Health Drugs	$278.85	$303.72	$315.92	$325.00	$330.08	$332.62	$343.44	$345.21	$320.57	$284.91	$326.82	$335.07	$320.18

Multi-Source Drug Use Percentage	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Multi-Source Drug Use Percentage	91.7%	91.9%	92.0%	92.1%	92.1%	92.2%	92.2%	92.1%	91.8%	91.6%	91.9%	91.9%	92.0%
Mental Health Carve-Out Drugs	90.7%	90.4%	90.4%	90.2%	90.2%	90.1%	90.2%	90.1%	90.1%	89.8%	90.0%	89.8%	90.2%
FFS Physical Health Drugs	91.4%	91.6%	91.7%	91.9%	91.9%	92.0%	91.8%	92.0%	91.9%	91.8%	92.1%	92.0%	91.8%
Encounter Physical Health Drugs	92.0%	92.3%	92.5%	92.6%	92.7%	92.7%	92.7%	92.6%	92.2%	92.0%	92.3%	92.4%	92.4%

Preferred Drug Use Percentage	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Avg Monthly
Preferred Drug Use Percentage	86.89%	86.96%	87.02%	87.03%	84.96%	84.97%	84.97%	84.89%	84.69%	84.60%	84.51%	84.42%	85.5%
Mental Health Carve-Out Drugs	73.18%	73.12%	73.06%	73.08%	71.91%	71.19%	71.10%	71.23%	71.26%	70.92%	71.09%	71.12%	71.9%
FFS Physical Health Drugs	92.37%	92.48%	92.18%	92.29%	91.11%	91.37%	91.24%	91.56%	91.78%	91.47%	91.34%	91.46%	91.7%
Encounter Physical Health Drugs	89.58%	89.72%	89.83%	89.96%	87.71%	87.86%	87.87%	87.67%	87.37%	87.14%	86.99%	87.21%	88.2%

Last Updated: July 17, 2014

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2014

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$9,450,692	21.8%	11,696	$808	V
2	DULOXETINE HCL	Antidepressants	$4,064,168	9.4%	17,519	$232	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,543,585	3.6%	2,868	$538	V
4	INTUNIV	ADHD Drugs	$1,525,519	3.5%	5,983	$255	V
5	LATUDA	Antipsychotics, 2nd Gen	$1,361,260	3.1%	1,966	$692	V
6	STRATTERA	ADHD Drugs	$1,124,435	2.6%	4,389	$256	Y
7	INVEGA SUSTENNA	Antipsychotics, 2nd Gen	$850,126	2.0%	670	$1,269	V
8	INVEGA	Antipsychotics, 2nd Gen	$716,008	1.7%	886	$808	V
9	Factor Viii Recombinant Nos	Physican Administered Drug	$664,131	1.5%	22	$30,188	
10	DIVALPROEX SODIUM ER	Antiepileptics	$594,398	1.4%	3,699	$161	Y
11	RISPERDAL CONSTA	Antipsychotics, 2nd Gen	$404,633	0.9%	635	$637	V
12	BUPROPION XL	Antidepressants	$373,266	0.9%	12,473	$30	V
13	SERTRALINE HCL	Antidepressants	$360,730	0.8%	30,695	$12	Y
14	MODAFINIL	ADHD Drugs	$357,555	0.8%	669	$534	V
15	SAPHRIS	Antipsychotics, 2nd Gen	$335,107	0.8%	709	$473	V
16	FLUOXETINE HCL	Antidepressants	$332,234	0.8%	27,672	$12	Y
17	PRISTIQ ER	Antidepressants	$325,726	0.8%	1,530	$213	V
18	LAMOTRIGINE ER	Antiepileptics	$322,095	0.7%	652	$494	V
19	TRAZODONE HCL	STC 11 - Psychostimulants, Antidepressants	$296,651	0.7%	32,064	$9	
20	Xyntha Inj	Physican Administered Drug	$281,178	0.6%	11	$25,562	
21	BUPROPION HCL SR	Antidepressants	$263,341	0.6%	10,907	$24	Y
22	LAMOTRIGINE	Antiepileptics	$262,441	0.6%	17,405	$15	Y
23	LANTUS	Insulins	$254,039	0.6%	926	$274	Y
24	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$244,513	0.6%	10,426	$23	Y
25	ZIPRASIDONE HCL	Antipsychotics, 2nd Gen	$244,213	0.6%	2,119	$115	V
26	CITALOPRAM HBR	Antidepressants	$238,145	0.5%	28,942	$8	Y
27	HUMIRA	Targeted Immune Modulators	$234,953	0.5%	101	$2,326	Y
28	VENLAFAXINE HCL ER	Antidepressants	$213,277	0.5%	11,128	$19	Y
29	CLOZAPINE	Antipsychotics, 2nd Gen	$207,839	0.5%	2,589	$80	Y
30	PROAIR HFA	Asthma Rescue	$204,982	0.5%	3,961	$52	Y
31	LORAZEPAM	Benzodiazepine Anxiolytics	$203,445	0.5%	20,502	$10	
32	VIIBRYD	Antidepressants	$198,675	0.5%	1,153	$172	V
33	RISPERIDONE	Antipsychotics, 2nd Gen	$197,255	0.5%	11,129	$18	Y
34	Trastuzumab Injection	Physican Administered Drug	$191,041	0.4%	68	$2,809	
35	ATRIPLA	STC 33 - Antivirals	$190,935	0.4%	99	$1,929	
36	VENLAFAXINE HCL ER	Antidepressants	$175,927	0.4%	1,346	$131	V
37	ABILIFY MAINTENA	Antipsychotics, 2nd Gen	$174,659	0.4%	123	$1,420	V
38	Infliximab Injection	Physican Administered Drug	$174,030	0.4%	112	$1,554	
39	TRUVADA	STC 33 - Antivirals	$172,999	0.4%	155	$1,116	
40	ESCITALOPRAM OXALATE	Antidepressants	$169,739	0.4%	12,391	$14	V
		Aggregate	**$43,362,474**		**658,224**	**$334**	

Notes
- FFS Drug Costs only, rebates excluded
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class

Last updated: July 17, 2014

ProDUR Report for April to June 2014

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	53	21	0	32	0.05%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,715	467	0	1,246	1.55%
DD (Drug/Drug Interaction)	Set alert/Pay claim	338	90	0	246	0.31%
ER (Early Refill)	**Set alert/Deny claim**	75,599	13,960	92	61,546	68.26%
ID (Ingredient Duplication)	Set alert/Pay claim	19,112	4,795	1	14,287	17.26%
LD (Low Dose)	Set alert/Pay claim	1,087	216	0	871	0.98%
LR (Late Refill/Underutilization)	Set alert/Pay claim	153	106	0	47	0.14%
MC (Drug/Disease Interaction)	Set alert/Pay claim	2,306	938	0	1,366	2.08%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	909	259	0	647	0.82%
PG (Pregnancy/Drug Interaction)	**Set alert/Deny claim**	2,668	1,704	2	962	2.41%
TD (Therapeutic Duplication)	Set alert/Pay claim	6,809	1,964	0	4,837	6.15%
	Totals	**110,749**	**24,520**	**95**	**86,087**	**100.00%**

ProDUR Report for April to June 2014							
Top Drugs in Each DUR Alerts							
DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
DC	Haloperidol	193	57	136	2,456	7.9%	29.5%
	Wellbutrin (Bupropion)	496	82	414	38,524	1.3%	16.5%
	Diazepam	135	40	95	12,829	1.1%	29.6%
DD	Geodon (Ziprasidone)	126	32	94	5,069	2.5%	25.4%
	Celexa (Citalopram)	54	8	46	39,660	0.1%	14.8%
ER	Hydrocodone/APAP	475	100	375	11,774	4.0%	21.1%
	Oxycodone	244	109	135	4,071	6.0%	44.7%
	Lorazepam	1,901	418	1,483	28,674	6.6%	22.0%
	Alprazolam	1,545	289	1,256	22,144	7.0%	18.7%
	Lamictal (Lamotrigine)	3,262	595	2,667	28,047	11.6%	18.2%
	Abilify (Aripiprazole)	2,175	406	1,769	17,810	12.2%	18.7%
	Seroquel (Quetiapine)	2,645	564	2,081	20,181	13.1%	21.3%
	Risperdal (Risperidone)	2,190	488	1,702	16,525	13.3%	22.3%
	Wellbutrin (Bupropion)	3,256	481	2,775	38,524	8.5%	14.8%
	Zoloft (Sertraline)	4,329	753	3,576	43,613	9.9%	17.4%
	Celexa (Citalopram)	3,374	431	2,943	39,660	8.5%	12.8%
	Prozac (Fluoxetine)	3,528	544	2,984	38,269	9.2%	15.4%
	Trazodone	4,452	664	3,788	42,875	10.4%	14.9%
	Cymbalta (Duloxetine)	2,406	385	2,021	27,280	8.8%	16.0%
ID	Lamictal (Lamotrigine)	1,084	236	847	28,047	3.9%	21.8%
	Seroquel (Quetiapine)	1,167	311	856	20,181	5.8%	26.6%
	Risperdal (Risperidone)	821	240	581	16,525	5.0%	29.2%
	Zoloft (Sertraline)	1,014	243	771	43,027	2.4%	24.0%
	Prozac (Fluoxetine)	975	223	751	38,269	2.5%	22.9%
PG	Lorazepam	234	178	56	28,674	0.8%	76.1%
	Alprazolam	169	125	44	22,144	0.8%	74.0%
TD	Lamictal (Lamotrigine)	474	121	353	28,047	1.7%	25.5%
	Depakote (Divalproex Sodium)	362	98	262	14,855	2.4%	27.1%
	Seroquel (Quetiapine)	576	160	416	20,181	2.9%	27.8%
	Zyprexa (Olanzapine)	448	123	325	12,265	3.7%	27.5%
	Risperdal (Risperidone)	384	127	257	16,525	2.3%	33.1%

ProDUR Report for April to June 2014

Top Drugs in Early Refill

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	4	18	51	5	62	0
	Hydrocodone Bit/APAP	4	3	47	0	28	0
	Oxycodone HCl	6	6	56	0	49	1
	Lorazepam	12	14	157	2	151	0
	Alprazolam	12	22	107	2	84	1
	Diazepam	3	8	78	0	54	0
	Buspar (Buspirone)	5	12	81	2	61	0
	Lamictal (Lamotrigine)	24	24	220	3	164	1
	Depakote (Divalproex Sodium)	13	9	110	2	174	0
	Clonazepam	4	1	18	0	19	0
	Gabapentin	10	9	51	1	65	0
	Abilify (Aripiprazole)	17	19	110	4	174	0
	Seroquel (Quetiapine)	27	37	139	1	218	0
	Risperdal (Risperidone)	16	22	153	11	172	0
	Zyprexa (Olanzapine)	10	13	80	3	136	0
	Geodon (Ziprasidone)	5	2	33	3	50	0
	Albuterol	1	6	22	0	32	0
	Lithium Carbonate	14	8	82	5	87	0
	Wellbutrin (Bupropion)	30	29	618	4	169	0
	Prilosec (Omeprazole)	3	2	18	2	48	1
	Zoloft (Sertraline)	36	42	317	8	197	0
	Celexa (Citalopram)	26	36	139	6	141	0
	Prozac (Fluoxetine)	28	34	190	5	161	0
	Lexapro (Escitaloprim)	16	26	81	2	90	0
	Paxil (Paroxetine)	14	9	47	3	46	0
	Trazodone	33	31	247	7	258	0
	Cymbalta (Duloxetine)	18	33	123	4	122	1
	Effexor (Venlafaxine)	13	22	60	4	114	0
	Amitriptyline	12	13	102	3	84	0
	Straterra (Atomoxetine)	4	4	25	1	26	0
	TOTALS	**420**	**514**	**3562**	**93**	**3236**	**5**

Drug Use Research & Management Program
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Retro-DUR Intervention History by Quarter FFY 2013 - 2014

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified		59	61	9
		Profiles Sent		31	38	6
		Responses Received		10	11	0
		Response Rate		32%	29%	0%
		Information Useful or Will Change Practice		5	5	0
		Patient Not With Office		0	0	0
		Already Scheduled		5	10	0
		Will Not Schedule		0	0	0
		Requested No Future Notifications		1	4	0
	Antipsychotic Metabolic Monitoring	Members Identified		707	900	432
		Profiles Sent		706	866	432
		Members With Response		165	46	0
		Response Rate		23%	5%	0%
		Newly Scheduled		95	9	0
		Provider Contacted		76	386	164
		Provider Responses		16	17	
		Provider Agreed with Recommendation		4	6	0
		Patient Not With Office		20	7	0
	Polypharmacy	Members Identified		404	65	219
		Profiles Sent		387	54	0
		Responses Received		195	21	0
		Response Rate		50%	39%	
		Information Useful or Will Change Practice		37	2	0
		Patient Not With Office		18	3	0
		Not Helpful, waste of time		23	1	

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Retro-DUR Intervention History by Quarter FFY 2013 - 2014

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Profile Review	Children under age 12 antipsychotic	Profiles Reviewed	122	98	108	
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	33	24	14	
	Children under age 18 on any psychotropic	Profiles Reviewed	195	92	94	
	Children under age 6 on any psychotropic	Profiles Reviewed	5	10	10	
	Lock-In	Profiles Reviewed	41	84	19	
		Letters Sent To Providers	6	3		
		Provider Responses	0	0		
		Provider Agreed / Found Info Useful	0	0		
		Locked In	17	56	19	

Drug Use Research & Management Program

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2012 - 2013

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	1,479	3,097	48%	1,431	3,052	47%	1,601	2,538	63%	1,420	2,923	49%
Five or more concurrent psychotropics	152	10,588	1%	153	10,939	1%	154	9,076	2%	164	10,201	2%
Three or more concurrent psychotropics	2,033	10,588	19%	2,075	10,939	19%	1,980	9,076	22%	1,882	10,201	18%
Two or More Concurrent Antipsychotics	149	10,588	1%	147	10,939	1%	121	9,076	1%	113	10,201	1%
Under 18 years old on any antipsychotic	3,115	10,588	29%	3,069	10,939	28%	2,956	9,076	33%	2,937	10,201	29%
Youth five years and younger on psychotropics	266	10,588	3%	283	10,939	3%	294	9,076	3%	257	10,201	3%

7/29/2014

Important: Totals for each quarter are generated three months after the end of the quarter to allow for delays in claim submission. Therfore, totals in this report may differ from dashboard reports, which do not account for

Note: The metric "Under 18 years old on any antipsychotic" counts children with or without diabetes receiving antipsychotics. The metric "Children on antipsychotics without diabetes screening" excluded children with pre-existing diabetes.

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Drug Use Research & Management Program

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2013 - 2014

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	1,356	2,833	48%	1,438	2,889	50%						
Five or more concurrent psychotropics	143	9,970	1%	140	10,911	1%						
Three or more concurrent psychotropics	1,992	9,970	20%	1,979	10,911	18%						
Two or More Concurrent Antipsychotics	110	9,970	1%	113	10,911	1%						
Under 18 years old on any antipsychotic	2,841	9,970	28%	2,899	10,911	27%						
Youth five years and younger on psychotropics	223	9,970	2%	242	10,911	2%						

7/29/2014

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Fee For Service

Fiscal Year 2012 - 2013

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	367	622	59%	344	577	60%	721	527	137%	303	492	62%
Five or more concurrent psychotropics	30	2,163	1%	29	2,152	1%	54	2,049	3%	27	1,824	1%
Three or more concurrent psychotropics	354	2,163	16%	350	2,152	16%	627	2,049	31%	313	1,824	17%
Two or More Concurrent Antipsychotics	28	2,163	1%	21	2,152	1%	48	2,049	2%	27	1,824	1%
Under 18 years old on any antipsychotic	623	2,163	29%	578	2,152	27%	933	2,049	46%	493	1,824	27%
Youth five years and younger on psychotropics	49	2,017	2%	54	2,152	3%	97	2,049	5%	54	1,824	3%

7/29/2014

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Fiscal Year 2013 - 2014

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	311	529	59%	384	621	62%						
Five or more concurrent psychotropics	19	1,969	1%	27	2,414	1%						
Three or more concurrent psychotropics	381	1,969	19%	439	2,414	18%						
Two or More Concurrent Antipsychotics	30	1,969	2%	24	2,414	1%						
Under 18 years old on any antipsychotic	531	1,969	27%	623	2,414	26%						
Youth five years and younger on psychotropics	49	1,969	2%	70	2,414	3%						

7/29/2014

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Second Generation Antipsychotics: Are these drugs effective in treating PTSD?

By Ramona Shayegani and Vivian Tang Pharm.D. Candidates 2014, Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

The National Comorbidity Survey Replication recently estimated an increase in lifetime prevalence of Posttraumatic Stress Disorder (PTSD) among adult Americans to be 6.8% compared to the previous rate of 3.5%.[1] This rise may be due to the increasing incidence of combat-related PTSD within recent years. Studies have found a prevalence of up to 19.6% in veterans returning from service in Iraq and Afghanistan.[1,2]

Typical symptoms of PTSD include persistent re-experiencing of traumatic events (e.g., flashbacks, nightmares), and avoidance of thoughts and feelings related to the event.[3] Other symptoms include decreased concentration, insomnia, irritability and hypervigilance.[3] Psychotherapy with or without pharmacotherapy is considered standard of care to improve symptoms and daily functioning in PTSD patients.[5]

Selective serotonin reuptake inhibitors (SSRIs) or venlafaxine are recommended first line for PTSD treatment. Sertraline and paroxetine are the only SSRIs approved by the Food and Drug Administration (FDA) for PTSD.[5] Some patients, particularly combat veterans, respond poorly to this class of drugs.[6,7] Also, a majority of PTSD patients present with psychiatric comorbidities.[8] In light of this, many clinicians seek augmentation strategies with a variety of medications to enhance medication response in patients with SSRI resistant PTSD symptoms. Adjunct treatment options include tricyclic antidepressants, monoamine oxidase inhibitors, non-SSRI antidepressants (mirtazapine and nefazodone) and prazosin.[5] Second-generation antipsychotic (SGAs) are often utilized for treatment of psychotic symptoms in PTSD despite the limited amount of evidence. The purpose of this review is to explore the literature on the use of SGAs as an augmentation therapy in the management of SSRI resistant PTSD patients.

The Evidence

Use of SGAs in PTSD is strongly correlated to the presence of comorbid psychotic, bipolar or cognitive disorders and recent psychiatric hospitalization.[9] A study at a single Veterans Affairs (VA) medical center found that SGAs were most commonly prescribed for their perceived "efficacy" and the goal of "[improving] sleep or sedation" in individuals with PTSD.[10] Another study which looked at multiple VA sites reported 19.9% of PTSD patients were prescribed an antipsychotic medication with 93.6% of these prescriptions being an SGA.[11]

In clinical practice, the selection of the most appropriate SGAs has been left up to the clinician's discretion and patient preferences. According to 2004 American Psychiatric Association (APA) guidelines, risperidone, olanzapine, and quetiapine are recommended as possible adjunct treatment options for PTSD, however, the supporting evidence for this recommendation is limited.[4] On the other hand, the 2012 revised VA/Department of Defense (DoD) PTSD Clinical guidelines do not recommend any SGAs due to lack of evidence.[5]

Risperidone

The largest body of evidence for the use of SGAs as augmentation treatment for PTSD comes from trials of risperidone. A meta-analysis of seven double blind placebo controlled trials suggested that both monotherapy and augmentation therapy with olanzapine and risperidone is efficacious in improving symptoms of PTSD, measured by the Clinician Administered PTSD Scale (CAPS) (standard mean difference, SMD, -0.94; 95% CI -0.75 to -0.14).[12] However, there was no difference in responder rate. The evidence was limited based on a small number of diverse trials.

The most recent randomized trial by Krystal et al., in 2011 compared the efficacy of risperidone versus placebo for the treatment of SSRI-resistant PTSD as measured by the CAPS change in baseline.[13] The study was conducted at 23 VA medical centers from 2007 to 2010 and included 247 highly symptomatic veterans despite having received at least 2 adequate SSRI treatments (4 weeks of therapy) prior to the study enrollment.[13] They were allowed to be on other pharmacotherapy agents including prazosin, trazodone, nefazodone, quetiapine and mirtazapine.[13] Participants were randomized to either a target dose of risperidone 4 mg daily (n=133) or placebo (n=134).[13] After 6 months of therapy, no significant difference was found with change in CAPS scores from baseline between risperidone (-16.3; 95% CI, -19.7 to -12.9) and placebo (-12.5; 95% CI, -15.7 to -9.4; mean difference 3.74; 95% CI, -0.86 to 9.35; p = 0.11).[13] Both groups were also receiving a similar number of other pharmacotherapy agents (risperidone 3.09 vs. placebo 2.86) during this trial.[13] The most common side effects were self-reported weight gain (risperidone 15.3%; placebo 2.3%), fatigue (risperidone 13.7%; placebo 0%), somnolence (risperidone 9.9%; placebo 1.5%) and hypersalivation (risperidone 9.9%; placebo 0.8%).[13] This study failed to show any additional benefits when risperidone was used in combination with SSRIs in treating PTSD.[13] This RCT was higher quality of evidence and included a much larger sample size (n=247) compared to the trials used in the previous meta-analysis which most included less than 40 subjects. The Va/DoD clinical practice guidelines originally recommended off-label risperidone, olanzapine, or quetiapine for the adjunctive treatment of patients with PTSD.[5] However, based on the negative results of this recent VA study, the 2012 revised VA/DoD PTSD Clinical Practice Guideline "recommend against the use of risperidone as adjunctive therapy.", stating insufficient evidence as an adjunctive therapy for the treatment of PTSD.[5]

Quetiapine

Of the SGAs, quetiapine has the largest proportion of off-label use (42.9%) for treatment of PTSD in the VA system.[11] However, supporting evidence is low quality, with mostly open-label, small studies. A six-week open-label trial (n=20) by Hamner et al., was the first to show a significant reduction in PTSD symptoms when quetiapine was used as an adjunct treatment.[14] Another open-label, 8 week study (n=15) by Ahearn et al., reported a 42% overall improvement in PTSD symptoms in patients with refractory symptoms on background SSRI therapy,. as measured by CAPS scores and significant improvement in each symptom cluster including re-experiencing, hyperarousal and avoidance.[15] The use of quetiapine has also been studied as an adjunctive treatment to reduce PTSD-related nightmares. In 2010, a prospective cohort trial and the first comparative study examined the long-term efficacy and safety of quetiapine versus prazosin for treatment of nighttime symptoms in combat veterans with PTSD.[16] Patients in this study (n=237) received either prazosin (n=62) or quetiapine (n=175).[16] Efficacy of the drug was identified through physician notation that "patient's nighttime symptoms improved" or "frequency of nightmares decreased."[16] The prazosin and quetiapine groups had similar short-term efficacy (61.3% vs 61.7%; p= 0.54) with symptomatic improvement within 6 months.[16] However, the prazosin group had significantly greater long-term efficacy (48.4%) compared with those receiving quetiapine therapy (24%; P <0.001; OR 3.0; 95% CI, 1.62-5.45) as therapy continued for approximately 3 to 6 years.[16] In terms of concurrent therapies, there were more patients in the prazosin group than the quetiapine group who were receiving sleep agents (32% vs. 18%; P = 0.02) such as diphenhydramine, trazodone, mirtazapine, zolpidem, and/or a benzodiazepine.[16] Patients in the quetiapine group were more likely to have been on an SSRI at baseline (69% vs. 53%; p = 0.02) or had an SSRI added on at baseline (80% vs. 61%; p = 0.005).[16] The prazosin group was less likely to discontinue therapy due to adverse events compared to

those receiving quetiapine (17.7% vs. 34.9%; p = 0.008).[16] The most frequent adverse effect resulting in therapy discontinuation in the quetiapine group was sedation (21% vs. prazosin 1.6%; p < 0.001).[16] There were also significantly more patients in the quetiapine group that discontinued therapy due to metabolic effects (9.1% vs. prazosin 0%; p = 0.014).[16] At the end of the study, 25% of quetiapine patients were switched to prazosin; whereas only 8% of prazosin patients were switched to quetiapine.[16] Based on the results of this study the authors concluded that prazosin should be used as the first line adjunctive treatment for PTSD-related sleep disturbances due to its superior long-term efficacy and safety.[16] The American Academy of Sleep Medicine as well as VA/DoD guidelines highly recommended the adjunctive use of prazosin for treatment of resistant sleep problems and nightmares in PTSD patients.[5,17]

Olanzapine

Previously, the evidence supporting the role of olanzapine in treating PTSD symptoms was limited to only case reports and small studies, as emphasized in the meta-analysis by Pae et al.[12] One of these small randomized, double-blind placebo controlled study examined the effect of adjunctive use of olanzapine (mean dose: 15 mg/day) versus placebo in 19 male veterans with SSRI resistant PTSD.[18] Olanzapine was associated with a significant improvement in CAPS score (14.80 vs placebo 2.67; p < 0.05).[18] In particular, sleep disturbances as measured by self-report Pittsburgh Sleep Quality Index (PSQI -3.29 vs 1.57; p = 0.01) and depressive symptoms as measured by self-rated Center for Epidemiologic Studies Depression Scale (CES-D 5.25 vs 4.88; p < 0.03) were significantly reduced in olanzapine group versus placebo.[18] However, participants receiving adjunctive treatment with olanzapine exhibited a significantly greater weight gain (13.2 lb vs -3.0 lb; p = 0.001).[18]The authors concluded that adjunctive use of olanzapine was superior compared to placebo in reducing PTSD symptoms particularly sleep disturbances and depressive symptoms.[18] However, this clinical benefit may come at the cost of weight gain and other metabolic disturbances.[18]

Aripiprazole

In 2005, Lambert et al published a case series examining the efficacy of aripiprazole in addition to ongoing treatment with cognitive behavioral therapy or with sertraline in five PTSD patients.[19] The authors reported that adding aripiprazole 15 or 30 mg at bedtime significantly improved symptoms in four out of five patients.[19] One patient reported agitation and inability to sleep on aripiprazole 15 mg and thus discontinued therapy.[19] The authors did not report the duration of follow-up for patients.[19] Recently, a 12-week, open-label trial conducted in veterans with severe PTSD demonstrated that using aripiprazole as adjunct treatment significantly reduced symptoms in 53% of the 17 subjects leading to a 20% reduction in total CAPS scores.[20] Another recent 12-week retrospective chart review examined PTSD symptom improvement in 27 military veterans as measured by total PTSD Checklist-Military Version (PCL-M) scores: a 17-item self-report measure completed by participants.[5] This study demonstrated that the addition of aripiprazole (average dose of 12.40 mg daily) to standard PTSD treatment decreased total PCL scores from 56.11 at baseline to 46.85 ($p < 0.0001$).[21]

Conclusion

Off-label use of antipsychotics for the treatment of PTSD remains controversial based on low quality evidence, including very small studies of limited duration. Most studies have focused on war veterans with PTSD and therefore it is challenging to extrapolate the results to the general population (e.g. civilians and women). Furthermore, combat related PTSD may be more resistant to SSRI treatment. All SGAs can cause significant side effects and therefore routine monitoring is required to safely use these medications. More robust evidence is needed to clarify the potential utility of these medications in the treatment of PTSD. Risks and benefits should be carefully considered before prescribing SGAs.

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New Cholesterol Guidelines: A Significant Shift in Cholesterol Management

By Yennie Quach, Pharm.D., Janine Lee Pharm.D. Candidate 2014, Megan Herink, Pharm.D., and Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

The recently published cholesterol treatment guidelines developed by the American College of Cardiology (ACC) and the American Heart Association (AHA) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) have recommend substantial changes from the 2004 Third Adult Treatment Panel (ATP III) guidelines.[1] The new guidelines abandon specific cholesterol treatment goals and instead focus on four high-risk groups that are most likely to benefit from statin therapy. The new guidelines also emphasize that overall risk of heart disease and stroke should be evaluated on an individual basis and recommend only using medications that have been proven to reduce atherosclerotic cardiovascular disease (ASCVD) risk.

To write the new guidelines, the expert panel focused heavily on high quality evidence from randomized controlled trials (RCTs) and systematic reviews of RCTs to create evidence-based recommendations, while the previous guidelines also included observational studies.[2] This approach led to more uncertainties in areas where high quality evidence is not available.

Should We Continue to Treat-to-Target?

The guidelines argue that multiple RCTs have shown that ASCVD events are reduced by optimizing fixed doses of statin therapy rather than obtaining pre-specified LDL-C goals.[3–5] However, a meta-analysis that evaluated the effects of statin therapy in lowering LDL-C in individuals with low risk for vascular disease conducted by the Cholesterol Treatment Trialists (CTT) Collaborators, supports LDL-C lowering goals.[6] Results showed that incremental reductions in LDL-C produced reductions in major vascular events, such as non-fatal myocardial infarction (MI) or coronary deaths (RR 0.79; 95% CI 0.77-0.81; p<0.0001, per 1.0 mmol/L reduction).[6] Nonetheless, the guideline panel concluded that there is insufficient evidence from RCTs that titration of LDL-C to specific targets further reduces coronary heart disease (CHD) or ASCVD beyond that achieved by simply giving a high-intensity statin. The guidelines also acknowledge that treating to cholesterol targets could potentially result in overtreatment with non-statin therapies which have failed to show a reduction in secondary ASCVD and could result in adverse effects from the use of multiple medications.[6,7]

Furthermore, when evaluating these trials further, the Treating to New Target (TNT) study and Pravastatin or Atorvastatin Evaluation of Infection Therapy (PROVE-IT) trial do indeed seem to support use of further lowering of target LDL-C levels for the reduction in risk of CV outcomes. The TNT study compared the CV benefits of atorvastatin 80 mg verses the lower dose of 10 mg in patients with stable CHD.[3] Results from TNT study demonstrated that treating to a mean target LDL-C of 75 mg/dL reduced the risk of nonfatal MI (HR=0.78; 95% CI 0.66-0.93; p=0.004) and fatal or nonfatal stroke (HR=0.75; 95% CI 0.59-0.96; p=0.02) compared to a target LDL-C of 100 mg/dl with fixed dose statins. [3] The PROVE-IT trial compared the risk reduction in death and CV events in individuals with an acute coronary syndrome taking pravastatin 40 mg with an LDL-C goal of 100 mg/dL compared to atorvastatin 80 mg with an LDL-C goal of 70 mg/dL.[4] Similarly to the TNT study, the results of the PROVE-IT trial suggests that a median LDL-C of 62 mg/dl significantly reduced the risk for requiring revascularizations (RR 0.87; 95% CI 0.76-0.99; p=0.04) and recurrent unstable angina (RR 0.74; 95% CI 0.55-0.99; p=0.02) when compared to a mean LDL-C of 95 mg/dL [4]

Focusing on Risk

The guidelines identified four high-risk populations that benefit from statin therapy: 1) individuals with known ASCVD, 2) adults with LDL-C ≥ 190 mg/dL, 3) individuals with diabetes who are 40 to 75 years old with LDL-C between 70 to189 mg/dL, 4) individuals who are 40 to 75 years old with a 10-year ASCVD risk greater than 7.5% and LDL-C between 70 to 198 mg/dL.[1] These risk categories make it easier to identify individuals who are most likely benefit from treatment with a statin. Rather than focusing on LDL-C targets, the new guidelines take into consideration a patient's overall CV risk.

Based on a review of RCTs included in the CTT meta-analysis, high-, moderate-, and low-intensity statin therapy were defined as a goal percent reduction in LDL-C by approximately ≥50%, 30-50%, and <30%, respectively (Table 1).[1] The meta-analysis provided high quality evidence that atorvastatin 40 mg to 80 mg reduced ASCVD risk significantly more than atorvastatin 10mg, pravastatin 40mg, or simvastatin 20 to 40 mg twice daily (moderate-intensity).

Table 1: Recommended Statins and Doses[8]

High-Intensity Therapy	Moderate-Intensity Therapy	Low-Intensity Therapy
Atorvastatin 40-80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20-40 mg** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10-20mg** **Lovastatin 20 mg** *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

*Statins and doses that are **Bold** were evaluated in RCTs.
**Statins and doses that are *Italics* are approved by the U.S. FDA, but not tested in RCTs reviewed by the guideline panel

It is recommended that patients with established ASCVD and those with LDL-C ≥ 190 mg/dL (groups 1 and 2) should be initiated on high intensity statin therapy. They also recommend considering moderate intensity statin therapy in older patients (>75 years old) with ASCVD and in individuals with diabetes with LDL-C between 70 to 189 mg/dl. In those >75 years old, it is reasonable to continue statin therapy in those who are tolerating it, as the recommendation for starting a lower dose is based on expert opinion and the potential for an increased risk of adverse effects and drug-drug interactions. In those who are intolerant to a high-intensity statin and/or who are receiving concomitant medications that can potentially increase risk of statin related adverse events, moderate intensity therapy is also recommended. There is good evidence to support a benefit from moderate intensity statins if a patient cannot tolerate the higher dose. The guidelines also acknowledge that non-statin drug therapy has not shown a reduction in ASCVD events in RCTs. The lack of evidence for other medications as well as the minimal safety concerns associated with statins is cited as reason for the major emphasis on statin therapy in the guidelines.

For primary prevention in those without clinical ASCVD and LDL-C 70-189 mg/dl (group 4), the expert panel provides a new risk calculator to assess the estimated 10-year risk for an ASCVD event and to identify candidates for statin therapy.[1] Patients calculated as having >7.5% 10-year ASCVD risk are included as a major statin benefit group. [1] This recommendation that people at lower risk for CV should receive a statin comes from the CTT meta-analysis.[6,9] The authors concluded that the significant benefit of statins in low risk patients (five year risk <10%) outweighed any known risks of therapy, based on a reduction in major coronary events (RR 0.61; 99% CI 0.50-074; p<0.0001). However, the data did not demonstrate a significant effect on overall mortality (RR 0.95; 95% CI 0.86-1.04) in low risk patients. A recent article argued that the data supporting this conclusion was based on soft

outcomes such as coronary revascularization procedures, with an increased risk of bias from RCTs predominantly funded by the manufacturer of the statin being studied.[9] In addition, although the meta-analysis resulted in similar adverse effects between placebo and statin groups, generalizing this data to the real world population may be difficult. Study patient selection often results in exclusion of elderly patients, those with medical comorbidities or potential drug-drug interactions, and women.[10]

The peer-reviewed calculator uses the Pooled Cohort Equations which were developed by the Risk Assessment Workgroup of the guidelines. Controversy over the calculator's validity has been raised as it has only been peer-reviewed. There is no high quality evidence supporting its use, but rather the recommendation is based on expert opinion and outdated studies.[9,11] In addition, there has never been a RCT that uses a risk prediction score as inclusion criteria However, this calculator has both strengths and weaknesses. The guidelines state that use of the Pooled Cohort Equations more adequately represents women and African Americans when compared to Framingham calculations.[1] Furthermore, the new risk calculator may also overestimate risk and significantly broaden the patient pool that will qualify for statin treatment; a result that may lead to various unknown implications.

Implications to Practice

The new ACC/AHA recommendations are essentially based on the same body of evidence used by previous ATPIII guidelines, just excluding certain data based on study design. They have taken many steps in the right direction, including focusing on the prevention of stroke as well as heart disease, emphasizing statin therapy rather than agents with no proven benefit on clinical outcomes, and stating the importance of intensive treatment with statins.[12] Conversely, the recommendations for primary prevention and the concern for overestimation of risk remain contentious.

A recent study published by Pencina et al. used data from the National Health and Nutrition Examination Survey to estimate the number of individuals who would be candidates for statin therapy according to the new guidelines, as compared with the previous ATP III guidelines.[13] Of the study sample, 42% of subjects would be eligible for a statin on the basis of the ATP III guidelines, as compared to 56.5% based on the new ACC/AHA guidelines. When extrapolated to U.S. adults, an estimated 56 million adults (48.6% of U.S. population; 95% CI 46.3-51) adults would be eligible for statin therapy based on the ACC/AHA recommendations compared to 43 million (37.5%; 95% CI 35.3-39.7) per the ATP III guidelines [13] This indicates that almost 13 million additional individuals are now eligible for statin therapy; the majority of which now qualify as a result of the new risk calculator. In patients without CV disease, the biggest difference in eligibility was found in older adults between 60 and 75 years of age.

The National Committee for Quality Assurance is proposing retirement of LDL-C monitoring from HEDIS 2015 Criteria in patients 18 to 75 years old with overt ASCVD based upon the recommendation to move away from the treat-to-target method.[14] If approved, this proposal would result in vast changes in the monitoring and quality improvement initiatives involving these patients.

The current pipeline of new lipid lowering drugs is extremely immense, with over 50 new drugs currently in development.[15] Many of these drugs, such as the PCSK9 inhibitors and the cholesterol ester transfer protein (CETP) inhibitors, have novel mechanisms of action. Some of these agents are demonstrating drastic reductions in LDL-C levels (up to 70%).[16] Nevertheless, with the guidelines' shift in focus to ASCVD outcomes rather than reductions in LDL, they may not fit into future guidelines and recommendations unless they can demonstrate ASCVD risk reduction.

In conclusion, the recent ACC/AHA cholesterol guidelines have the potential to greatly simplify and improve care for those patients at a higher risk. The new risk assessment tool significantly expands the number of low risk patients on statin therapy for primary prevention. With the conflicting evidence and uncertainties in the guidelines, it remains essential that health care providers consider the risk benefit ratio for each individual patient until further data is available.

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Recent Additions to the First DataBank (FDB) Drug File

Following is a list of agents recently added to the FDB drug file which were not subject to previous PA criteria. In accordance with OAR 410-121-0040(5)(b)

> *If the new drug is indicated for a condition below the funding line on the Prioritized List of Health Services, PA shall be required to ensure that the drug is prescribed for a condition funded by OHP*

These medications require a Prior Authorization to ensure use only for funded conditions.

Week of:	Generic	Brand	FDA Approved Indication(s)	ICD9 Code	HERC Funding Line
6/13/2008	Cyclosporine	Restasis	Suppressed tear production	375	537
6/19/2014	efinaconazole	Jublia	Dermatophytosis of nail	110.1	517

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Abbreviated Class Update: Hepatitis C

Month/Year of Review: July 2014
Current PDL Class: Hepatitis C Agents

Last Review: March 2014
Source Document: OSU College of Pharmacy

- **Preferred Agents:** BOCEPREVIR (VICTRELIS®), TELAPREVIR (INCIVEK®), SOFOSBUVIR (SOLVALDI®), SIMEPREVIR (OLYSIO®), PEGINTERFERON ALPHA-2A (PEGASYS®), PEGINTERFERON ALPHA-2A SUBQ (PEGASYS®, PEGASYS PROCLICK®), PEGINTERFERON ALFA-2B, PEGINTERFERON ALFA-2B, RIBAVIRIN
- **Non-Preferred Agents**: INTERFERON ALFACON-1 (INGERGEN®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

Current PA: Prior authorizations are currently in place or have been recommended for pegylated interferon and ribavirin (PR), for the oral protease inhibitors, and for sofosbuvir (Appendix 1) to ensure treatments are supported by the medical literature.

Research Questions:
- Is there any new evidence about comparative effectiveness of antiviral regimens, in long term clinical outcomes such as mortality and hepatitis C complications or in sustained virologic response (SVR) in adult patients being treated for chronic Hepatitis C virus (HCV)?
- Is there any new evidence about comparative harms of antiviral regimens in adult patients being treated for chronic HCV?
- Are there subpopulations of patients with HCV for which one antiviral regimen is more effective or associated with less harm?

Conclusions:
- New guidelines recommend prioritization of HCV patients for treatment based on disease severity, including those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations.[1,2]
- There remains insufficient evidence evaluating treatment with sofosbuvir or simeprevir in patients with decompensated cirrhosis. New guidelines recommend that those with decompensated cirrhosis not on a transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy and safety outcomes have not yet been established for this group.[3]
- There is new low quality evidence that simeprevir in combination with peginterferon alfa and ribavirin results in a higher SVR rate compared to peginterferon plus ribavirin dual therapy in GT1 chronic HCV patients, both treatment naïve and previous relapsers.[4,5]
- There remains insufficient evidence evaluating sofosbuvir in subpopulations and comorbidities including those with decompensated cirrhosis, HBV or HIV co-infection, treatment experienced patients, patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, and renal disease.[6]
- There is a lack of comparative evidence and evidence from randomized controlled trials evaluating the efficacy and long term safety of sofosbuvir in patients with genotype 1 HCV. New guidance from the National Institute for Health and Care Excellence and the German Institute for Quality and Efficiency in

Healthcare have concluded they cannot decide if sofosbuvir is a cost-effective use of resources, particularly in genotype 1 patients, until more comparative evidence is available.[7,8]

Recommendations:

- Recommend including additional changes to PA criteria (Appendix 1), including ensuring the patient is seen by or in consultation with hepatologist only.
- Consider excluding patients with decompensated cirrhosis due to lack of evidence in this patient population or only patients with decompensated cirrhosis on the transplant list who are more severe and need treatment.
- Continue to prioritize patients for treatment based on disease severity and stage of fibrosis.

Previous Conclusions and Recommendations:

- In Genotype 1 treatment naïve patients and treatment experienced patients, there is insufficient to low quality evidence that simeprevir does not appear to significantly improve the SVR12 compared with triple therapy with boceprevir and telaprevir, and its effectiveness is diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. [9] Simeprevir requires peginterferon and ribavirin (PR) and cannot be used to treat interferon-ineligible patients. There is an ongoing randomized trial comparing simeprevir to telaprevir is the first trial directly comparing 2 antiviral agents. Sofosbuvir therapy appears to have the highest SVR12 in this population (83%; 95% CI 79% to 87%).[9]
- There is insufficient evidence to evaluate the use of simeprevir or sofosbuvir in treatment-naïve genotype 1 patients who are interferon-ineligible.
- There is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients or simeprevir plus PR.
- There is low quality evidence that in genotypes 2 CHC, sofosbuvir-based therapy improves SVR rates compared to dual therapy with pegylated interferon and ribavirin.
- There is low quality evidence, based on one unpublished open-label trial, that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks results in high SVR12 rates (79-96%) in HCV genotype 1 null responders with METAVIR F0-F2 fibrosis.[10]
- There is insufficient evidence that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks is efficacious in HCV genotype 2 treatment naïve and null responder patients with METAVIR F3-F4 fibrosis. Only preliminary data is available demonstrating SVR4 rates of 96-100%; SVR12 rates have not yet been released.[10]
- There is insufficient evidence evaluating the safety and efficacy of simeprevir in HCV patients with moderate or severe hepatic impairment. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 ULN or lower, and transaminase level of 10 x ULN or lower. It should be limited to patients with compensated liver disease.
- There is insufficient data evaluating sofosbuvir in patients with severe renal impairment (CrCl <30 ml/min) or those who require hemodialysis. There is no dosing data currently available for this patient population.

Reason for Review: The evidence and clinical practice guidelines for the treatment of chronic Hepatitis C continues to evolve. New evidence, including systematic reviews and clinical guidelines, will be reviewed for further decision-making.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[11] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels

following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer. [11] The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. The studies evaluating sofosbuvir use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.[12] Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post treatment.[6]

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients. [11] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[13] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[14]

Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (Metavir fibrosis stage 2 or greater). Patients with compensated cirrhosis are at risk of progressing to decompensation, hepatocellular carcinoma or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.[15]

Simeprevir is a recently approved protease inhibitor used in combination with pegylated interferon and ribavirin for the treatment of adult patients with genotype 1 CHC. This includes patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon therapy with or without ribavirin. There are trials underway evaluating its use in genotype 4 infection and HCV/HIV co-infection. Studies investigating the use of simeprevir as part of interferon-free regimens have also been intiated.[16] Simeprevir structurally binds to a target enzyme which is different than telaprevir and boceprevir (14-membered macrocycle). It is given orally once a day with any type of food for 12-48 weeks depending on whether the patient is treatment-naïve, a prior relapse, or a nonresponder.

Sofosbuvir is a nucleotide inhibitor of HSV NS5B RNA-dependent RNA polymerase with broad genotypic activity. Sofosbuvir was given breakthrough therapy designation as the first potential interferon-free CHC therapy from the FDA that allowed an expedited approval program.[12] The criteria for a breakthrough therapy designation from the FDA is that a) it is used for a serious condition, and b) preliminary clinical evidence demonstrates substantial improvement over available therapy on one more clinically significant endpoints. Unlike the other available protease inhibitors, there is no response guided therapy criteria for its use.

Methods:
A Medline literature search beginning February 2014 (since the most recent Hepatitis C Class Update) and ending June 2014 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC), telaprevir (TVR), simeprevir (SIM), and sofosbuvir (SOF) was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
The Oregon Center for Evidence-based Policy recently evaluated sofosbuvir for the treatment of hepatitis C.[6] Ten studies were identified, as well as three studies cited in the FDA review which have not been published. Since the release of this report, the VALENCE trial has been published and is described in Table 3.[17] There was one placebo controlled trial and one study that compared sofosbuvir plus ribavirin to peginterferon plus ribavirin. These included patients with HCV genotypes 2 and 3. All other studies were designed to refine drug dose, drug combination or duration of treatment and did not include a control group. Studies included populations with favorable prognostic factors and only one study with HCV/HIV co-infected patients was identified. However, this study was from the FDA review and has not been published. All included studies were rated with a high risk of bias (poor quality) and only one study was rated as having fair applicability. Only one study had a comparator arm.

Response rates from the published studies, using SVR12, ranged from 10% to 89% for patients with HCV-1, 82% to 95% for HCV-2, and 30% to 84% for patients with HCV-3.[6] Relapse rates were not reported consistently and often only in per-protocol analyses. Rates ranged from 5% in treatment naïve genotype 2 patients treated with sofosbuvir plus ribavirin to 90% in treatment experienced genotype 1 patients. Only 6 studies tested one of the four FDA approved treatment regimens, shown below in table 1. The evidence for interferon-free treatment in genotype 1 comes from one study with only 60 patients. The genotype 2 regimen has the most supporting evidence with the sofosbuvir plus ribavirin 12 week regimen (n=1051; 4 trials).[6]

Table 1: FDA approved treatment regimens and response rates[6]

Genotype	Treatment	SVR12	Relapse	# of Studies (Study name)	Study N
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

Overall, discontinuations of therapy due to adverse events were low in studies and the most common side effects were fatigue, anemia, nausea, rash, headache, insomnia, and pain. A total of 34 patients (2.6%) experienced a treatment-emergent, serious adverse event, with no significant patterns identified. Nonetheless, patients included in the studies were healthier than the general population and studies were small and of short duration. The authors state a potential bias in under-representing the true effect of adverse events and that larger and longer term studies are needed to better describe the harms profile of sofosbuvir. [6]

The authors also searched for ongoing trials through ClinicalTrials.gov. They found no studies which compare sofosbuvir-based treatment to the current standard of care, no evidence on sofosbuvir, interferon, and ribavirin treatment in genotype 1 patients who have failed previous treatment, and no studies conducted by other groups other than pharmaceutical companies. [6]

Who to Treat and When to Treat:
The authors comment that using the study inclusion and exclusion criteria might help select patients who are more likely to respond to treatment. Six studies excluded patients with cirrhosis, and in the studies including patients with cirrhosis, none had decompensated cirrhosis. Other exclusion criteria included HIV or HBV co-infection, significant alcohol or drug use within the past 12 months, excessive current alcohol use, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, and significant renal disease.

The authors list the following factors to consider when developing treatment and coverage criteria: [6]

- Limit use to genotype 2 and 3, until comparative trials are available for genotype 1.
- Do not use sofosbuvir as monotherapy
- Limit use to patients who failed or did not tolerate current standard of care regimens or in whom peginterferon is contraindicated
- Confirm degree of liver fibrosis or cirrhosis prior to authorization of treatment
- Treat only patients at greatest risk of progressing to cirrhosis
- Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
- Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease
- Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection

Clinical Guidelines:

World Health Organization (WHO)
In April 2014, the World Health Organization produced its first guidelines for the screening, care and treatment of persons with hepatitis C infection.[2,18] The guidelines are targeted primarily toward policy makers and physicians in low- and middle-income countries. Both sofosbuvir and simeprevir were given strong recommendations for use based on high quality evidence. It was recommended that sofosbuvir be given in combination with ribavirin with or without pegylated interferon in genotypes 1, 2, 3, and 4 HCV infections rather than pegylated interferon and ribavirin alone. Simeprevir is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than pegylated interferon and ribavirin alone. However, at the time, pricing information was not available so this was not taken into consideration of making the recommendations.

The guideline panel recommends that patients with advanced fibrosis and cirrhosis (METAVIR stages F3 and F4) should be prioritized for treatment as they are at higher risk of developing cirrhosis and hepatocellular carcinoma. If resources permit, then persons with less advanced fibrosis could also be considered for treatment.

EASL Clinical Practice Guidelines:

In April 2014, the European Association for the Study of the Liver (EASL) updated its HCV treatment guidelines.[1] These guidelines were developed by a panel of experts and peer-reviewed by external expert reviewers. They were established using evidence and when not available, experts' experiences and opinion. The GRADE system was used to evaluate the strength of recommendations. The guideline panel provides the following recommendations on who to treat:

- All treatment naïve and experienced patients with compensated chronic liver disease and who have no contraindications to treatment should be considered for therapy (A1 Recommendation).
- Those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations should be prioritized for treatment (A1 Recommendation).
- For patients with minimal or no fibrosis, treatment may be deferred.
- Interferon-free treatment may also be considered in patients with decompensated cirrhosis, although limited data is available in this population. Patients on the transplant list should be considered (A1 Recommendation). Interferon-free treatment in patients with decompensated disease should only be attempted in experienced centers until further safety and efficacy date is available.
- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (A1 Recommendation).

Treatment of genotype 1 CHC:

Option 1:

- A combination of pegylated interferon, ribavirin, and sofosbuvir for 12 weeks is recommended (A1 recommendation)

Option 2:

- A combination of pegylated interferon, ribavirin, and simeprevir for 12 weeks (A1 Recommendation).

Option 3:

- Patients with HCV genotype 1, subtype 1b can be treated with pegylated interferon, ribavirin, and daclatasvir for 24 weeks (Recommendation B1).

Interferon-intolerant or –ineligible

- Ribavirin and sofosbuvir for 24 weeks (Recommendation B2). This should be proposed when no other interferon-free option is available.
- Patients can be treated with sofosbuvir and simeprevir for 12 weeks (Recommendation B1). Ribavirin should be considered in patients with predictors of poor response, especially prior non-responders and/or patients with cirrhosis.
- Combination of sofosbuvir and daclatasvir for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (Recommendation B1). Ribavirin should be considered in patients with predictors of poor response, especially prior non-responders and/or patients with cirrhosis.

Treatment of genotype 2 CHC:

- The combination of sofosbuvir and ribavirin for 12 weeks is recommended. In settings where this is not an option, the combination of pegylated interferon and ribavirin remains acceptable.
- Cirrhotics and/or treatment-experienced patients could be treated with pegylated interferon and ribavirin and sofosbuvir for 12 weeks.

Treatment of genotype 3 CHC:

- The combination of pegylated interferon, ribavirin, and daily sofosbuvir for 12 weeks appears to be more effective than 24 weeks of the combination of sofosbuvir and ribavirin, which should be option 2. (Recommendation A2). This therapy (sofosbuvir plus ribavirin for 24 weeks) is suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option.
- Patients can be treated with an interferon-free combination of daily sofosbuvir and daily daclatasvir for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients as option 3 (Recommendation B1). Adding daily ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

Monitoring:

- A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy.
- For patients on the combination of pegylated interferon, ribavirin, and sofosbuvir, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy (Recommendation A2).
- In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2(assessment of adherence), week 4, week 12 or 24, and 12 or 24 weeks after the end of therapy.
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs, or men who have sex with men with on-going risk behavior

Liver Transplant:

- Patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) can be treated with daily ribavirin and sofosbuvir until liver transplantation in experienced centers under close monitoring.
- In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2(assessment of adherence), week 4, week 12 or 24, and 12 or 24 weeks after the end of therapy.
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs, or men who have sex with men with on-going risk behavior
- Patients with decompensated cirrhosis not on a transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy and safety outcomes have not yet been established for this group (Recommendation B1).

Co-Morbidities:

- Patients who inject drugs should be considered for HCV treatment on an individualized basis and delivered within a multidisciplinary team setting (Recommendation A1).
- Pre-Therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition, and drug and alcohol use. Patients who inject drugs should be linked into social support services and peer report.
- Drug and alcohol users or any other patients with ongoing social issues or history of psychiatric disease are at risk of lower adherence and reduced likelihood of achieving SVR. They need to be monitored more closely during therapy and need more intensive multidisciplinary support (Recommendation B1).

Federal Bureau of Prisons:

The Federal Bureau of Prisons released interim guidance for the management of Chronic HCV infection in May 2014.[19] They provide the following groups that should be prioritized for treatment:

- Advanced hepatic fibrosis/cirrhosis
- Liver transplant recipients
- HIV co-infection
- Comorbid medical conditions associated with HCV (cryoglobulinemia and certain types of lymphomas)
- Continuity of care for newly incarcerated inmates who are being treated at the time of incarceration

National Institute for Health and Care Excellence (NICE):

In draft recommendations, NICE is asking for more information on sofosbuvir for the treatment of chronic hepatitis C.[7] Draft guidance states that available evidence demonstrates that sofosbuvir is effective in certain patients; however, evidence is lacking in subgroup populations and there are substantial uncertainties. Without further information, they cannot decide if sofosbuvir is a cost-effective use of resources. The committee concluded the following:

- Recommends further analysis comparing sofosbuvir in combination with ribavirin, with or without peginterferon alfa compared with peginterferon alfa and ribavirin in genotype 1 and genotype 3 CHC.

Institute for Quality and Efficiency in Health care (IQWiG**):**

The IQWiG, the German equivalent of NICE, released a preliminary report on the effectiveness of sofosbuvir.[8] Due to the lack of comparative studies, IQWiG concluded that there was insufficient evidence to assess effectiveness of treatment in genotype 1 and genotypes 3-6. The guideline found a positive effect of sofosbuvir treatment in genotype 2 based on one comparative study, but insufficient evidence to conclude that sofosbuvir had a better harms profile. The FISSION trial compared 12 weeks of sofosbuvir plus ribavirin to 24 weeks of peginterferon alfa plus ribavirin. Overall, they assessed the risk of bias of this study as high.

Department of Veterans Affairs (VA)

The VA National Hepatitis C Resource Center Program released treatment considerations for Chronic HCV earlier in 2014.[3] The purpose of this was to provide a detailed algorithmic approach to assist in clinical decision-making based on specific patient characteristics. For considerations for selecting patients for treatment, the guideline gave the highest strength of evidence to patients with: hepatocellular carcinoma, post-transplant recipients with cirrhosis, and for carefully evaluating treatment in patients with decompensated cirrhosis. It is recommended that some patients be deferred treatment, including those without cirrhosis. They recommend that patients with severe mental health conditions should be considered for therapy on a case-by-case basis and all patients should be evaluated for current alcohol and other substance use. Patients with active substance or alcohol-use disorders should be considered for therapy on a case-by-case basis.

The VA also includes the following criteria to use to determine whether a patient is interferon ineligible or intolerant:

- Platelet count <75,000/mm3
- Decompensated liver cirrhosis (Child-Turcotte-Pugh Class B or C, CTP score ≥ 7)
- Severe mental health conditions that may be exacerbated by interferon or respond poorly to medical therapy

- Autoimmune diseases that may be exacerbated by interferon
- Inability to complete a prior treatment course due to documented interferon-related adverse effects

Lastly, the VA provides laboratory monitoring recommendations. They recommend that patients should have HCV RNA assessed at week 4 of treatment. If the HCV RNA is detectable at week 4 or any time point thereafter, reassess in 2 weeks. If HCV RNA increases at any time point or if the 8-week level remains detectable, discontinuation of all treatment should be strongly considered (Strong recommendation; expert opinion).

UK Consensus Guidelines

New 2014 expert UK guidelines were developed to provide clinicians with an expert opinion of the current best standard of care.[20] The panel group consisted of members of leading hepatology and infectious disease societies. All but one of the 16 authors disclosed personal relationships with pharmaceutical companies and funding came from 13 pharmaceutical companies, adding risk of bias to the recommendations. Both published studies and unpublished studies from abstract presentations were included. Overall, 25 of the 26 treatment recommendations include the newer agents' sofosbuvir and simeprevir. Recommendations also include faldaprevir, which is not yet approved in the US. The costs and pricing structures was not taken into account and it was assumed that these drugs were deemed cost effective for NHS use by Scottish Medicines Consortium (SMC) and NICE. After this, NICE did not conclude that it was cost effective until further data was released. The following table provides a summary of the recommendations from the UK guidelines. There was no grading of the evidence or strength of the recommendation given, reiterating that these are meant to be expert opinion and are not necessarily evidence-based. No preference was given to one regimen over another, stating that each is a viable option.

Table 2: Summary of Recommendation from UK expert guidelines

Genotype	Treatment naïve	Treatment experienced	Cirrhosis or severe fibrosis
1a	12 weeks SOF + PR 12 week SMF, 24 weeks PR 12 weeks FDV, 24 weeks PR	12 weeks SMV, 24 or 28 weeks PR (RGT) 12 weeks SOF and PR	12 weeks SOF and PR
1b	12 weeks SOF and PR 12 weeks SMV, 24 weeks PR 12 weeks FDV, 24 weeks PR	12 weeks SMV, 24 or 48 weeks PR (RGT) 12 weeks SOF and PR	
2	12 weeks SOF and RBV	12 weeks SOF and RBV	12 weeks SOF and RBV
3	12 weeks SOF and PR 24 weeks PR 24 weeks SOF and RBV	12 weeks SOF and PR 24 weeks SOF and RBV	24 weeks SOF and RBV
4,5,6	12 weeks SOF and PR 12 weeks SMV, 24 or 48 weeks PR (RGT)	12 weeks SOF and PR 12 weeks SMV, 24 or 48 weeks PR (RGT)	12 weeks SOF and PR
SOF: sofosbuvir; SMV: simeprevir, PR: pegylated interferon and ribavirin, FDV: faldaprevir, RGT: response guided therapy, RBV: ribavirin			

Simeprevir and Sofosbuvir Combination Therapy:

There is one small unpublished phase IIa study (COSMOS) evaluating the combination of simeprevir and sofosbuvir in the treatment of previous null responders and treatment naïve patients.[10] Currently, only the abstract is available. The study is an open-label, randomized, phase II study in genotype 1 patients (n=167) with METAVIR scores F0-F2 who were prior null responders to PR (Cohort 1) or treatment-naïve patients and prior null responders with F3-F4 (Cohort 2). Patients in both cohorts were also randomized to simeprevir + sofosbuvir (with or without ribavirin for 12 weeks of simeprevir + sofosbuvir (with or without ribavirin) for 24 weeks. SVR 12 rates in the F0-F2 groups ranged from 79.2% to 96.3%. The lowest SVR 12 was in the most intense (24 weeks of the combination with ribavirin) treatment group and appears to be due to participants lost to follow-up, but the details of the data are not clear at this point. The highest SVR12 rate was in the simeprevir + sofosbuvir + ribavirin for 12 weeks group and SVR 12 was only 88.9% in those with the Q80K polymorphism. The results in the Cohort 2 patients with METAVIR F3-F4 fibrosis scores have not been released yet, although the preliminary SVR4 rates appear high. This preliminary data suggests that there may be no benefit from adding ribavirin to simeprevir and sofosbuvir and that 12 weeks of treatment may results in similar benefits compared to 24 week treatment. The most common adverse events were fatigue, headache, and nausea and anemia occurred mostly in the ribavirin-containing treatment groups. SVR 12 rates from the COSMOS trial are shown below in table 2.

Table3: SVR12 Results from Cosmos Trial[6]

COSMOS SVR12 Results Presented at AASLD and EASL Conferences					
Cohort	**Citation**	**SOF + SMV 12 weeks**	**SOF+SMV+RBV 12 weeks**	**SOF + SMV 24 weeks**	**SOF+SMV+RBV 24 weeks**
1	AASLD 2013 (Jacobson 2013b)	92.9% (13/14)	96.3% (26/27)	100% (14/14)	79.2% (19/24)
	EASL 2014 (Sulkowski 2014)	92.9% (13/14)	96.3% (26/27)	100% (13/13)	90.5% (19/21)
2	EASL 2014 (Lawitz 2014)	92.9% (13/14)	92.6% (25/27)	100% (16/16)	93.3% (28/30)

Randomized Controlled Trials:

Seven potentially relevant RCTs were evaluated from the literature search. After further review, 4 RCTs[21–24] included drugs not yet FDA approved and were therefore excluded. The remaining 3 RCTs are briefly described in the table below.

Table 4: Description of RCTs

Study	Comparison	Population	Primary Outcome	Results	Study Quality
Zeuzem et al.[17] VALENCE RCT, phase III, open-label, no placebo group or comparator	Sofosbuvir plus ribavirin (24 weeks for genotype 3 and 12 weeks for genotype 2).	HCV genotype 2 and 3, tx experienced or tx naïve; up to 20% with cirrhosis, HCV RNA > 10,000 IU/ml'(n=419)' 41% women 21% cirrhosis 58% previously treated, of whom 30% had no response	SVR12	SVR12 GT2: 68/73, 93% (85 to 98%) * GT3: 213/250, 85% (82 to 91%)** *All 68 patients maintained SVR at week 24 **206 (96.7%) maintained SVR at week 24 -Lowest response rate in GT 3 previously treated patients with cirrhosis (62%) Relapse: GT2: 5/73 (7%) GT3: 33/250 (13%)	Poor • Descriptive, open-label study with no placebo group, comparator, or hypothesis testing • Revised study design resulted in no formal statistical comparisons • Small number of patients with characteristics associated with a poor response rate
Manns, et al.[5] QUEST-2 Phase III, RCT, DB, PC	Simeprevir vs. placebo, both in combination with peginterferon alfa plus ribavirin	Treatment naïve, GT1 patients Decompensated cirrhosis, HIV, HBV were excluded (n=391)	SVR12	SVR12 SMV: 209/257 (81%) Pla: 67/134 (50%) P<0.0001 Relapse: SMV: 30/236 (13%) Pla: 21/88 (24%)	Fair • Randomized and concealment of allocation using computer-generated randomization schedule and interactive voice response system • Patients and investigators blinded • Higher withdraw in placebo group than tx (12.6% vs. 4.7%)
Forns, et al.[4] RCT, DB, PC, phase III	Simeprevir vs. placebo, both in combination with peginterferon alfa plus ribavirin	HCV GT 1 patients who had relapsed after 24 weeks or more of interferon based therapy	SVR12	SVR12 SMV: 206/260 (79.2%) Pla: 48/133 (36.1%) P<0.001	Fair • Centrally randomized; unclear allocation concealment • Patients blinded

		(n=393)		Relapse: SMV: 46/249 (18.5%) Pla: 45/93 (48.4%)	investigators blinded up to week 72 • Outcome assessors unblinded

Ongoing Trials:

A randomized trial comparing simeprevir to telaprevir in treatment-experienced patients is underway. This will be the first study to compare the new DAAs to the current standard of care for treating HCV genotype 1.[9]

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Sofosbuvir (Sovaldi®)

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature and where there is medical evidence of effectiveness and safety

Length of Authorization

- Initial trial of 12 weeks
- Continuation of therapy up to 24-48 weeks of total therapy based on therapy regimen, genotype, and patient population

Requies PA:

- Sofosbuvir

Approval Criteria		
1. What diagnosis is being treated?	**Record ICD9 code**	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (Not covered by the OHP)
3. Is the request for treatment of Chronic Hepatitis C?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Is the request for continuation of therapy?	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #5
5. Is the medication being prescribed by or in consultation with a ~~specialist in the field of gastroenterology, infectious disease, or hepatitis C~~ hepatologist?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. If the patient has been treated with peginterferon and ribavirin before, do they have documented noncompliance to their previous treatment?	**Yes:** Pass to RPh, Deny For Appropriateness	**No:** Go to #7
7. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 3 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins). Note: Occasional patients with HCV and hepatocellular carcinoma who do not have advanced fibrosis (Stage 3-4) should be included for treatment. Discuss with physician to confirm these particular cases.	**Yes:** Go to #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a HIV coinfection?	**Yes:** Go to #9	**No:** Go to #10
9. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #10	**No:** Pass to RPh; Deny (medical appropriateness)
10. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for	**Yes**: Go to #11	**No:** Pass to RPh, Deny for

≥ 6 months?		appropriateness
11. Does the patient have significant renal impairment (CrCl < 30 ml/min) or end stage renal disease (ESRD)?	**Yes:** Pass to RPh; Deny for appropriateness	**No:** Go `to #12
12. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #13	
13. Does the patient have genotype 1 or 4 chronic hepatitis C?	**Yes:** Go to # 14	**No:** Go to #17
14. Is the medication being used as triple therapy with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #15
15. Is the medication being used with ribavirin or simeprevir?	**Yes:** Go to #16	**No:** Pass To Rph; Deny for Appropriateness
16. Is the patient interferon ineligible defined by having one of the following conditions: • Previous adverse reaction or hypersensitivity to interferon • Decompensated liver disease • Severe or uncontrolled psychiatric disorder in consult with a psychiatrist • Autoimmune hepatitis or other autoimmune disorders • Unstable cardiac disease Note: Patient's or prescribers not wanting to go through treatment with interferon does not meet the criteria for being "interferon ineligible"	**Yes:** Approve initial trial of 12 weeks for total therapy of 12 weeks for sofosbuvir + simeprevir combination **OR** a total of 24 weeks for sofosbuvir + ribavirin therapy	**No:** Pass To Rph; Deny for Appropriateness
17. Does the patient have genotype 2 chronic hepatitis C?	**Yes:** Go to #18	**No:** Go to #19
18. Is the medication being used with ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Pass To Rph; Deny for Appropriateness
19. Does the patient have genotype 3 chronic hepatitis C?	**Yes:** Go to #20	**No:** Pass To Rph; Deny for Appropriateness
20. Is the medication being used with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #21
21. Is the medication being used with only ribavirin and the patient is interferon ineligible as defined by the conditions listed above in #15?	**Yes:** Approve for 12 weeks initial fill for a total 24 weeks of therapy	**No:** Pass To Rph; Deny for Appropriateness

Continuation of Therapy- Sofosbuvir		
Has the patient been adherent to and tolerated initial therapy?	**Yes**: Approve for additional 12 weeks in genotype 3 patients and genotype 1 patients who are interferon ineligible (refer to dosage and administration table below). If patient is awaiting liver transplantation, approve for up to additional 24 weeks or until liver transplantation, whichever occurs first.	**No:** DENY (Medical Appropriateness)

Dosage and Administration:

Genotype 1 and 4	Sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Genotype 2	Sofosbuvir + ribavirin	12 weeks
Genotype 3*	Sofosbuvir + ribavirin	24 weeks
Genotype 1 and interferon ineligible	Sofosbuvir + ribavirin	24 weeks
Those with hepatocellular carcinoma awaiting liver transplantation	Sofosbuvir + ribavirin	Up to 48 weeks or until ilver transplantation, whichever occurs first

*Certain patients with genotype 3 (nonresponders with advanced fibrosis) can also be treated with sofosbuvir + peginterferon alfa + ribavirin for 12 weeks if deemed appropriate by physician

P&T Board Action: 1/30/13 (MH)
Revision(s): 3/27/13, 7/31/14
Initiated:

Hepatitis C Oral Protease Inhibitors/Triple Therapy

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of 8-12weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

Requires PA:

- Telaprevir
- Boceprevir
- Simeprevir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the prescription for simeprevir?	**Yes: Go to #4**	**No: Go to #6**
4. Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline?	**Yes: Go to #5**	**No:** Pass to RPh, Deny For Appropriateness. Recommend that the screening take place.
5. Does the patient have the genotype 1 Q80K polymorphism virus?	**Yes:** Pass to RPh, Deny for Appropriateness	**No:** Go To #6
6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #8
8. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #10	**No:** Pass to RPh, Deny For Appropriateness
10. If the patient has been treated with peginterferon and ribavirin before, do they	**Yes:** Go to #11	**No:** Pass to RPh, Deny For

have documented compliance/adherence to their previous treatment?		Appropriateness
11. Does the patient have a biopsy to indicate moderate to severe fibrosis (Metavir score of 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins)?.	**Yes:** Go to #12	**No:** Pass to RPh, Deny For Appropriateness
12. Does the patient have a HIV coinfection?	**Yes:** Go to #13	**No:** Go to #14
13. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #14	**No:** Pass to RPh; Deny (medical appropriateness)
14. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #15
15. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #16 (If dose is different pass to RPh for appropriateness)
16. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Go to #17 (If dose is different pass to RPh for appropriateness)
17. Is the request for simeprevir 150 mg once daily for 12 weeks?	**Yes: Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks**	**No: Pass to RPh; Deny for appropriateness**

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at

		Treatment Week 24.
3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
***TREATMENT FUTILITY RULES** Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks) Week 24: Detectable Discontinue peginterferon and ribavirin. If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued		

Continuation of Therapy- Boceprevir		
1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)

***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

Continuation of Therapy- Simeprevir: Simeprevir in combination with peginterferon alfa and ribavirin should only be given for 12 weeks. No more simeprevir should be approved. The following are the recommended duration of treatments for dual therapy with peginterferon alfa and ribavirin after the initial 12 weeks of triple therapy		
1. Is the patient treatment-naïve or a prior relapse and has undetectable HCV RNA (< 25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.
2. Is the patient a prior non-responder (including partial and null responders) and has an undetectable HCV RNA (<25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.		

Interferons and Ribavirins

Goal(s):

Cover drugs only for those clients where there is medical evidence of effectiveness and safety

Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months

Requires pa: All drugs in HIC3 = W5G

Preferred Alternatives: See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Is peginterferon requested preferred?	**Yes:** Go to #4	**No:** Go to #2.
2. Will the prescriber consider a change to a preferred product? Message: - Preferred products are evidence-based reviewed for comparative effectiveness & safety Oregon Pharmacy and Therapeutics (P&T) Committee	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	**No:** Go to #3.
3. If the request is for interferon alfacon-1, does the patient have a documented trial of a pegylated interferon?	**Yes:** Go to #4.	**No:** Deny; Pass to RPH (Medical Appropriateness)
4. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code: (571.40; 571.41; 571.49)	**Yes:** Go to #5.	**No:** Go to #11
5. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #6
6. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment?	**Yes:** Forward to DMAP Medical Director	**No:** Go to #7

Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.		
7. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy? • severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy • untreated hyperthyroidism • severe renal impairment or transplant • autoimmune disease • pregnancy • unstable CVD	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #8
8. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes:** Go to #9	**No:** Deny; Pass to RPH (Medical Appropriateness)
9. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date:	**Yes:** Go to #10	**No:** Deny; Pass to RPH (Medical Appropriateness)
10. Does the patient have a documented HCV Genotype? Record Genotype:	**Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only	**No:** Deny; Pass to RPH (Medical Appropriateness)
11. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?	**Yes:** Go to #11	**No:** Deny; Pass to RPH (Medical Appropriateness)
12. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #12
13. Has the member received previous treatment with pegylated interferon?	**Yes:** Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

Continuation of Therapy- HCV

1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?

Yes: Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

Genotype	Approve for	Apply
1 or 4	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).
2 or 3	**An additional 12 weeks** or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).
For all genotypes and HIV co-infection	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).

No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

Clinical Notes:

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.
-

Stage is indicative of fibrosis:			Grade is indicative of necrosis:	
Stage 0	No fibrosis			

Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild
Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate
Stage 4	Cirrhosis		Stage 4	Marked

The following are considered investigational and/or do not meet medical necessity criteria:

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

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Hepatitis C Readiness to Treat

Recommendations

- Accept changes to the Hepatitis C readiness to treat assessment to supplement the drug prior authorization process (Appendix 1).
- Consider the following potential alternatives for delivery methods of the readiness to treat assessment:
    - Create document to be administered by the primary clinician as a referral process to the hepatologist or hepatitis C specialist. Require completion of a compliance contract similar to the example in Appendix 2 and adapt the referral form in Appendix 3 to evaluate access and allow for tracking.
    - Develop readiness to treat assessment to be administered at the hepatology center by specialists and their team of clinicians.
    - Have an OHA dedicated case manager administer the readiness to treat assessment and follow patients to promote adherence and identify any potential barriers.

Background

Hepatitis C virus (HCV) has a significant health burden with an estimated 3% of the world's population infected and disproportionately impacts marginalized groups.[1] Due to the complexity of the disease and treatment regimens, many psychosocial factors can potentially interfere with treatment adherence, treatment effectiveness, and therefore incur unnecessary and significant costs. There are higher rates of psychiatric and substance use disorders and cognitive impairment (risk factors for non-adherence) in persons with chronic HCV infection than in the general population.[2] Mental health issues, particularly depression and anxiety disorders, should be assessed and managed before initiating treatment. Success for HCV treatment is also dependent on treatment of addiction, as alcohol use leads to failed treatment and increased morbidity and mortality. In addition, HCV treatment side effects often result in early treatment discontinuation which reduces rates of cure. The term "readiness" is highlighted as an important concept in an individual's decision-making to undergo treatment, but there is little consensus on its definition.

The use of an initial assessment for readiness to treat has been studied, however; most of the literature occurs in the prison setting[1,3,4] or in those with HCV/HIV co-infection.[5–7] Still, standardized protocols or treatment guidelines are lacking. A recent study evaluated Australian inmates with HCV to identify why they refused, deferred, delayed or discontinued HCV treatment in prison. [1] Interviews of 116 inmates showed that stress, lack of knowledge, perceptions of treatment, treatment related fears, substance use, employment and accommodation, lack of continuity, access to care, lack of support, treatment comorbidities, and methadone use were reasons given to defer or discontinue treatment. There are also many provider barriers to treating HCV, including psychiatric illness, depression, cognitive impairment, history of substance use problems, and suspected poor adherence. Many different initial assessments are being used and developed to assess a patient's readiness to being HCV treatment. The Psychosocial Readiness Evaluation and Preparation for Hepatitis C Treatment (PREP-C) has been developed for this very reason and meant to occur in parallel to the medical work-up being conducted. The goal of PREP-C is to improve psychosocial functioning prior to HCV treatment initiation, to optimize treatment adherence and the achievement of sustained virologic response (SVR).

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The PREP-C clinical interview includes interview components which require intervention to improve treatment readiness related to the following assessment areas:

1. Motivation
2. Information
3. Medication Adherence
4. Self-Efficacy
5. Social Support and Stability
6. Alcohol and Substance Use
7. Psychiatric Stability
8. Energy Level
9. Cognitive Functioning

The PREP-C was used in 50 patients in 2011 being evaluated for HCV treatment at a primary-care based liver clinic. Patients most frequently rated Satisfactory in the Motivation domain and least frequently in the Information domain.[8] The number of domains rated Satisfactory did not differ by sex, race, or by HIV-co-infection status. Twenty one patients (42%) began HCV treatment within 6 months of PREP-C. Specific interview questions as part of PREP-C are included in Appendix 4. The University of Washington, through funding from the Centers for Disease control and Prevention also provides a checklist to use to assess a patient's readiness to start therapy (Appendix 5).[9]

Current prior authorization is in place for medications used in the treatment of HCV. The criteria include a thorough assessment of disease, significant medical comorbidities, clinical manifestations, liver fibrosis, and history of prior treatment. In general, only patients with advanced fibrosis should be treated at this time. The prior authorization criterion also addresses some of the psychosocial concerns, including: good evidence of adherence, no active drug or alcohol use, and severe or unstable psychiatric disorders. The readiness to treat should include an additional assessment of the psychosocial issues.

Conclusions

- Certain risk factors are known to negatively effect treatment adherence to HCV medications, as well as SVR rates. This includes such things as alcohol and drug use, psychiatric disease
- There is a lack of standardized protocols or guidelines to assess the readiness to treat of a patient with HCV
- A readiness to treat assessment should be done along with the drug PA process to address additional psychosocial concerns to optimize response to treatment. The readiness to treat assessment should help identity red flags that may affect treatment adherence and cure rates of hepatitis C virus.

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Appendix 1: Readiness to Treat Assessment

1. Does the patient have any of the following significant risk factors (See Clinical Notes for more details)?

□ Alcohol ~~use~~ abuse in the last 6 months
□ IV Drug use in the last 6 months
□ Active or uncontrolled depression, psychosis, or suicidality without proper care and coordination with Mental Health providers.
□ Homeless or Home Status at Risk (unless the patient and provider can ensure adherence to clinic visits)
□ A likely or expected major life event expected in the next 6 months (changing jobs, moving, health procedure, etc.)

If any of the above are checked, treatment is not recommended until corrected. Do not refer patient to specialist.

2. Does the patient have any of the following risk factors?

Risk Factors
□ Alcohol ~~use~~ abuse in the last 6-12 months
□ IV drug use in the last 6-12 months
□ Actively treated, but controlled or history of depression
□ History of poor compliance with medications
□ History of poor compliance with office visits
□ ED visit or hospitalization related to chronic Hepatitis C in the last 6 months
□ Previous treatment failure in part due to side effects (if treating includes peginterferon)
□ A likely or expected major life event expected in the next 6 months (changing jobs, moving, health procedure, etc)
□ Inadequate transportation system, unstable housing, and/or no telephone services for the duration of evaluation and treatment
□ At risk for reinfection
□ Pending legal situation that could result in incarceration
□ Developmental mental delay or decrease cognition or lack of support to properly understand medication instructions.
~~□ Please evaluate patient's social support system~~

3. Add the total ~~of points~~number of risk factors together from question 2.

~~**Points**~~**Risk Factors**	**Treatment Recommended**
0	Treatment ready; complete referral form for specialist (Appendix 2).
1-3	~~Treatment not recommended until other issues corrected~~Recommend patients are closely tracked to optimize full treatment and follow-up, including prevention of re-infection. Complete referral form (Appendix 2)
4+	Treatment not recommended until risk factors addressed and corrected.

4. Have the patient read and sign the compliance contract. If patient is unwilling to sign, do not refer patient to a specialist.

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Clinical Notes:

- All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT C or CAGE. The presence of current heavy alcohol use (> 14 drinks per week for men or > 7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol-use disorders should be carefully considered for therapy in coordination with substance-use treatment specialists.
- Patients with severe mental health conditions should be engaged in mental health treatment and should be managed in collaboration with mental health providers to determine the risks versus benefits of treatment and potential treatment option.
- For patients with a history of poor compliance with office visits or other transportation issues should consider using the Non-Emergent Medical Transportation (NEMT) program. More information is available at: http://www.oregon.gov/oha/healthplan/pages/nemt.aspx"

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Appendix 2: Patient Compliance Contract

CONSENT FOR HCV GENOTYPE 2 TREATMENT

I am requesting Hepatitis C treatment with Sofosbuvir and Ribavirin based therapy.

- I am willing to take each dose of my medication as directed, to give myself the best chance of clearing the virus.
- I understand that therapy has many known side effects; some of them can be serious and rarely may even result in death.
- Although a great deal is known about treating viral hepatitis, unknown risks may still exist.
- I am aware that many side effects can be reduced by carefully following my provider's instructions.
- I am aware that in some cases, medications such as Erythropoietin Stimulating Agents and/or Granulocyte Colony-Stimulating Factors may be needed to support blood cell levels. Such use is considered "off label" by the FDA and has associated risks.
- I understand that I need to call the Hepatology Clinic before starting any new medications/supplements as there can be interactions with treatment meds.
- I understand that pregnancy must be avoided in myself and my sexual partners during treatment and for 6 months after completion.
- I agree to use two non-hormonal birth control methods if I am capable of becoming pregnant or causing pregnancy.
- I am aware that I must not use alcohol during treatment and I may be screened for alcohol or drug use during treatment.

Some of the known side effects of Hepatitis C Therapy include:

Decreased Appetite	Headache	Rash/Skin Reaction
Irritability	Fatigue/Difficulty Sleeping	Nausea/Vomiting
Hemolytic Anemia	Cough/Shortness of Breath	Birth Defects
Diarrhea		

Ribavirin is an oral medication used to improve viral clearance.

- Ribavirin should not be used alone for the treatment of viral hepatitis.
- In most cases, this medication will be taken twice a day with food.
- I am aware that ribavirin can cause birth defects and abortion.

Typical treatment schedule

- I understand that regular clinic visits and blood draws are required to monitor for safety and effectiveness of therapy.
- A typical schedule will look like this but more frequent visits and blood draws may be required.

I have read and understand the above information (both sides)

Failure to comply may affect my chances of clearing the virus and/or result in discontinuation of treatment.

Signature_____ Date_____

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Appendix 3: Primary Care Provider Referral to a Specialist for Hepatitis C Treatment Evaluation

Directions: Primary care providers referring a patient to a specialist for HCV treatment evaluation should provide the following medical information to the specialist prior to the first appointment. Information may be placed on the form or provided via attachment or excerpt from the medical record.

Patient				**Date**	
Address					
Phone				Mobile	
Allergies				**DOB**	
Height		Weight		BMI	

CONCOMITANT MEDICAL Diagnoses	**Current Medications**

health maintenance		
1.	Smoking	
2.	Use of alcohol	
3.	Substance use	
4.	Mental health assessment	
5.	Pregnancy/ Contraception	

Reccomended Labroatroy testing prior to initial appointment with specialist					
HCV Genotype		ALT	Date:	Creatinine	
HCV RNA	Date:	AST	Date:	Platelet Count	
Albumin		Total bilirubin		Hemoglobin	

ASSESSMENT OF LIVER (COMPLETE IF AVAILABLE)		
Test performed	**Date**	**Findings/ Results**
Liver biopsy		
Ultrasound		
Transient Elastography		

Other Recommendations/Referrals

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Appendix 4: PREP-C Interview Questions

Motivation
1. What are the reasons you want to start Hepatitis C treatment?
2. What are your main concerns about hepatitis C Treatment?
3. How important is it to you to being hepatitis C treatment?
Information
1. Can you tell me what medications are used to treat Hepatitis C?
2. How are these medications taken and how often?
3. How long have you been told that your Hepatitis C treatment will last?
4. What are some of the possible side effects of hepatitis C treatment you are aware of?
5. Can you tell me what the goal of hepatitis C treatment is?
6. What is your hepatitis C genotype?
7. What is your Hepatitis C viral load?
8. What is your stage of liver disease, according to your last biopsy or FibroScan if you have had one of these?
Medication Adherence
1. Tell me all the medications that your doctors have told you to take and the number of times per day you were told to take them.
2. Put a cross on the line below at the point showing your best guess of about how much of your total prescribed medication you have taken in the last month.
3. When you do miss medication doses, what are the two most common reasons why?
Self-Efficacy
1. How confident are you that you will be able to take your Hepatitis C medication in addition to any current medications you are taking?
How confident are you that you will be able to deal with the side effects of the Hepatitis C medication?
How confident are you that you will take your Hepatitis C medication even if you aren't feeling well?
How confident are you that you will take your Hepatitis C medication if the side effects begin to interfere with your daily activities?
What are your main concerns about self-injecting medication?
Social Support and Stability
Are you currently having problems with money?
Are you currently having problems with health insurance or benefits?
Will you have out-of pocket expenses for your treatment visits and medications/
Are you concerned that you might not be able to pay for transportation to get to Hepatitis C medical appointments?
What type of housing do you live in?
Do you have a refrigerator at home where you will feel comfortable keeping your weekly injections of pegylated interferon?
Do you expect to have any changes in your housing situation in the next year?
How many days in the last month, if any, have you not had enough food to eat?
If you have ever been arrested or incarcerated (even if for only one night), when was the last time?
Are you the main person responsible for taking care of anyone? (Such as a child or elderly person.)
Would you be able to take time off for your HCV treatment if needed given your current work, caretaking, or other responsibilities?
How confident are you that these people will be available to provide you with emotional support during Hepatitis

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C treatment?
How confident are you that these people will be available to provide you with practical support during Hepatitis C treatment? *Such as: go with you to appointments, help with daily activities, remind you take your medications*
How do the people you are closest to feel about your starting treatment for Hepatitis C?
If this is your first time on this specific HCV treatment, do you know anyone who has been treated with this HCV treatment who can tell you what the treatment was like for them?
Alcohol and Substance Use
During the past year, on average how often did you use... Alcohol/Beer
During the past month, how often did you drink any alcohol (including beer)?
How confident are you that you will be able to stop all use of alcohol and beer during the entire time you are on Hepatitis C treatment?
If you have ever injected drugs, when is the last time you did so?
In the last 30 days, have you been enrolled in any form of alcohol/substance abuse treatment or counseling program? Such as: alcohol, drug, methadone, or buprenorphine treatment program
Psychiatric Stability
Are you currently receiving help for any type of mental health problem?
Would you like to have more help than you do now dealing with any mental health problem?
During the last month, was there a time when you felt sad, down, depressed or hopeless?
During the last month, was there a time when you felt like a bomb, ready to explode?
During the last month, was there a time when you had thoughts that you would be better off dead or thoughts of hurting yourself in some way?
During the last month, was there a time when you have been bothered by feeling nervous, anxious, on edge, or worrying a lot about different things?
During the last month, was there a time when you experienced an anxiety attack - suddenly feeling fear or panic?
Have you ever been psychiatrically hospitalized?
Have you ever made an attempt to end your life?
Are you currently taking any type of medication for anxiety, depression, hearing voices, or for any other emotional problem?
Have you taken any type of medication for anxiety, depression, hearing voices, or for any other emotional problem in the past?
Energy Level
During the past seven days, on how many nights do you feel that you have gotten enough sleep?
During the past two weeks, I have found I am easily fatigued or tired.
During the past two weeks, I have found fatigue or being tired interferes with my daily activities, work, family, or social life.
Cognitive Functioning
Is English your primary language?
How often is it difficult for you to understand or communicate with your health care provider due to language problems?
How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy? (Confirm that answer given is not due to vision problems)
In the last month, did you have difficulty reasoning and solving problems, for example, making plans, making decisions, and learning new things?
In the last month, did you forget things that happened recently, for example, where you put things, appointments?

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Appendix 5: Screening Checklist

Checklist Before Starting Treatment for Hepatitis C
❑ No history of decompensated cirrhosis (CPT score > 7, ascites, variceal bleeding)
❑ Psychiatrically stable
❑ No active drug abuse or problem alcohol use
❑ No baseline cytopenias
❑ Normal thyroid function
❑ No active autoimmune disease
❑ Good evidence of adherence and willing to comply with follow-up
❑ Perform dilated retinal exam if history of diabetes mellitus, hypertension, or retinal issues
❑ If HIV-infected, the HIV is well-controlled
❑ Potential drug-drug interactions addressed and plan in place to monitor
❑ Adequate psychosocial support
❑ Financial aspects of therapy and ability to work addressed
❑ Not pregnant or planning to become pregnant during therapy and for 6 months afterwards
❑ If patient or partner of child-bearing potential, has ≥2 reliable methods of birth control
❑ No significant cardiac or respiratory issues

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DRUG USE EVALUATION: UTILIZATION OF BOTULINUM TOXIN

There are currently four botulinum toxin (BoNT) products available in the United States: abobotulinumtoxinA (ABO), incobotulinumtoxinA (INC), onabotulinumtoxinA (ONA), and rimabotulinumtoxinB (RIM). They are used for a variety of FDA approved and off label indications. The goal of this drug use evaluation is to quantify the use of BoNT in OHP that lacks evidence for benefit or is not currently funded by OHP in order develop prior authorization criteria for the FFS program.

Background:

There are seven serologically distinct forms of BoNT, A through G. Each neurotoxin works at a distinct site. Botulinum toxins now play a role in the management of a variety of medical conditions.[1] Three distinct serotype A botulinum toxin (BoNT A) products, ABO, INC, ONA, and one serotype B botulinum toxin (BoNT B) product, RIM, have been approved by the U.S. Food and Drug Administration (FDA) (Table 1). The most recent preparation approved is INC in 2010. Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each BoNT product and cannot be compared or converted into units of another product. In addition, there are no universally accepted safe dose conversion ratios. BoNTs are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, where the goal of therapy is to reduce contraction of striated or smooth muscle. [1] All of the products have a black box warning in their labeling regarding the risk of BoNT spreading beyond the site of injection, resulting in adverse events and death in some cases. BoNT A has become first line therapy for cervical dystonia and blepharospasm.[2] Not all patients respond well to BoNT A though, and 5 to 10% become resistant to it.[3] In these cases, BoNT B is an alternative to BoNT A. [2] Head to head studies comparing the efficacy and safety of different BoNT formulations are limited.[4] However, there is evidence that ABO and ONA are similar in efficacy for the treatment of cervical dystonia, blepharospasm, and spasticity.[5]

Table 1: FDA approved Indications

Drug	FDA approved indications*
OnabotulinumtoxinA (Botox®)	Prophylaxis of chronic migraines, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, bladder dysfunction (detrusor over activity associated with a neurologic condition or overactive bladder), blepharospasm, strabismus
AbobotulinumtoxinA (Dysport®)	Cervical dystonia
RimabotulinumtoxinB (Myobloc®)	Cervical dystonia
IncobotulinumtoxinA (Xeomin®)	Cervical dystonia, Blepharospasm

The use of BoNT has been evaluated for prophylaxis treatment of migraines. Common prophylactic treatments for migraines include beta-blockers, tricyclic antidepressants, antiepileptic drugs, and lifestyle management. ONA is the only BoNT approved by the FDA for the prophylactic treatment of chronic migraine. There is lower quality evidence that unspecified BoNT A products may be associated with benefit in the prophylaxis of chronic daily migraine headaches (15 or more headaches per month), but results are inconsistent.[6–8] In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headaches per month.[6] A recent draft technology assessment on controversies in migraine management by the Institute for Clinical and Economic Review (ICER) confirms this.[9] The systematic review and meta-analysis demonstrated a small clinical improvement with BoNT compared to placebo injections, with a reduction in 2.3 migraine headache days per month.[9] None of the BoNT formulations are approved for the prophylactic treatment of chronic tension-type headache or intermittent migraine attacks, and there is moderate quality evidence of no benefit of prophylaxis with BoNT A in these patients.[6–8]

There are additional uses of BoNT that may be considered appropriate for patients who have tried and failed other more conservative or more effective treatments. This includes use in anal fissures, and urinary incontinence due to detrusor over activity associated with a neurologic condition.[5] Table 4 also describes indications in which there is no evidence to support the use of BoNT or evidence of no benefit. Cosmetic procedures involving BoNT injections and treatment of primary axillary hyperhidrosis are not covered by OHP. BoNT has been studied in a number of other disorders where there is evidence of no benefit or insufficient evidence to recommend its use. This includes gastroparesis, restless legs syndrome, benign prostatic hyperplasia, lower back pain, and spasmodic dysphonia.[5]

Methods:

This is a descriptive, observational study to determine prevalence of diagnoses associated with patients with BoNT claims. The study population includes all patients with 1 or more paid FFS or encounter drug, professional or outpatient claim for BoNT (Appendix 1) in the calendar year 2013. Patients were excluded if they were also enrolled in Medicare Part D as identified by a benefit package of BMM or BMD or if they were eligible for less than 75% of days during the calendar year.

In addition, professional and outpatient claims from January 1, 2012 through April 30, 2014 were used to classify each patient into the mutually exclusively categories in Table 4 in priority: 1) Evidence-supported first-line use 2) Evidence-supported second-line use 3) Unclear benefit 4) Limited evidence of no benefit and/or not funded by OHP and 5) no identified diagnosis. Patients could have more than one diagnosis within each of the 5 categories.

Profiles in the Second-Line and Unclear categories were manually reviewed to make a final determination of the indication that BoNT was used for and the appropriateness of that therapy. Patients using BoNT for

migraine were deemed "appropriate" if there was claims evidence of a trial of 3 alternative prophylactic medications. It was not possible to determine the number of migraines experienced per month from claims data, and relied on the ICD-9 codes for "Chronic" vs "Episodic" to make the assumption that patients with "Chronic" migraines experienced at least 15 episodes per month. Patients using BoNT for neurogenic bladder were deemed "appropriate" if there was claims evidence of a neurological cause and a prior trial of antimuscarinic drug.

Results:

There were 558 unique patients identified for this study. After exclusion of 275 Medicare patients and 24 patients that were eligible for Medicaid coverage less than 75% of the study period, there was a unique study population of 272 patients.

Table 2 displays the demographics. The majority of study patients were adults (73%), Caucasian (84%), female (65%) and were enrolled in Coordinating Care Organizations [CCO] (84%). The study population is similar to all Medicaid BoNT users with the exception of age and CCO enrollment. The Medicare exclusion resulted in a study population that was generally younger than all BoNT users (mean age 31.5 years versus 43.3 years). Children were also more prevalent in the study population (27% versus 14%). Study patients were also more likely to be enrolled in a CCO (84% versus 68%).

TABLE 2: PATIENT DEMOGRAPHICS

		All BoNT Patients		Study BoNT Patients	
	n=	**558**	**%**	**272**	**%**
Age					
	Mean (min-max)	43.3	0-90	31.5	0-67
	< 13	52	9.3%	49	18.0%
	13-18	24	4.3%	24	8.8%
	19-64	397	71.1%	196	72.1%
	> 64	85	15.2%	3	1.1%
Sex					
	M	196	35.1%	95	34.9%
	F	362	64.9%	177	65.1%
Ethnicity					
	Caucasian	482	86.4%	227	83.5%
	Non-Caucasian	76	13.6%	45	16.5%
Claims Source*					
	FFS	183	32.8%	43	15.8%
	Encounter	381	68.3%	229	84.2%

* 6 patients from the "All BoNT Patients" group had both FFS and Encounter claims. So, the total percent is >100%.
BoNT = botulinum toxin

Table 3 displays utilization by product and claim source. As expected, most were billed on professional or outpatient claims and more than $709,000 was reimbursed to providers during calendar year 2013. Of this number, about $541,000 was paid on CCO claims and the $168,000 was paid on FFS claims. The average CCO claim cost of $627 was $173 (28%) more than the average FFS claim cost of $454. Finally, over 86% of market share by claim count is associated with ONA.

TABLE 3: **All BoNT Product Utilization - Pharmacy and Medical, Calendar Year 2013**

Pharmacy		**FFS**			**CCO**		
HSN	**Description**	**Patient Count**	**Claim Count**	**Sum Amt Paid***	**Patient Count**	**Claim Count**	**Sum Amt Paid***
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)	2	2	$191	2	2	$2,146
036477	ABOBOTULINUMTOXINA (DYSPORT)	1	1	$157			
036687	INCOBULINUMTOXINA (XEOMIN)						
021869	RIMABOTULINUMTOXINB (MYOBLOC)						
Medical		**FFS**			**CCO**		
Proc Code	**Description**	**Patient Count**	**Claim Count**	**Sum Amt Paid***	**Patient Count**	**Claim Count**	**Sum Amt Paid***
J0585	Injection, Onabotulinumtoxina, 1 Unit	163	308	$157,322	346	746	$483,150
J0586	Injection, Abobotulinumtoxina, 5 Units	13	35	$7,098	13	39	$11,195
J0587	Injection, Rimabotulinumtoxinb, 100 Units	1	3	$0	3	7	$18,739
J0588	Injection, Incobotulinumtoxin A, 1 Unit	10	21	$3,305	24	70	$26,191
	Unique by Plan Type	183	370	$168,073	381	864	$541,420
	Unique, FFS/MCO Combined	558	1234	$709,493			

* Rebate revenues are not included in this figure.

Table 4 displays the number of unique patients by exclusive diagnostic evidence category. Prior to the manual review, the prevalence of diagnoses were similar in the study and all BoNT users (not shown). Over 73% of study patients had a claim for a diagnosis supported by evidence and <4% had claims for diagnoses that are not funded by the OHP or evidence of no benefit of BoNT. BoNT was used by a single patient for "Other disorder of binocular eye movements", a diagnosis where BoNT has unclear benefit. Of note, 22.8% of study patients used BoNT for diagnoses where it is not recommended first-line and the majority had a migraine diagnoses. Not shown in Table 4 is that of the total 43 FFS patients included in this study, 90.7% (n=39) of the patients were prescribed therapy according to supported evidence. This is in comparison to just

67.7% (n=155) of the 229 CCO patients. In CCO patients, the second most common category was in second line use of BoNT.

TABLE 4: DIAGNOSTIC CATEGORY DISTRIBUTION

ICD-9	Diagnostic Category	n=	%
Evidence or guidelines supporting BoNT use first-line		**199**	**73.2**
333.6x *333.7x* *333.81* *333.83* *333.89*	*Genetic torsion dystonia* *Acquired torsion dystonia* *Blepharospasm* *Spasmodic torticollis* *Other fragments of torsion dystonia*	86	31.6
 340.xx *341.0* *342.xx* *343.xx* *344.0x* *344.1* *344.2* *344.4x* *344.5* *378.73*	*Secondary spasticity and strabismus in other neuromuscular disorders* *Multiple sclerosis* *Neuromyelitis optica* *Spastic hemiplegia, Other specified hemiplegia,* *Cerebral palsy* *Quadriplegia and quadraparesis* *Parapalegia,* *Diplegia of upper limbs,* *Monoplegia of upper limb,* *Unspecified monoplegia* *Strabismus in other neuromuscular disorders*	132	48.5
Evidence for BoNT use is second-line or in specific circumstances only		**62**	**22.8**
596.5x, *788.3x*	*Other functional disorders of bladder (e.g. Hypertonicity of bladder, Neurogenic bladder NOS, Detrusor sphincteric dyssynergia).* *Urinary incontinence*	9	3.3
346.xx	*Migraine*	46	16.9
530.0 *530.5*	*Achalasia and cardiospasm* *Dyskinesia of esophagus*	4	1.5
728.85 *727.81*	*Spasm of muscle;* *Contracture of tendon (sheath)*	3	1.1
527.7	*Disturbance of salivary secretion (sialorrhea)*	0	0.0
Low quality or insufficient evidence of unclear benefit		**1**	**0.4**
787.2x	*Dysphagia*	0	0.0
378 (excluding 378.73)	*Other disorders of binocular eye movements (e.g. Esotropia, Exotropia, mechanical strabismus, sixth nerve palsy).*	1	0.4
Limited Evidence of no benefit and/or not funded OHP indications		**10**	**3.7**
333.xx (excluding 333.6x, 333.7x,333.81, 333.83,333.89) *307.2x* *351.xx* *478.75* *478.79*	*Other extrapyramidal disease and abnormal movement disorders (excluding torsion dystonias)* *Tics* *Facial nerve disorders* *Laryngeal spasm* *Spastic Dysphonia*	8	2.9
705.xx *780.8*	*Disorders or sweat glands (e.g. Focal hyperhidrosis)* *Generalized hyperhidrosis*	1	0.4
565.0	*Anal fissure*	0	0.0
723.xx *724.xx* *729.1*	*Other disorders of cervical region* *Other and unspecified disorders of back* *Myalgia and myositis, unspecified*	2	0.4
339.xx *307.8x*	*Other headache syndromes (e.g. tension headache)* *Pain disorders related to psychological factors (e.g. tension headache)*	0	0.0
536.3	*Gastroparesis*	0	0.0
600.xx	*Hyperplasia of prostate*	0	0.0
335.20	*Amyotrophic sclerosis.*	0	0.0
None of selected conditions		**0**	**0**

Sixty-two patients (22.8%) were using BoNT for a second line therapy. The two most common conditions were either overactive bladder (9 patients, 3.3%) or migraine (46 patients, 16.9%). Upon manual review of the migraine patients, 14 (30.4%) met criteria for appropriate BoNT use, while 32 (69.6%) did not. Of the 9 patients categorized under overactive bladder, 4 (44.4%) were classified as having neurogenic etiology, with prior use of antimuscarinic therapy, and 5 (55.6%) failed to meet this criteria. Three patients had diagnoses of both contracture of tendon and abnormality of gait, not associated with an associated musculoskeletal condition such as cerebral palsy. There is insufficient evidence evaluating the efficacy and safety of BoNT for these conditions not associated with a neurologic or musculoskeletal condition.[10] Lastly, there were 4 patients using BoNT for achalasia (1.5%). BoNT could be appropriate in achalasia patients who are not candidates for the other surgical treatments (older patients with multiple comorbidities).[11] It could not be determined if these patients were appropriate from the claims data.

Discussion:

Overall, the patients utilizing BoNT carry multiple, complex medical problems and many were severely disabled. From these data it was determined the majority of patients using BoNT (73.2%) were associated with diagnoses with strong supporting evidence, and an additional 6.6% utilized BoNT appropriately for second line therapy. The remaining 20.2% either had unclear benefit, no benefit, or used BoNT inappropriately for secondary treatment according to treatment guidelines.[8,9,12,13,14] Literature describing BoNT utilization, as well as use of other appropriate preventive medications, in Medicaid programs is lacking.[15]

The off-label indications continue to expand for BoNT in both neurological and non-neurological disorders. This could greatly impact the future OHP costs associated with BoNT. The majority of BoNT cost was in the CCO patient population ($541,420), as was the majority of inappropriate use (~33% of CCO patients versus 9% of FFS patients). Much of the inappropriate use in the CCOs was associated with chronic migraine where the clinical benefit is debatable.[9] The remaining inappropriate use was largely in patients with overactive bladder, but to a much smaller degree than chronic migraine.

Due to the retrospective and descriptive design of this study, there are certain limitations of importance. It should be noted that claim data can only associate patients with the same drugs and diagnoses but does not indicate the specific diagnosis a drug is prescribed for. In addition, the study period only extends back to January 1, 2012 and it is possible that prior utilization may reduce the amount of "inappropriate" use for migraine or neurogenic bladder. A total of 18% of the Medicaid study patients were less than 13 years of age. Medicare patients were excluded. This, in addition to the high-risk nature the population, could result in a higher percentage of appropriate use than what might be seen in non-Medicaid populations.

Overall the majority of patients in our study population had claims evidence of using BoNT appropriately. However, a significant portion (20.2%), primarily from CCOs, did not. This is predominantly driven by use for prevention of chronic migraine. Currently, prior authorization for use of BoNT in chronic migraine and other

off-label indications is required in many other state Medicaid programs and could help curb inappropriate use in the Oregon Medicaid population.[16]

Recommendation:

1) Consider implementing prior authorization criteria in FFS to limit use to evidence supported diagnoses.

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DRUG USE EVALUATION: UTILIZATION OF BOTULINUM TOXIN

Appendix 1:– Drug Identifiers

HSN	Generic Drug Name
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)
036477	ABOBOTULINUMTOXINA (DYSPORT)
021869	RIMABOTULINUMTOXINB (MYOBLOC)
036687	INCOBULINUMTOXINA (XEOMIN)

ProcCode	Descriptions
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit
52287	Cystourethroscopy, with injection for chemodenervation of the bladder
64612	Chemodenervation of muscle; muscle(s) innervated by facial nerve, unilaterial (For blepharospasm, hemifacial spasm)
64615	Chemodenervation of muscle; muscle(s) innervation by facial trigeminal, cervical spinal and accessory nerves, bilaterial (For chronic migraine)
64616	Chemodenervation of muscle; neck muscle(s) excluding muscles of the larynx, unilateral
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous, includes guidance by needle
64642-64647	Chemodenervation of extremity or truck muscles
64650	Chemodenervation of endocrine glands; both axillae
64653	Chemodenervation of endocrine gland; other areas
67345	Chemodenervation of extraocular muscle
46505	Chemodenervation of internal anal sphincter
95873	Electrical Stimulation for guidance in conjunction with chemodenervation
95874	Needle electromyography for guidance in conjunction with chemonervation

Botulinum Toxins (BoNT)

Goal(s):

- Approve BoNT only for funded OHP diagnoses which are supported by the medical literature (e.g. various dystonias and spasticity associated with certain neurological diseases).

Length of Authorization:

- 90 days up to lifetime

Requires PA:

Use of BoNT without associated dystonia or neurological disease diagnosis in last 12 months (i.e. 333.6x, 333.7x, 333.81, 333.83, 333.89, 340.xx, 341.0, 342.xx, 343.xx, 344.0x, 344.1, 344.2, 344.3x, 344.4x, 344.5, 344.89, 359.0-2, 438.2x-5x or 378.73)

HSN	Generic Drug Name
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)
036477	ABOBOTULINUMTOXINA (DYSPORT)
021869	RIMABOTULINUMTOXINB (MYOBLOC)
036687	INCOBULINUMTOXINA (XEOMIN)

ProcCode	Descriptions
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria	
1. What diagnosis is being treated?	Record ICD-9 Code

Approval Criteria		
2. Does client have diagnosis of certain dystonias or spasticity associated with other neurological diseases that make BoNT a first-line treatment option? Examples: 333.6x (genetic torsion dystonia) 333.7x (acquired torsion dystonia), 333.81 (blepharospasm) 333.83 (spasmodic torticollis) 333.89 (other fragments of torsion dystonia) 438.2x – 432.5x (paralysis associated with CVD) 340.xx (multiple sclerosis) 341.0 (neuromyelitis optica) 342.xx (spastic hemiplegia, other specified hemiplegia), 343.xx (cerebral palsy), 344.0x (quadriplegia and quadraparesis), 344.1 (parapalegia), 344.2 (diplegia of upper limbs) 344.3x (monoplegia of lower limb) 344.4x (monoplegia of upper limb) 344.5 (unspecified monoplegia) 344.89 (other specified paralytic syndrome) 359.0x – 359.2x (muscular dystrophies) 378.73 (strabismus in other neuromuscular disorders)	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3
3. Does client have diagnosis of chronic migraine based on clinical symptoms; at least 15 headache days per month, of which, at least 8 of those days are considered migraine days?	Yes: Go to #6	No: Go to #4
4. Does client have diagnosis of overactive bladder related to neurological causes? Document neurological cause	Yes: Go to #7	No: Go to #5

Approval Criteria		
5. Does client have any of the following diagnoses? <u>Insufficient evidence of benefit:</u> 787.2x (dysphagia) 333.xx (other extrapyramidal disease and abnormal movement disorders excluding 333.6x, 333.7x, 333.81, 333.83, 333.89 and 333.82, 333. 84, 333.94-333.99) 378 excluding 378.73 (other disorders of binocular eye movements (e.g. esotropia, exotropia, mechanical strabismus, sixth nerve palsy) 307.2x (tics) 478.75 (laryngeal spasm), 723.0 and 723.4 (Spinal stenosis in cervical region or Brachial neuritis or radiculitis NOS) 728.85 (spasm of muscle [in absence of neurological diagnoses]), 727.81 (contracture of tendon – sheath [in absence of neurological diagnoses]) 335.20 (amyotrophic sclerosis), 724.00-724.09, 724.4 (clinically significant spinal deformity or disorders of spine with neurological impairment) 600.xx (hyperplasia of prostate), <u>Unfunded OHP condition:</u> 333.82, 333. 84, 333.94-333.99 (neurologic conditions with no or minimally effective treatment or not treatment is necessary) 351.xx (facial nerve disorders), 478.79 (spastic dysphonia) 565.0 (anal fissure), 705.xx (disorders of sweat glands e.g. focal hyperhidrosis), 723.xx except 723.4 (other disorders of cervical region), 705.0-705.1,705.21-705.9,780.8 (disorders of sweat glands) 724.1, 724.2, 724.4-724.6, 727.70-724.9 (acute and chronic disorders of the spine without neurologic impairment) 729.0-729.2 (disorders of soft tissue) 307.81,339.10-339.89,784. (tension headaches) 536.3 (gastroparesis),	Yes: Pass to RPH; Deny (Medical Appropriateness) (Condition not funded by OHP)	No: Go to #8

Approval Criteria		
6. Has the client not responded or are they contraindicated to at least one drug in three of the following drug classes? • B-blocker (metoprolol, atenolol, nadolol, propranolol, timolol) • Tricyclic antidepressant (nortriptyline, amitriptyline) • Anticonvulsant (valproic acid, divalproate, carbamazepine, topiramate, gabapentin) • Calcium Channel Blocker (verapamil, diltiazem, nimodipine)	Yes: Approve for 180 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (www.orpdl.org).
7. Has the client tried or are they contraindicated to at least two of the following urinary incontinence antimuscarinic therapies? (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium)	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (www.orpdl.org).
8. Pass to pharmacist to evaluate for evidence support and OHP funding level.	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness)

P&T / DUR Action: *7/31/2014*
Revision(s):
Initiated:

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
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Oregon Health Authority

Alcohol Use Disorder Treatment: Abbreviated Class Review

Month/Year of Review: July 2014 **End date of literature search:** June 2014
Drugs Included: Acamprosate (Campral®), disulfiram (Antabuse®), and naltrexone injectable and oral (Vivitrol®, Revia®)

Current Management: Naltrexone depot injection (Appendix 1) is non-preferred with prior authorization criteria to expand access to opioid addiction treatment, allow for use in alcohol use disorder until a subsequent full evidence review can be presented, deny for use in pain and for below the line indications.

Research Questions:

- What is the comparative efficacy and safety evidence comparing different pharmacologic treatment options for alcohol use disorder?
- What is the efficacy and safety evidence of different pharmacologic treatment options for alcohol use disorder when compared to placebo or active control?
- Are there subgroups of patients where one treatment option may be more effective or safer?

Conclusions:

- There is moderate level of evidence from five meta-analyses, that oral naltrexone reduced the chance of relapses measured by return to heavy drinking (NNT = 13)[1], any drinking (NNT = 25)[1], drinking days and reduced heavy drinking days, drinking days or number of drinks per drinking days[1–5] One meta-analysis indicated naltrexone increased the chance of abstinence compared with placebo with psychosocial co-interventions (OR: 1.46, 95% CI [1.07, 2.00]; p = 0.00182)[3] and one analysis[4] suggested oral naltrexone was associated with a significant decrease in risk of relapse to heavy drinking in non-abstinent drinkers compared to placebo (NNT = 8)[4].
- There is moderate level of evidence from four meta-analyses, that acamprosate reduced the risk of relapse to heavy drinking after detoxification in alcohol dependent patients compared to placebo.[1,4,6] It significantly reduced the risk of any drinking with NNT of 9[6] or 10[1], significantly reduced the risk of relapse to heavy drinking with NNT of 9[4], significantly reduced the risk of first drinking after abstinence with NNT of 7[4], and in non-abstinent drinkers there was no significant difference in risk of heavy drinking between acamprosate and placebo (RR 0.98, 95% CI: 0.94, 1.02)[4].
- There is moderate level of evidence[1,6] that there is no statistically significant difference between acamprosate and oral naltrexone (50-100mg/day) for consumption outcomes (return to any drinking RR 1.03 (95% CI 0.96 to 1.10); cumulative abstinence duration MD 2.98 (95% CI -7.45 to 13.42); return to heavy drinking RR 1.04 (95% CI 0.95 to 1.15))[6]after detoxication from analyses on head-to-head comparisons.
- There is low strength of evidence that naltrexone injection decreases return to any drinking and return to heavy drinking, and insufficient evidence for percent drinking days.

- There is moderate level of evidence that the side effects of naltrexone and acamprosate were mainly gastrointestinal and sedative effects[1,2]. In head-to-head studies, the risk of headache was higher for naltrexone than for acamprosate (risk difference -0.06; 95% CI: -0.15, 0.03)[1].
- There is moderate level of evidence from one meta-analysis that men and women did not differ on any measure of acamprosate efficacy, safety, or tolerability.[7]
- There is low quality evidence suggesting supervised disulfiram has some beneficial effect on short-term abstinence and days until relapse when compared to placebo, nothing or other abstinence-supportive treatments.[1,8] There is insufficient evidence that dilsulfiram improves return to heavy drinking, percent of days drinking, quality of life or function, or mortality.
- There is insufficient evidence comparing depot injection of naltrexone to oral naltrexone form for efficacy and safety.
- There is insufficient evidence with any treatment on improving health outcomes, including accidents, injuries, quality of life, function, or mortality.

Recommendations:

- Oral naltrexone and acamprosate should be considered for inclusion on PDL based on moderate level evidence to support the similar efficacy and safety for the treatment of alcohol use disorder.
- Maintain injectable naltrexone as a treatment option for those patients unable or unwilling to take oral therapy or are not likely to adhere with oral naltrexone therapy.
- Maintain naltrexone depot injection prior authorization criteria (Appendix 1).

Reason for Review:

Naltrexone depot injection was recently reviewed for its role in the treatment of opioids dependence. There are several agents including naltrexone available for the treatment of alcohol use disorder. However none of these agents are currently on the Preferred Drug List (PDL). This review will examine their place in therapy for PDL placement.

Background:

Alcohol use disorder is a cluster of somatic, behavioral and physical symptoms, which are classified as mild, moderate and severe categories based upon the presence of a pre-defined list of symptoms.[9] Alcohol misuse is a widespread psychiatric disorder with lifetime prevalence estimates of 7-12.5% in most Western countries.[10,11] In the United States, about 18 million people have an alcohol use disorder.[12] Alcohol use disorder is reported to be the third leading preventable cause of death in the US, which results in significant morbidity and approximately 88,000 deaths annually. Excessive alcohol use is responsible for 2.5 million years of potential life lost (YPLL) annually, or an average of about 30 years of potential life lost for each death.

Although abstinence is the ultimate outcome for the treatment of alcohol use disorder, goals such as decreasing the drinking incidence, shortening the course, reducing episode severity, and preventing relapse are essential. Recently reduction in the frequency of heavy drinking was recognized as the major factor for decreasing disease burden and improving quality of life.[13] Traditionally the most recognized strategy for the treating alcohol use disorder was

specialty treatment programs using psychosocial therapy.[14] However using psychotherapy without an adjunct pharmacological treatment gives a poor clinical outcome, with up to 70% of patients resuming drinking within a year.[2,15,16] Medications currently approved by the Food and Drug Administration (FDA) for the treatment of alcohol use disorder include disulfiram, naltrexone and acamprosate.

The Substance Abuse and Mental Health Services Administration (SAMHSA) provides robust and comprehensive treatment guidelines/protocols for the management of alcohol disorder. Its treatment Improvement Protocol (TIP) 49[17] recognizes three pharmacological options: disulfiram, naltrexone, and acamprosate.

Disulfiram

Disulfiram was the first medication approved by the FDA to treat chronic alcohol dependence. Disulfiram is an alcohol-aversive or alcohol-sensitizing agent, which causes an acutely toxic physical reaction when mixed with alcohol. Disulfiram inhibits the liver enzyme aldehyde dehydrogenase. Alcohol intake during treatment leads to the accumulation of acetaldehyde, which possibly causes the disulfiram-ethanol reaction in the form of increased pulse and respiration, tachycardia, facial flushing, nausea, committing, hypotension, and cardiovascular collapse in the worst case.[18] Disulfiram has only limited clinical utility for patients with high motivation, good health and good cooperation. Even in highly motivated individuals, disulfiram may only partially improve alcohol-dependent patients in some aspects such as drinking frequency and amount of alcohol consumption[19].

Naltrexone

Oral naltrexone was approved by the FDA in 1994 for the treatment of alcohol use disorder. It reduces both the rewarding effects of alcohol and the craving for it. In 2010 an extended-release, monthly, intramuscular injection of naltrexone (Vivitrol®) was approved by the FDA to overcome the documented poor compliance with the oral product. Naltrexone is a highly effective opioid antagonist that binds to mu-receptors. Consequently the endorphins released as a result of alcohol drinking can no longer stimulate the opioid receptors and cause euphoria.[20] Patients notice the futility of drinking and limit their intake of alcohol.

Acamprosate

The exact mechanism of action of acamprosate has not been clearly established, but it is thought that it interacts with the glutamate neurotransmitter system, reducing and normalizing the pathologic glutamatergic hyperactivity that occurs during protracted withdrawal from alcohol. It is hypothesized that this normalization leads to a reduction of common symptoms of protracted, or post-acute, withdrawal such as insomnia, anxiety, and restlessness—symptoms that may contribute to a patient's return to alcohol use.[21,22] It was also proposed that patients who returned to drinking while taking acamprosate drank less, and less frequently, than those taking placebo.[23]

Methods:

A MEDLINE Ovid search was conducted using the terms: alcohol dependence, alcohol use disorder, disulfiram, acamprosate and naltrexone. The search was limited to meta-analysis, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality

(AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Systematic Reviews and Meta-analyses: (See Appendix 2 for abstract)

Medical Treatment of Alcohol Use Disorder

AHRQ (2014 report)[1] conducted a systematic review and meta-analysis of the efficacy, comparative effectiveness, and harms of medications (both FDA-approved and others) for adults with alcohol-use disorders, and to evaluate the evidence from primary care settings. The review included 130 studies. Most patients met criteria for alcohol dependence; mean ages were in the 40s. Moderate strength of evidence (SOE) found both acamprosate and oral naltrexone are effective for improving alcohol consumption outcomes NNT 12 and 20, respectively). For return to heavy drinking, evidence did not support the efficacy of acamprostae. Oral naltrexone was efficacious for return to heavy drinking (NNT 12). There was low SOE that injectable naltrexone is efficacious for reducing percentage of heavy drinking days. For acamprosate and naltrexone including both oral and IM forms, numbers needed to treat (NNT) to prevent one person from returning to any drinking were 10 and 25, respectively (moderate strength of evidence (SOE)). NNT to prevent one person from returning to heavy drinking was 13 for naltrexone (moderate SOE). The meta-analyses of 3 head-to-head trials found no statistically significant difference between acamprosate and oral naltrexone (50-100mg/day) for consumption outcomes after detoxication (moderate SOE). Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting. Those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting. In head-to-head studies, the risk of headache was higher for naltrexone than for acamprosate (risk difference -0.06; 95% CI: -0.15, 0.03). Evidence was insufficient to determine comparative effectiveness of medications for subgroups. The authors concluded that acamprosate and naltrexone including both oral and IM forms have the best evidence of efficacy for improving alcohol consumption outcomes for patients with alcohol dependence; and that head-to-head trials have not consistently established superiority of one medication over the others. Thus, other factors may contribute to medication choices, such as frequency of administration, potential adverse events, coexisting symptoms, and availability of treatments.

Miller PM et. al. (2011)[5] performed a systematic review to examine the efficacy of pharmacological interventions alone or in combination with brief psychosocial interventions for the treatment of alcohol dependence in primary care and specialist medical settings. Eighty-five RCTs (18,937 participants) were included in the review. Follow-up ranged from 12 weeks to 15 months.

Disulfiram (11 RCTs): Nine trials were used to draw conclusions as two used a method of administration without proven efficacy. One of the nine trials had lower potential for bias. It was unclear whether disulfiram was an effective intervention. There were mixed findings for all comparisons with placebo and active interventions. Some outcome measures showed a statistically significant benefit and others did not.

Naltrexone (31 RCTs): Seventeen trials were judged to have a lower potential for bias. Oral Naltrexone was superior to placebo in most trials (25 trials), but no difference or mixed findings were found in some (five trials). Naltrexone combined with sertraline (an antidepressant) was effective in one trial that included participants with alcohol dependence and depression but not in another trial where the participants were not depressed. The two trials included depot injections and both found statistically significant benefit compared to placebo injections.

Acamprosate (24 RCTs): Fifteen trials were rated as having a low potential for bias. There were mixed findings in 11 trials that compared acamprosate with placebo. Six of these trials found some benefits for acamprosate and five trials found either no significant differences or mixed findings. There were mixed findings for the combination of acamprosate and naltrexone (two trials). One trial found no difference with naltrexone compared with other medications. The other trials found acamprosate to be less effective than naltrexone (one trial) and disulfiram (two trials). Adjunctive psychosocial interventions (11 RCTs): Most studies of pharmacological interventions summarised above included adjunctive psychosocial interventions. Eleven trials examined this separately and seven were judged to be of low risk of bias. There were mixed findings concerning the benefits of adjunctive psychosocial treatment. The authors concluded although effects are modest, pharmacological treatment for alcohol dependence with brief support or more intensive psychosocial interventions can be effective in primary care and specialist settings. Overall the review lacks clarity for the inclusion criteria and the lack of detail provided for outcome data mean that the authors' conclusions may not be reliable.

Acamprosate and Naltrexone Reviews:

Meta-analysis by Rösner S et. al (Jan. 2008)[4] included 21 RCTs evaluating acamprosate (n=5,280) and 20 RCTs evaluated oral naltrexone at 50mg/day (n=2,182). The primary review outcomes were: return to any drinking (defined as the first drink after a period of continuous abstinence); and return to heavy drinking (as defined in individual studies). Secondary review outcomes included days drinking per week, quantity consumed per day, time to first drink, time to first relapse and gamma-glutamyl transpeptidase (GGT) level. Naltrexone studies used a drug dose of 50 mg/day. All studies used psychosocial co-interventions concurrently for all groups. Treatment duration ranged from 51 days to one year. The mean age of patients was between 36 and 58 years. The risk of having a first drink after abstinence was reduced significantly with acamprosate compared to placebo (RR 0.84, 95% CI: 0.78, 0.91; NNT 8) and with naltrexone compared to placebo (RR 0.93, 95% CI: 0.88, 0.99; NNT 17). Significant heterogeneity was found for both analyses: $p<0.00001$, I^2 83.6% for acamprosate; and $p=0.08$, I^2 33.8% for naltrexone. The risk of relapse to heavy drinking was significantly reduced with acamprosate compared to placebo (RR 0.82, 95% CI: 0.73, 0.92; NNT 9) and for naltrexone compared to placebo (RR 0.80, 95% CI: 0.71, 0.91; NNT 8). Significant heterogeneity was found for both analyses ($p<0.0001$, I^2 75.5% for acamprosate and $p< 0.0001$, I^2 64.6% for naltrexone). For non-abstinent drinkers there was no significant difference in the risk of heavy drinking between acamprosate and placebo (RR 0.98, 95% CI: 0.94, 1.02), but the risk of heavy drinking was significantly reduced with naltrexone compared to placebo (RR 0.88, 95% CI: 0.80, 0.96; NNT to prevent one additional relapse to heavy drinking was nine). The funnel plot was asymmetrical suggesting the potential for publication bias, but Begg's test showed no significant evidence ($p=0.09$ and 0.31 for the two main analyses). The authors concluded abstinence rates were significantly increased by both naltrexone and acamprosate, but only naltrexone was associated with a significant decrease in the risk of relapse to heavy drinking in non-abstinent drinkers.

Disulfiram

Jørgensen,CH., et al (2011).[8] This systematic review included eleven randomized controlled trials (RCTs) with a total of 1,527 patients. The review compared disulfiram treatment with placebo, none or other abstinence-supportive treatments. Overall, 6 studies reported a significantly better effect on abstinence for patients treated with disulfiram. Six of 9 studies measuring secondary outcomes reported that patients treated with disulfiram had significantly more days until relapse and fewer drinking days, respectively. The quality of the included studies was moderate. Heterogeneity was significant in most of the meta-analyses, but statistically significant results were found regarding the effect of disulfiram versus placebo over 12 months and unsupervised disulfiram

versus other or no treatment. The vast majority of statistically significant studies were of shorter duration, while only 3 studies of 12 months were significant regarding more days until relapse and/or reduction in drinking days. The authors concluded supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. The authors suggested the need for more homogeneous and high-quality studies in the future regarding the efficacy of disulfiram.

Naltrexone

Cochrane Review by Rösner et al. (October 2010)[2]

The aim of this systematic review was to evaluate the effectiveness and tolerability of opioid antagonists (i.e. naltrexone/nalmefene) compared to placebo or active control in the treatment of alcohol dependence. A minimum of four weeks daily treatment was required to ensure an adequate implementation of the intervention. To allow clinically relevant conclusions on treatment stability, post-treatment evaluations had to include at least 12 weeks of observation. The study end-points of the primary effectiveness outcomes including, return to heavy drinking, return to any drinking, or drinking days were considered as constitutive for effectiveness conclusions. Based on a total of 50 RCTs with 7,793 patients, naltrexone including both oral (43 RCTs) and IM (4 RCTs) forms reduced the risk of heavy drinking versus the placebo group, RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14). Based on a limited study sample, the effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies, RR 0.90 (95% CI 0.78 to 1.05) did not significantly differ from those of non-profit funded trials, RR 0.84 (95% CI 0.77 to 0.91) and the linear regression test did not indicate publication bias (P = 0.765). The authors concluded naltrexone based on analysis on both forms appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

Meta-analysis by Jarosz et.al. (May 2013)[3]

The objective of this article was to review the clinical effectiveness of oral naltrexone as an adjunct therapy to psychotherapy for the treatment of alcohol dependency. This meta-analysis included 2,427 patients in 17 RCTs with a short-term observation period (12–16 weeks), which constitutes the core of the meta-analysis. Based on the results of the meta-analysis, naltrexone increased the chance of abstinence and reduced the chance of relapse in alcohol-dependent patients. The OR of abstinence rate was 1.46, 95% CI [1.07, 2.00] and reached statistical significance (p =.00182). The OR of relapse was 0.48, 95% CI [0.36, 0.64], demonstrating statistical significance (p <.0001) in favor of naltrexone. No statistically significant differences between groups in terms of efficacy and safety assessment were observed for medium and long observational periods. The authors acknowledge that the studies included in this analysis differ with respect to type of psychotherapy reported. Moreover, the same type of psychotherapy modality can differ in its structure and intensity. They concluded oral naltrexone (50 mg once daily) is an effective and safe therapy for the treatment of alcohol-dependent patients who are simultaneously undergoing psychotherapy.

Acamprosate

The Cochrane Review by Rösner S et. al (Sept. 2010)[6] Twenty-two RCTs with 6,915 participants fulfilled the criteria of inclusion and were included in the review. Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking, RR 0.86 (95% CI 0.81 to 0.91); NNT 9 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81). Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNT 9 (95% CI 7.69 to 11.11). Effects of industry-sponsored trials RR 0.88 (95% 0.80 to 0.97) did not significantly differ from those of non-profit funded trials RR 0.88 (95% CI 0.81 to 0.96). In addition, the linear regression test did not indicate a significant risk of publication bias (p = 0.861). The meta-analytic integrations based on head-to-head comparisons between acamprosate and oral naltrexone (50-100mg/day) did not indicate a superiority of one or the other drug (return to any drinking RR 1.03 (95% CI 0.96 to 1.10); cumulative abstinence duration MD 2.98 (95% CI -7.45 to 13.42); return to heavy drinking RR 1.04 (95% CI 0.95 to 1.15)). The authors concluded acamprosate appears to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent patients. The authors recognized the treatment effect sizes appear to be rather moderate, and they recommended the use of acamprosate should be valued against the background of the relapsing nature of alcoholism and taking into consideration of the limited therapeutic options currently available for its treatment.

Special Population: Sex-specific Meta-analysis

Mason B et. al. (March 2012)[7]: The objective of this study was to assess sex-specific differences in the efficacy, safety, and tolerability of acamprosate compared to placebo in the treatment of women and men with alcohol dependence. A sex-specific meta-analysis was conducted based on individual patient data. Individual records were obtained from 1,317 women and 4,794 men who participated in 22 eligible studies conducted in 18 countries. A meta-analyses of the data found a significant beneficial effect of acamprosate relative to placebo across all 4 efficacy end points: an incremental gain of 10.4% (95% CI 7.1 to 13.7, $p < 0.001$) in percentage of abstinent days, an incremental gain of 11.0% (7.4 to 14.6, $p < 0.001$) in percentage of no heavy drinking days, an odds ratio of 1.9 (1.6 to 2.2, $p < 0.001$) for rate of complete abstinence, and an odds ratio of 1.9 (1.6 to 2.3, $p < 0.001$) for rate of no heavy drinking, over the study duration. Acamprosate was also associated with significantly higher rates of treatment completion ($p = 0.004$) and medication compliance ($p < 0.001$) than placebo. Men and women did not differ on any measure of acamprosate efficacy, safety, or tolerability. The authors concluded that acamprosate has a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence. Further, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men and had a comparable safety and tolerability profile.

Treatment guidelines:

National Institute for Health and Clinical Excellence (NICE) released guidelines on diagnosis, assessment and management of harmful drinking and alcohol dependence in 2011.[24] The NICE guidelines recommended using benzodiazepines such as diazepam or chlordiazepoxide for assisted withdrawal. After a successful withdrawal, consider offering 1) acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioral therapies, behavioral therapies or social network and environment-based therapies) focused specifically for alcohol miseuse or 2) offering

Disulfiram in combination with a psychological intervention to users who have a goal of abstinence but acamprosate and oral naltrexone are not suitable or prefer disulfiram and understand the relative risk of taking the drug.

VA/DoD 2009 updated treatment guideline on substance abuse have the following recommendations on pharmacotherapy for alcohol dependence:[25] 1)routinely consider oral naltrexone, an opioid antagonist, and/or acamprosate for patients with alcohol dependence (level A); 2)medications should be offered combined with addiction-focused counseling(level A); 3)Injectable naltrexone should be considered when medication adherence is a significant concern in treating alcohol dependence and should be combined with addiction-focused counseling (level A); 4)if patient does not respond to one of the approved medications, a trial on one of the other approved medications is warranted; 5) because of the risk of significant toxicity and limited evidence of effectiveness, risk and benefits of disulfiram should be considered and disulfiram should only be used when abstinence is the goal and when combined with addiction-focused counseling (level B). The informed consent discussion with the patient should be documented.

World Federation of Societies of Biological Psychiatry (WFSBP) released guidelines for the treatment of alcoholism in 2008.[26] Among the medications used as relapse prevention, disulfiram has level C strength of evidence on its efficacy whereas both acamprosate and naltrexone have level A grading. The guidelines also recognized the value of using pharmacotherapy in conjunction with psychosocial treatment to increase abstinence rates and relapse rates.

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Appendix 1: Vivitrol Prior Authorization Criteria

Naltrexone Extended Release Inj. (Vivitrol)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization: Initial – 3 months; Renewal – one year

Covered Alternatives: Acamprosate, naltrexone tablets, disulfiram

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the member have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (AUD; DSM5)?	**Yes:** Go to #3.	**No:** Go to #4
3. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider and/or objective testing?	**Yes:** Go to #6	**No:** Deny, medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
4. Does the member have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (OUD; DSM5)?	**Yes:** Go to #5	**No:** Deny, medical appropriateness. Naltrexone extended release injection is only approved for alcohol and opioid dependence.
5. Has the patient tried and failed other oral agents for the treatment of opioid dependency (buprenorphine, methadone) **OR** Is the patient unable to take oral therapy or d~~D~~oes the patient require injectable therapy due to adherence issues?	**Yes:** Go to #6	**No:** Deny, medical appropriateness.

Approval Criteria		
6. Is the member part of a comprehensive treatment program for substance abuse that includes a psychosocial support system?	**Yes:** Go to #7	**No:** Deny, medical appropriateness. Naltrexone extended release injection therapy must be part of a comprehensive treatment program including psychosocial support.
7. Has the patient received any opioid prescription within the last 30 days from a prescriber other than the requesting provider based on prescription claims history?	**Yes:** Notify requesting provider of the opioid prescriber, drug, dose, prescription date and the day supply; Go to #8.	**No:** Go to #8
8. Has the patient abstained from the use of any opioids for at least 7 to 10 days, including street opioids such as heroin or prescription opioids as assessed by the provider and/or objective testing?	**Yes:** Approve for 3 months for initial therapy, 12 months for continuation therapy	**No:** Deny, medical appropriateness. Patient must be opioid free for 7 to 10 days prior to administration to minimize risk of acute opioid withdrawal syndrome.

Appendix 2: Abstract of Selected Systemic Reviews and Meta-analyses

1. **Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and meta-analysis.**
Jonas DE, Amick HR, Feltner C, et al. *JAMA*. 2014;311(18):1889-1900.

Abstract

Importance: Alcohol use disorders cause substantial morbidity and early mortality yet remain greatly undertreated. Medications are considerably underused.

Objective: To conduct a systematic review and meta-analysis of the benefits and harms of medications (US FDA-approved and others) for adults with alcohol use disorders.

Data Sources: PubMed, Cochrane Library, PsycINFO, CINAHL, EMBASE, FDA website, and clinical trials registries (January 1, 1970, to March 1, 2014).

Study Selection: Two reviewers selected randomized clinical trials (RCTs) with at least 12 weeks' duration that reported eligible outcomes and head-to-head prospective cohort studies reporting health outcomes or harms.

Data Extraction and Synthesis: We conducted meta-analyses using random-effects models and calculated numbers needed to treat for benefit (NNTs) or harm (NNHs).

Main Outcomes and Measures: Alcohol consumption, motor vehicle crashes, injuries, quality of life, function, mortality, and harms.

Results: We included 122 RCTs and 1 cohort study (total 22,803 participants). Most assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both. The NNT to prevent return to any drinking for acamprosate was 12 (95% CI, 8 to 26; risk difference [RD], -0.09; 95% CI, -0.14 to -0.04) and was 20 (95% CI, 11 to 500; RD, -0.05; 95% CI, -0.10 to -0.002) for oral naltrexone (50 mg/d). The NNT to prevent return to heavy drinking was 12 (95% CI, 8 to 26; RD -0.09; 95% CI, -0.13 to -0.04) for oral naltrexone (50 mg/d). Meta-analyses of trials comparing acamprosate to naltrexone found no statistically significant difference between them for return to any drinking (RD, 0.02; 95% CI, -0.03 to 0.08) or heavy drinking (RD, 0.01; 95% CI, -0.05 to 0.06). For injectable naltrexone, meta-analyses found no association with return to any drinking (RD, -0.04; 95% CI, -0.10 to 0.03) or heavy drinking (RD, -0.01; 95% CI, -0.14 to 0.13) but found an association with reduction in heavy drinking days (weighted mean difference [WMD], -4.6%; 95% CI, -8.5% to -0.56%). Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene (heavy drinking days per month: WMD, -2.0; 95% CI, -3.0 to -1.0; drinks per drinking day: WMD, -1.02; 95% CI, -1.77 to -0.28) and topiramate (% heavy drinking days: WMD, -9.0%; 95% CI, -15.3% to -2.7%; drinks per drinking day: WMD, -1.0; 95% CI, -1.6 to -0.48). For naltrexone and nalmefene, NNHs for withdrawal from trials due to adverse events were 48 (95% CI, 30 to 112) and 12 (95% CI, 7 to 50), respectively; risk was not significantly increased for acamprosate or topiramate.

Conclusions and Relevance: Both acamprosate and oral naltrexone were associated with reduction in return to drinking. When directly compared with one another, no significant differences were found between acamprosate and naltrexone for controlling alcohol consumption. Factors such as dosing frequency, potential adverse events, and availability of treatments may guide medication choice.

2. **The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder.**
Jørgensen, C. H., Pedersen, B. and Tønnesen, H. (2011), Alcoholism: Clinical and Experimental Research, 35: 1749–1758. doi: 10.1111/j.1530-0277.2011.01523.x

Abstract

Background: Alcohol use disorders (AUD) involving hazardous, harmful, and addictive misuse of alcohol are widespread in most parts of the world. The aim of this study was to review the effect of disulfiram in the treatment of patients with AUD. The effect of disulfiram was evaluated according to the primary outcome of an intake of alcohol below 30 and 20 g/d for men and women, respectively, as well as secondary outcomes such as days until relapse, alcohol intake, and numbers of drinking days.

Methods: A systematic review of the literature was conducted using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL).

Results: Eleven randomized controlled trials were included with a total of 1,527 patients. They compared disulfiram treatment with placebo, none or other abstinence-supportive treatments. Overall, 6 studies reported of a significant better effect on abstinence for patients treated with disulfiram. Six of 9 studies measuring secondary outcomes reported that patients treated with disulfiram had significantly more days until relapse and fewer drinking days, respectively. The quality of the included studies was moderate. Heterogeneity was significant in most of the meta-analyses, but valid results were found regarding the effect of disulfiram versus placebo over 12 months and unsupervised disulfiram versus other or no treatment. The vast majority of significant studies were of shorter duration, while only 3 studies of 12 months were significant regarding more days until relapse and/or reduction in drinking days.

Conclusions: Supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. However, there is a need for more homogeneous and high-quality studies in the future regarding the efficacy of disulfiram.

3. **Opioid antagonists for alcohol dependence.**
Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD001867. DOI: 10.1002/14651858.CD001867.pub3.

Abstract
Background: Alcohol dependence belongs to the globally leading health risk factors. Therapeutic success of psychosocial programs for relapse prevention is moderate and could be increased by an adjuvant treatment with the opioid antagonists naltrexone and nalmefene.

Objectives: To determine the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.

Search methods: We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL in January 2010 and inquired manufacturers and researchers for unpublished trials.

Selection criteria: All double-blind randomised controlled trials (RCTs) which compare the effects of naltrexone or nalmefene with placebo or active control on drinking-related outcomes.

Data collection and analysis: Two authors independently extracted outcome data. Trial quality was assessed by one author and cross-checked by a second author.

Main results: Based on a total of 50 RCTs with 7793 patients, naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Significant effects were also demonstrated for the secondary outcomes of the review including heavy drinking days, MD - 3.25 (95% CI -5.51 to -0.99), consumed amount of alcohol, MD - 10.83 (95% CI -19.69 to -1.97) and gamma-glutamyltransferase, MD - 10.37 (95% CI -18.99 to -1.75), while effects on return to any drinking, RR 0.96 (95 CI 0.92 to 1.00) missed statistical significance. Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14). Based on a limited study sample, effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies, RR 0.90 (95% CI 0.78 to 1.05) did not significantly differ from those of non-profit funded trials, RR 0.84 (95% CI 0.77 to 0.91) and the linear regression test did not indicate publication bias (P = 0.765).

Authors' conclusion: Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

4. **Naltrexone (50 mg) Plus Psychotherapy in Alcohol-Dependent Patients: A Meta-Analysis of Randomized Controlled Trials.**
Jarosz J, Miernik K, Wąchal M, Walczak J, Krumpl G. *Am J Drug Alcohol Abuse*. 2013;39(3):144-160. doi:10.3109/00952990.2013.796961.

Abstract

Background: Alcoholism is a chronic and potentially fatal disease. One of the therapeutic options is pharmacotherapy with the opioid antagonist naltrexone in combination with psychotherapy,

Objectives: The objective of this review was to compare the clinical effectiveness of naltrexone (50 mg/day) versus that of a placebo in alcohol-dependent patients receiving psychotherapy.

Methods: The clinical effectiveness of the treatment was assessed in accordance with the principles of systematic review, as outlined in the Cochrane Collaboration guidelines (Cochrane Reviewer's Handbook) and the guidelines of the Polish Agency for Health Technology Assessment (AHTAPol).

Results: Statistical significances in favor of the treatment modality were found in both the percentage of patients maintaining total abstinence and the percentage of relapsed patients.

Conclusion: The analysis herein demonstrates that for short (12–16 weeks) period of treatment, a combination of naltrexone administration and psychotherapy results in high clinical efficacy with a safety profile comparable to that of the placebo in the treatment of alcohol-dependent patients. The side effects of naltrexone treatment are usually mild and transient.

5. **Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials.**
Srisurapanont M, Jarusuraisin N. *Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP*. 2005;8(2):267-280. doi:10.1017/S1461145704004997.

Abstract

Many trials of naltrexone have been carried out in alcohol-dependent patients. This paper is aimed to systematically review its benefits, adverse effects, and discontinuation of treatment. We assessed and extracted the data of double-blind, randomized controlled trials (RCTs) comparing naltrexone with placebo or other treatment in people with alcoholism. Two primary outcomes were subjects who relapsed (including heavy drinking) and those who returned to drinking. Secondary outcomes were time to first drink, drinking days, number of standard drinks for a defined period, and craving. All outcomes were reported for the short, medium, and long term. Five common adverse effects and dropout rates in short-term treatment were also examined. A total of 2861 subjects in 24 RCTs presented in 32 papers were included. For short-term treatment, naltrexone significantly decreased relapses [relative risk (RR) 0.64, 95% confidence interval (CI) 0.51-0.82], but not return to drinking (RR 0.91, 95% CI 0.81-1.02). Short-term treatment of naltrexone significantly increased nausea, dizziness, and fatigue in comparison to placebo [RRs (95% CIs) 2.14 (1.61-2.83), 2.09 (1.28-3.39), and 1.35 (1.04-1.75)]. Naltrexone administration did not significantly diminish short-term discontinuation of treatment (RR 0.85, 95% CI 0.70-1.01). Naltrexone should be accepted as a short-term treatment for alcoholism. As yet, we do not know the appropriate duration of treatment continuation in an alcohol-dependent patient who responds to short-term naltrexone administration. To ensure that the real-world treatment is as effective as the research findings, a form of psychosocial therapy should be concomitantly given to all alcohol-dependent patients receiving naltrexone administration.

6. **Acamprosate for alcohol dependence.**
Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2.

Abstract

Background: Alcohol dependence is among the main leading health risk factors in most developed and developing countries. Therapeutic success of psychosocial programs for relapse prevention is moderate, but could potentially be increased by an adjuvant treatment with the glutamate antagonist acamprosate.

Objectives: To determine the effectiveness and tolerability of acamprosate in comparison to placebo and other pharmacological agents.

Search methods: We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL in January 2009 and inquired manufacturers and researchers for unpublished trials.

Selection criteria: All double-blind randomised controlled trials (RCTs) which compare the effects of acamprosate with placebo or active control on drinking-related outcomes.

Data collection and analysis: Two authors independently extracted data. Trial quality was assessed by one author and cross-checked by a second author. Individual patient data (IPD) meta-analyses were used to verify the primary effectiveness outcomes.

Main results: 24 RCTs with 6915 participants fulfilled the criteria of inclusion and were included in the review. Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking RR 0.86 (95% CI 0.81 to 0.91); NNT 9.09 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81), while secondary outcomes (gamma-glutamyltransferase, heavy drinking) did not reach statistical significance. Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNTB 9.09 (95% CI 7.69 to 11.11). Effects of industry-sponsored trials RR 0.88 (95% 0.80 to 0.97) did not significantly differ from those of non-profit funded trials RR 0.88 (95% CI 0.81 to 0.96). In addition, the linear regression test did not indicate a significant risk of publication bias (p = 0.861).

Authors' conclusions: Acamprosate appears to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent patients. Even though the sizes of treatment effects appear to be rather moderate in their magnitude, they should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

7. **Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes.**
Rösner S, Leucht S, Lehert P, Soyka M. *J Psychopharmacol Oxf Engl*. 2008;22(1):11-23. doi:10.1177/0269881107078308.

Abstract

Two pharmacological agents have repeatedly been shown to be efficacious for relapse prevention in alcohol dependence: The putative glutamate-antagonist acamprosate and the opioid-antagonist naltrexone. Clinical evidence for both drugs is based on various outcome criteria. Whereas for acamprosate primarily abstinence maintenance has been demonstrated, studies with naltrexone have mostly emphasised the prevention of heavy drinking. The remaining effects of both drugs are not always reported; accordingly the corresponding database is fragmentary. Thus, the primary objective of the present meta-analysis was to complete the efficacy profiles for acamprosate and naltrexone and to compare them with each other. Unreported results, requested from the study investigators and the drug manufacturers, were integrated in the computation of effect sizes. For the meta-analysis, emphasis was placed on the conceptual distinction between having a first drink and returning to heavy drinking. Naltrexone was found to have a significant effect on the maintenance of abstinence as well as the prevention of heavy drinking. Acamprosate was shown only to support abstinence; it did not influence alcohol consumption after the first drink. When the efficacy profiles of the two

drugs were compared, acamprosate was found to be more effective in preventing a lapse, whereas naltrexone was better in preventing a lapse from becoming a relapse. The superiority of either one drug or over the other one cannot be determined as a general rule, it rather depends on the therapeutic target. Benefits in the treatment of alcohol dependence might be optimized by matching the efficacy profiles of specific antidipsotropics with the motivational status of alcohol-dependent patients.

8. **Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data.**
Mason BJ, Lehert P. *Alcohol Clin Exp Res*. 2012;36(3):497-508. doi:10.1111/j.1530-0277.2011.01616.x.

Abstract

Background: It is unknown whether women derive comparable benefits and have a similar safety and tolerability profile as men from acamprosate, a widely prescribed drug for the maintenance of abstinence in alcohol dependence. The objective of this study was to assess sex-specific differences in the efficacy, safety, and tolerability of acamprosate in the treatment of women and men with alcohol dependence.

Methods: A sex-specific meta-analysis was conducted based on individual patient data (IPD). Data were obtained from double-blind, randomized controlled trials with quantitative drinking measures in patients with alcohol dependence receiving oral acamprosate or placebo. Sources included PubMed, PsychInfo, and Cochrane electronic databases; reference lists from retrieved articles and presentations at professional meetings; and direct access to authors and companies who provided IPD.

Results: Individual records were obtained from 1,317 women and 4,794 men who participated in 22 eligible studies conducted in 18 countries. IPD meta-analyses found a significant beneficial effect of acamprosate relative to placebo across all 4 efficacy end points: an incremental gain of 10.4% (95% CI 7.1 to 13.7, $p < 0.001$) in percentage of abstinent days, an incremental gain of 11.0% (7.4 to 14.6, $p < 0.001$) in percentage of no heavy drinking days, an odds ratio of 1.9 (1.6 to 2.2, $p < 0.001$) for rate of complete abstinence, and an odds ratio of 1.9 (1.6 to 2.3, $p < 0.001$) for rate of no heavy drinking, over the study duration. Acamprosate was also associated with significantly higher rates of treatment completion ($p = 0.004$) and medication compliance ($p < 0.001$) than placebo. Men and women did not differ on any measure of acamprosate efficacy, safety, or tolerability.

Conclusions: This sex-specific IPD meta-analysis provides evidence that acamprosate has a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence. Further, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men and had a comparable safety and tolerability profile.

9. **Medical treatment of alcohol dependence: a systematic review.**
Miller PM, Book SW, Stewart SH. *Int J Psychiatry Med*. 2011;42(3):227-266.

Abstract

Objective: To summarize published data on pharmacologic treatments for alcohol dependence alone and in combination with brief psychosocial therapies that may be feasible for primary care and specialty medical settings.

Methods: We conducted electronic searches of published original research articles and reviews in MEDLINE, SCOPUS, CINAHL, Embase, and PsychINFO. In addition, hand searches of reference lists of review articles, supplemental searches of internet references and contacts with experts in the field were conducted. Randomized controlled studies published between January 1960 and August 2010 that met our inclusion/exclusion criteria were included.

Results: A total of 85 studies, representing 18,937 subjects, met our criteria for inclusion. The evidence base for oral naltrexone (6% more days abstinent than placebo in the largest study) and topiramate (prescribed off-label) (e.g., 26.2% more days abstinent than placebo in a recent study) is positive but modest. Acamprosate shows modest efficacy with recently abstinent patients, with European studies showing better results than U.S. ones. The evidence-base for disulfiram is equivocal. Depot naltrexone shows efficacy (25% greater reduction in rate of heavy drinking vs. placebo, in one of the largest studies) in a limited number of studies. Some studies suggest that patients do better with extensive psychosocial treatments added to medications while others show that brief support can be equally effective.

Conclusions: Although treatment effects are modest, medications for alcohol dependence, in conjunction with either brief support or more extensive psychosocial therapy, can be effective in primary and specialty care medical settings.

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Class Update: Topical Androgens

Month/Year of Review: July 2014
PDL Class: Topical Androgens
Literature Search End Date: June 2014

Date of Last Review: September, 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred agents: Testosterone (Androgel®), testosterone gel (Testim®), testosterone cypionate injection and testosterone enathate injection.
- Non-preferred agents: Testosterone transdermal gel (Fortesta®), testosterone transdermal solution (Axiron®), testosterone patch (Androderm®).

Previous Conclusions/Recommendations:

- There is no new evidence that there is a difference in efficacy between the different testosterone products.
- Testosterone patches are associated with a higher incidence of adverse reactions related to administration.
- There is new low quality evidence that there is a potential increased risk of cardiovascular related events associated with testosterone therapy, and caution should be used in older men where cardiovascular disease is common.
- There is insufficient evidence that the new formulations (Axiron® , Androgel® 1.62%, and Fortesta®) have improved efficacy or safety than other available agents.
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

PA Criteria: A prior authorization criterion is currently in place for transdermal androgens to cover only for covered diagnosis and for medically appropriate conditions (Appendix 1). Use for body building and sexual dysfunction is not covered.

Conclusions:

- There is no new evidence that there is a difference in efficacy or safety between the different testosterone products.
- There is insufficient evidence that new depot formulation of testosterone (Aveed®) has improved efficacy or safety than other available agents. The new depot formulation of testosterone (Aveed®) offers less frequent dosing schedule, but at risk of serious pulmonary oil microembolism reactions and anaphylaxis.[1]

- The most recent FDA safety alert on potential risk of stroke, heart attack, and death in men taking testosterone supplementation was based on low quality evidence (2 observational trials).[2,3] There remains insufficient long term evidence assessing the long-term benefits and risk of testosterone therapy in men and further randomized controlled trials are needed.
- There is insufficient evidence to support androgen therapy as part of hormone therapy for the treatment of primary ovarian insufficiency.[4]

Recommendations:

- Re-evaluate safety of testosterone therapy once FDA concludes its review.
- Remove ovarian failure from list of covered diagnoses in PA criteria.
- Evaluate comparative costs in executive session.

Methods:

A MEDLINE OVID search was conducted using the following search terms: testosterone, testosterone, steroids, anabolic agents, androgens, hypogonadism, weight gain, and osteoporosis. The search is limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans from July 2013 to first week of May 2014.

The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New drugs:

None.

New Formulations/ Indications:

In March 2014, the FDA approved testosterone undecanoate (Aveed®), an injectable depot formulation, for use in men with hypogonadism who require testosterone replacement therapy.[1] The recommended dosage is 750 mg injected intramuscularly at 0 and 4 weeks, and then every 10 weeks thereafter.[1] An unpublished 84-week trial of testosterone undecanoate therapy in 130 hypogonadal men (mean age 54 years), found that 94% of those who participated in the study through week 24 maintained average serum testosterone concentrations in the normal range after the third injection of the drug. The average maximum testosterone concentration at steady state was 891 ng/dL and the average minimum was 324 ng/dL. The percentage of patients with maximum concentrations >1500 ng/dL was 7.7%.[1]

In clinical trials, the most common adverse effects of testosterone undecanoate injections that occurred in about 5% of patients included acne, injection site pain, and an increase in prostate specific antigen levels above 4 ng/mL. Postmarketing surveillance of testosterone undecanoate products approved in other countries found that some patients developed pulmonary oil microembolism (POME) reactions that have included cough, dyspnea, throat tightening, chest pain, dizziness, and syncope occurring during or immediately after injection of the drug. Some of these episodes lasted several hours, and some required

hospitalization. Life-threatening anaphylactic reactions have also been reported. As a result, the FDA labeling includes boxed warning requiring that patients be observed for 30 minutes after injections of Aveed®, and use of the drug is restricted to healthcare providers and settings certified through a Risk Evaluation and Mitigation Strategy (REMS) program.[1] This new depot formulation of testosterone offers less frequent dosing schedule, but at risk of serious pulmonary oil microembolism reactions and anaphylaxis.

In June 2014, the FDA approved another testosterone gel (Vogelxo™) that is available in tube, unit dose packet or meter dose gel pump. It is dosed once daily topically. At time of this review, there is no published RCTs evaluating its efficacy and safety. Based on product prescribing information, the FDA approval was based on one multi-center RC trial in 406 patient for 90 days[5]. The study was double-blind for the doses of testosterone gel and placebo, but open label for the nonscrotal testosterone transdermal system. During the first 60 days, patients were evenly randomized to testosterone gel 50 mg, testosterone gel 100 mg, placebo gel, or testosterone transdermal system. At Day 60, patients receiving testosterone gel were maintained at the same dose, or were titrated up or down within their treatment group, based on 24-hour averaged serum testosterone concentration levels obtained on Day 30. Of 192 hypogonadal men who were appropriately titrated with testosterone gel and who had sufficient data for analysis, 74% achieved an average serum testosterone level within the normal range (300 to 1,000 ng/dL) on treatment day 90[5].

New FDA safety alerts:
January 2014 FDA released a safety alert on the investigation of the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products.[6] This alert was based on the recent publication of two separate observational studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy.[2,3] At this time, FDA has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death. Patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals. FDA encourage weighing the benefits vs. potential risks of treatment before prescribing.

The first study was a retrospective cohort study in the VA system including men with low serum testosterone (<300 ng/dl) who were undergoing coronary angiography, to assess for coronary artery disease. Some of the men received testosterone treatment while others did not and the primary outcome was a composite of all-cause mortality, myocardial infarction (MI), and ischemic stroke. On average, the men who entered the study were about 60 years old, and many had underlying cardiovascular disease (more than 80% had coronary artery disease). This study suggested a 30 percent increased risk of stroke, heart attack, and death in the group that had been prescribed testosterone therapy (HR 1.29; 95% CI 1.05-1.58; p=0.02).[2] The absolute risk differences in events were 1.3% (95% CI -7.1% to 9.7%) at 1 year, 3.1% (95% CI -4.9% to 11.0%) at 2 years, and 5.8% (95%CI -1.4% to 13.1%) at 3 years. There are many limitations to this study, including the retrospective study design and use of ICD-9 codes to determine outcomes.

A second observational cohort study reported an increased risk of MI in older men, as well as in younger men with pre-existing heart disease, who filled a prescription for testosterone therapy.[3] The study reported a two-fold increase in the risk of heart attack among men aged 65 years and older in the first 90 days following the first prescription (RR 2.19; 95% CI 1.27 to 3.77). Among younger men less than 65 years old with a pre-existing history of heart disease, the study reported a two- to three-fold increased risk of MI in the first 90 days following a first prescription. Younger men without a history of heart disease who filled a prescription for testosterone, however, did not have an increased risk of MI (RR 1.17; 95% CI 0.84 to 1.63).

On June 19, 2014, FDA released a general warning on potential venous clots while on testosterone products. The risk of venous blood clots is already included in the labeling of testosterone products as a possible consequence of polycythemia, an abnormal increase in the number of red blood cells that sometimes occurs

with testosterone treatment. Because there have been postmarket reports of venous blood clots unrelated to polycythemia, FDA is requiring a change to drug labeling of all testosterone products to provide a more general warning regarding venous blood clots and to ensure this risk is described consistently in the labeling of all approved testosterone products. Because these clots occur in the veins, this new warning is not related to FDA's ongoing evaluation of the possible risk of stroke, heart attack, and death in patients taking testosterone products[7].

New Systematic Reviews (Appendix 2):
Corona et.al. recently conducted a systematic review and meta-analysis of testosterone replacement therapy's (TRT) outcomes in late-onset hypogonadism (LOH).[8] This review examined the diagnostic criteria for hypogonadism, effects of lifestyle modification and weight loss in LOH and medical treatment of LOH including the effect of androgen supplementation on comorbidities including: type 2 diabetes (T2DM) and metabolic syndrome(MetS), HIV infection, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), osteoporosis, and cardiovascular diseases. Six RTCs specifically evaluated the effect of TRT on MetS enrolling 483 patients and 5 RCTs on T2DM with total 263 patients. The results showed TRT showed a significant reduction of fasting glycemia (mmol/L) (diff. in mean: -0.48; 95% CI -0.78 to -0.19; p = 0.00); triglycerides (nmol/L) (diff. in mean: -0.40; 95% CI -0.66 to -0.14; p = 0.00), and waist circumference (cm) (diff. in mean: -4.09); 95%CI -7.78 to -0.39; p = 0.03) in MetS. Accordingly, an improvement of fasting glycemia (mmol/L) (diff. in mean-1.09; 95% CI -1.84 to -0.35; p = 0.00), HbA1C (%) (diff. in mean: -0.62; 95% CI -1.0 to -0.24; p = 0.00) and triglycerides (nmol/L) (diff. in mean: -0.60; 95% CI -0.83 to -0.37; p = 0.00) was observed in subjects with T2DM. In patients with HIV infection, TRT significantly improved lean mass over placebo (kg) (diff. in mean: 0.91; 95 CI 0.15 to 1.66; p = 0.02) based on 6 RTCs. The studies of TRT in patients with CKD, COPD, CVD and osteoporosis are scarce, information about the benefits and risks of TRT is too limited to draw final conclusions.

In addition to above analysis, there was a clinical review by Su J et.al since last review, that evaluated the effect of TRT on CVDs[9] The review recognized most of the studies examining TRT and CVD were observational, cross sectional, or retrospective studies that cannot demonstrate cause and effect. The more recent control studies pointed toward a potential beneficial effect of TRT on CVD. TRT resulted in positive short- and long-term physiological and biochemical changes in patients with CVD. Favorable effects have been demonstrated on myocardial ischemia, chronic heart failure (CHF) exercise tolerance, and MetS. Clinical trials and meta-analysis investigating the benefits and risks of TRT have not demonstrated significant CV events in acute setting. However, its long term risks were raised in more recent studies. The authors concluded future randomized control studies are needed to better delineate the risks and benefits of TRT in CVD and establish the optimal protocol for TRT while comparing acute versus chronic adverse effects.

Guidelines:
None.

New Trials:
A total of 83 citations resulted from initial literature search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, no relevant head-to-head controlled clinical trials were identified.

Current PA Criteria Evaluation:
Ovarian failure is included as one of diagnoses that can be approved under current PA criteria. Estrogen therapy in combination with a progestin is the gold standard for the treatment in women with primary ovarian insufficiency (premature ovarian failure) with intact uterus.[10] The main purpose of estrogen therapy is to prevent bone loss. Women with primary ovarian insufficiency may have some degree of androgen deficiency when compared with young women without

ovarian insufficiency. However, the clinical consequences of this decrease in ovarian androgens and the possible role of androgen therapy have been extensively studies[10]. Androgen therapy had been reported in uncontrolled studies in the past to be beneficial for vasomotor flushes, cognitive function and mood, and bone mineral density. However, in a Cochrane review and meta-analyses of 54 studies by Somboonporn et al.[4], no evidence of benefit for any of these outcomes was observed in peri-postmenopausal women. The authors concluded there is good evidence that adding testosterone to hormone therapy has a beneficial effect on sexual function in post-menopausal women. However, the combined therapy is associated with a higher incidence of hair growth and acne and a reduction in HDL cholesterol. These adverse events may differ by the different doses and route of testosterone administration. There is insufficient evidence to determine the effect of testosterone in long term use.

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Author: B Liang, Pharm.D Date: July 2014

Appendix 1: Current PA Criteria

Hormones – Testosterone (Androgens)

Goal(s):

- Cover only for covered diagnosis and for medically appropriate conditions.
- Use for body building is not covered.
- Use for sexual dysfunction is not covered.

Length of Authorization: 6 months

Requires PA: All testosterones require PA for coverage verification

Covered Alternatives: Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Does the diagnosis for the medication requested include any of the following? ~~- Ovarian failure (256.31, 256.39)~~ - Testicular Hypofunction (257.2) - Hypopituitarism and related disorders (253.2, 253.4, 253.7, 253.8) - AIDS-related cachexia (253.2)	**Yes**: Go to #3	**No**: Pass to RPh. RPh go to #4

Author: B Liang, Pharm.D Date: July 2014

3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. Approve for 6 months.	**No**: Approved for 6 months.
4. RPH only All other indications need to be evaluated to see if they are above the line or below the line.	**If above the line or clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, (Not Covered by the OHP).

P&T / DUR Action: 2/23/12 (TDW), 9/16/10 (KS), 2/23/06, 2/21/01, 9/6/00
Revision(s): 5/14/12, 1/24/12, 1/1/11, 9/1/06
Initiated:

Appendix 2

1. **Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: Systematic review and meta-analysis of TRT outcomes. Best Practice & Research Clinical Endocrinology & Metabolism. 2013;27(4):557-579.**

Abstract

Late-onset hypogonadism (LOH) is a relatively common conditions affecting the aging male. The aim of this review is to summarize the available evidence regarding LOH and its interaction with general health. LOH is often comorbid to obesity and several chronic diseases. For this reason lifestyle modifications should be strongly encouraged in LOH subjects with obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) and good treatment balance of chronic diseases. Medical therapy of LOH should be individualized depending on the etiology of the disease and the patient's expectations. Available evidence seems to suggest that testosterone replacement therapy is able to improve central obesity (subjects with MetS) and glycometabolic control (patients with MetS and T2DM), as well as to increase lean body mass (HIV, chronic obstructive pulmonary disease), along with insulin resistance (MetS) and peripheral oxygenation (chronic kidney diseases). However, it should be recognized that the number of studies on benefits of T supplementation is too limited to draw final conclusions. Longer and larger studies are needed to better clarify the role of TRT in such chronic conditions.

2. **Su JJ, Park SK, Hsieh TM. The Effect of Testosterone on Cardiovascular Disease: A Critical Review of the Literature. *Am J Mens Health*. 2014.**

Abstract

Cardiovascular disease is the leading cause of death in the United States. Testosterone is the principal male sex hormone and plays an important role in men's health and well-being. Historically, testosterone was believed to adversely affect cardiovascular function. However, contemporary literature has refuted this traditional thinking; testosterone has been suggested to have a protective effect on cardiovascular function through its effects on the vascular system. Data from modern research indicate that hypogonadism is closely related to the development of various cardiovascular risk factors, including hyperlipidemia and insulin resistance. Several studies have demonstrated beneficial effects of testosterone supplementation therapy on reversing symptoms of hypogonadism and improving cardiovascular disease risk profiles. In this review, we perform a critical analysis on the association between testosterone and cardiovascular disease.

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Abbreviated Class Update: Oral/Inhalation Pulmonary Arterial Hypertension (PAH) Agents

Month/Year of Review: July 2014
Last Review: 2009 PAH Agents
2012 IV PAH Agents

End date of literature search: May 2014
Source Document: Provider Synergies
OSU DURM

New drugs reviewed: macitentan (Opsumit®) and riociguat (Adempas®)
New drug formulation reviewed: oral treprostinil (Orenitram®)

Current PDL Status:

Preferred

Drug Class	Drug
Endothelin Antagonist	**Bosentan**
Phosphodiesterase-5 Inhibitor	**Sildenafil citrate**

Non-preferred

Drug Class	Drug
Prostanoid	**Treprostinil (inhaled)**
Prostanoid	**Iloprost (inhaled)**
Phosphodiesterase-5 Inhibitor	**Tadalafil**
Endothelin Antagonist	**Ambrisentan**

Research Questions:

- Are macitentan, riociguat and/or oral treprostinil more effective than preferred PDL treatments for patients with pulmonary arterial hypertension (PAH)?
- Are macitentan, riociguat and/or oral treprostinil a safer alternative to preferred PDL treatments for patients with PAH?
- Are there indications or subpopulations where macitentan, riociguat and/or oral treprostinil may be more effective or safer than other available agents?
- Are there new guidelines and/or evidence that suggest that changes should be made to the PAH agents on the PDL?

Conclusions:

- There is insufficient evidence to directly compared riociguat to other PAH treatments. There is moderate strength of evidence that riociguat improved the 6 minute walk (6MW) distance in patients with chronic thrombotic/embolic disease (CTEPH) and low to moderate evidence in patients with PAH. Changes in 6MW distance ranged from 33 to 39 m, which is at the lower end of clinically significant improvement and consistent with PDE-5 inhibitors, which work by a similar mechanism of action. Adverse events, such as syncope and hypotension, are similar to other vasodilators.[1,2]
- There is no direct comparative evidence evaluating macitentan to other PAH treatments. There is moderate strength of evidence that macitentan improves the composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with IV or SQ prostanoids or worsening of PAH in patients with PAH based on one small study lasting approximately 2 years. This was primarily driven by worsening of PAH. Modest efficacy was demonstrated in the 6MW distance at 6 months with a treatment effect of 22m for the macitentan 10mg group. Patients on background PAH treatment and those with functional class III/IV symptoms received the most benefit from treatment. Common adverse events are anemia, headache and nasopharyngitis.[3]
- Studies comparing oral treprostinil to other PAH therapies are lacking. There is low strength of evidence that oral treprostinil improves the 6MW distance in patients not on other vasodilatory therapy for PAH compared to placebo, 26 m and 0 m, respectively.[4] Oral treprostinil use in patients taking other PAH therapies demonstrated no significant difference in the 6MW distance when compared to placebo. Oral treprostinil was associated with headache, nausea and diarrhea in clinical trials.[4,5,6]
- There is no new significant comparative evidence on other treatments for PAH. Evaluation of recent literature supports the current PDL placement of agents for PAH.

Recommendations:

- Prior authorize riociguat to ensure appropriate use by qualified providers (Appendix 2).
- Prior authorize macitentan to ensure appropriate use by qualified providers. Limited evidence is insufficient to prefer macitentan over bosentan for placement on PDL.
- Prior authorize oral treprostinil to ensure appropriate use by qualified providers.
- Continue to include an agent from each class on the PDL and evaluate comparative costs in executive session.

Reason for Review:

This review will update the recommendations for oral and inhalation treatments for PAH. Since the last review additional systematic reviews and guidelines have been published. New PAH treatments have also been approved. This review will analyze the comparative effectiveness of the PAH treatments and incorporate important updates and revisions as they are related to this class since the last review.

Previous Conclusions/February 2012:

- Comparative evidence was insufficient to preference one agent over another.
- An agent from each class should be offered for coverage (bosentan and sildenafil are on the PDL).

Background:

PAH is the result of constricted flow through the pulmonary vasculature resulting in increased pulmonary resistance. PAH is defined as a mean pulmonary artery pressure (mPAP) >25 mm Hg with a pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units.[7] The cause of PAH is not fully understood but includes idiopathic, heritable (often from a mutation in

the bone morphogenic protein receptor-2), drug and toxin induced or PAH caused by an underlying medical condition (e.g. connective tissue diseases and HIV infection).[8] Regardless of the etiology, PAH is usually progressive with the most common cause of death being right ventricular failure.[9]

Changes in vascular structure and function within the pulmonary arteries account for the common symptoms of PAH including dyspnea, syncope, fatigue, edema and others. Exercise tolerance, as measured by the 6 minute walk (6MW) distance, and hemodynamic improvements are indicators of survival.[7] The 6MW is the most common outcome measured, which reflects the distance walked in meters. The 6MW distance is a measure of functional status and has been shown to correlate with morbidity and mortality in some studies but recent data suggests a lack of correlation between the 6MW distance and clinical outcomes.[10,11] The inability to detect treatment changes in patients with less severe PAH and to identify treatment differences when trials are short and have small sample sizes are some of the limitations of the 6MW distance as a surrogate endpoint. In PAH trials the minimum meaningful clinical improvement has been shown with a 6MW distance of 33 m.[12,13] Studies of PAH agents have demonstrated 6MW distance improvements of 33-50 m.[7] Other outcomes measured in clinical trials are: mortality, World Health Organization (WHO) functional class changes, hospitalizations, changes in pulmonary vascular resistance, dyspnea (assessed by Borg dyspnea score), and quality of life. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels have been shown to correlate with the presence of PAH but it is unknown if these levels can be used to help manage PAH treatment.[7] Baseline functional class and combined clinical events (i.e. hospitalizations, mortality and rescue treatments) are recommended, in addition to the 6MW distance, to determine effectiveness of PAH therapies.[14]

The World Health Organization classifies pulmonary hypertension (PH) into five groups based on etiology. WHO Group 1 includes PAH caused by idiopathic PAH (IPAH), heritable PAH, and PAH as a result of connective tissue diseases, HIV and portal hypertension. These same groups of PAH were formerly referred to as primary pulmonary hypertension (Table 1).[9] Group 4 PAH caused by CTEPH will also be covered in this review. PH caused by other secondary sources are included in Groups 2, 3 and 5 and won't be the focus of this review. The WHO functional assessment classification system for PH has been adapted from the New York Heart Association (NYHA) functional classification. Both systems are utilized in guidelines and studies to classify patients based on symptoms as well as for treatment guidance (Table 2).[15]

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)[9]

WHO Group 1: Pulmonary Arterial Hypertension	
1. Pulmonary arterial Hypertension	1.4 Associated with
1.1 Idiopathic PAH (IPAH)	1.4.1 Connective tissue diseases
1.2 Heritable	1.4.2 HIV infection
1.2.1 Bone morphogenetic protein receptor (BMPR) type 2	1.4.3 Portal hypertension
1.2.2 Activin receptor-like kinase 1 (ALK1) endoglin (with or without hereditary hemorrhagic telangiectasia)	1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.2.3 Unknown	1.4.6 Chronic hemolytic anemia
1.3 Drug induced	1.5 Persistent pulmonary hypertension of the newborn 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
WHO Group 4: Pulmonary Arterial Hypertension	
4. Chronic thromboembolic pulmonary hypertension (CTEPH)	

Table 2. WHO Functional Assessment Classification[15]

Class	**Description**

I	Patients with PH with no limitation in physical ability
II	Patients with PH with slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
III	Patients with PH with marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
IV	Patients with PH unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest

Significant advances in therapeutic options to treat WHO Group 1 PAH have evolved over the last 15 years including the use of combination therapy. Patients with symptomatic PAH are provided treatment based on functional class. Standard treatment options include: anticoagulants, diuretics, digoxin, and oxygen.[16] PAH-specific therapies are: prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (ERAs) (bosentan and ambrisentan), phosphodiesterase (PDE)-5 inhibitors (sildenafil and tadalafil) and calcium channel blockers (for those responsive to acute vasoreactivity testing).[7] Patients who respond well to acute vasodilator testing during cardiac catherization are good candidates for calcium channel blocker therapy. This usually applies to small subset of patients with IPAH with a sustained response to CCB therapy (functional class I or II with normal or near-normal hemodynamics after several months of treatment). Long-acting nifedipine or diltiazem or amlodipine are recommended. Of the treatments for PAH, epoprostenol is the only agent that has been shown to decrease mortality, improve exercise capacity and improve hemodynamic measures.[7] The PDE-5 inhibitors and ERA antagonists have been shown to decrease hospitalizations, improve exercise capacity and improve hemodynamic measures.[12] Before the approval of riociguat, there were no approved medical therapies for CTEPH. The standard treatment for CTEPH is pulmonary endarterectomy, which can be curative. Atrial septostomy or lung transplantation is an option for advanced PAH, unresponsive to other treatments.[7,12] Bosentan has been studied in patients with CTEPH, demonstrating an increase of 36 m in 6MW distance after 3-6 months (95% CI, 33.6 to 38.2; $p<0.001$).[17]

Methods:

A Medline literature search ending in May 2014 for new systematic reviews and randomized controlled trials (RCTs) for PAH treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: one treatment guideline[7], four systematic reviews[12,14,18,19] and six RCTs.[1-6]

Systematic Reviews:

AHRQ – Pulmonary Arterial Hypertension: Screening, Management and Treatment[12]

AHRQ recently conducted a comparative effectiveness review for PAH. The focus of the review was to update new data on combination therapies and treatments for PAH. Included studies were assessed for quality and graded using the Cochrane Risk of Bias tool. More than 3,600 patients were studied in 28 randomized, controlled trials (96% were rated good or fair quality). The review included the following treatments: bosentan, sildenafil, iloprost, epoprostenol, tadalafil, ambrisentan, treprostinil and vardenafil. The analysis found that there was low strength of evidence that patients on monotherapy benefited more from combination therapy instead of continuing monotherapy. There was limited evidence that prostanoids provided a mortality benefit (low strength of evidence). There was insufficient evidence to draw mortality conclusions with the ERAs and PDE-5 inhibitors. There was moderate strength of evidence that

ERAs, PDE-5 inhibitors and prostanoids improved 6MW distance. Hospitalizations were reduced with ERAs and PDE-5 inhibitors (moderate strength of evidence). All classes improved hemodynamic measures, however, clinical significance of these measures still needs to be delineated.

COCHRANE – Endothelin Receptor Antagonists for Pulmonary Arterial Hypertension (Review)[18]

A systematic review was done to analyze the efficacy of ERAs for PAH. Twelve double-blind, placebo-controlled, randomized controlled trials lasting 12 weeks to 6 months studying bosentan, sitaxsentan (removed from the market due to hepatic toxicity) and ambrisentan were included. A total of 1471 patients with predominately idiopathic PAH and WHO functional class II and III were studied. Eleven of the studies were placebo controlled trials and one study compared bosentan to sildenafil. Average improvement in the 6MW distance was 33.71 meters (95% CI 24.90 to 42.52meters) compared to placebo. Statistically significant improvements in functional class were found and there was a trend toward a mortality benefit. There was no significant difference found between bosentan and sildenafil, however, small sample size in the study limits the ability to draw strong conclusions. ERAs were well tolerated and there was a low occurrence of hepatic toxicity.

CADTH – Drugs for Pulmonary Arterial Hypertension: A Systematic Review of Clinical-Effectiveness of Combination Therapy[19]

A 2009 Canadian Agency for Drugs and Technologies in Health performed a systematic review on the use of combination treatment for idiopathic PAH. Four studies lasting 12 weeks to 6 months and two guidelines were included. Combinations studied were; sildenafil and epoprostenol, inhaled iloprost and bosentan, bosentan and epoprostenol and bosentan and sildenafil. Combination therapy demonstrated a benefit in 6MWdistance (treatment difference of 26 to 28.8 m). Due to limited evidence, guidelines recommend combination therapy be reserved for patients failing monotherapy, those with severe disease and as part of a clinical trial.

Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension[14]

Barst, et al, reviewed PAH trials and graded the evidence to support a treatment algorithm. Recommendations were based on the quality of the evidence and the net benefit of therapy. Calcium channel blockers were moderately recommended for patients in WHO Class I-IV who are responsive to acute vasoreactivity testing. Ambrisentan, bosentan, and sildenafil are strongly recommended for patients in WHO Class II and these same agents, in addition to IV epoprostenol and iloprost inhalation, are strongly recommended for patients in WHO Class III. Tadalafil, SQ treprostinil and sitaxsentan (no longer available) are moderately recommended for patients in WHO Class III. Epoprostenol IV is strongly recommended for patients in WHO Class IV patients based on evidence of a survival benefit. Inhaled iloprost is moderately recommended for WHO class IV patients. Iloprost IV and treprostinil IV are moderately recommended based on expert opinion. Combination therapy is appropriate for patients who remain in WHO Class III despite monotherapy. Atrial septostomy and lung transplantation are an option for patients who fail to respond to medical treatments.

New Guidelines:

ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension[7]

The ACCF/AHA Consensus document recommends an evidence-based treatment algorithm for the management of PAH. Recommendations are based on available studies and expert opinion. Therapies included are; background therapies (anticoagulation, diuretics, oxygen and digoxin), calcium channel blockers, epoprostenol, treprostinil, iloprost, bosentan, sitaxsentan, ambrisentan, and sildenafil (tadalafil, macitentan and riociguat not approved at time of guideline publication). General recommendations include warfarin for anticoagulation, diuretics for patients with right ventricular (RV) volume overload and oxygen if needed to maintain saturations above 90%. Calcium channel blockers should be given to appropriate patients, based on acute vasodilator testing. Patients that are considered lower risk should be offered oral ERA or PDE-5 inhibitor therapy. High risk patients should be given an IV prostacyclin first line. Critically ill patients should be given IV epoprostenol based on evidence of improved exercise capacity, hemodynamics and survival benefit. ERAs or PDE-5 inhibitors are

appropriate for patients at lower risk (functional class II or III). Both ERAs and PDE-5 inhibitors have been shown to improve exercise capacity in patients with PAH. Combination therapy may be an option for PAH patients not responding to monotherapy. Lung transplantation and/or atrial septostomy can be considered for those patients who fail medical management.

ACCP – Updated Treatment Algorithm of Pulmonary Arterial Hypertension[20]

Recommendations from the most recent World Symposium on Pulmonary Hypertension (WSPH) are summarized in this update. Evidence was graded using the European Society of Cardiology grades of recommendations (Class I- recommended; Class II- conflicting evidence regarding usefulness; Class IIa – should be considered; Class IIb – may be considered; Class III – not recommended). Levels of evidence were also incorporated (level A to level C; A being the strongest). Supportive therapy with anticoagulants, diuretics, oxygen and digoxin should be considered for patients with PAH. Pharmacotherapy recommendations are based on available evidence and WHO functional class. PAH specific treatment is indicated in those unresponsive to vasodilatory testing or those not responding to calcium channel blocker therapy. For patients with WHO-FC II symptoms the following therapies are considered recommended based on a level A or B recommendation; ambrisentan, bosentan, macitentan, riociguat, sildenafil, and tadalafil. Ambrisentan, bosentan, epoprostenol IV, iloprost inhaled, macitentan, riociguat, sildenafil, tadalafil, and treprostinil s.c. and inhaled are recommended for patients with WHO-FC III patients (Class I; evidence level A and B). Class IIa, evidence C recommendations for WHO-FC III patients are iloprost IV and treprostinil IV and beraprost is recommended for these same patients based on a Class IIb, evidence level B. Lastly, combination therapy can be considered in WHO-FC III patients (Class IIb; evidence level C). Survival benefit have been demonstrated with IV epoprostenol and should be first-line therapy for WHO-FC IV patients (Class I; evidence level A or B). Ambrisentan, bosentan, iloprost inhaled/IV, macitentan, riociguat, sildenafil, tadalafil and treprostinil SC/IV/inhaled are alternatives for WHO-FC IV patients (Class IIa; evidence level C). Initial combination therapy can also be considered for patients with WHO-FC IV symptoms (Class IIb; evidence level C). Patients experiencing an inadequate response to combination therapy should be considered for lung transplantation.

New Primary Literature:

New Drug Evaluation- Riociguat (Adempas®)

FDA Indications[21]:

Riociguat is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class or PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Clinical Efficacy Data (see evidence table below) [1,2]:

Riociguat has been studied in two, phase III trials for FDA approval. PATENT-1 was in patients with WHO group I PAH and the second study was CHEST-1, which included patients in WHO group 4 PAH. The primary outcome measure was the change from baseline to the end of week 12 in the 6MW distance in PATENT-1 and 16 weeks in CHEST-1.

Pulmonary Arterial Hypertension

In the fair-good PATENT-1 study, 443 patients were randomized to receive riociguat titrated to a maximum of 2.5 mg three times daily (R2.5), riociguat titrated to a maximum of 1.5 mg three time daily (exploratory only, not included in the efficacy analysis) or placebo in patients with symptomatic PAH for 12 weeks. Patients were eligible is they had a pulmonary vascular resistance >300 dyn·sec·cm^{-5}, a mean pulmonary-artery pressure of at least 25 mm Hg and a baseline 6-

minute walk distance of 150 to 450 m. Patients were allowed to take ERAs or prostanoids (excluding IV prostanoids) at doses that had been stable for at least 90 days. The majority of patients were white females with and the average age of 51 years and PAH WHO functional class II or III. Fifty percent of patients were receiving other treatments for PAH (44% ERAs and 6% prostanoids). For the primary endpoint, the 6MW distance increased 30 m in the R2.5 group compared to 6 m in the placebo group (lease square mean difference [LSMD] 36 m, 95% CI 20 to 52, p<0.001). The change from baseline in the 1.5 mg maximum dose group was similar to the 2.5 mg group with a 6 MWD of 31 m. There were more patients in the 1.5 mg group who moved to a lower functional class compared to the 2.5 mg group, 24% (ARR 10%, NNT 10) and 21% (ARR 7%, NNT 14), respectively. Patient with WHO functional class III and IV and on background prostanoids received the most benefit from riociguat therapy. Efficacy results were similar for patients on other treatments for PAH and for those only on riociguat and for treatment naïve patients. PATENT-2 is an ongoing extension trial, including eligible patients from PATENT-1. An unpublished interim analysis showed a further increase in 6MW distance during the first 12 weeks.

In PATENT-1 there were 9% more patients with WHO functional class III PAH in the R2.5 group compared to placebo. This could favor the efficacy results of R2.5, being that this group received the most benefit from treatment. Data from ongoing extension studies will be helpful to determine efficacy beyond 12-16 weeks. Additional studies are needed to determine the comparative effectiveness to other PAH therapies.

Chronic Thromboembolic Pulmonary Hypertension

In the good quality CHEST-1 trial, patients were randomized in a 1:2 ratio to riociguat 0.5 – 2.5 mg three times daily (R) or placebo for 16 weeks. Two hundred sixty one patients with inoperable chronic thromboembolic PAH or persistent or recurrent PAH after pulmonary endarterectomy were studied for 16 weeks. Patients on background PAH treatment within three months of study initiation were excluded. The mean age was 59 years and the majority (66%) of patients were female. At week 16, 77% of patients enrolled were taking riociguat 2.5 mg three times daily. The primary endpoint was significantly improved in patients taking riociguat over placebo (LSMD 46m; 95% CI 25 to 67, p<0.001). Riociguat significantly improved WHO functional class compared to placebo (ARR 18%, NNT 6). Patients in WHO functional class 3 or 4 had a better response in the 6MW distance than those in class 1 or 2, LSMD 54 (95% CI 28 to 79) and 24 (95% CI -14 to 63), respectively. Patients in the postoperative CTEPH subgroup were shown to not have a significant benefit from treatment (LSMD 26, 95% CI -16 to 68). Improvement in functional class was significantly improved compared to placebo, 33% vs. 15%, respectively.

Clinical Safety (see evidence table below)[1,2]:

Withdrawals due to adverse events were low (3%) in both studies. Adverse events seen in ≥10% of patients in the riociguat group were headache, dyspepsia, peripheral edema, nausea, dizziness, diarrhea, vomiting, nasopharyngitis, and hypotension. The most common serious reactions were syncope, worsening PAH, chest pain, right ventricular failure and hemoptysis. The following rare, but serious adverse events were associated with riociguat; increased hepatic enzymes, acute renal failure, syncope, esophageal pain and swelling, supraventricular tachycardia and right ventricular failure. Dose-dependent decreases in blood pressure and hypotension are concerns when riociguat is used in a non-study setting.

Additional data on mortality and long-term studies would be helpful in defining the role of riociguat in patients with Group 4 PAH.

Conclusion

There is moderate strength of evidence that riociguat improved 6MW distance in patients in with CTEPH (WHO Group 4). There was low to moderate strength of evidence that riociguat improved the 6MW distance in patients with PAH (WHO Group 1). Changes in 6MW distance ranged from 33 to 39 m, which is at the lower end of clinically significant improvement and consistent with PDE-5 inhibitors which work by a similar mechanism of action. Adverse events, such as syncope and hypotension, are similar to other vasodilators. Interim analyses of long term extension studies (PATENT-2 and CHEST-2 ongoing) suggest

persistence of effect up to 9 months. It has been suggested that the efficacy of riociguat would be superior to PDE-5 inhibitors, due to the lack of dependence of riociguat on nitric oxide concentrations, which can be reduced in PAH. There are no head to head studies to validate this assumption at this time.

New Drug Evaluation- Macitentan (Opsumit®)

FDA Indication[22]:

Macitentan is an ERA indicated for the treatment of PAH (WHO Group 1) to delay disease progression. Macitentan is a structural modification of the ERA, bosentan. Macitentan affinity for endothelin receptors and time of receptor occupancy is greater than other ERAs but clinical significance of this is unknown.

Clinical Efficacy Data (see evidence table below)[3]:

Macitentan was studied in one, phase III, good quality trial (SERAPHIN) lasting an average of 96 weeks. Patients (N=742) with idiopathic or heritable PAH, whom were predominately female and average age of 46 years, were randomized to macitentan 3 mg daily, 10 mg daily or placebo. Most patients had functional class II or III PAH and 60% were on background PAH therapy (excluding subcutaneous and intravenous prostanoids and ERAs). The primary outcome was the time from initiation of treatment to the first occurrence of the composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with subcutaneous or intravenous prostanoids, or worsening PAH (decreased 6MW distance, worsened PAH symptoms, and need for additional PAH treatment). The composite primary endpoint occurred in 31.4%, 38.0% and 46.4% of patients in the macitentan 10mg, macitentan 3mg and placebo groups, respectively. Macitentan 10 mg was found to be significantly better than placebo (HR 0.55, 95% CI 0.39 to 0.76, $p<0.001$), where the 3 mg dose was not. The most common primary endpoint event was worsening PAH. The change in 6MWD was modest with most benefit seen in the macitentan 10 mg group, followed by macitentan 3 mg and a decrease in the placebo group, 12.5 m, 7.4 m, and -9.4 m, respectively. Mortality rates were not significantly different between groups for macitentan 3 mg, macitentan 10 mg and placebo, 8.4%, 5.8% 7.6%, respectively (study underpowered to show effect on mortality alone). Macitentan efficacy was consistent with the 10mg dose in patients with or without background PAH therapy and irrespective of etiology for the primary endpoint. Subgroup analysis showed macitentan 10 mg to be statistically significantly better than placebo in patients on background therapy for the change in 6MWD and for patients with WHO functional class III/IV symptoms. In North American study sites, macitentan treatment was not statistically different from placebo.[23]

Clinical Safety Data (see evidence table below):

The most common side effect seen in the study with macitentan was anemia, headache and nasopharyngitis.[3] In general ERAs are linked to increased LFT elevations. Macitentan has only weakly been associated with this adverse effect but continued monitoring and surveillance is recommended due to the small study population and limited trial experience.[22] Discontinuations due to adverse events were low, 12.4%, 13.6% and 10.7% in the placebo, macitentan 3mg and macitentan 10mg group, respectively.[3] Serious adverse effects were lower in the macitentan 3 mg and macitentan 10 mg group compared to placebo, 52%, 45% and 55%, respectively.

Conclusion:

There is moderate strength of evidence that macitentan 10mg improves morbidity in patients with PAH based on one small study lasting approximately 2 years. Only modest efficacy was demonstrated in the change in 6MWD. Common adverse events are anemia, headache and nasopharyngitis. Study design limitations include lack of details on blinding, treatment allocation concealment, and randomization.

New Drug Formulation - Treprostinil (Orenitram®)

FDA Indication[24]: Oral treprostinil is indicated for the treatment of PAH (WHO Group I) to improve exercise capacity. Study data was mostly conducted in patients with WHO functional class II-III symptoms and with idiopathic or heritable forms of PAH or PAH associated with connective tissue disease. Use of oral

treprostinil as monotherapy showed small exercise benefits. Studies with oral treprostinil in combination with other vasodilator therapy produced no additional benefit.

Clinical Efficacy Data (see evidence table below) [4,5,6]

The oral form of treprostinil was studied in three, phase III, PC, randomized-controlled trials. In two trials (FREEDOM-C and FREEDOM-C2) treprostinil was combined with ERAs and/or PDE-5 inhibitors. In these trials no additional benefit of adding oral treprostinil was found. In the third study, FREEDOM-M, treprostinil 1mg twice daily (titrated to clinical efficacy) was compared to placebo in 349 patients for 12 weeks. Patients were predominantly female with an average 6MW distance of 329m. Patients were allowed to continue on conventional PAH treatments but prostacyclins, ERAs and PDE-5 inhibitor use was prohibited. The primary endpoint was change in 6MW distance at 12 weeks. The median difference in favor of treprostinil was 26m (95%CI, 10.0 to 41.0, p= 0.0001) in the ITT population. The combined 6MWD/Borg score at weeks 4, 8 and 12 was the only significantly improved secondary outcome in the ITT population.

Clinical Safety Data (see evidence table below):

The most common adverse events seen in clinical trials were nausea, headache and diarrhea. Severe adverse seen in trials were right ventricular failure, dyspnea, lower respiratory tract infection and worsening PAH. Discontinuations due to adverse events were higher in the treprostinil group compared to placebo. Studies that had lower strength tablets (0.25mg) available for initiation and titration resulted in better tolerability and efficacy.

Conclusion:

There is low strength of evidence that oral treprostinil improves exercise capacity in patients with PAH. There is moderate strength of evidence that treprostinil added no additional benefit to ERAs and/or PDE-5 inhibitor therapy when used in combination. Adverse events were common with treprostinil therapy and led to treatment discontinuation in 10-14% of patients.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1.) Exercise tolerance
2.) Disease progression
3.) Mortality

Study Endpoints:

1.) Change from baseline in 6MW distance
2.) Change in WHO functional class
3.) Composite endpoint of death, atrial septostomy, lung transplantation, initiation of SQ/IV prostanoids or worsening PAH

Evidence Table

PATENT-1[1]

Ghofrani, et al Phase III, RCT, DB, PC 30 Countries	1. Riociguat up to 2.5 mg three times daily (R2.5) 2. Riociguat up to 1.5 mg three times daily (R 1.5)* 3. Placebo QD (P) * Included for exploratory purposes; not included in the efficacy analysis	Mean Age: 51 Female: 79% Baseline 6-Min walk distance(m): 368±69 **Inclusion**: Patients 18-80 years old with symptomatic Group I PAH if pulmonary vascular resistance was >300 dyn·sec·cm^{-5}, a mean pulmonary- artery pressure of at least 25 mm Hg and a 6-minute walk distance of 150 to 450 m and if on no other PAH treatment or endothelin-receptor antagonist or prostanoids at stable doses for 90 days. **Exclusion**: Patients taking intravenous prostanoids or phosphodiesterase type 5 inhibitors, history of pulmonary or cardiac disease, pregnancy, PAH associated with HIV, schistosomiasis and chronic hemolytic anemia.	1. 254 2. 63 3. 126	12 weeks	Change from baseline at week 12 (m): R2.5:+30 R1.5: +31.1 P: -6 LSMD (R2.5 vs. P): 36 (95% CI, 20 to 52, p<0.001) LSMD (R1.5 vs. P): 37.35 (95% CI, 12 to 63, p<0.001) Improvement in WHO functional class: R2.5: 53 (21%) R1.5: (24%) P: 18 (14%) P=0.003 (R2.5 vs. P) RR: 1.5 (R2.5 vs P) RR: 1.7 (R1.5 vs P) Clinical Worsening: R2.5: 8 (6%) P: 3 (1%) P= 0.005 Borg Dyspnea Score: R2.5: -0.4 P: 0.1 P=0.002	NA R2.5 vs P ARR: 7 NNT: 14 R1.5 vs P ARR: 10% NNT: 10 ARR: 5 NNT: 20 NA	Serious Adverse Events: R2.5: 8 (3%) R1.5: 2 (3.25%) P: 5 (4%) Withdrawal due to Adverse Events: R2.5: 8 (3%) R1.5: 1 (1.6%) P: 9 (7%)	NA NA	**Quality Rating: Fair-Good** **Internal Validity: RofB** Selection: Patient randomized and allocation concealment done using a computer-generated random code and interactive voice response system. Groups similar at baseline. Performance: Double-blind treatment design. Patients and investigators were blinded. Sham dosage adjustments using IVR system based on blood pressure done to maintain blinding. Detection: Sponsor and contract research personnel blinded. Unclear on outcome assessors. Attrition: mITT analysis was used with LOCF for missing data. Overall 7-12% discontinued treatment prior to 12 weeks. **External Validity** Recruitment: recruited from 30 countries. US sites accounted for 6.5% of patients. Patient Characteristics: most patients were white females with idiopathic PAH. Most patients were WHO class II and III. Patients with more severe disease (WHO class III and IV) saw the most benefit from treatment. Fifty percent were on other treatments for PAH. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
CHEST-1[2]									
Ghofrani, et al Phase III, RCT, DB, PC	1. Riociguat 0.5 – 2.5 mg three times daily (R) 2. Placebo (P)	Age: 59 years Female: 66% Baseline 6-Min walk distance(m): 347±80 Inclusion:	1. 173 2. 88	16 weeks	Change from Baseline in 6 MW distance at 16 weeks (m): R: +39 P: -6 LSMD: 46m (95% CI 25 to 67, p<0.001)	NA	Serious Adverse Events: R: 6 (3%) P: 2 (1%) Withdrawal due to	NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Patient investigators and

26 countries		Patients 18-80 years with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endoarterectomy and pulmonary vascular resistance was >300 dyn·sec·cm^{-5}, a mean pulmonary-artery pressure of at least 25 mm Hg and a 6-minute walk distance of 150 to 450 m. Exclusion: Use of endothelin receptor antagonists, prostacyclin analogues, phosphodiesterase -5 inhibitors or nitric oxide donor within previous 3 months and pulmonary and cardiovascular disease and pregnancy.			Improvement in WHO functional class: R: 57 (33%) P: 13 (15%) P=0.003 Clinical Worsening: R2.5: 4 (2%) P: 5 (6%) P= 0.17 Borg Dyspnea Score: R2.5: -0.8 P: 0.2 P=0.004	ARR: 18 NNT: 6 NS NA	Adverse Events: R: 4 (3%) P: 2 (2%)	NA	sponsor/contract research personnel blinded. Detection: Patient investigators and sponsor/contract research personnel blinded. Unclear on outcome assessors. Attrition: mITT analysis was used with LOCF for missing data. Attrition was low in both groups. **External Validity:** Recruitment: 89 centers in 26 countries. Approximately 6% from US centers. Patient Characteristics: Seventy-seven percent of patients were receiving the maximal riociguat dose (2.5 mg three times daily) at week 16. Most patients had functional class III PAH and inoperable CTEPH. Patients with inoperable CTEPH and higher functional class (III or IV) received the most benefit from treatment. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
SERAPHIN[3]									
Pulido, et al Phase III, DB, PC	1. Macitentan 3 mg daily (M3) 2. . Macitentan 10 mg daily (M10)	Age: 46 years Female: 77% Baseline 6-Min walk distance(m): 360±100.2	1. 250 2. 242	1. 100 weeks 2. 104 weeks	Composite endpoint of death, atrial septostomy, lung transplantation, initiation of SQ/IV prostanoids or worsening PAH : M3: 95 (38%)		Serious Adverse Events: M3: 130 (52%) M10: 109 (45%) P: 137 (55%) Withdrawal due to	NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized by a central randomization system via interactive voice response or interactive web response. Performance: double-blind treatment design was

39 countries	3. Placebo (P)	Inclusion: Patients 12 years and older with idiopathic or heritable PAH, confirmed PAH by right hear catheterization, 6 MW distance of ≥5(m, class II, III or IV WHO functional class. PAH medications not mentioned below were allowed. Exclusion: Use of endothelin-receptor antagonists, intravenous or subcutaneous prostanoids.	3. 250	3. 85 weeks	M10: 76 (31.4%) P: 116 (46.4%) HR M3 vs. P : 0.70 (95% CI 0.52 to 0.96, P=0.011*) HR M10 vs. P: 0.55 (95% CI 0.39 to 0.76, p<0.001) * Overall alpha set at p=0.01 Death from any cause: M3: 21 (8.4) M10: 16 (6.6) P: 17 (6.8) Change from Baseline in 6 MW distance at 6 months: M3: 7.4 m P: -9.4 m P=0.01 M10: 12.5 m P: -9.4 m P=0.008 Improvement in WHO functional class from baseline to month 6: M3: 20% P: 13% P=0.04 M10: 22% P: 13% P=0.006 Hospitalizations for PAH: M3: 56 (22) M10: 45 (19) P: 79 (32)	NA M10 ARR: 15 NNT: 7 NA NA NA M10 ARR: 9 NNT: 11 NA	Adverse Events: M3: 34 (13.6%) M10: 26 (10.7%) P: 31 (12.4%)	NA	stated with matching treatment and placebo and identical medication kits. Detection: results were adjudicated by blinded clinical event committee. Attrition: ITT analysis with LOCF was used for data analysis. A total of 13% of patients discontinued the study early. **External Validity:** Recruitment: from 159 centers in 39 countries. Patient Characteristics: Most patients (77%) were female and had predominantly WHO functional class II or III PAH. Over 60% of patients were on background treatments for PAH. Outcomes: event-driven study using morbidity and mortality endpoint. Composite endpoint can exaggerate treatment effect.

FREEDOM-C[5]									
Tapson, et al Phase III, DB, PC, RCT 72 centers	1. Treprostinil 1mg twice daily (starting dose) [T] 2. Placebo (P) * Treatment given in combination with a PDE-5 inhibitor and/or an ERA	Age: 50 years Female: 82% Mean baseline 6-Min walk distance(m): 346 <u>Inclusion:</u> Patients 12-70 years with symptomatic idiopathic PAH, familial PAH, PAH associated with congenital heart disease, connective tissue disease or HIV, a 6 MW distance of 100 to 450m, stable use of PDE-5 inhibitor and/or ERA therapy within 90 days of study. <u>Exclusion:</u> Pregnancy, nursing, investigational therapy use and other PAH diseases not mentioned in inclusion.	1. 174 2. 176	16 weeks	<u>Median change from Baseline in 6 MW distance at 16 weeks (m):</u> T: 14.5 P: 4.8 (median difference 11m, 95%CI 0.0 to 22.0, P= 0.07) <u>Improvement in WHO functional class:</u> T: 31 (18%) P: 26 (15%) P= 0.94 <u>Clinical Worsening:</u> T: 8 (5%) P: 12 (7%) P = 0.49 <u>Borg Dyspnea Score:</u> T: -0.03 P: 0.38 P= 0.07	N/A N/A N/A N/A	<u>Any Adverse Event:</u> T: 173 (99%) P: 157 (90%) <u>Withdrawal due to Adverse Events:</u> T: 25 (14%) P: 8 (5%)	NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients randomization details were not disclosed. Performance: Study was double-blind with no details on blinding of care providers. Detection: No details on the blinding of outcome assessors were provided. Attrition: mITT analysis was used but methodology for missing data imputation was not provided. Attrition was 22% in the treprostinil group and 14% in the placebo group. **External Validity:** Recruitment: 72 centers in 14 countries. Patient Characteristics: Majority (76%) of patients had WHO functional class III symptoms. Thirty percent of patients were receiving concomitant ERA therapy and 25% were receiving concomitant PDE-5 inhibitor and 45% were taking both. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
FREEDOM-M[4]									
Jing, et al Phase III, DB, PC, RCT 81 centers	1. Treprostinil 1mg twice daily (T)* 2. Placebo (P) * Changed to initiation dose of treprostinil 0.5mg twice daily and then later to	Age: 41 years Female: 75% Mean baseline 6-Min walk distance(m): 329 <u>Inclusion:</u> Patients 12-75 years with idiopathic PAH, hereditary PAH,	1.233 2.116	12 weeks	<u>Change from Baseline in 6 MW distance at 12 weeks (m) for ITT population:</u> T: 26 P: 0 (median difference 26m, 95%CI 10.0 to 41.0, P= 0.0001) <u>Clinical Worsening for ITT</u>	NA	<u>Serious Adverse Events:</u> T: 41 (18%) P: 26 (22%) <u>Withdrawal due to Adverse Events:</u> T: 23 (10%) P: 3 (3%)	NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients randomization details were not disclosed. Performance: Study was double-blind with no details on blinding of care providers. Detection: No details on the blinding of outcome assessors were provided. Attrition: ITT and mITT analysis was used with LOCF applied to missing data. Attrition was 23% in the treprostinil group and 16% in the placebo group.

	0.25mg twice daily	PAH associated with congenital heart disease, connective tissue disease or HIV, a 6 MW distance of 100 to 450m, and stable use of convention PAH therapies. Exclusion: Use of PDE-5 inhibitors, ERAs or prostacyclin therap within 30 days, significant left-sided heart disease or parenchymal lung disease.			population: T: 22 (9%) P: 15 (13%) Death for ITT population: T: 13 (6%) P: 8 (7%) Hospitalization/new therapy for ITT population: T: 9 (4%) P: 5 (4%)	N/A N/A N/A			**External Validity:** Recruitment: Patients were from 81 centers in 7 countries. Patient Characteristics: Majority (61%) of patients had WHO functional class III symptoms. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
FREEDOM-C2[6]									
Tapson, et al Phase III, DB, PC, RCT 94 centers	1. Treprostinil 0.25mg twice daily* (T) 2. Placebo (P) * Dose was titrated if clinically indicated	Age: 51 years Female: 78% Mean baseline 6-Min walk distance(m): 333 Inclusion: Patients 18-75 years with idiopathic PAH, familial PAH, PAH associated with congenital heart disease, connective tissue disease or HIV, a mean pulmonary- artery pressure of at least 25 mm Hg, a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure o ≤15 mm Hg, pulmonary vascular	1.157 2.153	16 weeks	Placebo adjusted change from Baseline in 6 MW distance at 16 weeks (m): Median difference between T and P: 10 m (95% CI, -2.0 to 22.0, P=0.89) Clinical Worsening: T: 11 (7%) P: 10 (7%)	NA N/A	Any Adverse Event: T: 157 (100%) P: 136 (89%) Withdrawal due to Adverse Events: T: 23 (10%) P: 3 (3%)	NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients randomization details were not disclosed. Performance: Study was double-blind with no details on blinding of care providers. Detection: No details on the blinding of outcome assessors were provided. Attrition: analysis was used with LOCF applied to missing data. Attrition was 23% in the treprostinil group and 16% in the placebo group. **External Validity:** Recruitment: Patients were from 94 centers. Patient Characteristics: Majority (73%) of patients had WHO functional class III symptoms. The mean dose of treprostinil was 3.1mg twice daily. Newly diagnosed patients received the most improved 6MW distance. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.

		resistance >3 Wood units and the absence of unrepaired congenital heart disease, use of ERA or PDE-5 inhibitors ≥90 days and stable doses for ≥30 days and baseline 6MW distance of 150-425 m. <u>Exclusion:</u> Pregnancy, nursing, left-sided heart disease or significant parenchymal lung disease, FEV1/FVC ratio <50%, use of investigation medication or change of PAH medication within 14 days.							

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group
[2]**Results abbreviations**: HR = Hazard Ratio, ARR = absolute risk reduction, LSMD= least square mean difference
NNT = number needed to treat, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: PAH = pulmonary arterial hypertension, WHO= World Heath Organization

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Appendix 1: Drug Information

NDE: Riociguat (Adempas®)[19]

Pharmacology: Riociguat is a soluble guanylate cyclase inhibitor (sGC) stimulator, an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). Riociguat is proposed to work by sensitizing sGC to endogenous NO and by stimulating sGC by binding to a site independent of NO.

Table 1. Pharmacokinetics[19]

Parameter	Riociguat	Parameter	Riociguat
Half-Life	7-12 Hours	**Renal Dose Adjustment**	Safety and efficacy has not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis.
Elimination	40% renal and 53% hepatic		
Metabolism	CYP1A1,CYP3A, CYP2C8, CYP2J2	**Hepatic Dose Adjustment**	Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child-Pugh class C).

Contraindications/Warnings:

- **Black box warning:** Riociguat should not be given to pregnant females because it may cause fetal harm. Females must acquire riociguat through a REMs program and be using adequate contraception.
- **Contraindications:** Riociguat is contraindicated in pregnancy, use with nitrates or nitric oxide donors in any form, and use with phosphodiesterase inhibitors.
- **Warning:** Caution should be used when prescribing riociguat in patients with symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease. Dose titration should be done cautiously due to varying inter-patient concentrations.

Dose

The recommended dose of riociguat is a starting dose of 1 mg taken three times daily. For patients who can not tolerate the hypotensive effects, the dose should be administered at 0.5 mg three times daily. If systolic blood pressure remains above 95 mmHg and the patient has no signs or symptoms of hypotension, up titrate the dose by 0.5 mg three times a day. Dose increases should be no sooner then 2 weeks apart. If tolerated the dose may be increased to 2.5 mg, three times a day. Intra-patient variability of drug concentrations and metabolism requires individualized dose titration. Dose may need to be adjusted when riociguat is given with CYP3A4 inhibitors/inducers and in patients who smoke.

NDE: Macitentan (Opsumit®)[20]

Pharmacology: Macitentan is an ERA antagonist that prevents binding of endothelin (ET)-1 to its receptors. This prevents harmful effects of ET-1, such as vasoconstriction, fibrosis, proliferation, hypertrophy and inflammation seen in PAH where the ET system is up regulated.

Table 2. Pharmacokinetics[20]

Parameter	Macitentan	Parameter	Macitentan
Half-Life	16 hours and 48 hours (active metabolite)	**Renal Dose Adjustment**	None recommended
Elimination	50% renal and 24% hepatic		
Metabolism	CYP3A4 and CYP2C19	**Hepatic Dose Adjustment**	None recommended

Contraindications/Warnings:

- **Black box warning:** Macitentan may cause fetal harm and should not be given to pregnant females.
- **Contraindications:** Macitentan should not be used in pregnant females.
- **Warning:** Liver enzymes should be monitored, as other ERAs have been shown to cause hepatotoxicity. Macitentan may cause decreases in hemoglobin and pulmonary edema in patients with pulmonary veno-occlusive disease (discontinue treatment if confirmed). ERAs have been shown to cause decreases in sperm count.

Dose

The recommended dose is macitentan 10mg orally once daily.

New Drug Formulation: Treprostinil (Orenitram®)[22]

Pharmacology: Oral treprostinil is a prostacyclin vasodilator indicated for PAH Group 1 to improve exercise capacity.

Table 3. Pharmacokinetics[22]

Parameter	Treprostinil	Parameter	Treprostinil
Half-Life	Dose-proportional	**Renal Dose Adjustment**	None recommended
Elimination	Oxidation, renal (0.19%) and hepatic (1.3%)		
Metabolism	CYP2C8 and CYP2C9	**Hepatic Dose Adjustment**	Mild impairment initiate treprostinil at 0.125mg dose twice daily and increase every 3-4 days. Avoid use in moderate hepatic impairment and use is contraindicated in severe hepatic impairment.

Contraindications/Warnings:

- **Contraindications:** Severe hepatic impairment (Child Pugh Class C).
- **Warning:** Do not discontinue abruptly, increased risk of bleeding especially if receiving anticoagulants, do not take with alcohol and potential for tablets to be lodged in diverticulum in patients with diverticulosis.

Dose

The recommended starting dose for treprostinil is 0.25mg twice daily with food. Dose may be increased by 0.25-0.5mg twice daily every 3-4 days to achieve optimal clinical response. Maximum doses in clinical studies were 12-21 mg twice daily. Avoid abrupt discontinuation.

APPENDIX 2:
Suggested PA Criteria

Oral/Inhalation Pulmonary Arterial Hypertension Agents

Goal(s): Approve therapy for covered diagnoses which are supported by the medical literature.
- Erectile dysfunction is not covered by OHP

Length of Authorization:
Up to 12 months

Requires PA:
- Non-preferred drugs

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis?	Record ICD10 code**.**	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No**: Pass to RPH. Deny, (Not covered by the OHP)
3. Does the patient have a diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH)?	**Yes:** Go to #8	**No:** Go to #4.

4. Does the patient have a diagnosis of WHO Group 4 PAH?	**Yes**: Go to #5	**No:** Pass to RPH. Deny (Medical Appropriateness)
5. Is the request for riociguat (Adempas®)?	**Yes**: Go to #6	**No:** Pass to RPH. Deny (Medical Appropriateness)
6. Is the drug being prescribed by a pulmonologist or cardiologist?	**Yes**: Go to #7	**No:** Pass to RPH. Deny (Medical Appropriateness)
7. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Approve for 12 months.	**No:** Pass to RPH. Deny (Medical Appropriateness)
8. Will the prescriber consider a change to a preferred product?	**Yes**: Inform provider of alternatives in class.	**No**: Go to #9
9. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Go to #10	**No:** Pass to RPH. Deny (Medical Appropriateness)
10. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months.	**No:** Go to #11

11. RPH Only: Is the diagnosis above the line and has the clinic provided supporting literature for use?	**Yes:** Approve for length of treatment.	**No:** Deny (not covered by the OHP)

WHO Functional Classification of Pulmonary Hypertension*

Class I—
- Patients with pulmonary hypertension but without resulting limitation of physical activity.
- Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or syncope.

Class II—
- Patients with pulmonary hypertension resulting in slight limitation of physical activity.
- They are comfortable at rest.
- Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or syncope.

Class III—
- Patients with pulmonary hypertension resulting in marked limitation of physical activity.
- They are comfortable at rest.
- Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or syncope.

Class IV—
- Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms.
- These patients manifest signs of right heart failure.
- Dyspnea and/or fatigue may even be present at rest.
- Discomfort is increased by any physical activity.

*Table adapted from "Classification of Pulmonary Hypertension.
" Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed. Peter Libby et al. 2007.web. 21 Oct 2010.

DUR Board Action: 7/24/14 (KS), 3/27/14 (KS), 2/23/12 (TW), 9/16/10 (KS)
Revision(s): 5/14/12, 1/24/12
Initiated: 1/1/11

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Abbreviated Class Update: Anticoagulants

Month/Year of Review: July 2014
Last Review: March 2013

End date of literature search: June 2014
Source: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: lovenox (branded product), dalteparin (Fragmin®), unfractionated heparin (UFH), warfarin
- Non Preferred Agents: enoxaparin, fondaparinux (Arixtra®), rivaroxaban (Xarelto®), dabigatran (Pradaxa®), apixaban (Eliquis®)

Current PA: Oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (apixaban and rivaroxaban) are subject to prior authorization criteria to promote safe and effective use among patients requiring anticoagulation (Appendix 2).

Research Questions:

- Is there any new evidence of efficacy differences between approved anticoagulants in adults requiring treatment or prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE), orthopedic prophylaxis of venous thromboembolism (VTE), or patients with atrial fibrillation (AF)?
- Is there evidence of differences in harms between the available anticoagulants products?
- Are there indications or subpopulations where one agent may be more effective or safe than other available agents?

Conclusions:

- The new oral anticoagulants (dabigatran, apixaban and rivaroxaban) have been shown to be superior or non-inferior to warfarin for the prevention of stroke and systemic embolism in patient with non-valvular AF based on high strength of evidence (SOE)[1], however, clinical differences remain small.[2] Guidelines recommend warfarin in preference to the newer agents or offer that patient characteristics and discussion of the risks and benefits of all treatments be the determining factors in anticoagulant selection.[3,4]
- For the treatment of VTE, apixaban demonstrated non-inferiority to conventional therapy in one good quality study with reduced rates of major bleeding (moderate SOE).[5] For extended VTE treatment, dabigatran proved to be non-inferior to warfarin with less risk of major or clinically relevant bleeding and that dabigatran is superior to placebo (NNT 19) but with increased risk of bleeding (moderate SOE).[6,7] Low molecular weight heparins (LMWH) are preferred for long-term VTE prophylaxis in patients with cancer, based on high SOE.[8]
- Meta-analysis data in patients undergoing total hip or total knee surgery that require VTE prophylaxis, demonstrated that factor Xa inhibitors (apixaban and rivaroxaban) reduced the rate of symptomatic DVT to a greater extent than LMWH (4 fewer events per 1000 patients) based on high SOE, with a higher occurrence of major bleeding compared to LMWH (2 more events per 1000 patients treated), based on moderate evidence.[9] There was no significant difference in efficacy outcomes between LMWH and dabigatran 220mg daily (strength not available).[9]

- Based on low strength of evidence, rivaroxaban was shown to be as effective as enoxaparin at day 10 and superior to enoxaparin at day 35 when used for thrombus prevention in patients who were medically ill. Enoxaparin treatment was associated with less risk of bleeding compared to rivaroxaban based on low strength of evidence. There is insufficient evidence for the use of rivaroxaban long-term in this population.[10]

Recommendations:

- **Atrial Fibrillation:** Recommend warfarin as first-line therapy and offer dabigatran and apixaban as non-preferred agents subject to PA approval. No changes to the PDL are recommended.
- **VTE treatment:** Recommend warfarin or enoxaparin first line with dabigatran, rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
- **Orthopedic Prophylaxis:** Recommend LMWH as an appropriate first-line treatment option. Recommend rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
- **Medically Ill:** If continued anticoagulation is warranted in medically ill patients recommend warfarin as first-line option. Fourteen day supply of rivaroxaban allows transition to preferred therapy in current PA criteria. No changes to the PDL are recommended.

Reasons for the Review:

As the range of treatment options for patients requiring anticoagulation expands, new evidence becomes available. Data on newer oral anticoagulants (NOA) continues to evolve with the additional FDA approved indications and additions to the literature. The recent Drug Effectiveness Review Project (DERP) scan will be reviewed with applicable literature added. New indications and safety alerts since the last drug class update in 2013 will summarized.

Previous Conclusions and Recommendations:

Atrial Fibrillation

- There is moderate level of evidence that the new oral anticoagulants are superior (dabigatran and apixaban) or non-inferior (rivaroxaban) to warfarin in patients with non-valvular AF as demonstrated by the reduced risk of stroke and systemic embolism.[11-13] The risk of major bleeding was less with the NOAs compared to warfarin based on moderate strength of evidence. There are no studies directly comparing the new oral agents. Treatment beyond two years has not been studied. Concerns over lack of antidote for the new oral anticoagulants, unexplained increases in coronary events with dabigatran and limited clinical experience in the general population remain. Clinical prior authorization criteria are required for the utilization of the new oral anticoagulants while warfarin is available without restrictions.

Acute or Chronic DVT or PE Treatment

- Based on four, fair- good quality studies the NOAs have been shown to be non-inferior to warfarin (±previous enoxaparin therapy) for acute and chronic DVT and PE treatment based on moderate level of evidence.[14-17] Direct comparison among the new agents is lacking. Patients with severe renal disease and those at high risk of bleeding have not been studied. Guidelines favor the use of warfarin followed by LMWH for this indication and these treatments are available without restriction.[18] Dabigatran and rivaroxaban are available upon meeting clinical PA requirements.

VTE Prophylaxis in Orthopedic Surgery (Total Knee Replacement [TKR] and Total Hip Replacement [THR)

- Data from five studies suggested NOAs are non-inferior or superior to enoxaparin when used for orthopedic prophylaxis in patients undergoing THR.[19-23] Studies of the NOAs in patients undergoing TKR have shown conflicting results with evidence suggesting non-inferiority or superiority of the NOAs over enoxaparin when the 40 mg daily dose for enoxaparin is used.[24,25] Studies utilizing the US enoxaparin recommended dose for TKR, 30 mg twice daily, has

shown the NOAs to be inferior to enoxaparin with the exception of rivaroxaban which has demonstrated superiority based on moderate strength of evidence.[26-29] No direct comparisons are available, however, indirect data suggests apixaban, dabigatran, and rivaroxaban prevent symptomatic VTEs to a similar extent based on moderate SOE.[30] Guidelines favors LMWH over fondaparinux, apixaban, dabigatran, rivaroxaban, or UFH based on moderate evidence.[18] LMWH are considered an appropriate first-line treatment and are not subject to PA criteria. Rivaroxaban is considered the most appropriate second-line option.

Background:

Anticoagulants are used in the prevention and treatment of a variety of medical conditions. Thrombosis results from damage to the endothelial lining of blood vessels which trigger activation of the coagulation cascade leading to thrombus formation.[30] Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors.[30] Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) or factor Xa inhibition (rivaroxaban and apixaban).[32-35] Commonly used oral and injectable anticoagulants are presented in table 1.

Table 1. Anticoagulants – FDA Approved Indications[32-36]

Drug	DVT/PE Prophylaxis	DVT/PE Treatment	Atrial Fibrillation	Cardiac Valve Replacement	Post- MI
Warfarin (Coumadin®)	+	+	+	+	+
Dabigatran (Pradaxa®)	---	+	+ (nonvalvular only)	---	---
Rivaroxaban (Xarelto®)	+ (Studied in THR and TKR)	+	+ (nonvalvular only)	---	---
Apixaban (Eliquis®)	+ (Studied in THR and TKR)	---	+ (nonvalvular only)	---	---
Enoxaparin (Lovenox®)	+	+	---	---	+

* MI- myocardial infarction, DVT – deep vein thrombosis, THR- total hip replacement, TKR- total knee replacement

The most important outcomes in assessing therapy for treatment and prevention of VTE include the occurrence or reoccurrence of VTE, major bleeding and all-cause mortality. Additional relevant outcomes include: minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. When evaluating anticoagulation therapies for patients undergoing hip or knee replacement surgeries current literature has incorporated the use of the surrogate outcome, asymptomatic DVT, detected by mandatory venography.[36] The American College of Chest Physicians (ACCP) guidelines find this outcome "fundamentally unsatisfactory" due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding.[18] The guidelines provide suggestions to estimate reductions in symptomatic thrombosis, dependent upon available evidence. Many studies that evaluate the effectiveness of anticoagulants in surgery patients rely on

asymptomatic DVT events to determine treatment differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates.[37]

Rates of stroke, systemic embolisms and mortality are appropriate outcomes in evaluating treatment for AF. Secondary outcomes of interest are rates of ischemic and hemorrhagic strokes and incidence of myocardial infarctions (MI). Important safety outcomes include major bleeds, clinically relevant non-major bleeds and gastrointestinal bleeding.

VTE Prophylaxis

For patients undergoing THR or TKR, prophylactic anticoagulants are considered standard practice. ACCP guidelines recommend the use of LMWHs over other available anticoagulants (moderate evidence).[18] A minimum treatment duration of 10-14 days is recommended (moderate evidence).[18] There is moderate evidence suggesting thromboprophylaxis be continued for up to 35 days from the day of the surgery.[17] The FDA approved doses for subcutaneous enoxaparin prophylaxis in patients undergoing hip replacement surgery is 30 mg every 12 hours or 40 mg once daily and for knee replacement surgery is 30 mg given every 12 hours.[36] This is in contrast to the common European dosing regimen of enoxaparin 40 mg given once daily for prophylaxis in patients undergoing knee replacement, which is used in some trial designs. Dabigatran has demonstrated similar efficacy to LMWH, while rivaroxaban has shown superiority to LMWH in a comparative effectiveness review evaluating patients undergoing orthopedic surgery.[37]

For patients who are medically ill and at risk for VTE, prophylaxis is recommended with one of the following therapies; LMWH, unfractionated heparin (UFH) or fondaparinux.[18]

Acute VTE Treatment

ACCP guidelines recommend the use of LMWH, fondaparinux, intravenous (IV) UFH or subcutaneous UFH for the acute treatment of DVT and PE. The treatment duration is indication dependent, however, long-term anticoagulation is recommended, ranging from 3 months to extended therapy.[17] Treatment with vitamin K antagonists (VKA) are recommended over LMWH for extended anticoagulation in most patients (Grade I, low evidence), except those with cancer in which LMWHs are preferred, based on moderate evidence.[18]

Atrial Fibrillation

Patients with AF are at increased risk of stroke and systemic embolism. Risk estimates are based on the $CHADS_2$ and CHA_2DS_2-VASc Classification Scheme (Table 2).[2] The $CHADS_2$ risk stratification scheme has demonstrated a 2% increase in stroke rate for each one point increase in score. The $CHADS_2$ system designates intermediate risk to those with a score of 1, lacking a clear risk assessment for those at lowest risk.[2] Those with prior history of prior stroke may have their risk underestimated by $CHADS_2$ classification. The CHA_2DS_2-VASc scoring system has a wider scoring system which correlates to better predictability of risk in those with a lower initial stroke risk. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and a $CHAD_2$ score ≥1 and the AHA/ACC/HRS guidelines recommend anticoagulation for those with prior stroke, TIA or CHA_2DS_2-VASc score ≥2.[2,18]

Table2. $CHADS_2$ and CHA_2DS_2-VASc Classification Risk Stratification Scores for Subjects with Nonvalvular AF[2,18]

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc			
$CHADS_2$ acronym	**Score**	**CHA_2DS_2-VASc acronym**	**Score**

Congestive HF	1	Congestive HF	1
Hypertension	1	Hypertension	1
Age ≥75yr	1	Age ≥75yr	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
Maximum Score	**6**	Vascular disease (prior MI, PAD, or aortic plaque)	1
		Age 65-75 y	1
		Sex category (i.e., female sex)	1
		Maximum Score	**9**

Methods:

A Medline literature search beginning January 2013 (since last anticoagulant drug class update) and ending May 2014 for new systematic reviews and randomized controlled trials (RCTs) of anticoagulant therapies was performed. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Veterans Affairs - Comparative Effectiveness of New Oral Anticoagulants and Standard Thromboprophylaxis in Patients Having Total Hip or Knee Replacement[9]

A recent systematic review compared the efficacy and harms new oral anticoagulants to standard treatment (LMWH) in patients undergoing THR or TKR. Literature was analyzed and graded using the Assessment of Multiple Systematic Reviews and QUOROM (Quality of Reporting of Meta-analyses) criteria. Six, good-quality reviews were included in the analysis. The new oral anticoagulants studied included: apixaban, dabigatran, rivaroxaban, and edoxaban (not available in the United States [US]). All studies used a LMWH as a comparator. Factor Xa inhibitors were found to reduce the rate of symptomatic DVT to a greater extent than LMWH based on high SOE (4 fewer events per 1000 patients; OR 0.46; 95% CI 0.30-0.70). The risk of non-fatal PE (OR 1.07; 95% CI 0.65 to 1.73) and death (OR 0.95; 95% CI 0.55 to 1.63) were similar. There was moderate SOE that factor Xa inhibitors were associated with a non-significant higher occurrence of major bleeding compared to LMWH (2 more events per 1000 patients treated; OR 1.27; 95% CI 0.98 to 1.65). The direct thrombin inhibitor, dabigatran, was not statistically different from LMWH, regardless of outcome studied (based on low and moderate SOE). Rivaroxaban was shown to reduce the risk of VTE to a greater extent than dabigatran and apixaban, based on indirect comparisons.

COCHRANE – Factor Xa Inhibitors Versus Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients with Atrial Fibrillation[3]

In a 2013 review, the Cochrane Collaboration evaluated the efficacy and safety of factor Xa inhibitors compared to VKAs in stroke and systemic embolism prevention. Ten, moderate to high quality trials involving 42,084 participants with AF were included. Apixaban and rivaroxaban studies accounted for approximately 80% of the factor Xa inhibitors studied, however, studies of therapies not approved in the US were also included (betrixaban, darexaban, edoxaban and idraparinux). The primary outcome of composite strokes and systemic embolism was reported in nine of the studies. Factor Xa inhibitors were

found to be statistically superior to warfarin for the composite primary outcome of stroke and systemic embolic events (OR 0.81, 95% CI 0.72 to 0.91; 9 studies), as well as the individual components. These results translate into of number needed to treat (NNT) of 304 per year for apixaban and 369 for rivaroxaban, when including only larger studies with follow-up of at least a year. Major bleeding was also found to be significantly less with factor Xa inhibitors compared to warfarin (OR 0.81, 95% CI 0.81 to 0.98). Due to high heterogeneity, a second analysis was performed and showed that major bleeds were not significantly less with factor Xa inhibitors (OR 0.92, 95% CI 0.63 to 1.34). Clinically relevant non-major bleeding was not statistically different between the two groups. Intracranial hemorrhage rates and all-cause death were also found be significantly less with factor Xa inhibitors compared to warfarin. Quality of anticoagulation (time in therapeutic range) with warfarin did not effect the efficacy results when compared to rivaroxaban and apixaban. Authors note that while factor Xa inhibitors were shown to be more effective than warfarin the clinical difference between the agents remains very small.

Ruff et al - Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials[39]

Apixaban, dabigatran, edoxaban, and rivaroxaban were included in a recent meta-analysis evaluating the efficacy and safety of these agents in patients with AF. In dabigatran and edoxaban studies, two dosing schemes were used and therefore analyzed in separate analyses: low dose (dabigatran 110mg twice daily and edoxaban 30mg once daily) and high dose (dabigatran 150mg twice daily, edoxaban 60mg once daily, rivaroxaban 20mg once daily and apixaban 5mg twice daily). There were 42,411 patients who received new oral anticoagulants and 29,272 who received warfarin. The mean ages included in the trials ranged from 70-73 with approximately one-third being women. The mean baseline $CHADS_2$ score was 2.1 in studies with dabigatran and apixaban, 2.8 with edoxaban and highest with rivaroxaban with a score of 3.5. Time in therapeutic range (TTR) was 58-68% across the trials. Follow-up ranged from 1.8 to 2.8 years.

The meta-analysis comparative efficacy combined results for stroke and systemic embolism favored high-dose NOAs over warfarin (RR 0.81, 95% CI 0.73 to 0.91, $p < 0.0001$). As in many of the individual trials, the results were driven by reductions in hemorrhagic stroke. All cause mortality rates were also significantly reduced in the patients allocated to the high-dose NOAs compared to those in the warfarin groups (RR 0.90, 95% CI 0.85 to 0.95, p = 0003). Safety findings illustrated a reduction in major bleeding (RR 86, 95% CI 0.73 to 1.00, p = 0.06) and intracranial hemorrhage (RR 0.48, 95% CI 0.39 to 0.59, $p < 0.0001$). Gastrointestinal bleeding was significantly higher in high-dose NOAs compared to warfarin (RR 1.25, 95% CI 1.01 to 1.55, p = 0.043). The efficacy benefits seen with high dose NOAs compared to warfarin were consistent across subgroups (age, sex, diabetes, previous stroke or TIA, creatinine clearance, $CHADS_2$ score, VKA status and center-based TTR). Safety findings were also consistent across subgroups except for the center-based TTR. In centers where TTR was less than 66%, relative reductions in major bleeding were even greater with the NOAs compared to warfarin. The results for the low-dose NOAs comparison to warfarin demonstrated similar efficacy findings as the high-dose, however, ischemic stroke rates were greater in the low-dose NOA groups. More MIs were reported in the low-dose NOAs group compared to warfarin. For the safety analysis, major bleeding and gastrointestinal bleeding rates were not significantly different between groups.

AHRQ – Stroke Prevention in Atrial Fibrillation[1]

An AHRQ comparative effectiveness review evaluated the efficacy and harms of treatment options for patients with nonvalvular AF. Investigators evaluated studies for quality and applicability and graded the evidence. Ninety-two studies related to bleeding risk, predicting thrombosis, thrombosis prevention and anticoagulation in patients undergoing procedures were included in the analysis. Dabigatran 150 mg had a significantly lower risk of stroke and systemic embolism than warfarin (RR 0.66; 95% CI 0.53 to 0.82) based on high SOE. There was high SOE that major bleeding was similar between warfarin and dabigatran groups (RR 0.93; 95% CI 0.81 to 1.07). Apixaban was also found to be superior to warfarin for stroke and systemic embolism reduction (HR 0.79; 95% CI 0.66 to 0.95) and major bleeding (HR 0.69, 95% CI 0.60 to 0.80) based on high SOE. All-cause mortality was found to be reduced with apixaban compared to warfarin

(HR 0.89, 95% CI 0.80 to 0.998) based on moderate SOE. Apixaban was shown to be superior to aspirin based on high SOE (HR 0.45, 95% CI 0.32 to 0.62). Rivaroxaban was shown to be noninferior to warfarin for stroke and systemic embolism prevention based on moderate evidence with similar rates of major bleeding and death (high SOE). Limitations to the review were the inclusion of a small number of trials and the lack of direct comparisons between the new agents. There was insufficient evidence on patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulation after a major bleeding event.

New Guidelines:

2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[2]

A newly released guideline from the collaborate effort of the American Heart Association (AHA), American College of Cardiology (ACC) and Heart and Rhythm Society (HRS) provides updated guidance on the management of AF. For the purpose of this drug class update, only anticoagulant therapies will be reported. The guidelines incorporate multiple data analysis methods for formulation of recommendations. The Class of Recommendations (COR) is an estimate of the size of treatment effect and the Level of Evidence (LOE) is an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. An additional designation of *guideline-directed medical therapy* (GDMT) is used for optimal therapy options. Anticoagulation recommendations are provided by class, as listed below. Additional recommendations not pertaining directly to anticoagulation therapies are provided in table 3.

Class I Recommendations

In patients with mechanical heart valves, warfarin is recommended with an INR goal based on type and location of prosthesis (LOE B). Oral anticoagulants are recommended for all AF patents with prior stroke, transient ischemic attack (TIA) or CHA_2DS_2-VASc score ≥2. Oral anticoagulant options include warfarin (LOE A), dabigatran, rivaroxaban or apixaban (LOE B). INR evaluations for patients on warfarin should be done weekly upon initiation and monthly when stable (LOE A). Direct thrombin or factor Xa inhibitors are suggested for those patients who are unable to maintain a therapeutic INR on warfarin (LOE C). Renal function evaluation should be performed prior to direct thrombin or factor Xa inhibitor initiation and re-evaluate when clinically indicated, and at least annually (LOE B). The recommendations for anticoagulation for atrial flutter are the same as for AF (LOE C).

Class IIa Recommendations

In patients who require anticoagulation with CHA_2DS_2-VASc scores ≥2 and end-stage chronic kidney disease (CrCl <15 mL/min) or on hemodialysis, warfarin is a reasonable choice (LOE B).

Class IIb Recommendations

Consideration may be given to no treatment, anticoagulants, or aspirin therapy in patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1 (LOE C). In patients with a CHA_2DS_2-VASc score of ≥2 who have undergone a coronary revascularization, it may be reasonable to use clopidogrel in combination with oral anticoagulants, but not aspirin (LOE B).

Class III: No benefit

Due to lack of evidence from clinical trials and the balance of risks and benefits, dabigatran and rivaroxaban are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis (LOE C).

Class III: Harm
Dabigatran should not be used in patients with mechanical heart valves (LOE B).

Table 3. AHA/ACC/HRS Guidelines – Non-drug Recommendations for the Prevention of Thromboembolism in Patients with AF[2]

Recommendations	Class of Recommendation	Level of Evidence
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences	I	C
Antithrombotic therapy selection based on risk of thromboembolism	I	B
Re-evaluate the need for anticoagulation at periodic intervals	I	C
Bridging therapy with LMWH or UFH recommended with mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks or stroke and bleeding.	I	C
Without mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated	I	C
With nonvalvular AF and CHA2DS2-VAc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B
For percutaneous coronary intervention (see 2011 guideline for specifics on type of stent and duration of dual antiplatelet therapy recommendations) bare-metal stent may be considered to minimize duration of dual antiplatelet therapy	IIb	C

** Table adapted from January CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. J of Amer C of Cardiol 2014, doi: 10.1016/j.jacc.2014.03.022.*

Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update[8]
The 2007 evidence-based guideline produced by the American Society of Clinical Oncology (ASCO) was updated in 2013. Forty-two systematic reviews and randomized controlled trials were included and assessed for risk of bias. Recommendations regarding VTE treatment and prophylaxis will be reported. There was strong evidence to support the use of LMWH over UFH for initial anticoagulation (5-10 days) in patients with cancer with newly diagnosed VTE and no renal impairment. LMWH is preferred for long-term anticoagulation, lasting at least 6 months, over VKAs (strong SOE). However, VKAs are an option if LMWH is unavailable. There is insufficient evidence to recommend anticoagulation beyond 6 months. The use of NOAs for prevention or treatment of VTE is not recommended due to insufficient evidence.

AHA/ASA Guideline – Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack (TIA)[40]
The American Heart Association (AHA) and the American Stroke Association (ASA) released updated guidelines on managing secondary prevention patients with a history of TIA or stroke. The data pertaining to anticoagulation treatment will be summarized. Recommendations are based on two components; the Class of Recommendations (COR) is an estimate of the size of treatment effect and the Level of Evidence (LOE) is an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. The Class of Recommendations (COR) is an estimate of the size of treatment effect and the Level of Evidence (LOE) is an estimate of certainty or precision of

effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. Table 4 highlights changes from previous recommendations.

Table 4. Updated Recommendations for Stroke Prevention in Patients with Stroke and TIA[40]

Indication	Therapy	Class of Recommendation	Level of Evidence
Nonvalvular AF (paroxysmal or permanent)	VKA Therapy (INR 2.0-3.0)	I	A
	Apixaban	I	A
	Dabigatran	I	B
	Rivaroxaban	IIa	B
Nonvalvular AF and CAD	VKA/Newer Agents and antiplatelet therapy	IIb	C
Ischemic stroke or TIA and MI and Thrombus*	VKA therapy for 3 months	IIb	C
	For patients intolerant to VKAs appropriate alternatives to consider are; LMWH, dabigatran, rivaroxaban or apixaban for 3 months	IIb	C
Ischemic stroke or TIA and Cardiomyopathy*	VKA for ≥3 months for left atrial or left ventricular thrombus	I	C
	VKA therapy for mechanical LVAD	IIa	C
	Dabigatran, rivaroxaban, apixaban therapy for dilated cardiomyopathy, restrictive cardiomyopathy, or mechanical LVAD has uncertain effectiveness compared to VKA treatment	IIb	C
Ischemic stroke or TIA and Valvular Heart Disease	VKA therapy for rheumatic mitral valve disease and AF	I	A
	VKA therapy may be considered for those with rheumatic mitral valve disease or another likely cause for symptoms without AF	IIb	C
Ischemic stroke or TIA and Prosthetic Heart Valve	VKA therapy recommended for mechanical aortic valves in patients with stroke or TIA history before valve insertion	I	B
Pregnancy and High Risk Condition	LMWH, UFH throughout pregnancy or up until the 13th week, followed by a VKA until close to delivery and then LMWH or UFH is resumed	IIa	C
Breastfeeding and High Risk Condition	Warfarin, UFH, or LMWH	IIb	C

* See guideline for specific circumstances regarding therapy recommendations.

LMWH- low molecular weight heparin, VKA- vitamin K antagonist, UFH-unfractionated heparin, LVAD-left ventricular assist device , AF-atrial fibrillation

Table adapted from Kernan et al, Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45:00-00. Doi:10.1161/STR.0000000000000024.

Patient specific characteristics such as risk factors, cost, tolerability, patient preference, drug interactions, ability to maintain a therapeutic INR and renal function should be considered when selecting an anticoagulation regimen. Initiation of anticoagulation in patients with a history of TIA or stroke should be considered in most patients within in 14 days of initial symptoms.

AHA/ASA – Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association[41]

Stroke risks and treatments were summarized in a recent guideline from the AHA/ASA pertaining exclusively to women. The guidelines incorporate multiple data analysis methods for formulation of recommendations. The Class of Recommendations (COR) is an estimate of the size of treatment effect and the LOE is

an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. Data pertaining to anticoagulants will be summarized.

VKAs are recommended for women with acute cerebral venous thrombosis (CVT) for at least 3 months and possibly indefinitely dependent upon etiology. Pregnant women with CVT should receive LMWH during pregnancy, followed by vitamin K antagonists for ≥6 weeks post partum (Class I; Level of Evidence A). For women with paroxysmal or permanent AF with pre-specified risk factors, NOAs are an alternative to VKA therapy in patients without prosthetic heart valves or hemodynamically significant valve disease, severe renal failure, lower weight (<50 kg) or advanced liver disease (Class I; Level of evidence C). Data on NOA use in women is minimal, as none of the studies were powered to determine a difference in efficacy according to sex, but evidence suggests that efficacy is similar to that in men.

NICE – Atrial Fibrillation: the Management of Atrial Fibrillation[4]

June 2014 marked the release of updated guidance from NICE for the management of patients with AF. Evidence was assessed for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. Recommendations for anticoagulation will be discussed. Anticoagulation should be considered in patients with a CHA_2DS_2VASc stroke risk score equal to 1 in men and offered to all patients with a CHA_2DS_2VASc score of ≥2. Choice of anticoagulant should be chosen based on patient preference, clinical characteristics and consideration of benefits and risks of all treatments. Evidence comparisons between warfarin and non-vitamin K antagonists have been discussed in single technology appraisals. Bleeding risk, based on the HAS-BLED score, should be taken into account when offering anticoagulation. For patients on VKAs, TTR should be determined every visit and calculated over a maintenance period of at least 6 months. If adequate anticoagulation can't be maintained, other treatment options should be considered. Non-vitamin K anticoagulation options are presented below (table 5). Aspirin monotherapy is not recommended for stroke prevention.

Table 5. Non-vitamin K Antagonists for Patients with Atrial Fibrillation[4]

Treatment	Patient Characteristics
Apixaban	Nonvalvular AF and one or more of the following risk factors: prior stroke, age ≥75 years, hypertension, diabetes or symptomatic heart failure
Dabigatran	Nonvalvular AF and one or more of the following risk factors: previous stroke, TIA, or systemic embolism, left ventricular EF <40%, symptomatic HF of NYHA class ≥2, ≥75 years, ≥65 years with one of the following: diabetes, coronary artery disease or hypertension
Rivaroxaban	Nonvalvular AF and one or more of the following risk factors: CHF, hypertension, ≥75 years or older, diabetes or prior stroke or TIA
AF- atrial fibrillation, TIA – transient ischemic attack, EF – ejection fraction, NYHA – New York heart classification, CHF – congestive heart failure	

New FDA Alerts:

DABIGATRAN- Black Box Warning[35]

Labeling changes were made in April of 2013 to dabigatran. A black box warning was added to alert providers of the increased risk of thrombotic events, including stroke, upon discontinuation of dabigatran. Coverage with a different anticoagulant is recommended unless pathological bleeding is present. Epidural or spinal hematomas may occur in patients treated with dabigatran who are receiving neuraxial anesthesia or undergoing spinal puncture.

RIVAROXABAN- Black Box Warning[42]

In August of 2013 the black box warning for rivaroxaban was changed to include an increased risk of thrombotic events upon premature discontinuation of rivaroxaban, regardless of indication.

Warnings and precautions section was updated to advise against the use of rivaroxaban in patients with prosthetic heart valves as it has not been studied and therefore not recommended.

APIXABAN – Dosing Recommendations[33]
In January of 2014 dosing recommendations for apixaban when used in end-stage renal disease maintained on hemodialysis was updated based on pharmacokinetic and pharmacodynamic studies. Apixaban 5mg twice daily is recommended when undergoing dialysis. As previously recommended, patients ≥80 years of age or body weight of ≤60 kg should be given 2.5 mg twice daily.

APIXABAN- Black Box Warning[33]
The warning of the risk for epidural or spinal hematoma, potentially causing paralysis, is increased in patient using apixaban and undergoing spinal epidural anesthesia or spinal puncture was added in March 2014.

DABIGATRAN – Drug Safety Communication – Lower risk for Stroke, and Death, but Higher Risk for GI Bleeding Compared to Warfarin[43]
An observational cohort study of 134,000 Medicare patients (65 years and older) was conducted by the FDA to compare dabigatran to warfarin for risk of stroke, major GI bleeding, MI and death. Patients were newly diagnosed with AF within 6 months of medication claim for anticoagulation. Data was derived from administrative and insurance claims data. Adjustments were made for potential confounding variables. Dabigatran (150 mg and 75 mg dose) was found to be associated with a lower risk of ischemic stroke (HR 0.80; 95% CI 0.67 to 0.96), intracranial hemorrhage (HR 0.34; 95% CI 0.26 to 0.46) and death (HR 0.86; 95% CI 0.77 to 0.96) compared to warfarin. Risk for GI bleeding was higher for dabigatran (HR 1.28; 95% CI 1.14 to 1.44) compared to warfarin and MI risk was similar (HR 0.92; 95% CI 0.78 to 1.08). These findings are similar to the RE-LY study with the exception of the MI risk being similar for the two treatments instead of an elevated risk for dabigatran. The increased risk of GI bleeds associated with dabigatran was similar to the RE-LY study but differs from data found in the Mini Sentinel Modular Program analysis which found less risk of GI bleeds with new users of dabigatran compared to warfarin.

New Indications:
APIXABAN-
Apixaban gained a new indication in March 2014 for prophylaxis of DVT which may lead to PE in adult patients who have undergone hip or knee replacement surgery. One fair quality study (ADVANCE-1) and two good quality studies (ADVANCE-2 and ADVANCE-3) were used as evidence for the approval of apixaban for this expanded indication. [22,25,26] The approved dose for prophylaxis is 2.5mg twice daily.

ADVANCE TRIALS – Orthopedic Prophylaxis

The good quality ADVANCE studies were previously evaluated in the Anticoagulant Abbreviated Class Update (Appendix 1), which was presented to the Oregon Health Plan P&T Committee in March 2013.[42] The clinical efficacy and safety of apixaban use in orthopedic prophylaxis was demonstrated in three phase III, randomized, double-blind, double-dummy clinical trials involving 11,659 patients (ADVANCE 1-3).[22,25,26] Patients were eligible for the trials if they were scheduled for TKR or revision (ADVANCE 1-2) or THR or revision (ADVANCE 3). Mean treatment durations were 11-12 days in the TKR trials and 34 days in the

THR trial. The primary endpoint was the rate of symptomatic and asymptomatic DVT, non-fatal PE and all-cause mortality. The primary safety endpoint was bleeding rates.

ADVANCE-1 randomized patients undergoing TKR to apixaban 2.5mg twice daily compared to enoxaparin 30mg every 12 hours.[25] Apixaban was show to be inferior to enoxaparin based on primary endpoint occurrence (RR 1.02; 95% CI 0.78 to 1.32, p=0.06 for noninferiority). In ADVANCE-2 the European dosing regimen of enoxaparin 40mg daily was compared to apixaban 2.5 mg twice daily and was found to be noninferior and superior to enoxaparin (RR 0.62; 95% CI 0.51 to 0.74, p<0.001 for superiority).[26] In ADVANCE-3 patients received enoxaparin 40 mg daily or apixaban 2.5 mg twice daily for THR for a mean duration of 34 days. Apixaban was found to be noninferior and superior to enoxaparin (RR 0.36, 95% CI 0.22 to 0.54, p<0.001).[22]

Pooling data of the ADVANCE trials showed both apixaban and enoxaparin to have a similar rate of adverse reactions and discontinuation due to adverse events. ADVANCE-1 showed apixaban to be associated with significantly less major bleeds and clinically relevant non-major bleeds compared to enoxaparin. These same safety outcomes were found to be similar between apixaban and enoxaparin in ADVANCE-2 and 3.

Conclusion:
Apixaban was found to be superior to the European dosing regimen of enoxaparin, based on one fair quality trial, but not to the US approved dosing regimen of enoxaparin, in patients requiring thromboprophylaxis for TKR (low SOE). One good quality trial found use of apixaban, in patients undergoing THR, to be superior to enoxaparin (moderate SOE). Rates of bleeding were found to be similar for apixaban and enoxaparin in patients requiring thromboprophylaxis for TKR or THR (moderate SOE).

DABIGATRAN – Reduction in Recurrent VTE[6]

Dabigatran recently received approval for the reduction in risk of recurrent DVT and PE in individuals who have already been treated. Dosing recommendations for this indication are dabigatran 150mg twice daily. Evidence for this approval was based on two studies (REMEDY and RESONATE).[6]

Dabigatran was studied in two good quality studies for the extended treatment of VTE in patients previously treated for 3 months with dabigatran or other anticoagulant. In REMEDY 2866 patients were randomized to dabigatran 150 mg twice daily or warfarin (target INR of 2.0 to 3.0) and in RESONATE 1353 patients were assigned to dabigatran 150 mg twice daily or placebo. Both studies had the same design and patient inclusion and exclusion criteria were similar. Patients deemed to be at higher risk for recurrent VTE were enrolled in the active treatment study. Patients were predominately white with a slight majority being male. A higher percentage of patients in the dabigatran group had a history of coronary artery disease, diabetes and hypertension compared to warfarin. DVT was the most common reason for inclusion followed by PE. In the active treatment study therapy ranged from 6 to 36 months and in the placebo study follow-up was to 12 months. The primary efficacy outcomes was recurrent symptomatic and objectively verified VTE or death associated with VTE (or unexplained death in the placebo-control study). Secondary outcomes of importance include symptomatic DVT, non-fatal symptomatic PE, VTE-related death and all deaths. Important safety outcomes included major bleeding, clinically relevant non-major bleeding and acute coronary events.

Dabigatran was found to be non-inferior to warfarin with the primary outcome occurring in 1.8% and 1.3%, respectively (HR 1.44, 95% CI 0.78 to 2.64, p=0.01). Major bleeding was less with dabigatran than warfarin but not significantly so. In the placebo controlled trial primary outcome rates were lower for dabigatran compared to placebo, 0.4% and 5.6%, respectively. Major bleeding was less with dabigatran compared to warfarin but not significantly so. The composite endpoint of major or clinically relevant bleeding was significantly less with dabigatran compared to warfarin (HR 0.54, 95% CI 0.41 to 0.71, p<0.001). As anticipated, major bleeding rates were higher with dabigatran compared to placebo. Major or clinically relevant nonmajor bleeding was also higher with

dabigatran than placebo, 5.3% vs. 1.8%. Acute coronary events were found to be higher in the dabigatran group (0.9%) compared with warfarin (0.2%), however event rates were similar in placebo controlled trial. Limitations to the studies include a large noninferiority margin for the hazard ratio (2.85) which proved dabigatran to be noninferior to warfarin even with an increase in risk of almost 3. Most patients enrolled had normal renal function and were Caucasian, limiting extrapolation of results to the general population. The role associated with the increased risk of coronary events seen with dabigatran is still unknown. Future studies including patients with strong indications for continued anticoagulation would be helpful in determining the role of dabigatran for the prevention of VTE long term.

Conclusion: There is moderate SOE that dabigatran is non-inferior to warfarin for the extended treatment of VTE with less risk of major or clinically relevant bleeding and that dabigatran is superior to placebo but with increased risk of bleeding.

RE-COVER II- Dabigatran for the Treatment of VTE[7]

Dabigatran 150 mg twice daily has received FDA approval for use in the treatment of DVT and PE in patients receiving 5to 10 days of parenteral anticoagulation. The RECOVER and RECOVER II studies were used for data to support this indication.[17,7]

In RECOVER II dabigatran was compared to warfarin in 2589 patients, previously treated with LMWH or unfractionated heparin for 5 to 11 days, for the treatment of VTE. In this double-blind, double-dummy, non-inferiority, randomized controlled trial, patients were provided dabigatran 150 mg twice daily or warfarin adjusted to an INR of 2-3 for 6 months. The non-inferiority margin was set at a HR of 2.75 and an absolute risk margin of 3.6 percentage points for the primary outcome. Patients were an average age of 55 years with the majority (61%) being male. Baseline characteristics were well-matched except for a higher percentage of patients in the dabigatran group had prior history of VTE than those in the warfarin group, 19% and 16%, respectively. TTR was 57% for patients randomized to warfarin therapy. The primary efficacy outcomes were recurrent symptomatic and objectively verified VTE or death. Major bleeding was the primary safety endpoint with any bleeding being a secondary safety outcome.

For the primary outcome dabigatran was shown to be non-inferior to warfarin (HR 1.08, 95% CI 0.64 to 1.80, $p < 0.001$), which was consistent across subgroups. The risk of symptomatic DVT was higher in the dabigatran group compared to warfarin, 2.0% vs. 1.3%, respectively. The reverse was true for symptomatic nonfatal PE, with a lower risk demonstrated in the dabigatran group (0.5%) compared to warfarin (1.0%). Dabigatran was shown to be associated with lower major bleeding than warfarin, 1.2% and 1.7%, respectively (HR 0.69, 95% CI 0.36 to 1.32). Major or clinically relevant non-major bleeding and any bleeding occurred less commonly with dabigatran than with warfarin, with a significant difference found in the latter two outcomes. Dabigatran and warfarin groups were associated with a similar number of deaths and coronary events. A limitation to this study include a large non-inferiority margin which allowed for more than a 3% difference in efficacy . TTR for patients in the warfarin group was less than what has been commonly shown in other studies which would favor dabigatran.

For the pooled analysis of RE-COVER and RE-COVER II patients, recurrent VTE rates were similar with a HR of 1.09 (95%CI, 0.76 to 1.57). Baseline patient characteristics did not influence efficacy results to a significant extent, however, warfarin appeared to be more effective in patients under 60 years of age. For the outcome of clinically relevant bleeding, dabigatran demonstrated a significantly higher risk reduction in younger patients up to the age of 85 years.

Conclusion: There is moderate evidence that dabigatran is non-inferior to warfarin for acute VTE treatment with less major bleeding and significantly less major and clinically relevant non-major bleeds and any bleeding with dabigatran in comparison to warfarin.

NEW EVIDENCE:

Apixaban – VTE Treatment[5]

In AMPLIFY, 5395 patients with objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism were randomized to receive apixaban 10 mg twice daily for seven days followed by 5 mg twice daily for 6 months compared to conventional treatment with enoxaparin for at least 5 days and warfarin (target INR 2.0-3.0) for 6 months. The non-inferiority margin was set at a relative risk less than 1.8 and the risk difference below 3.5%. The mean age of included patients was 57 years old and the majority (69%) were males. Patients at high risk of bleeding, those with cancer, patients requiring extended treatment with an anticoagulant, those requiring long-term anticoagulation, or those with additional indications for anticoagulants were excluded. The majority of patients presented with unprovoked DVT. The primary outcome was recurrent symptomatic VTE or death related to VTE. Important secondary outcomes were the individual components of the primary composite outcome. Safety outcomes included major bleeding and the combined outcome of major bleeding plus clinically relevant non-major bleeding.

In this good quality trial, apixaban treatment was shown to be non-inferior to conventional treatment with enoxaparin and warfarin (RR 0.84, 95% CI 0.60 to 1.18, p<0.001). Non-fatal PE and DVT risk was lower with apixaban compared to conventional treatment, 1.8% vs. 2.2%, respectively. Major bleeding was found to significantly less in the apixaban group compared to conventional treatment (0.31, 95% CI 0.17 to 0.55, p < 0.001). Results were consistent regardless of diagnosis at study entry (DVT or PE). Patients randomized to warfarin were found to have therapeutic INRs 61% of the time, which corresponds to rates found in other studies. Withdrawals due to adverse effects were similar among treatment groups. External validity is limited to patients with normal renal function or mild renal impairment, low risk for bleeds and no cancer diagnosis.

Conclusion: There is moderate SOE that apixaban treatment is non-inferior to conventional therapy for VTE treatment and was found to be superior to conventional therapy for the safety outcome of major bleeding.

RIVAROXABAN – Thromboprophylaxis in Acutely Ill Medical Patients[10]

The MAGELLAN study compared rivaroxaban to enoxaparin in hospitalized, acutely ill, medical patients. In this fair quality study patients were randomized to SQ enoxaparin 40mg once daily for 10±4 days and oral placebo for 35±4 days or rivaroxaban 10 mg daily for 35±4 days and SQ placebo for 10±4 days. There were 8428 patients enrolled in the study which were a median age of 71, predominately white with most having normal renal function. The primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic VTE (asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE and VTE-related death) up to day 10 and up to day 35. Net clinical benefit or harm was an important secondary outcome.

Rivaroxaban was found to be non-inferior to enoxaparin at day 10 (RR 0.97, 95% CI 0.71 to 1.31, p = 0.003 for noninferiority). At day 35 rivaroxaban was shown to be superior to enoxaparin with occurrence of the primary outcome in 4.4% of rivaroxaban patients and 5.7% in those who received enoxaparin (RR 0.77, 95%CI 0.62 to 0.96, p=0.02 for superiority). For the analysis of net clinical benefit (efficacy and harms) enoxaparin was shown to have a benefit over rivaroxaban at day 10 and day 35. For the primary safety outcome of the composite of major or clinically relevant nonmajor bleeding, rivaroxaban was shown to have higher rates at day 10 (RR 2.3, 95% CI 1.63 to 3.17, p < 0.001) and day 35 (RR 2.5, 95% CI 1.85 to 3.25, p < 0.001) compared to enoxaparin. Limitations to this data include the

varying treatment durations of study groups and large subgroup of patients not available for ultrasonography (17-25%). The clinical relevance of asymptomatic VTE, included in the composite primary endpoint, is unknown. External validity is limited to elderly patients with normal renal function.

Conclusion: Based on low strength of evidence, rivaroxaban was shown to be as effective as enoxaparin at day 10 and superior to enoxaparin at day 35 when used for thrombus prevention in patients who were medically ill. Enoxaparin treatment was associated with less risk of bleeding compared to rivaroxaban based on low strength of evidence.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:
Mortality
Thromboembolic events (DVT, PE, stroke)
Cardiovascular events
Bleeding

Primary Study Endpoints:
Surgery Prophylaxis: Total VTE and mortality
DVT/PE Treatment: Recurrent VTE and mortality
AF: Stroke or systemic embolism and mortality
Medically Ill: Cardiovascular death, myocardial infarction or ischemic stroke
All studies: bleeding

Evidence Table

AMPLIFY[5]

Agnelli, et al Phase III, RCT, DB 28 Countries	1. Apixaban (A) - 10mg BID fo 7 days, then 5mg BID for 6 months 2. Conventional Therapy (CT) – SQ enoxaparin for at least 5 days followed by warfarin for 6 months (INR 2.0-3.0)	Age: 57 yrs Male: 59% Inclusion: Patients 18 and older with objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism. Exclusion: Bleeding disorder contraindication t warfarin or enoxaparin, cance and use of LMWH was planned, DVT or PE provoked without persistence risk factors for recurrence, less than 6 months of treatment planned, an additional indication for long term anticoagulation, ASA use of >165mg a day, or use of potent cytochrome P-450 3A4 inhibitors.	1. 2691 2. 2704	Median Tx duration: 6 months	<u>Recurrent Symptomatic VTE or Death related to VTE :</u> A: 59 (2.3%) CT: 71 (2.7%) RR: 0.84 (95% CI 0.60 to 1.18, p<0.001 for noninferiority) <u>Fatal PE:</u> A: 1 (<0.1%) CT: 2 (0.1%) <u>DVT:</u> A: 20 (0.8%) CT: 33 (1.3%) <u>Non-fatal PE with or without DVT:</u> A: 27 (10%) CT: 23 (0.9%)	NS NS NS NS	<u>Major Bleeding:</u> A: 15 (0.6%) E: 49 (1.8%) RR: 0.31 (95% CI 0.17 to 0.55, P<0.001 for superiority) <u>Major Bleeding and Clinically Relevant nonmajor bleeding:</u> A: 115 (4.3%) CT: 261 (9.7%) RR: 0.44 (95% CI 0.36 to 0.55, p<0.001) <u>Withdrawal due to Adverse Events</u> A: 162 (6.1%) E: 199 (7.4%)	ARI: 1.2% NNH: 83 ARI: 5.4% NNH: 19 NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: Interactive voice-response system Performance: double-dummy design used to conceal treatment assignments from patients and clinical monitors. INR monitoring was blinded and encrypted. Detection: independent committee, blinded to treatment assignment, adjudicated results Attrition: similar attrition rates were seen in both studies (14-15%). Sensitivity analysis accounting for missing data did not change results. **External Validity** Recruitment: recruited from 358 centers in 28 countries. Patient Characteristics: the majority of patients presented with unprovoked DVT. For patients on warfarin, INRs were therapeutic 61% of the time. Adherence to apixaban was >80% in 96% of patients. Outcomes: Primary endpoint and safety outcomes were appropriate for study.
REMEDY[6]									
Schulman, et al	1. Dabigatran (D) 150 mg daily 2. Warfarin (W)	Age: 54.5 years Female: 39% Duration of prior treatment: 199 days	1. 1430 2. 1426	Median Tx duration: 6-36 months	<u>Recurrent VTE or death:</u> D: 26 (1.8%) W: 18 (1.3%) HR: 1.44 (95% CI 0.78 to 2.64	NA	<u>Major Bleeding</u>: D: 13 (0.9%) W: 25 (1.8%) HR: 0.52 (95% CI 0.27 to 1.02,	NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system.

Phase III, DB, RCT 33 Countries	with target range of 2.0-3.0	Inclusion: Patients at least 18 years old with objectively confirmed, symptomatic, proximal DVT or PE and 3 months of initial therapy of an approved anticoagulant or dabigatran as part of the RE-COVER or RE-COVER II studies. Exclusion: Symptomatic DVT at screening, patients with PE etiology from source other than legs, use or anticipated use of vena cava filter, patients at excessive risk of bleeding, unstable co-morbidities.			P=0.01 for noninferiority) Recurrent DVT: D: 17 (1.2%) W: 13 (0.9%) HR: 1.32 (95% CI 0.64 to 2.71, p=0.46) Recurrent PE D: 10 (0.7%) W: 5 (0.4%) HR: 2.04 (95% CI 0.70 to 5.98, p=0.19)	NS NS	p=0.77) Major or Clinically Relevant Bleeding: D: 80 (5.6%) W: 145 (10.2%) HR: 0.54 (95% CI 0.41 to 0.71, P<0.001) Acute Coronary Syndrome: D: 13 (0.9%) W: 3 (0.2%) p=0.02 Withdrawal due to Adverse Events D: 145 (10.1%) W: 126 (8.8%)	ARI: 4.6% NNH: 22 ARI: 0.7% NNH: 143 NA	Performance: double-dummy design used to conceal treatment assignments from patients and clinical monitors. INR monitoring was blinded and encrypted. Detection: Outcomes were assessed by central adjudication committee that were unaware of treatment assignment. Large noninferiority margin for the hazard ratio (2.85) allowed for almost 3x the risk to be considered noninferior Attrition: Low rates of lost to follow-up. **External Validity:** Recruitment: Patients recruited from 265 sites from 33 countries. Patient Characteristics: Patients on warfarin in TTR 65% of the time. Patients had previously been exposed to treatments. Outcomes: Direct outcomes were used to determine treatment effect. Large non-inferiority margin was used which could show no difference, even if one exists.
RESONATE[6]									
Schulman, et al Phase III, DB, RCT 21 Countries	1. Dabigatran (D) 150 mg daily 2. Placebo	Age: 56 yrs Female: 44.5% Inclusion: Patients at least 18 years old with objectively confirmed, symptomatic, proximal DVT or PE and 3 months of initial therapy of an approved	1. 681 2. 662	Tx duration: 6 months	Recurrent VTE or death: D: 3 (0.4%) P: 37 (5.6%) HR: 0.08 (95% CI 0.02 to 0.25 P<0.001 for superiority) Recurrent DVT: D: 2 (0.3%) P: 22 (3.3%) Recurrent PE D: 1 (0.1%)	ARR: 5.2% NNT: 19	Major Bleeding: D: 3 (0.3%) P: 0 (0.0%) Major or Clinically Relevant Bleeding: D: 36 (5.3%) P: 12 (1.8%) HR: 2.92 (95% CI 1.52 to 5.60, p=0.001) Acute Coronary	NS ARI: 3.5 NNH: 29	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: Double-dummy design used to conceal treatment assignments from patients and clinical monitors. INR monitoring was blinded and encrypted. Detection: Outcomes were assessed by central adjudication committee that was unaware of treatment assignment. Attrition: Low rates of lost to follow-up.

		anticoagulant or dabigatran as part of the RE-COVER or RE-COVER II studies Exclusion: Symptomatic DVT a screening, patients with PE etiology from source other than legs, use or anticipated use of vena cava filter, patients at excessive risk of bleeding, unstable co-morbities and cancer.			P: 14 (2.1%)		Syndrome: D: 1 (0.1%) P: 1 (0.2%) Withdrawal due to Adverse Events D: 50 (7.3%) P: 81 (12.3%)		**External Validity:** Recruitment: Patients were recruited from 147 sites in 21 countries. Patient Characteristics: Patients were previously exposed to treatment. Outcomes: Direct outcomes were used to determine treatment effect.
MAGELLAN[10]									
The Cohen, e al Phase III, DB, DD, RCT 52 Countries	1. Rivaroxaban 10mg once daily (R) 2. Enoxaparin 40mg SQ once daily (E)	Median Age: 71 years Male: 55% Median hospital duration: 11 days Inclusion: patients 40 years and older, hospitalized with ar acute medical illness for less than 72 hours with reduced mobility and one additional risk factor for VTE. Exclusion: Elevated risk of bleeding, severe comorbidities, use of medications known to interact with rivaroxaban or enoxaparin, use of	1. 4050 2. 4051	Tx duration: 10 day for enoxaparin /35 days for rivaroxaban	Asymptomatic proximal o symptomatic VTE at day 10: R: 78 (2.7%) E: 82 (2.7%) RR: 0.97 (95% CI, 0.71 to 1.31, p=0.003, for noninferiority) Asymptomatic proximal o symptomatic VTE at day 35: R: 131 (4.4%) E: 175 (5.7%) RR: 0.77 (95% CI, 0.62 to 0.96, p=0.02 for superiority) VTE related death at day 10: R: 3 (0.1%) E: 6 (0.2%) VTE related death at day 35:	NA ARR: 1.3% NNT: 77 NA	Clinically relevant bleeding at day 10: R: 111 (2.8%) E: 49 (1.2%) RR: 2.3 (95% CI, 1.63 to 3.17, p<0.001) Clinical relevant bleeding at day 35: R: 164 (4.1%) E: 67 (1.7%) RR: 2.5 (95% CI, 1.85 to 3.25, p<0.001) Fatal Major Bleed at day 10: R: 5 (0.1%) E: 1 (<0.1%) Fatal Major Bleed at day 35: R: 7 (0.2%) E: 1 (<0.1%)	ARI: 1.6 NNH: 63 ARI: 2.4% NNH: 42 NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: Double-blind, double-dummy design helps to minimize risk of bias. Detection: Outcomes were assessed by centra adjudication committee that was unaware of treatment assignment. Attrition: 17-25% of patients excluded from mITT analysis due to lack of venography. **External Validity:** Recruitment: Patients were from 556 sites in 52 countries. Patient Characteristics: Similar baseline characteristics. Patients were elderly and predominately white. Outcomes: Clinical relevance of asymptomatic VTE is unknown.

		other anticoagulants or compression devices.			R: 19 (0.6%) E: 30 (1.0%)	NA			
RE-COVER II[7]									
Shulman et al. RCT, DD, DB 31 Countries	1. Dabigatran 150 mg twice daily (D) 2. Warfarin (W) – adjusted to INR of 2-3 * Patients in both groups previously treated with LMWH or unfractionated heparin for 5-11 days	Median Age: 55 years Male: 39% <u>Inclusion:</u> Patients 18 or older with acute, symptomatic, objectively verified proximal DVT of the legs or pulmonary embolism whom 6 mo. of anti-coagulation was deemed appropriate. <u>Exclusion:</u> Symptoms >14 days, PE with hemodynamic instability or requiring thrombolytics, additional warfarin indication, high risk of bleeding, unstable CV disease, and renal and liver abnormalities.	1.1279 2.1289	Tx duration: 6 months	<u>Recurrent Symptomatic VTE or death due to VTE:</u> D: 30 (2.3%) W: 28 (2.2%) HR: 1.08 (95% CI 0.64 to 0.1.80 P<0.001 for non-inferiority) <u>Symptomatic DVT:</u> D: 25 (2.0) W: 17 (1.3) HR: 1.48 (95%CI, 0.80 to 2.74) <u>Symptomatic nonfatal pulmonary embolism:</u> D: 7 (0.5) W: 13 (1.0) HR: 0.54 (95% CI 0.21 to 1.35) <u>Death:</u> D: 25 (2) W: 25 (1.9) HR: 0.98 (95% CI, 0.56 to 1.71)	NA NA NA NA	<u>Major Bleeding:</u> D: 15 (1.2%) W: 22 (1.7%) HR: 0.69 (95% CI 0.36 to 1.32) <u>Major or clinically relevant non-major bleeding:</u> D: 64 (5%) W: 102 (7.9%) HR: 0.62 (95% CI 0.4 to 0.84) <u>Any Bleeding:</u> D: 200 (15.6%) W: 285 (22.1%) HR: 0.67 (95% CI 0.56 to 0.81) <u>Dyspepsia:</u> D: 11 (1.0%) W: 3 (0.2%) <u>Acute Coronary Syndrome</u>: D: 4 (0.3%) W: 2 (0.2%) <u>Event Leading to Drug Discontinuation:</u> D: 100 (7.8%) W: 100 (7.8%) HR: 1.00 (95%CI 0.76 to 1.32)	NS NS NS	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized via interactive, computerized voice-response system and computer-generated randomization scheme. Performance: Double-blind, double-dummy design minimize risk of bias. Interactive voice-response system provided true or sham INR values. Detection: Outcomes were assessed by centra adjudication committee that was unaware of treatment assignment. Attrition: 17-25% of patients excluded from mITT analysis due to lack of venography. **External Validity:** Recruitment: Patients were from 208 sites in 31 countries. Patient Characteristics: Similar baseline characteristics except for a higher percent of dabigatran treated patients had prior history o VTE. Majority (66%) from Europe and North America. TTR for warfarin treated patients wa 56.9%. Outcomes: Clinical relevance of asymptomatic VTE is unknown.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.

[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, DVT- deep vein thrombosis, PE-pulmonary embolism, VTE- venous thromboembolism.

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Appendix 1: ADVANCE Studies

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:
Mortality
Thromboembolic events (DVT, PE, stroke)
Cardiovascular events
Bleeding

Primary Study Endpoints:
Recurrent VTE, clinically relevant bleeding
Mortality
Clinically relevant bleeding

Evidence Table

ADVANCE-1[7]								
1. Apixaban 2.5 mg twice daily* 2. Enoxaparin 30 mg every 12 hours* * Treatment started 12-24 hours post surgery	Mean Age: 66 years Female: 60% Inclusion: Patients ≥ 18 years of age scheduled for TKR on one or both knees. Exclusion: active bleeding, contraindications to anticoagulation, required ongoing anticoagulation or antiplatelet therapy, uncontrolled hypertension, active hepatobiliary disease, significant renal disease and contraindications to venography.	1. 1599 2. 1596	Mean Treatment: 11 days Mean start of medication: 20 hours	Composite of asymptomatic and symptomatic DVT, non-fatal PE or death from any cause: A: 104 (9.0%) E: 100 (8.8%) RR 1.02 (95% CI 0.78 to 1.32, p=0.06 for noninferiority) Symptomatic VTE and VTE related death: A: 19 (1.2%) E: 13 (0.81%) RR 1.46 (95% CI 0.72 to 2.95) All PE: A: 16 (1.0%) E: 7 (0.4%) Mortality: A: 3 (0.2%) E: 3 (0.2%)	NS NS NS	Major Bleeds: A: 11 (0.7%) E: 22 (1.4%) Risk Difference: -0.81 (95% CI -1.49 to 0.14, p=0.05) Major or clinically relevant non-major bleeding: A: 46 (2.9%) E: 68 (4.3%) Risk Difference: -1.46 (95% CI, -2.75 to 0.17, p=0.03)	NA NA	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via central, interactive telephone system. Well matched baseline characteristics. Performance: Use of double-blind, double-dummy design was used to minimize bias. Detection: Outcomes assessment done by blinded, independent central adjudication committee. Attrition: There was a high level of attrition (~30%) which was similar between groups and characteristic for studies dependent upon venography for primary outcome rates. **External Validity:** Recruitment: Included patients from 14 countries and 129 sites. Patient Characteristics: Most patients were white (95%), from North America and under went unilateral knee replacement. Mean hospital stay was 6 days. Outcomes: Use of composite outcomes can overestimate treatment effect. Endpoints were driven mostly by asymptomatic events, which clinical relevance is still unknown.
ADVANCE-2[8]								
1. Apixaban 2.5 mg twice daily (started	Mean Age: 66.5 years Female: 71.5%	1. 1528	Mean treatment: 12 days	Composite of asymptomatic and symptomatic DVT, non-		Major Bleeds A: 9 (0.6%) E: 14 (0.9%)	NS	**Study Rating: Good** **Internal Validity: RofB**

12-24 hours post surgery) 2. Enoxaparin 40 mg once daily (started 12 hours before surgery)	Inclusion: Patients ≥ 18 years of age scheduled to have unilateral or bilateral elective knee replacement, including revision. Exclusion: Same as above.	2. 1529		<u>fatal PE and all-cause death:</u> A: 147 (15.1%) E: 243 (24.4%) RR: 0.62 (95% CI 0.51 to 0.74, p<0.0001 for superiority) <u>Symptomatic VTE or VTE-related death:</u> A: 7 (0.46%) E: 7 (0.46%) RR: 1.00 (95% CI 0.35 to 2.85) <u>All PE:</u> A: 4 (0.26%) E: 0 (0%) Mortality: A: 2 (0.13%) E: 0 (0%)	ARR: 9.3% NNT: 11 NA NA	P= 0.30 Absolute Risk Difference: -0.33% (95% CI -0.95 to 0.29, p=0.301) <u>Major or clinically relevant non-major bleeding:</u> A: 53 (3.5%) E: 72 (4.8%) Absolute Risk Difference: -1.24% (95% CI -2.66 to 0.18, p=0.088)	NS	Selection: Patients randomized via an interactive, central telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. The European dosing regimen of enoxaparin 40 mg daily was used as the comparator. Detection: Outcome assessment done by assessors blinded to treatment assignment. Attrition: Approximately 35% of patients in both groups were not included in primary efficacy analysis. This rate is consistent with other studies with a similar design, however, higher than projection of 30%. **External Validity:** Recruitment: Patients were recruited from 27 countries and 125 sites. Patient Characteristics: Patients were recruited from non-US sites and majority of patients were white females. Mean hospital stay and treatment duration was 12 days, therefore, majority of drug treatments were done as an inpatient. Outcomes: Use of composite outcomes may overestimate treatment benefit. More clinically relevant symptomatic VTE rates were the same, however, trial was not powered to determine superiority.
ADVANCE-3[9]								
1. Apixaban 2.5 mg twice daily (started 12-24 hours post surgery) 2. Enoxaparin 40 mg every 24 hours (started 12 hours before surgery)	Mean Age: 60 yrs. Female: 52% Inclusion: Patients ≥ 18 years of age scheduled for elective total hip replacement or revision of previous inserted hip prosthesis. Exclusion: active bleeding, contraindications	1. 1949 2. 1917	Mean treatment duration: 34 days	<u>Composite of asymptomatic or symptomatic DVT, non-fatal PE or all-cause mortality:</u> A: 27 (1.4%) E: 74 (3.9%) RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority) <u>Symptomatic VTE and VTE-related death:</u> A: 4 (0.1%)	ARR: 2.5% NNT: 40 NS	<u>Major Bleeds</u> A: 22 (0.8%) E: 18 (0.7%) Absolute Risk Difference: 0.1 (95% CI -0.3 to 0.6, p=0.54) <u>Major or clinically relevant non-major bleeding:</u> A: 129 (4.8%) E: 134 (5.0%) Absolute Risk Difference: 0.2 (95% CI -1.4 to 1.0 p=0.72)	NS NS	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via an interactive telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. Detection: Blinding of outcome assessors was not described. Attrition: There were 28% of apixaban treated patients and 29% of enoxaparin treated patients that had venograms that could not be evaluated and were excluded from the analysis.

	to anticoagulation or required ongoing anticoagulation or antiplatelet therapy.			E: 10 (0.4%) RR: 0.40 (95% CI 0.01 to 1.28, p=0.11) <u>All PE:</u> A: 0 (0%) E: 4 (0.2%) Mortality: A: 3 (0.1%) E: 1 (<0.1%)				**External Validity:** Recruitment: Patients were recruited from 21 countries and 160 sites. Patient Characteristics: Patients were predominately white and primarily treated in Europe and North America. Mean hospitalization days were 9. Outcomes: Use of composite outcomes may overestimate treatment benefit.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, DVT- deep vein thrombosis, PE-pulmonary embolism, VTE- venous thromboembolism.

APPENDIX 2:
Suggested PA Criteria

Oral Direct Factor Xa Inhibitors (Rivaroxaban and Apixaban)

Goal(s):

- Promote safe and effective use of oral direct factor Xa inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
What diagnosis is the factor Xa being prescribed for?	Record the ICD9 code:	
1. Does the patient have a diagnosis requiring short-term (<45 days) anticoagulation (i.e. total knee replacement: ICD9 - 81.54 or 81.55) or total hip replacement: ICD9 – 81.51 or 81.52)?	**Yes**: Go to #2	**No:** Go to #3
2. Will the prescriber consider a change to a preferred product LMWH?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Approve for up to 35 days.
3. Does the patient have a diagnosis of nonvalvular atrial fibrillation (ICD9 – 427.3x)?	**Yes:** Go to #4	**No:** Go to #7
4. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #5

5. Is the patient unable to tolerate the preferred oral anticoagulants due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Go to # 6	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
6. Is the request for the second line agent, apixaban?	**Yes:** Approve for 1 year.	**No:** Deny with the allowance of a 14 days of rivaroxaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of apixaban.
7. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #8	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*.
8. Will the prescriber consider a change to a preferred anticoagulant?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #9
9. Is the patient unable to tolerate the preferred anticoagulant due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.

***** Patients switching from rivaroxaban or apixaban to other anticoagulants have been shown to have an increased risk of thrombotic events. Adequate anticoagulation is recommended during the switch from rivaroxaban or apixaban to another anticoagulant. Rivaroxaban and apixaban effect INR measurements, therefore, the appropriate dose of warfarin based on INR can not be used. Adding a parenteral anticoagulant, in addition to warfarin, at the time the next dose of rivaroxaban or apixaban is due is recommended.

P&T Action: 7/24/14 (KS), 3/28/13 (KS), 8/30/12 (KS), 1/26/12(KS)
Revision(s):
Initiated: 4/9/12

Oral Direct Thrombin Inhibitors (Dabigatran)

Goal(s):

- Promote safe and effective therapies for oral direct thrombin inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes:** Go to #2	**No:** Go to #6
2. Will the prescriber consider a change to a preferred product warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #3
3. Is the patient unable to take warfarin therapy due to one of the following: - unstable INR - warfarin allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects	**Yes:** Go to #4	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.

4. Does the patient have normal renal function (CrCl >30 mL/min) and is prescribed dabigatran 150mg twice daily or reduced renal function (CrCl 15-30 mL/min) and is prescribed dabigatran 75mg twice daily?	**Yes:** Go to #5	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
5. Does the patient have a mechanical prosthetic heart valve?	**Yes:** Deny (Contraindicated)	**No:** Approve for up to 1 year.
6. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #7	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
7. Will the prescriber consider a change to the preferred anticoagulant?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #8
8. Is the patient unable to tolerate the preferred anticoagulant due to one of the following: - unstable INR - allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
***** Patients switching from dabigatran to other anticoagulants have been shown to have an increased risk of thrombotic events. Adequate anticoagulation is recommended during the switch from dabigatran to another anticoagulant. Dabigatran can increase INR measurements. See package insert for dosing recommendations.		

DUR Board Action: *7/24/14 (KS), 3/28/13(KS), 1/26/12(KS)*
Revision(s):
Initiated: *1/26/12 (KS)*

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Oregon Health Authority

Abbreviated Class Update: Antiplatelet Drugs

Month/Year of Review: July 2014 **End date of literature search:** April 2014
New drug(s): vorapaxar (Zonitivity™) **Manufacturer:** Merck

Current Status of PDL Class:

- Preferred Agents: ASPIRIN, CLOPIDOGREL, DIPYRIDAMOLE, DIPYRIDAMOLE ER 200MG/ASPIRIN 25MG (D-ER/ASA)
- Non Preferred Agents: TICAGRELOR, PRASUGREL, TICLOPIDINE

Research Questions:

- Is there new comparative evidence that antiplatelet drugs differ in effectiveness for adult patients with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack (TIA), or symptomatic peripheral arterial disease (PAD)?
- Is there any new evidence that antiplatelet drugs differ in harms for adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease?

Conclusions:

- There is no new comparative effectiveness evidence for clopidogrel, prasugrel, ticagrelor ticlopidine, aspirin, dipyridamole or D-ER/ASA.
- There is moderate quality evidence that vorapaxar produces lower rates of a composite of cardiovascular (CV) deaths, myocardial infarction (MI) or stroke at 3 years versus placebo when added to standard antiplatelet therapy for secondary prevention in patients experiencing a stroke, PAD or MI patients who have not undergone percutaneous coronary intervention (PCI) (HR 0.87 95% CI 0.80 - 0.94, ARD 1.1%, NNT 91). Significance was driven primarily by the MI component (HR 0.83 95% CI 0.74 – 0.90, ARD 0.8%, NNT 125). There is moderate quality evidence that vorapaxar does not prevent cardiovascular complications in patients with unstable angina or non-ST elevated MI (UA/NSTEMI).
- There is no new comparative safety evidence for clopidogrel, prasugrel, ticagrelor ticlopidine, aspirin, dipyridamole or D-ER/ASA.
- There is moderate quality evidence that vorapaxar increases moderate to severe bleeding rates at 3 years compared to placebo (HR 1.35 95% CI 1.16 -1.58, ARD 1.6%, NNH 63). The trial was stopped 6 months early because of more hemorrhagic stroke for vorapaxar (HR 2.73 95% CI 1.22 – 6.14, ARD 0.2%, NNH 500).

Recommendations:

- Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit for multiple indications (Coronary Artery Disease [CAD], ACS, stroke and PAD).
- Evaluate other antiplatelet drugs in executive session for potential inclusion.

Reason for Review:
Two new drugs have been reviewed by the FDA (vorapaxar in January 2014 and cangrelor in February 2014) and a new Drug Effectiveness Review Project (DERP) scan of the literature was published.[1]

Previous P&T Conclusions (November 2011[2,3]):

- There was high strength evidence prasugrel reduced target-vessel revascularization more than clopidogrel at 15 months in patients with acute coronary syndrome (ACS) undergoing revacularization (HR 0.66 95% CI 0.54 – 0.81). There was moderate-high strength evidence of no significant differences between prasugrel and clopidogrel in the most important effectiveness outcomes of all-cause mortality (HR 0.95 95% CI 0.78 – 1.16) and cardiovascular mortality (HR 0.89 95% CI 0.70 – 1.12). There was moderate evidence of ticagrelor superiority over clopidogrel for all-cause mortality (HR 0.78 95% CI 0.69-0.89) and cardiovascular mortality (HR 0.79 95% CI 0.69 – 0.91) but concerns regarding a lack of benefit in the United States arm of the study.
- There was moderate strength evidence of more major bleeding with prasugrel than clopidogrel (RR 1.32 95% CI 1.03 – 1.68). There was moderate evidence of no difference in major bleeding with the use of ticagrelor versus clopidogrel (RR 1.04 95% CI 0.94-1.13).
- There was no evidence of effectiveness for prasugrel or ticagrelor for other indications (i.e. secondary stroke prevention, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

Background:
Antiplatelet drugs are recommended to prevent cardiovascular events and premature death in patients who have experienced Acute Coronary Syndrome (ACS), transient ischemic attacks (TIA), thromboembolic stroke, MI or symptomatic peripheral arterial disease (PAD).[4] The FDA approved indications are represented in Table 1 below.

Table 1 – FDA Approved Indications

	2° Stroke	2° PAD	2° MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

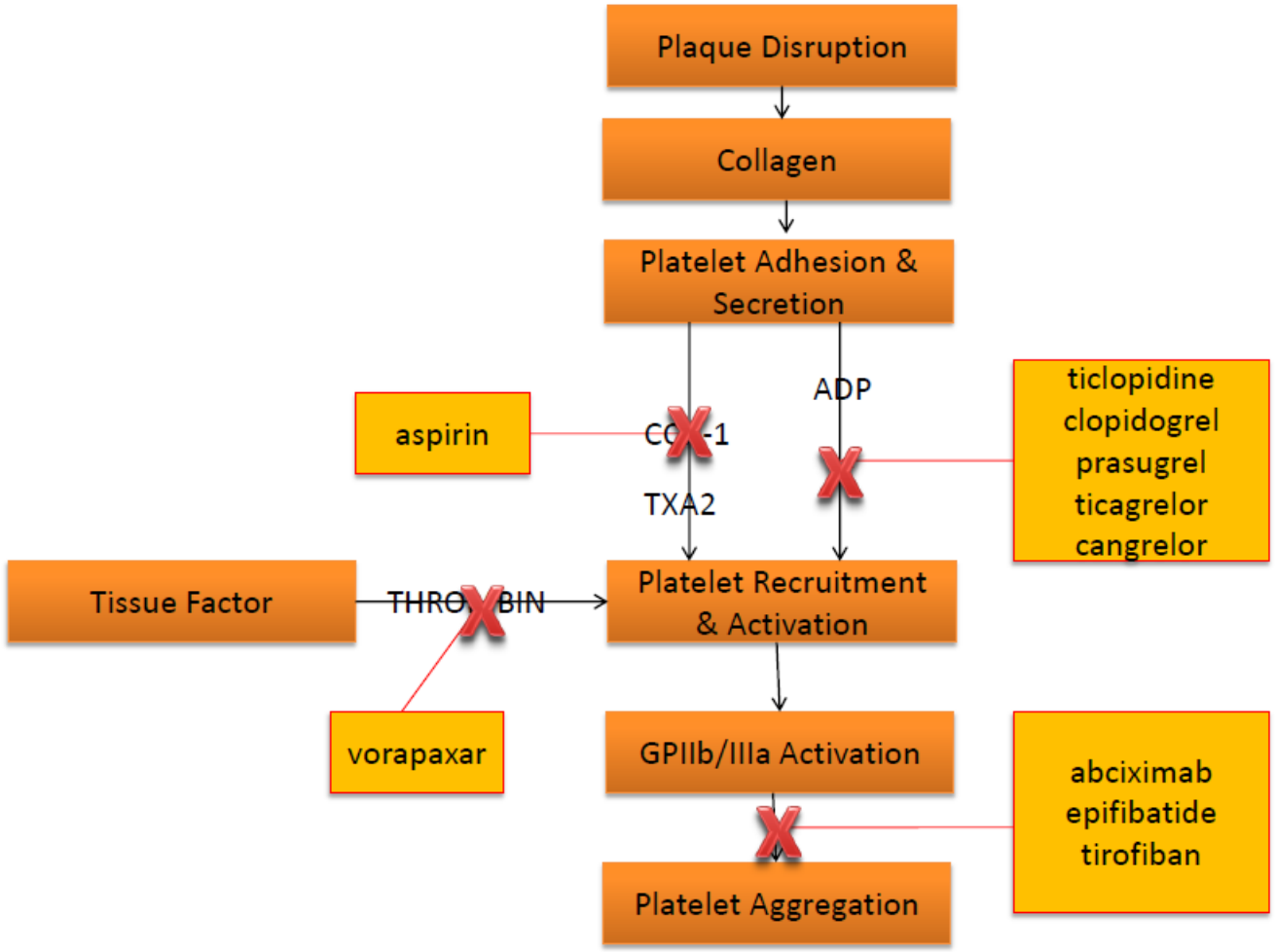
X = FDA indicated; CI=contraindication; ACS=Acute Coronary Syndrome; PCI=Percutaneous Intervention

Figure 1 below is adapted from Goodman and Gilman and identifies the site of action of the various antiplatelet drugs.[5] Ticlopidine, clopidogrel, and prasugrel irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Ticlopidine causes rare, but serious, neutropenia and is rarely prescribed. Clopidogrel, is the only generically available $P2Y_{12}$ inhibitor but is limited by a slower onset of action, incomplete platelet inhibition and poor response in some patients. Cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Cangrelor is a new rapid acting injectable intended for percutaneous interventional (PCI) use and will not be covered in this review. Vorapaxar is a new selective antagonist of the protease-activated receptor-1 (PAR-1), the primary thrombin receptor and, a novel site of action.

The multiple guidelines for treatment of CAD recommend aspirin 75-162mg daily for all patients[6,7,8] and clopidogrel 75mg daily as an alternative for patients intolerant to aspirin.[7,8] Dual antiplatelet therapy ($P2Y_{12}$ inhibitor plus aspirin) is recommended for ACS.[6,9] The recommendation of which $P2Y_{12}$ inhibitor to use in various ACS patient types is evolving and varies depending on the guideline source interpretation of the PLATO trial.[10]

Either aspirin (50-325mg) or D-ER/ASA is recommended over anticoagulants for secondary non-cardioembolic stroke prevention.[6,11] Clopidogrel is an option for aspirin intolerant patients. Aspirin 75-325mg daily or clopidogrel 75mg daily is recommended for symptomatic PAD patients to reduce the risk of myocardial infarction, stroke or vascular death.[6,12] Neither prasugrel or ticagrelor have evidence to support their use for PAD or stroke patients.[2,3]

Figure 1: Sites of action of antiplatelet drugs adapted from Goodman & Gilman[5]



Methods:
The DERP scan searched Ovid MEDLINE from September 2012 to January 2014 for new systematic reviews and randomized controlled trials (RCTs) comparing any of the antiplatelet agents.[1] An additional search through April 2014 was done. Agency for Healthcare Research and Quality (AHRQ),[13] Cochrane Collection, National Institute for Health and Clinical Excellence (NICE),[14] Department of Veterans Affairs, Clinical Evidence, Up To Date,[15,16] Dynamed,[4] and the Canadian Agency for Drugs and Technologies in Health (CADTH)[17] resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
The DERP Scan[1] tabulated the potentially relevant new RCTs by drug comparison and population. Important RCTs identified and not included in other systematic reviews were the TRILOGY ACS trial comparing prasugrel to clopidogrel for ACS without revascularization and the TRACER[18]and TRA 2P[19] placebo controlled Phase III trials for vorapaxar. They will be reviewed in detail below. The other trials are summarized in Appendix 2.

Acute Coronary Syndrome
UpToDate recommends ticagrelor or prasugrel over clopidogrel for NSTEMI or STEMI ACS patients who have had PCI and ticagrelor in patients without PCI except when patients are at high risk for bleeding or concurrent fibrinolytic therapy is used and then clopidogrel is recommended.[15,16]

AHRQ published a comparative effectiveness review of antiplatelet and anticoagulant treatments for UA/NSTEMI.[13] It included an extensive literature search through July 2012 and all publications were subject to quality assessments. Both prasugrel and ticagrelor were superior to clopidogrel after 1 year in terms of reduction of composite ischemic endpoints based upon moderate strength of evidence from the TRITON-TIMI 38[20] and PLATO[10] trials. Only prasugrel showed an increase in major bleeding events and it was only studied in patients who had PCI. High strength evidence supports the use of dual antiplatelet therapy for 6 months to one year reduces rates of composite ischemic outcomes but there is insufficient evidence to recommend short-term over long-term therapy. The findings are mixed for composite ischemic events for proton-pump inhibitor use with antiplatelet therapies based on low strength evidence.

CADTH summarized the evidence for clinical effectiveness, cost effectiveness and recent guidelines for clopidogrel, prasugrel and ticagrelor in adults with ACS.[17] The literature search extended from January 2007 thru May 2012 and was limited to RCTs, systematic reviews, technology assessments, meta-analyses, economic evaluations and guidelines that were appraised for quality. Aspirin plus clopidogrel was found to reduce the risk of CV events and was cost-effective compared to aspirin alone in ACS patients with UA/NSTEMI or STEMI whether clinically managed or revascularized. Prasugrel (TRITON-TIMI 38[20]) and ticagrelor (PLATO[10]) were more effective than standard clopidogrel doses but with a higher risk of bleeding. It was noted that the PLATO[10] trial had no difference for the composite primary outcome in the North American subpopulation and was theorized this was due to higher aspirin doses but that this hypothesis has yet to be proven. CADTH authors concluded that clopidogrel and aspirin remain the recommended therapy for ACS patients but that ticagrelor or prasugrel may be considered in STEMI patients you have not received antiplatelet therapy prior to arrival in catheterization lab or high risk NSTEMI patients where quick onset of action is a concern.

Stroke

A recent meta-analysis investigating the effectiveness of combination clopidogrel and aspirin therapy compared to aspirin alone for stroke prevention concluded it reduced the risk of total stroke without increasing the risk of intracranial hemorrhage.[21] In the overall population, those with CV disease with or without previous CV events, 2.2% of aspirin patients and 1.8% of combination therapy patients experienced a stroke at a median of 12 months of follow-up (RR 0.80; 95% CI 0.73-0.88; I^2=28% for 10 RCTs, n=93405).[21] For the secondary stroke prevention cohort, data from 7 RCTs, 13237 patients and 12 months of follow-up found 9.2% of aspirin patients and 7.0% of combination therapy patients experienced a stroke (RR 0.76; 95% CI 0.68-0.86, I^2=0%).[21] However, the result of this review need to be interpreted cautiously as explicit RCT quality assessment was not reported. Intracranial bleeding was evaluated but other safety outcomes such as all-cause mortality and other bleeding outcomes were not. Intracranial bleeding was also sometimes included in the composite total stroke outcome of included studies.

New Guidelines:

Acute Coronary Syndrome

NICE recommends ticagrelor as a treatment alternative to clopidogrel post MI for up to 12 months.[14] This was based upon a technology assessment of ticagrelor that estimated a cost less than £10,000 per Quality Adjusted Life Year gained over clopidogrel for the treatment of ACS.[22]

The American College of Chest Physicians published their 9th edition of antithrombotic therapy which incorporated prasugrel and ticagrelor recommendations.[6] They recommend ticagrelor over clopidogrel for patients the first year after ACS (2B recommendation based upon unclear or close risk/benefit balance and moderate quality evidence) and recommend against prasugrel for patients less than 60kg, over 75 years old or with a previous stroke history. Patients undergoing elective PCI and stent placement are recommended clopidogrel plus aspirin for 6-12 months.

The American Heart Association/ American College of Cardiology Foundation (AHA/ACCF) gives all three $P2Y_{12}$ inhibitors equal weight for ACS with or without stent placement but recommends avoiding prasugrel in patients with a history of stroke or TIA (IIIB recommendation –harmful treatment based upon a single randomized controlled trial).[7]

The European Cardiology Society recommends ticagrelor for all ACS NSTEMI patients at moderate to high risk of ischemic events (Level B – single RCT).[23] Prasugrel is recommended for patients who are naïve to $P2Y_{12}$ inhibitors and known to be progressing to PCI (Level B – single RCT). Clopidogrel is recommended for patients not able to receive either ticagrelor or prasugrel (Level A).

Noncardioembolic Ischemic Stroke or Transient Ischemic Attack

The AHA/ACCF published updated guidelines for secondary prevention of stroke on May 1, 2014.[11] The update includes a new recommendation to consider a dual antiplatelet therapy with aspirin and clopidogrel within 24 hours of a minor ischemic stroke or transient ischemic attack (TIA) (Level B). This recommendation is based upon the results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial which enrolled patients within 24 hours of a minor ischemic stroke or TIA.[24] Patients were assigned aspirin plus clopidogrel or aspirin plus placebo for 90 days. There were fewer primary outcomes of ischemic or hemorrhagic stroke in the combination group (8.6%) compared to the aspirin group (11.7%) [HR 0.68; 95% CI 0.57 - 0.81].[24] Rates of bleeding were similar.[24] Additionally, Level C evidence highlights the uncertainty of adding antiplatelet therapy to vitamin K antagonist for patients with a history of ischemic stroke, transient ischemic attack, atrial fibrillation or CAD.[11]

Peripheral Artery Disease

The AHA/ACCF recommends aspirin or clopidogrel daily for symptomatic PAD.[7,12] Combination aspirin and clopidogrel may be considered for patients with symptomatic lower extremity PAD who are at perceived high CV risk (Level B evidence).[12] Antiplatelet therapy in asymptomatic PAD is not supported in patients with ankle-brachial indexes 0.91-0.99 (Level A evidence) and potentially beneficial in ankle-brachial indexes ≤ 0.90 (Level C evidence).

Randomized Controlled Trials:

The TRILOGY ACS[25] was a fair quality, randomized, double-dummy active control trial that evaluated whether prasugrel 10mg daily was superior to clopidogrel 75mg daily for UA/NSTEMI patients 75 years old or younger and selected for medical management. The median duration of exposure to a study drug was 14.8 months (interquartile range, 8.2 to 23.6). All patients were on concurrent daily aspirin. Median follow-up time was 17 months. The Kaplan-Meir (K-M) hazard ratio (HR) at 30 months for the composite outcome of CV death, MI or stroke was 0.91 95% CI (0.79–1.05). Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening (not CABG related) K-M HR at 30 months was 0.94 95% CI (0.44 – 1.99). Prasugrel did not significantly reduce the primary endpoint compared to clopidogrel and the bleeding rates were similar.

New FDA Safety Alerts:

Aspirin

May 2, 2014[26]: Use of Aspirin for Primary Prevention of Heart Attack and Stroke

"The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke."

Clopidogrel:

December 2013[27]: Thienopyridine Cross - Reactivity

"Hypersensitivity including rash, angioedema or hematologic reaction has been reported in patients receiving Plavix, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines"

December 2011[28]: Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

"Proton Pump Inhibitors - Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix"

Prasugrel:

September 2011[29]:

"WARNINGS AND PRECAUTIONS

Hypersensitivity including angioedema has been reported in patients receiving Effient, including patients with a history of hypersensitivity reaction to other thienopyridines."

Vorapaxar New Drug Evaluation:

Vorapaxar (Zontivity™) was reviewed by the FDA Cardiovascular and Renal Drugs Advisory Committee on January 15, 2014.[30] It was approved May 8, 2014 "for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR)."[31]

The TRACER[18,32,33] trial was a good quality Phase III, placebo controlled, randomized, superiority trial that evaluated vorapaxar efficacy and safety when added to standard antiplatelet therapy to prevent cardiovascular complications in patients with UA/NSTEMI. It reported no difference between vorapaxar and placebo for the primary outcome, a composite of cardiovascular deaths, MI, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization using K-M time to event analysis at 2 years (HR 0.92 95% CI 0.85 - 1.01). Only the MI component showed a significant reduction (HR 0.88 95% CI 0.79 – 0.98, ARD 1.2%, NNT 83). GUSTO moderate to severe bleeding rates using K-M time to event analysis at 2 years were significantly higher for vorapaxar (HR 1.35 95% CI 1.16 - 1.58, ARD 1.6%, NNH 63). The trial was stopped 6 months early because of more hemorrhagic stroke for vorapaxar (HR 2.73 95% CI 1.22 – 6.14, ARD 0.2%, NNH 500). TRACER was internally valid with significant power (95%) which reduces the likelihood of β-error and strengthens the negative finding. There remains a risk of attrition bias due to the early discontinuation of the trial (69% of follow-up achieved) which means late developing differences between groups may have gone undetected. The GUSTO bleeding risk (NNH 63) was higher than the reduction in MI (NNT 83). The most generous interpretation of results suggests the benefit does not outweigh the risk. The study was limited to a subset of ACS patients and excluded those at higher risk of bleeding.

TRA2P-TIMI50[19,34,35] was a good quality Phase III, placebo controlled, randomized, superiority trial that evaluated vorapaxar efficacy and safety added to standard antiplatelet therapy for secondary prevention after stroke, PAD or in MI patients who have not undergone percutaneous coronary intervention (PCI). It reported significantly lower rates of the primary outcome, a composite of CV deaths, MI or stroke using K-M time to event analysis at 3 years for vorapaxar versus placebo (HR 0.87 95% CI 0.80 - 0.94, ARD 1.1%, NNT 91). This was driven primarily by the MI component (HR 0.83 95% CI 0.74 – 0.90, ARD 0.8%, NNT 125). GUSTO moderate to severe bleeding rates using K-M time to event analysis at 3 years were significantly higher for vorapaxar (HR 1.66 95% CI 1.43 - 1.93, ARD 1.3%, NNH 76). The trial was stopped after 2 years in patients with history of stroke due to an excess of intracranial bleeding for vorapaxar (HR 1.94 95% CI 1.39 – 2.70, ARD 0.3%, NNH 333). There was low and balanced attrition (2.1%) but high and balanced non-adherence (40%) due to the discontinuation of stroke patients. There was a median of 30 months (83%) of follow-up. The GUSTO bleeding risk (NNH=76) was higher than the reduction in the composite outcome (NNT=91). The study applicability was broadened by inclusion of several qualifying diagnoses, but notably excluded ACS patients undergoing PCI and patients at higher risk of bleeding. It reliably predicts the addition of vorapaxar to the standard antiplatelet regimens does reduce clinically relevant CV events, especially MI, but increases risk of serious bleeding, especially for those with history of stroke.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) CV-related deaths
2) MI
3) Stroke
4) Major bleeding

Primary Study Endpoints:

1) Composite of CV-related deaths, MI, Stroke
2) GUSTO moderate to severe bleeding

Study	Population	Intervention	Analysis	Results	Safety	Comments
TRACER[18,32,33] RCT, PC, PG, DB To determine whether the addition of vorapaxar to standard therapy would be superior to placebo in reducing recurrent ischemic cardiovascular events and to determine its safety profile in patients with acute coronary syndromes without ST-segment elevation.	Target Population: Patients with acute coronary syndromes within 24 hours of hospital presentation, without ST-segment elevation. Setting: - Multinational, 818 sites in 37 countries Region of enrollment: North America (26.3%), South America (6.6%), Western Europe (45.1%), Eastern Europe (11.5%), Asia (7.2%), Australia or New Zealand (3.3%) - presumably hospitals settings Inclusion criteria: >18 yo -current clinical manifestation of NSTE ACS confirmed by biomarker or EKG + 1 or more CV risk factors (>55yo; DM, previous MI, PCI or CABG, or PAD) Exclusion criteria: -PG or breast feeding -Concurrent or anticipated treatment with warfarin, oral factor Xa inhibitor, or oral direct thrombin inhibitor. -Concurrent or anticipated treatment with a potent CYP3A4 inducer or inhibitor. -an unusual susceptibility to bleeding w/in 30 days -Hx of intracranial hemorrhage, intracranial or spinal cord surgery, or a central nervous system tumor or aneurysm.	Experimental Intervention Description: V: 40mg @ randomization & at least 1 hour prior to procedure, then 2.5 mg x 1 year Control Intervention Description: P: Matching loading dose and matching daily tablets x 1 year Other Care Provided: -Investigators were encouraged to follow current practice guidelines of professional societies (i.e. ASA & clopidogrel) – add-on therapy. - stratified by intention to use a glycoprotein IIb/IIIa inhibitor (vs. none) and the intention to use a parenteral direct thrombin inhibitor (vs. other antithrombin agents). Follow-up Time: - Patients were followed until the final visit or the last assessment of end points. -Median follow-up period was 502 days (interquartile range, 349 to 667).	ITT V: 6473 P: 6471 Total: 12944 PP (Safety): V: 4628 P: 4715 Attrition: V: 336 (5.2%) P: 396 (6.1%) Total: 732 (5.7%) Non-Adherence: V: 1818 (28.1%) P: 1726 (26.7%) Total: 3544 (27%) Power: Calculated a minimum of 1900 primary events would provide a power of more than 95% to detect a 15% hazard reduction in the vorapaxar vs placebo. Power goals met with 2133 events. Trial stopped 6 months early with unplanned safety review and terminated study drug in patients with a history of stroke. Statistical Tests:	Primary Outcome: Composite of r. K-M HR @ 2 years: 0.92 95% CI (0.85–1.01) p-value: 0.07 V: 1031 (15.9%) P: 1102 (17.0%) RR: 0.94 RD: 1.1% NNT: NS Component Outcomes: Cardiovascular deaths: K-M HR @ 2 years: 1.00 95% CI (0.83–1.22) p-value:0.96 V: 208 (3.2%) P: 207 (3.2%) RR: 1.00 RD: 0% NNT: NS Myocardial infarction K-M HR @ 2 years: 0.88 95% CI (0.79–0.98) p-value: 0.02 V: 621 (9.6%) P: 698 (10.8%) RR: 0.89 RD: 1.2% NNT: 83 Stroke K-M HR @ 2 years: 0.93 95% CI (0.70–1.23) p-value: 0.61 V: 96 (1.5%) P: 103 (1.6%) RR: 0.94 RD: 0.1% NNT:NS	Withdrawals d/t ADE: V: 649 (10.0%) or (14% PP) P: 489 (7.6%) or (10.4% PP) RR 1.31 p-value: NR RD: 2.4% NNH: p NR GUSTO mod/sev bleeding: K-M HR @ 2 years: 1.35 95% CI (1.16–1.58) p-value: <0.001 V: 391 (6.1%) or (8.4% PP) P: 290 (4.5%) or (6.2% PP) RR 1.36 RD: 1.6% NNH: 63 TIMI clinically significant bleeding: K-M HR @ 2 years: 1.43 95% CI (1.31-1.57) p-value: <0.001 V: 1065 (16.5%) or (23% PP) P: 755 (11.7%) or (16% PP) RR 1.41 RD: 4.8% NNH: 21 Hemorrhagic Stroke: K-M HR @ 2 years: 2.73 95% CI (1.22 – 6.14) p-value: 0.02 V: 22 (0.3%) or (0.5% PP) P: 8 (0.1%) or (0.2% PP) RR: 3.00 RD: 0.2% NNH: 500	Overall Study Quality: **GOOD** Risk of Bias: Selection: Low- assumed computer generated randomization; allocation concealment via IVR; groups well matched at baseline. Performance: Low- described as double-blind with noted "matched placebo" Detection: Low- central committee blinded with adjudication protocols; objective outcome Attrition: Mod- Attrition was low (5.7%) and even between groups. But, non-adherence was high (27%) and median f/u was 502/650 days (77%). Used time to event analysis at 2 years to impute missing data for ITT. RR and HR are similar indicating imputed data did not significantly change results. Trial stopped 6 months early for safety. External Validity: Recruitment:. Details not provided; Recruitment from December 18, 2007, and ended on June 4, 2010. Patient Characteristics: Confirmed NSTE ACE without significant comorbidities, a likely population to be treated with vorapaxar. Excluded patients at higher risk of bleeding and those concurrent anticoagulants which exclude likely patients to be treated. Setting: multi-center, multi-national hospitals doing heart procedures. Unclear how other country demographics and treatment standards apply to US population.

	-sustained severe hypertension w/in 10days - Severe valvular heart disease - Hx of major surgery other than mentioned above or of ischemic (presumed thrombotic) stroke w/in 2 weeks - Hx thrombocytopenia w/in 30 days - active hepatobiliary disease w/in 30 days - serious illness or any condition that the investigator feels would (a) pose a significant hazard to the subject if investigational therapy were initiated -the subject's life expectancy is <24 months. - current substance abuse <u>Baseline Comparison:</u> Groups were compared on significant factors (e.g. age, race, gender, weight, CV risk factors and disease history). No factor differed by more than 0.7%.		Cox proportional-hazards model used to calculate HR and 95% CIs for event rates of time to the first occurrence of any component of the composite end points and presented as 2-year Kaplan–Meier HR.	<u>Recurrent ischemia with rehospitalization</u> <u>K-M HR @ 2 years:</u> 1.14 95% CI (0.83–1.58) p-value: 0.42 V: 79 (1.2%) P: 69 (1.1%) RR: 1.09 RD: 0.1% NNT: NS <u>Urgent coronary revascularization</u> <u>K-M HR @ 2 years:</u> 1.07 95% CI (0.88–1.31) p-value: 0.49 V: 203 (3.1%) P: 189 (2.9%) RR: 1.07 RD: 0.2% NNT:NS		<u>Intervention:</u> Patients managed with local practice standards. Unclear how other country treatment standards apply to US population. <u>Outcomes:</u> Primary composite outcome driven by MI component. Rehospitalization and revascularization components less severe than others. Multiplicity of outcomes planned for. Hemorrhagic stroke obscured by composite bleeding outcomes but composite bleeding outcomes appropriate and validated in previous studies.

Study	Population	Intervention	Analysis	Results	Safety	Comments
TRA2P-TIMI50[19,34,35] RCT, PC, DB Does vorapaxar reduce atherothrombotic events in patients with established atherosclerosis who were receiving standard therapy.	Target Population: Patients with a known history of atherosclerotic disease receiving standard therapy Setting: -1032 sites in 32 countries Inclusion: 1. At least 18 years old 2. Evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems: a. CAD: presumed spontaneous MI ≥ 2 wk but ≤ 12 m prior, or b. CVD: ischemic (presumed thrombotic) stroke ≥ 2 wk but ≤ 12 m prior, or c. PAD: history of intermittent claudication and i. An ABI of b0.85, or ii. Amputation or revascularization of the extremities secondary to ischemia 3. Able and willing to give appropriate informed consent 4. A woman of child-bearing potential who is sexually active must agree to use contraception -stopped enrolling patients with stroke or PAD when reached 15% Exclusion: 1. Clinically unstable at the	Experimental Intervention Description: Patients received Vorapaxar (2.5 mg po qd) in a blinded fashion until the end of follow-up Control Intervention Description: Patients received matched placebo po qd in a blinded fashion until the end of follow-up. -Therapy DC'd in both groups if patient needed a potent CYP3A4 inhibitor or warfarin concurrent with a thienopyridine Follow-up Time: -Primary and secondary outcomes assessed at 3 years. -Median follow up time was 30 months. Average follow up time was 18-24 months. Other Care Provided: -All concomitant medical therapy, including the use of other antiplatelet agents, was managed by the clinicians at the study sites who were responsible for the care of the patients, according to local standards of care. Stratified by qualifying diagnosis and physician's intent to administer thienopyridine.	ITT: V: 13,225 P: 13,224 Total: 26,479 PP (Safety): V: 7,818 P: 8,028 Attrition Total: 549 (2.1%) V: 272 (2.1%) P: 292 (2.2%) Non-Adherence: Total: 10603 (40%) V: 5407 (40.9%) P: 5196 (39.3%) Power Analysis: -1400 events needed 85% power to detect 15% RR difference in primary endpoint. -protocol amended and primary endpoint changed after review of TRACER study results. Multiplicity hierarchy reversed. -DSMB stopped trial at a median of 24 months of follow-up d/t excess of intracranial hemorrhage in patients with stroke Hx in the	Primary Outcome: Composite of CV death, MI or stroke K-M HR @ 3 years: 0.87 95% CI (0.80–0.94) p: < 0.001 V: 1028 (7.8%) P: 1176 (8.9%) RR: 0.88 ARR: 1.1% NNT: 91 CV Death: K-M HR @ 3 years: 0.89 95% CI (0.76–1.04) p: 0.15 V: 285 (2.2%) P: 319 (2.4%) RR: 0.92 ARR: 0.2% NNT: NS MI: K-M HR @ 3 years: 0.83 95% CI (0.74–0.93) p: 0.001 V: 564 (4.3%) P: 673 (5.1%) RR: 0.84 ARR: 0.8% NNT: 125 Stroke: K-M HR @ 3 years: 0.97 95% CI (0.83–1.14) p: 0.73 V: 315 (2.4%) P: 324 (2.5%) RR: 0.96 ARR: 0.1%	Withdrawals d/t ADEs: V: 1381 (10.4%) or (17.7% PP) P: 1299 (9.8%) or (16.2% PP) RR: 1.06 ARR: 0.6% p: NR NNH: NA GUSTO moderate or severe: K-M HR @ 3 years: 1.66 95% CI (1.43–1.93) p: <0.001 V: 438 (3.3%) P: 267 (2.0%) RR: 1.65 ARR: 1.3% NNH: 76 TIMI Clinically significant bleeding: K-M HR @ 3 years: 1.46 95% CI (1.36–1.57) p: <0.001 V: 1759 (13.3%) P: 1241 (9.4%) RR: 1.41 ARR: 3.9% NNH: 26 Intracranial bleeding: K-M HR @ 3 years: 1.94 95% CI (1.39–2.70) p: <0.001 V: 102 (0.7%) P: 53 (0.4%) RR: 1.75 ARR: 0.3% NNH: 333	Overall Study Quality: **GOOD** Risk of Bias: Selection: Low- good randomization but unclear allocation concealment; groups well matched at baseline. Performance: Low-blinding by "matched placebo". Detection: Low- central committee blinded and objective outcome. Attrition: Mod- Low attrition (2.1%) and even but very high non-adherence (40%) d/t mid-study protocol change for safety. Used time to event analysis at 3 years to impute missing outcome data. RR and HR are similar indicating imputed data did not significantly change results. Low power (85%) for primary outcome. External Validity: Recruitment:. Not described Patient Characteristics: Diverse population including positive history for atherosclerosis except those with planned PCI (a likely group to use). Patients with common co-morbidities excluded, especially those on anticoagulants & at higher risk of bleeds (common risks with treatment population). Setting: multi-center, multi-national. Unclear how foreign demographics apply to US population. Intervention: Locat treatment standards used. Unclear if standard of care similar in other countries. Outcomes:. Primary composite outcome appropriately conceived of

	time of enrollment 2. Planned coronary revascularization or peripheral intervention 3. Concurrent or anticipated treatment with warfarin, oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrollment 4. Concurrent or anticipated treatment with a potent inducer or potent inhibitor of CYP3A4 isoenzymes 5. History of a bleeding diathesis, or evidence of active abnormal bleeding within 30 d before enrollment 6. History at any time of intracranial hemorrhage, intracranial or spinal cord surgery, or a central nervous system tumor or aneurysm 7. Documented sustained severe hypertension (systolic blood pressure N200 mm Hg or diastolic blood pressure N110 mm Hg) at enrollment or within the previous 10 d 8. Severe valvular heart disease 9. History within 2 wk prior to enrollment of major surgery or ischemic stroke 10. Known platelet count b100 000/mm3 within 30 d before enrollment 11. Known active hepatobiliary disease, or unexplained persistent increase in ALT or AST activity ≥2× ULN 12. Any serious illness or any condition that the investigator feels would (a) pose a significant hazard to the subject if investigational therapy were initiated or (b) would limit the prognosis		vorapaxar group and recommended discontinuation of the drug in all patients with stroke. <u>Statistical Test for primary outcome:</u> Cox proportional-hazards model used with the study group and stratification factors at randomization as covariates. Cumulative event rates calculated with Kaplan–Meier method at 3 years.	NNT: NS		equal severity and driven by MI component. Bleeding composites validated in previous studies.

	of the subject, regardless of investigational therapy 13. Any serious medical comorbidity (eg, active malignancy) such that the subject's life expectancy is b24 m <u>Baseline Group Comparison:</u> Similar in all known demographic and prognostic factors					

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Appendix 1: Specific Drug Information[31]

CLINICAL PHARMACOLOGY

Vorapaxar is a reversible antagonist of the PAR-1 receptor. This is a novel site of antiplatelet action and thus, theoretically, a rational add-on therapy for patients needing additional antiplatelet activity. There are many other cell types that express PAR-1 receptors, including endothelial cells, neurons, and smooth muscle cells, but the vorapaxar effects in these cell types have not been evaluated.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	100%
Protein Binding	>99%
Elimination	58% of metabolized dose recovered in feces; 25% in urine
Half-Life	Multi-exponential disposition; steady-state achieved in 21 days; terminal half-life is ~8 days.
Metabolism	Metabolized by CYP3A4 and CYP2J2

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
2.08mg (equivalent to 2.5mg vorapaxar sulfate)	Oral tablets	Daily	No adjustment needed	Not recommended for patients with severe hepatic impairment due to bleeding risk.	Use not established	No Adjustment needed	B	-Use with aspirin and/or clopidogrel. There is limited experience with other antiplatelet drugs or as monotherapy. -Give without regard to food.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

BBW: Do not use in patients with a history of stroke, TIA, intracranial hemorrhage (ICH) or active pathological bleeding. Antiplatelet drugs increase the risk of bleeding, including ICH and fatal bleeding.

Contraindications:

History of Stroke, Transient Ischemic Attack (TIA), or Intracranial Hemorrhage (ICH)
Active Pathologic Bleeding

Warnings and Precautions:

Antiplatelet agents, including vorapaxar, increase the risk of bleeding, including ICH and fatal bleeding.
Strong CYP3A inhibitors increase and inducers decrease vorapaxar exposure. Avoid use with either.

Look-alike / Sound-alike (LA/SA) Error Risk Potential: NA

Appendix 2: RCTs identified by DERP Scan[1]

Table 1. New Trials of Antiplatelet Drugs in Previous Report

Study	Population	Comparison
ACS		
Wallentin 2009 (PLATO)	ACS	Ticagrelor vs Clopidogrel
Cannon, 2007 (DISPERSE-2)	non-ST-segment elevation ACS	Ticagrelor vs Clopidogrel
Roe, 2012 (TRILOGY ACS)	ACS without revascularization	Prasugrel vs clopidogrel
Coronary Revascularization		
Isshiki, 2012 (CLEAN) Japan	PCI in patients with stable angina or recent MI	Clopidogrel vs Ticlopidine
Mannacio, 2012 (CRYSSA)	Off-pump CABG patients	Clopidogrel+ASA vs ASA
Patti, 2013	Reloading clopidogrel prior to PCI	Clopidogrel vs Placebo
Stroke/TIA		
Benavente, 2012	Lacunar Infarct	Clopidogrel +ASA vs ASA
Wang, 2013	Minor stroke or TIA	Clopidogrel +ASA vs ASA
Peripheral Artery Disease		
Tepe, 2012	PAD with endovascular therapy	Clopidogrel+ASA vs ASA

Secondary publications of trials listed above or included in report previously

Study	Subgroup or Secondary Outcome	Comparison
JASAP	**Stroke**	
Uchiyama, 2011	full publication of results	ER Dipyridamole + ASA vs ASA
CHARISMA	**High risk patients**	Clopidogrel + ASA vs ASA
Berger, 2011	Bleeding and cause of mortality	
Hankey, 2011	Stroke or TIA patients	
PLATO	**ACS**	Ticagrelor vs Clopidogrel
Goodman, 2012	PPI and CV outcomes	
Becker, 2011	Bleeding risk	
James, 2010	Diabetes	
James, 2010	Renal disease	
James, 2011	Non-invasive management	
James, 2012	Stroke or TIA patients	
Mahaffey, 2011	Geographic variation	
Scirica, 2011	bradyarrhythmias	
Steg, 2010	ACS with ST-elevation	
Storey, 2011	Dyspnea events	
Storey, 2011	Pulmonary function	
Varenhorst, 2012	Factors associated with mortality	
Husted, 2012	Patients > 75 years	
Cornel, 2012	Smoking status	
Steg, 2013	Stent thrombosis	
Levin, 2013	Quality of life	
Kohli, 2013	Combined primary endpoint analysis	
Brilakis, 2013	Prior CABG	
TRITON-TIMI-38	**ACS**	Prasugrel vs Clopidogrel
Ruff, 2012	Geographic regions	
Wiviott, 2011	Standard dose vs dose by age/weight,	
Smith, 2012	Effect of timing of drug withdrawal	
TRILOGY ACS		Prasugrel vs Clopidogrel
Wiviott, 2013	Unstable angina, non-ST elevation MI with/without angiography	

Table 2. Trials of Vorapaxar

Author, Year	Indication	Outcomes
TRA 2° P-TIMI 50 Trial; N = 26,449; Follow-up 3 years		
Morrow, 2012	History of myocardial infarction, ischemic stroke, or peripheral arterial disease	Composite of cardiovascular death, myocardial infarction, or any stroke
Bonaca, 2013	PAD (subgroup)	
Morrow, 2013	Prior Ischemic Stroke (subgroup)	
Scirica, 2012	Previous myocardial infarction (subgroup)	
TRACER Trial; N = 12 944; Follow-up 16 months (mean)		
Tricoci, 2012	Non-ST-segment elevation Acute coronary syndromes	Cardiovascular death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization
Leonardi, 2013	Non-ST-segment elevation MI (subgroup)	
Phase II studies; 60 days duration with Primary outcomes = adverse events, Major and minor bleeding		
Becker, 2009	PCI	Clinically significant major or minor bleeding
Hinohara, 2012	Previous ischemic stroke	Overall incidence of adverse events
Goto, 2010	Non-urgent PCI	TIMI major and minor bleeding

Platelet Inhibitors

Goal(s):

- Approve platelet inhibitors for covered diagnoses which are supported by medical literature

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3	No: pass to RPh, Deny for OHP coverage.
3. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class.	No: Go to #4
4. Is this continuation of hospital treatment?	Yes: Approve for 30 days only and inform provider of preferred products.	No: Go to #5
5. Is the patient unable to take clopidogrel due to one of the following: • clopidogrel allergy • contraindications to clopidogrel therapy e.g. poor metabolizers of CYP2C19 (document) • drug-drug interactions e.g. omeprazole (document) • intolerable side effects (document)	Yes: Go to #6	No: Pass to RPh. Deny Recommend clopidogrel trial

Approval Criteria		
6. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	Yes: Deny (Medical Appropriateness)	No: Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other antiplatelet drugs or as monotherapy.

FDA Approved Indications (May 2014)

	2° Stroke	2° PAD	2° MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

X = FDA indicated; CI=contraindication; ACS=Acute Coronary Syndrome; PCI=Percutaneous Intervention

P&T / DUR Action: *7/31/2014 (KK); 11/17/11(KS)*
Revision(s): _____
Initiated: *4/9/12 (KS)*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
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Class Update: Asthma/COPD Medications

Month/Year of Review: July 2014
PDL Classes: Asthma Controller, Asthma Rescue, COPD
New drug(s): Anoro® Ellipta® (umeclidinium/vilanterol)

Last Oregon Review: May 2012/November 2013
Source Documents: OSU College of Pharmacy
Manufacturer: GSK/Theravance
Dossier Received: Yes

Current Status of PDL Classes:

Chronic Obstructive Pulmonary Disease (COPD):

- **Preferred Agents**: IPRATROPIUM BROMIDE HFA AER AD, IPRATROPIUM BROMIDE SOLUTION, IPRATROPIUM/ALBUTEROL SULFATE AMPUL-NEB, TIOTROPIUM BROMIDE(SPIRIVA®) CAP W/DEV, IPRATROPIUM/ALBUTEROL (COMBIVENT®) RESPIMAT
- **Non-Preferred Agents**: AFORMOTEROL (BROVANA®), FORMOTEROL (PERFOROMIST), ROFLUMILAST (DALIRESP®), INDACATEROL (ARCAPTA®) NEOHALER, ACLIDINIUM (TUDORZA®) PRESSAIR, VILANTEROL/FLUTICASONE (BREO®) ELLIPTA

Asthma Controllers and Asthma Rescue

- **Preferred Agents**: BECLOMETHASONE DIPROPIONATE(QVAR®), BUDESONIDE (PULMICORT FLEXHALER®), BUDESONIDE / FORMOTEROL FUMARATE (SYMBICORT®), FLUTICASONE PROPIONATE(FLOVENT HFA®), FLUTICASONE PROPIONATE(FLOVENT DISKUS®), FLUTICASONE/SALMETEROL(ADVAIR DISKUS®), FLUTICASONE/SALMETEROL(ADVAIR HFA®), FORMOTEROL (FORADIL®) AEROLIZER, MONTELUKAST SODIUM TAB CHEW/TABLET, SALMETEROL XINAFOATE (SEREVENT®), ALBUTEROL SULFATE SOLUTION/VIAL NEBS, PIRBUTEROL ACETATE, PROAIR® HFA, VENTOLIN® HFA
- **Non-preferred Agents**: CICLESONIDE (ALVESCO®), TRIAMCINOLONE ACETONIDE, ZILEUTON, ARFORMOTEROL, FORMOTEROL FUMARATE/EFORMOTEROL, OMALIZUMAB (XOLAIR®), INDACTEROL, MOMETASONE FUROATE (ASMANEX®) MOMETASONE/FORMOTEROL, BUDESONIDE/FORMOTEROL, MOMETASONE/FORMOTEROL (DULERA®), ZAFIRLUKAST

Research Questions:

- Is there new comparative efficacy and effectiveness in the treatment of persistent asthma or COPD?
- Is there any new comparative evidence of a meaningful difference in harms of medications used to treat persistent asthma or COPD?
- Is there any evidence that umeclidinium/vilanterol is more effective or safer than other long acting beta agonist/ long acting muscarinic agonist (LABA/LAMA) combination products in adults with COPD?
- Are there subgroups of patients in which umeclidinium/vilanterol is more effective or safer than other available treatments for the treatment of COPD in adults?

Conclusions:

- Overall findings from the DERP systematic review did not suggest that a single medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class in the treatment of persistent asthma or COPD.[1]
- There is moderate quality evidence that ICSs do not differ in their ability to control asthma symptoms, prevent asthma exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. There are no head to head trials comparing ICSs in the treatment of COPD. [1]
- For patients with COPD, results indicated that monotherapy with ICS and LABAs are similarly effective and have similar risk of experiencing any adverse event. However, there was low-strength evidence that treatment with ICS increases the risk of serious pneumonia.[1]
- Umeclidinium demonstrated a statistically and clinically significant increase in mean change from baseline in the change from baseline FEV1 relative to placebo (115 mL; 95% CI 76 to 155). There is insufficient comparative evidence demonstrating superior efficacy or safety of umeclidinium to other available agents.
- There is low quality evidence that mometasone (Asmanex®) HFA improves change from baseline mean trough FEV1 at 12 weeks versus placebo (mometasone HFA 100mg difference from placebo 0.12 L; 95% CI 0.05 to 0.2). There is insufficient evidence to determine the efficacy and safety of mometasone HFA compared to mometasone Twisthaler.
- There is moderate quality evidence that once daily umeclidinium/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the change from baseline in trough FEV1 compared to placebo (0.17 L; 95% CI 0.13-0.21; p <0.001). Trials have been short-term, and the long-term safety and efficacy of umeclidinium/vilanterol is unknown. There is insufficient evidence to determine the comparative efficacy of umeclidinium/vilanterol. There is insufficient evidence to draw conclusions about the ability of umeclidinium/vilanterol to decrease exacerbations, reduce shortness of breath, or improve quality of life.
- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain and chest pain (all ≥1% of patients and more common than with placebo.
- There is insufficient evidence for differences in subpopulations in which umeclidinium/vilanterol is more effective or safer.

Recommendations:

- Due to no evidence demonstrating clinical superiority of umeclidinium/vilanterol over current agents, recommend making it non-preferred.
- Recommend including umeclidinium/vilanterol in the prior authorization criteria to ensure it is being used appropriately and limiting to patients who have COPD (appendix 2).
- Due to no evidence demonstrating clinical superiority of safety of umeclidinium over current agents, recommend making it non-preferred.
- Due to no evidence demonstrating clinical superiority or safety of mometasone HFA over current agents, recommend making it non-preferred.
- Due to no strong comparative effectiveness of superiority between other agents, recommend comparing costs in executive session.
- Reorganize PDL classes based on drug class.

Reason for Review:
The Pacific Northwest Evidence-Based Practice Center Drug Effectiveness Review Project (DERP) published a drug class review on drugs to treat asthma and chronic obstructive pulmonary disease (COPD) in April 2014. This update will summarize findings from the DERP class review and identify other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines, as well as review the evidence for umeclidinium/vilanterol (Anoro® Ellipta®), a new drug (combination of a long acting anticholinergic and LABA) approved in December 2013 and two new formulations, umeclidinium (Incruse® Ellipta®) and mometasone (Asmanex®) HFA. Changes to the PDL pulmonary drug class classification will also be reviewed. Currently, the classes are "Asthma Controller", "Asthma Rescue" and "COPD". Many medications in these classes are used for both asthma and COPD and the classes do not reflect current use.

Previous P&T Conclusions for Asthma Controllers (May 2012):

- Inhaled corticosteroids (ICS) are recommended for adults and children with persistent asthma. ICS are considered the most potent and effective long-term control treatment. ICS have been shown to reduce the symptoms of asthma severity, improve quality of life, improve lung function, prevent exacerbations, reduce healthcare utilization, and reduce the risk of death due to asthma.
- Long-acting beta-agonists (LABA) are the preferred adjunctive therapy, when combined with an ICS, in adults and children with persistent asthma not controlled with an ICS alone. Systematic reviews and guidelines suggest the addition of LABA improve airway function, quality of life and reduce asthma symptoms and short-acting rescue inhaler use. New safety data recommends that equal consideration should be given to increasing the dose of ICS or adding a LABA in patients with uncontrolled persistent asthma. FDA labeling states that ICS/LABA combination products are indicated for patients not adequately controlled on other asthma controller medications.
- Asthma controller medications that are alternatives, but not preferred options, for patients requiring step 2 care (persistent asthma) include: cromolyn sodium, nedocromil, montelukast, zafirlukast, zileuton and theophylline.
- Anti-IgE therapy, i.e., omalizumab, is recommended for patients whom have a specific sensitivity to a relative allergen and require step 5 or 6 care (persistent asthma on high-dose ICS, LABA or montelukast +/- oral steroids).
- Additional data on the safety of LABA, especially in children, is needed to help delineate the risks and benefits of treatment.

Previous P&T Conclusions for COPD (November 2013):

- There is moderate to high quality evidence based on a very recent Cochrane review that compared to ipratropium, tiotropium results in improved lung function, fewer COPD exacerbations (OR 0.71, 95% CI 0.52 to 0.95), fewer hospital admissions (OR 0.34, 95% CI 0.15 to 0.76) and improved quality of life. There was also moderate quality evidence of no difference in all-cause mortality (OR 1.30, 95% CI 0.44 to 4.39).
- There is low quality evidence of no difference between tiotropium and LABAs in mortality (OR 0.82, 95% CI 0.60 to 1.13), and overall hospitalizations (OR 0.93, 95% CI 0.57-0.93). However, there is moderate quality evidence that tiotropium was associated with fewer COPD exacerbations compared with LABA (OR 0.86, 95% CI 0.79 to 0.93). There was insignificant evidence to conclude whether tiotropium or LABAs result in improved quality of life and insignificant evidence to compare the combination of tiotropium plus LABA with tiotropium alone
- Published trials use the surrogate marker of change in FEV1 to evaluate the efficacy of fluticasone/vilanterol, while mortality remains most desired clinical outcome. There remains insufficient evidence to determine its effects on mortality and other patient-related outcomes.

- There is moderate quality evidence that once daily fluticasone/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the weighted mean FEV1 (0-4 h post-dose) after 24 weeks of treatment compared to placebo (0.173 L, p<0.001). Trials have been short-term, and the long-term safety and efficacy of fluticasone/vilanterol is unknown.
- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pneumonia, decrease in bone mineral density, nasopharyngitis, upper respiratory tract infection, oral candidiasis and headache (all seen in ≥5% of patients).
- There is insufficient evidence for differences in subpopulations in which fluticasone/vilanterol is more effective or safer.
- There is moderate quality evidence that fluticasone/vilanterol is non-superior to fluticasone/salmeterol 250/50 ug after 12 weeks of therapy in change in FEV1 after 12 weeks.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, and limited long term effectiveness or safety evidence of aclidinium bromide compared to tiotropium.
- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and long acting agents. Choice of agent should be based on availability, cost of medication and the patient's response.

Background:

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation and increased airway responsiveness. As a result of inflammation, individuals with asthma may experience symptoms such as wheezing, difficulty breathing, or coughing. The airway obstruction which occurs with asthma is generally reversible spontaneously or with treatment. The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) asthma categories are intermittent and persistent (subdivided into mild, moderate or severe).

COPD is another chronic lung disease, characterized primarily by persistent airflow limitation. Smoking is the most common risk factor. COPD is more common over the age of 40 and is usually progressive, becoming more severe over time, and is usually associated with an increased inflammatory response to smoke and other airborne particles. Chronic inflammation may destroy lung tissue, causing emphysema, and/or lead to small airway damage and obstruction. However, the current COPD definition from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not describe emphysema and chronic bronchitis as COPD subtypes, as has been done in the past. Instead, COPD is defined as a mixture of airflow obstruction, alveolar destruction and chronic inflammation. The GOLD classification was updated to include grades A-D (A being low risk of exacerbations and D being a high risk of exacerbations) based upon a combination of clinical symptoms, most notably dypsnea, FEV1 and number of yearly exacerbations.

Many current medications available to treat persistent asthma target the inflammatory process caused by multiple inflammatory cells and mediators including lymphocytes, mast cells and eosinophils, among others. There are currently two categories of medications used for asthma treatment, controller medications and quick relief (or rescue) medications. All patients with persistent asthma should have a short-acting relief (or rescue) medication for the treatment of exacerbations and a controller medication for long-term control. Inhaled corticosteroids (ICS) are the preferred agents for long-term control in all stages of persistent asthma. Long-acting beta-2 agonists (LABAs) are agents used in combination with ICSs to obtain control in persistent asthma. The NAEPP expert panel advocates for the use of LABAs as the preferred adjunct with an ICS in individuals ≥12 years old for persistent asthma. LABAs may also be used in preventing exercised-induced bronchospasm, but are not approved or recommended for relief of acute asthma symptoms or for use as monotherapy for persistent asthma. Leukotriene modifiers can also be used to help control asthma symptoms.

Pharmacotherapy recommendations for COPD differ from those for asthma, although the drugs used overlap. Either a LABA or a long-acting anticholinergic (also known as a long-acting muscarinic agonist or LAMA) are used as first-line therapy, rather than an ICS. The GOLD guidelines recommend treatment sequencing for patients with disease of increasing severity of (1) LABA or LAMA, (2) ICS/LABA *or* LAMA, and (3) ICS/LABA *and/or* LAMA. They also include roflumilast (a phosphodiesterase-4 [PDE-4] inhibitor) as an option to prevent exacerbations, given in combination with long-acting bronchodilators as an alternative to ICS treatment. LAMA/LABA combination may be considered when symptoms are not improved with a single agent. Long-term treatment with an ICS is recommended for patients with severe and very severe airflow limitations and patients with frequent exacerbations that are not adequately controlled by a LAMA or LABA. The American College of Physicians and collaborating organizations consider evidence for combination therapy weaker than that for monotherapy and state that clinicians may consider combination therapy.

There are many drugs used in both asthma and COPD, but there are a few drugs that are only used in one of these diseases. Tiotropium (a LAMA) and roflumilast (a PDE-4 inhibitor) are approved for the treatment of COPD, but not for asthma. Leukotriene modifiers (leukotriene receptor antagonists and 5-lipoxygenase inhibitors), cromolyn sodium, nedocromil, montelukast, theophylline and omalizumab are used in the treatment of asthma only.

Many trials for asthma and COPD use a surrogate endpoint of change in FEV1 because it is highly reproducible in a majority of patients. However, FEV1 measurements do not always correlate with clinically relevant outcomes such as dyspnea, health status, exercise capacity, quality of life, exacerbations or hospitalization, and changes in lung volume can occur without concomitant changes in FEV1.[2] The American Thoracic Society/European Respiratory Society (ATS/ERS) suggests a minimally important difference of 100-140 ml is an appropriate value, although this value remains poorly defined in COPD patients.[3]

Umeclidinium/vilanterol 62.5/25 mcg is a new combination inhalation product comprised of a LAMA and a LABA and is delivered with the dry powder inhaler Ellipta®. Neither component is currently marketed as a single-ingredient inhalation product, although vilanterol is a component in fluticasone/vilanterol (Breo® Ellipta®), an ICS/LABA combination inhaler approved for use in COPD. This is the first LAMA/LABA combination product that is approved for the treatment of COPD. It is not approved for use in patients with asthma, although it may be used off-label, and carries a safety warning in patients with asthma, as LABAs increase the risk of asthma-related death.[4]

In planning for efficacy studies, the investigators planned a step-down closed statistical testing procedure a priori. This accounts for multiplicity across treatment comparisons and ensures that statistical significance is truly achieved, rather than the appearance of statistical significance through chance. A step-wise statistical testing hierarchy was used whereby (1) the highest combination dose was compared to placebo, (2) the lowest combination product was compared to placebo, (3) the highest combination was compared to each component and (4) the lowest combination was compared to each component. Each comparison had to be statistically significantly different in order for subsequent tests to have statistical significance.

Methods:
A Medline literature search was conducted for new systematic reviews and randomized controlled trials (RCTs) comparing beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, triamcinolone, mometasone, formoterol, arformoterol, salmeterol, indacaterol, montelukast, zafirlukast, zileuton, phosphodiesterase-4, roflumilast, tiotropium and aclidinium since the date of the literature search included in the DERP report (January 2014). The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, UpToDate, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and

relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches,

Systematic Reviews:
Drug Effectiveness Review Project (DERP) Report

A systematic review as performed to compare the efficacy and safety of ICSs, LABAs, leukotriene modifiers (LMs), long-acting anticholinergics, phosphodiesterase-4 inhibitors, and combination products for people with persistent asthma or COPD. [1] However, as it was a streamlined report, only direct comparisons were included. Placebo controlled trials were excluded from the review. Overall, the authors concluded that the evidence does not suggest that one medication within any of the classes is more effective or harmful than another medication.[1] Results support starting treatment for persistent asthma with an ICS, followed by the addition of a LABA as the next step. [1] In the treatment of COPD, monotherapy with ICS and LABAs are similar in efficacy and have similar risk of adverse events. [1] There is low strength evidence that treatment with ICS increases the risk of serious pneumonia and the evidence for newer medications is of insufficient or low strength for most outcomes. [1]

Inhaled Corticosteroids

Overall, efficacy studies provide moderate quality evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. [1] Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits) or quality of life outcomes. [1] There was moderate strength of evidence from 2 studies that fluticasone reduces the risk of exacerbations better than beclomethasone.[1] Long-term data (beyond 12 weeks) is lacking for most comparisons. [1] In children, head-to-head trials do not show a difference in health outcomes, but data were only available for 5 comparisons (3 systematic reviews and 7 RCTs): beclomethasone compared with fluticasone, beclomethasone compared with budesonide, budesonide compared with ciclesonide, budesonide compared with fluticasone and ciclesonide compared with fluticasone. [1]

There are no ICS products approved by the FDA for the treatment of COPD. No head-to-head trials comparing ICS with another were identified.[1]

Leukotriene Modifiers

Limited head-to-head evidence from 2 short-term (12 week) studies does not support differences between leukotriene modifiers (montelukast and zafirlukast) in ability to decrease rescue medicine use or improve quality of life in patients with asthma, although symptoms improve slightly more with zileuton than montelukast in patients in India (low quality evidence). [1] There were no head-to-head trials comparing zafirlukast to zileuton identified, or any trials in patients with COPD.[1]

LABAs

Results from 3 efficacy studies provide moderate evidence that LABAs do not differ in their ability to prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients ≥ 12 years with persistent asthma not controlled on ICSs alone.[1] In children, direct evidence is limited to 1 fair-quality trial enrolling children and adolescents age 6-17. [1] The trial reported no difference in exacerbations, quality of life, missed work, or missed school in subjects treated with formoterol compared to those treated with salmeterol.[1]

There is low quality evidence that arformoterol and formoterol are associated with similar exacerbation rates and improvements in quality of life in patients with COPD. [1] Nebulized formoterol is similar to formoterol via dry powder inhaler in its effects on exacerbations and quality of life. Formoterol and indacaterol have similar impacts on exacerbations and quality of life (low quality evidence). [1] There was a trend towards improved exacerbation and quality of life outcomes for formoterol versus arformoterol.

ICS/LABA

Overall, results from 4 large trials of up to 6 months duration provide moderate strength evidence that there is no significant difference in efficacy between fixed-dose combination treatment with budesonide/formoterol and fluticasone/salmeterol. [1] There is no statistically significant difference between the risk of exacerbations requiring oral steroids (OR 1.11; 95% CI 0.95 to 1.3) or exacerbations requiring emergency visits or hospital admissions (OR 0.74; 95% CI 0.53 to 1.03). [1] Quality of life measures specific to asthma also found no difference between these treatments.[1] Moderate strength evidence from 2 trials (12 weeks and 52 weeks) indicated no difference in asthma deteriorations (emergency visits, hospitalizations or requiring additional medicine) between mometasone/formoterol and fluticasone/salmeterol at medium doses. [1] Low strength evidence from only the 52-week study also suggests no difference between mometasone/formoterol and fluticasone/salmeterol at high doses. A single study of fluticasone/salmeterol and fluticasone/vilanterol provides low strength evidence of no difference in quality of life between the treatments. [1]

No head-to-head trials comparing 2 or more fixed-dose combination products of ICS/LABA in patients with COPD that reported efficacy or effectiveness outcomes were found. [1]

LAMAs

No reviews or head-to-head RCTs comparing LAMAs in patients with either COPD or asthma were found. [1]

ICS vs Leukotriene Modifiers

No evidence comparing ICSs with leukotriene modifiers in patients with COPD was found. [1] In patients with asthma, efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over LMs for the treatment of asthma as monotherapy for both children and adults for exacerbations and quality of life (high strength evidence).[1] Results for rescue medicine use and asthma symptoms also favored ICSs. [1]

ICSs vs LABAs

Overall, efficacy studies provide consistent evidence favoring ICSs over LABAs for the treatment of asthma monotherapy in children and adults (high strength evidence). [1] Those treated with LABAs had significantly higher odds of experiencing an exacerbation than those treated with ICSs (OR 2.12; 95% CI 1.53-2.95; 7 studies). [1] There was no statistically significant differences in measures of symptoms or rescue medicine use in the meta-analysis, although the majority of individual RCTs included in this review reported no differences or favorable results for those treated with ICSs compared to those treated with LABAs for almost all outcomes.[1] LABAs are not recommended or approved for use as monotherapy for persistent asthma. [1]

In COPD, there is low quality evidence of no difference between ICS and LABA in mortality (OR 1.17; 95% CI 0.97-1.42).[1] There is moderate quality evidence of no difference between ICS and LABA in exacerbations (OR 0.96; 95% CI 0.89-1.02) or in hospitalizations due to exacerbations (RR 1.07; 95% CI 0.91-1.26).[1]

Leukotriene Modifiers vs LABAs

There is insufficient evidence to draw any firm conclusions about the comparative efficacy of leukotriene modifiers and LABAs for uses as monotherapy for persistent asthma. [1] Neither are recommended nor approved for use as monotherapy for persistent asthma. [1]

No head-to-head trials comparing leukotriene modifiers with LABAs in COPD were identified. [1]

LABAs vs LAMAS

There is low strength evidence that step-up therapy with either tiotropium or salmeterol in patients whose asthma was not controlled by ICS alone does not differ in its effects on exacerbations or quality of life. [1] Evidence was insufficient to support conclusions about mortality and hospitalizations. [1]

In COPD, evidence for mortality is insufficient to support any conclusions about the comparative effects of tiotropium and LABAs. [1] Compared with salmeterol, there is moderate strength evidence that tiotropium is associated with fewer patients experiencing 1 or more exacerbations and low strength evidence that tiotropium and salmeterol do not differ in hospitalizations and proportions of patients with clinically significant improvement in quality of life. [1] Compared with indacaterol, there is low strength of evidence that tiotropium was associated with significantly lower proportions of patients with clinically significant improvement in quality of life, but the drugs did not differ in hospitalizations or exacerbations. [1] There is low strength of evidence that tiotropium and formoterol do not differ in exacerbations and insufficient evidence to draw conclusions about hospitalizations and quality of life. [1]

ICS vs PDE-4 Inhibitors

There is low strength of evidence that more patients taking roflumilast experienced exacerbations than did those taking beclomethasone in patients with asthma. [1] There were no trials of this comparison in COPD patients. [1]

ICS/LABA vs Higher Dose ICS

There is high strength of evidence that there is greater efficacy with the addition of a LABA to an ICS than increasing the dose of the ICS for adults and adolescents with persistent asthma. [1] There is insufficient evidence in children with asthma and no trials with this comparison in patients with COPD. [1]

ICS/LABA vs LAMA

There was no evidence of this comparison in patients with asthma.[1]

In patients with COPD, there is low strength evidence that, compared with tiotropium, fluticasone/salmeterol was associated with lower risk of mortality, higher risk of hospitalization and a lower proportion of patients with a clinically significant improvement in quality of life and no difference in effects on exacerbations. [1] There is low strength evidence that tiotropium and fluticasone/vilanterol do not differ in their effects on mortality and insufficient evidence to draw conclusions about how tiotropium and fluticasone/vilanterol compare for hospitalizations, exacerbations and quality of life.[1] For the comparison of umeclidinium

bromide/vilanterol vs tiotropium, there is low strength evidence of no statistically significant difference in risk of mortality and insufficient evidence to draw conclusions about other effectiveness outcomes. [1]

ICS/Leukotriene Receptor Antagonist vs ICS

The addition of leukotriene receptor antagonists to ICSs compared to continuing the same dose of ICS in patients with asthma resulted in improvement in rescue medicine use and a non-statistically significant trend toward fewer exacerbations requiring systemic steroids. [1] There is no apparent difference in symptoms, exacerbations, or rescue medicine use between the two groups. [1] There were some conflicting results and further research may alter the results. There was no evidence in patients the COPD for this comparison. [1]

ICS/LABA vs Leukotriene Modifier

The combination of fluticasone/salmeterol is more efficacious than montelukast for the treatment of persistent asthma.[1] No studies in patients with COPD were found for this comparison. [1]

Addition of LABA compared to Leukotriene Receptor Antagonist as Add-On Therapy to ICS

There is high strength evidence that the addition of a LABA to ICS therapy prevents exacerbations in more patients than does the addition of a leukotriene receptor antagonist to ICS therapy for adolescents and adults with persistent asthma.[1] There was high strength of evidence that the choice of a LABA versus a leukotriene receptor antagonist did not affect quality of life.[1]

Addition of LABA to ICS compared to switching ICS

There is low strength of evidence of no difference in exacerbations between fluticasone/vilanterol versus fluticasone propionate in patients with asthma. [1] There were no comparisons in patients with COPD. [1]

Subgroup Analyses-Asthma

Age: See above for specific differences in efficacy or adverse events between children and adolescents or adults. For children under 4 years of age, no head-to-head studies were found, but one study included a subgroup analysis of patients age 2 to 4. This analysis suggested more exacerbations per patient and more patients with serious adverse events for montelukast compared with budesonide, with risk differences greater among the younger patients (low strength).

Elderly: There were no head –to-head studies comparing the safety and efficacy of older adults treated with ICS. One case-control study on older adults found 2-fold increase in serious pneumonia with fluticasone compared to controls with a dose-response relationship. Budesonide had 17% increase in serious pneumonia compared to controls without a dose-response effect (low strength of evidence).

Racial groups: A trial including 63 African American and 375 Caucasian patients with COPD suggested higher risk of serious adverse events and withdrawals due to adverse events among African American patient taking aformoterol compared with formoterol, though there were few events in this small subgroup. These risk differences were not apparent among Caucasians (low strength of evidence).

Gender: One observational study suggested that the effects on montelukast compared with ICSs budesonide or fluticasone on linear growth velocity do not differ between boys and girls (low strength of evidence).

Pregnancy: No head-to-head studies were found. Budesonide is the only ICS labeled pregnancy category B; the other ICSs are category C. LABA and lower dose ICS were not associated with low birth weight, preterm birth or small for gestational age babies. Higher dose ICS increased the risk of having a low birth weight or small for gestational age baby. (Low strength of evidence)

New Guidelines:
An update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was published in January 2014.[5] Changes in pharmacologic recommendations focus around medications approved since the GOLD guidelines were first published in 2011. [5] Among long-acting anticholinergics, aclidinium and glycopyrronium appear to have a similar action on lung function and breathlessness as tiotropium but less data are available for other outcomes.[5] Combinations of a long-acting beta2-agonist and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact on patient reported outcomes is still limited. [5] There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations. [5] While there were no changes to the treatment algorithm, there is a suggestion of using two short comprehensive symptom measures (COPD Assessment Test, CAT, and COPD Control Questionnaire, CCQ) as one tool to stratify a patient into a Patient Group (A-D) in order to guide the initial pharmacologic management. [5]

New Safety Alerts, Indications:
None

New Formulations:
Umeclidinium (Incruse® Ellipta®)

Umeclidinium was approved in April 2014 for the maintenance treatment of COPD.[6] It is the same strength and in the same delivery device as umeclidinium/vilanterol (Anoro® Ellipta®) (see below).[6] Umeclidinium should be administered as 1 inhalation once daily.[6] FDA approval was based on one 24-week efficacy trial which included 698 patients with a mean age of 63, an average smoking history of 46 pack-years and 50% identified as current smokers.[6] The primary endpoint was change from baseline in trough FEV1 at Day 169 compared to placebo.[6] Umeclidinium demonstrated a statistically and clinically significant increase in mean change from baseline in the change from baseline FEV1 relative to placebo (115 mL; 95% CI 76 to 155).[6] Health-related quality of life was measured using St. George's Respiratory Questionnaire (SGRQ); umeclidinium demonstrated an improvement in mean SGRQ total score compared with placebo treatment at Day 168: -4.69 (95% CI: -7.07,-2.31).[6] There is insufficient comparative evidence demonstrating superior efficacy or safety to other available agents.

Mometasone (Asmanex®) HFA

Mometasone HFA was approved in April 2014 for the treatment of asthma.[7] It contains slightly different doses than delivered by the Twisthaler® device already on the market at 100 mcg and 200 mcg doses, compared to 110 mcg and 220 mcg contained in the Twisthaler®.[7] The safety and efficacy of mometasone HFA was demonstrated in two randomized, double-blind, placebo- or active-controlled multi-center clinical trials of 12 and 26 weeks' duration, conducted as part of a mometasone/formoterol (Dulera®) 100/5 mcg or 200/5 mcg combination product development program. [7] One trial evaluated 781 patients, of which 192 patients received mometasone HFA 100 mcg and 196 patients received placebo. [7] Patients ranged from 12 to 76 years of age, 59% were female, 72% were Caucasian, and all had persistent asthma and were not controlled on medium dose of inhaled corticosteroids prior to randomization. [7] Mean FEV1 and mean

percent predicted FEV1 were similar among all treatment groups (2.33 L, 73%).[7] The change from baseline to week 12 in the mean trough FEV1 was greater among patients receiving mometasone HFA 100 mcg than among those receiving placebo (treatment difference from placebo 0.12 L; 95% CI 0.05 to 0.2).[7]

A second trial evaluated mometasone in combination with formoterol at both doses and did not contain a mometasone-only arm [7] In order to assess the added benefit of a higher dose of mometasone in the 200 mcg mometasone product compared to the lower dose 100 mcg product, trough FEV1 at 12 weeks was compared between the combination mometasone/formoterol 200/5 mcg and 100/5 mcg treatment groups as a secondary endpoint.[7] Improvement in trough FEV1 from baseline to week 12 in patients who received mometasone/formoterol 200/5 mcg was not statistically different than among patients who received mometasone/formoterol 100/5 mcg (treatment difference: 0.05 L; 95% CI -0.02 to 0.10).[7]

New Drug Evaluation: Anoro Ellipta (umeclidinium/vilanterol)

FDA approved indications: Umeclidinium/viltanterol is a combination of an anticholinergic and LABA, indicated for the long-term, once-daily maintenance treatment of COPD.

Potential Off-label Use: Maintenance treatment of asthma

Clinical Efficacy Data:
The approval of umeclidinium/vilanterol 62.5/25 mcg was based on four 24-week studies.[8–10] The primary endpoint in all 4 studies was the trough FEV1 at day 169, intending to show the benefit of the combination product over both single ingredients. [4] These studies included patients who had a diagnosis of moderate-to-severe COPD. Results of this primary endpoint showed a statistically significant difference between umeclidinium/vilanterol at both the 125/25 mcg and 62.5/25 mcg doses over each of the respective single ingredients, with a statistically significant difference from placebo in the single ingredient arms. However, there was not a statistically significant difference between the two combination doses (0.21 L vs 0.21 L in Decramer Study 2 and 0.22 L vs 0.21 L in Decramer Study 1 for the 125/25 mcg and 62.5/25 mcg doses, respectively).[9] The 62.5/25 mcg dose was the only dose that consistently showed statistically significant differences from placebo and its component parts and was granted FDA approval.[4] Only 3 studies[8,9] included this dose; the fourth study[10] only compared umeclidinium/vilanterol 125/25 mcg to its component parts and placebo.

Donahue et al[8] compared umeclidinium/vilanterol 62.5/25 mcg with placebo and the difference in the primary endpoint (change from baseline in trough FEV1) was 0.17 L (95% CI 0.13-0.21; p <0.001), which is clinically significant. The Decramer et al[9] studies compared umeclidinium/vilanterol 62.5/25 mcg to tiotropium 18 mcg and comparative differences were 0.09 L (95% CI 0.04-0.14; p=0.006) for study 1 and 0.06 L for study 2 (statistical significance for this difference cannot be claimed as a result of the failure of the predefined testing hierarchy in the clinical trial design).[4] Interestingly, a higher-than-approved dose of the LAMA component, umeclidinium 125 mcg, was tested against tiotropium 18 mcg in Celli et al[10] and there was not a statistically significant difference in mean change from baseline in trough FEV1 at day 169 for umeclidinium compared to tiotropium (0.04 L; 95% CI -0.01 to 0.09; p-value = 0.138).

There is insufficient evidence to draw conclusions about the ability of umeclidinium/vilanterol to decrease exacerbations, reduce shortness of breath, or improve quality of life.[4] Data on exacerbation rates are not available in the published trial or on the ClinicalTrials.gov website. The FDA stated that while umeclidinium/vilanterol showed some numerical benefit in improving exacerbations over umeclidinium and vilanterol in some studies, the results were not statistically significant. [4] The FDA also stated that umeclidinium/vilanterol did not show consistent, statistically significant differences from its component parts

in reducing shortness of breath based on Shortness of Breath with Daily Activities (SOBDA) scores, a daily patient recording of shortness of breath on 13 activities related to daily living. [4] There was also a lack of data supporting a claim for improvement in St. George's Respiratory Questionnaire (SGRQ), as umeclidinium/vilanterol was only shown to meet the threshold for clinically meaningful improvement (an increase of 4 units) in SGRQ scores from baseline in 1 of the 4 pivotal efficacy trials.[4]

Clinical Safety:

Overall, the most common adverse events seen in trials are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain and chest pain (all ≥1% of patients and more common than with placebo).[4] The total incidence of adverse events was comparable across treatment groups and respiratory events were the most commonly reported. [4] Rates of patients discontinuing due to an adverse event was also comparable across treatment groups. [4] There is low quality evidence that of no statistically significant difference in rates of mortality. One unpublished 52 week trial of umeclidinium/vilanterol 125/25 mcg showed similar adverse reactions as those in the efficacy trials and rates of adverse events were low across all groups. [4]

Due to the LABA component of this combination product, the FDA has issued a safety warning for its use in patients with asthma, as LABAs have been shown to increase asthma exacerbation and asthma-related death. [4] Since COPD is a disease that occurs only in adults, umeclidinium/vilanterol has not been specifically studied in the pediatric population, and as such no safety data for this population is available. [4]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of exacerbations
3) Health-related quality of life
4) Dyspnea

Primary Study Endpoint:

1) Mean change from baseline in pre-dose trough FEV1 at day 169

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Donohue et al[8] R, DB, PC 24-weeks	A: UMEC/VI 62.5/25 mcg U: UMEC 62.5 mcg V: VI 25 mcg P: Placebo Medications allowed: inhaled albuterol as rescue medication, ICS at stable dose	Demographics: Age: 63 70% male 50% current smokers at screening 46 pack-year history Inclusion Criteria: Established COPD ≥40 years old Current/former smoker ≥10 pack-year smoking history Post-albuterol FEV/FVC <0.70 Post-albuterol FEV1 ≤70% pred MMRC score ≥2 Exclusion Criteria: Asthma or other known respiratory disorders (including α-1antitrypsin deficiency, active TB, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary HTN, interstitial lung disease); any clinically significant uncontrolled disease (including CV-related, abnormal clinically significant ECG, or 24-h Holter ECG, abnormal clinical lab finding)	3:3:3:2 randomization ITT: A: 413 U: 418 V: 421 P: 280 Attrition: A: 81 (20%) U: 94 (22%) V: 103 (24%) P: 76 (27%)	LS Mean Change from Baseline in Trough FEV1 at Day 169 (L): **A**: 0.171 VS P: 0.167 (95% CI 0.128-0.207) p-value <0.001 **U**: 0.119 Vs P: 0.115 (95% CI 0.076-0.155) p-value <0.001 **V:** 0.076 Vs P: 0.072 (95% CI 0.032-0.112) p-value <0.001 **P**: 0.004	NA	SAE: A: 21 (5%) U: 27 (6%) V: 24 (6%) P: 9 (3%) Withdrawals due to AE: A: 23 (6%) U: 34 (8%) V: 24 (6%) P: 9 (3%)	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Central randomization schedule generated using validated computerized system, patients randomized using automated, interactive telephone-based system Performance: Patients randomized using interactive telephone-based system Detection: FEV1 and FVC were obtained using standard spirometry equipment that met or exceeded the minimal ATS performance recommendations Attrition: high (23.1% overall). Withdrawals similar to other COPD trials. **External Validity:** Recruitment: No details given Patient Characteristics: Baseline characteristics were similar across all groups. Majority of patients (91%) were GOLD stage II and III. Setting: 163 outpatient centers in 10 countries Outcomes: The accepted surrogate outcome of FEV1 was used for efficacy measure. No clinically important outcomes measured, including mortality, hospitalizations, and quality of life.

Decramer 2014[9] Study 1 R, DB, AC 24-weeks	A125: UMEC/VI 62.5/25 mcg U: UMEC 62.5 mcg T: Tiotropium 18 mcg V: VI 25 mcg Medications allowed: inhaled albuterol as rescue medication, ICS at stable dose	Demographics: Age: 63 70% male 50% current smokers at screening 46 pack-year history Inclusion Criteria: Established COPD ≥40 years old Current/former smoker ≥10 pack-year smoking history Post-albuterol FEV/FVC <0.70 Post-albuterol FEV1 ≤70% pred MMRC score ≥2 Exclusion Criteria: Asthma, α-1antitrypsin deficiency, any clinically significant uncontrolled disease, significant ECG or clinical lab finding, lower respiratory tract infection or recent COPD exacerbation	ITT: A125: 214 A62.5: 212 TIO: 208 VI: 209 Attrition: A125: 41 (19%) 62.5: 31 (15%) TIO: 31 (15%) VI: 44 (21%)	<u>LS Mean Change from Baseline in Trough FEV1 at Day 169 (L):</u> **A125**: 0.209 Vs VI: 0.088 (95% CI 0.036 to 0.140) p-value <0.001 Vs TIO: 0.090 (95% CI 0.036 to 0.140) p-value <0.001 **A62.5**: 0.211 Vs VI: 0.088 (95% CI 0.036 to 0.140) p-value <0.001 Vs TIO: 0.090 (95% CI 0.036 to 0.141) p-value <0.001 **TIO:** 0.121 **VI**:0.121	NA	<u>SAE:</u> A125: 5 (2%) A62.5: 7 (3%) TIO: 13 (6%) VI: 15 (7%) Withdrawals due to AE: A125: 15 (7%) A62.5: 10 (5%) TIO: 9 (4%) VI: 10 (5%)	NS NS	**Quality Rating: Poor** **Internal Validity:** <u>Selection:</u> Randomization schedule generated using computer software. Block randomization in groups of 8 were used. Allocation controlled by telephone system. <u>Performance:</u> Double-dummy design used, however tiotropium and placebo were not identical (placebo capsules lacked markings). <u>Detection:</u> Staff involved in safety and efficacy assessments were not present during dosing in clinic. No other details given. Many secondary outcomes were rater-administered with no details on training or standardization of scores given. <u>Attrition:</u> high (17% and 23% overall). **External Validity:** <u>Recruitment:</u> No details given <u>Patient Characteristics:</u> Baseline characteristics were similar across all groups. Most were in their mid-60's, male, GOLD stage II or III, and about half used inhaled corticosteroids. <u>Setting:</u> 91 outpatient centers in 9 countries (study 1); 95 outpatient centers in 10 countries (study 2) <u>Outcomes:</u> The accepted surrogate outcome of FEV1 was used for efficacy measure. No clinically important outcomes measured, including mortality, hospitalizations, and quality of life.

Decramer 2014[9] Study 2 R, DB, AC 24-weeks	A125: UMEC/VI 125/25 mcg A62.5: UMEC/VI 62.5/25 mcg TIO: Tiotropium 18 mcg UMEC: UMEC 62.5 mcg Medications allowed: inhaled albuterol as rescue medication, ICS at stable dose	Demographics: Age: 63 70% male 50% current smokers at screening 46 pack-year history Inclusion Criteria: Established COPD ≥40 years old Current/former smoker ≥10 pack-year smoking history Post-albuterol FEV/FVC <0.70 Post-albuterol FEV1 ≤70% pred MMRC score ≥2 Exclusion Criteria: Asthma, α-1antitrypsin deficiency, any clinically significant uncontrolled disease, significant ECG or clinical lab finding, lower respiratory tract infection or recent COPD exacerbation	A125: 215 A62.5: 217 TIO: 215 UMEC: 222 Attrition: A125: 49 (23%) A62.5: 54 (25%) TIO: 39 (18%) UMEC: 57 (26%)	<u>LS Mean Change from Baseline in Trough FEV1 at Day 169 (L):</u> **A125**: 0.223 Vs UMEC: 0.088 (95% CI 0.036 to 0.140) p-value 0.142 Vs TIO: 0.074 (95% CI 0.025 to 0.123) p-value 0.003 **A62.5**: 0.208 Vs UMEC: 0.022 (95% CI -0.018 to 0.072) p-value 0.377 Vs TIO: 0.060 (95% CI 0.010 to 0.109) p-value 0.018 **TIO:** 0.149 **UMEC**:0.186		<u>SAE:</u> A125: 15 (7%) A62.5: 22 (10%) TIO: 9 (4%) UMEC: 15 (7%) Withdrawals due to AE A125: 15 (7%) A62.5: 20 (9%) TIO: 13 (6%) UMEC: 17 (8%)		**SAME AS ABOVE**

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[4]

PHARMACOKINETICS

Parameter	Result
Protein Binding	Umeclidinium: 89%, Vilanterol: 94%
Elimination	Urine (vilanterol); feces (umeclidinium and vilanterol)
Half-Life	11 hours
Metabolism	CYP2D6 (umeclidinium) CYP3A4 (vilanterol)

DOSE & AVAILABILITY[4]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Umec/VI 62.5/25 mcg	INH	1 inhalation once daily	No adjustment	No adjustment (has not been studied in severe hepatic impairment)	NA	NA	Not for the relief of acute bronchospasm or for asthma treatment Device has to be discarded 6 weeks after it is removed from the foil tray

DRUG SAFETY[4]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning: May cause an increase in asthma-related death, which is considered a class effect of LABA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with fluticasone furoate /vilanterol has been conducted.

Contraindications: Patients with severe hypersensitivity to milk proteins or hypersensitivity to umeclidinium, vilanterol or any component of the product.

REMS: none

Warnings and Precautions:

- Should not be initiated in patients during rapidly deteriorating exacerbations.

- Should not be used as a rescue inhaler
- Should not use with any other LABA-containing medication
- Caution should be exercised when considering the coadministration with known strong CYP3A4 inhibitors because vilanterol is a CYP3A4 substrate
- May cause paradoxical bronchospasm
- May produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and cardiac arrhythmias
- May cause worsening of narrow-angle glaucoma
- May cause worsening urinary retention
- May cause increase in serum glucose

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Anoro Ellipta may be confused with Breo Ellipta, Alora
Ellipta may be confused with Ella®, Ellence®, eletriptan
Umeclidinium may be confused with Umecta®, aclidinium

Appendix 2: Current PA with Proposed Changes

~~LABA/ICS~~Combination Inhalers

Goal(s):

- Approve ~~LABA/ICS~~combination inhalers only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication).
- LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).

Initiative:

- ~~LABA/ICS~~Combination Inhaler Step Therapy

Length of Authorization:

Up to 12 months

Requires PA:

- All combination ~~inhaled corticosteroid/long-acting beta-agonist~~ inhalers

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Step Therapy Required Prior to Coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at (www.orpdl.org)

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at www.orpdl.org), DO NOT require prior authorization

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to #2	**No:** Go to #4
2. Is the medication for Breo Ellipta (fluticasone furoate/vilanterol) or Anoro Ellipta (umeclidinium/vilanterol)	**Yes:** Pass to RPH; Deny (Medical appropriateness)	**No:** Go to #3
3. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days?	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy	**No**: PASS TO RPH DENY (Medical Appropriateness).

	and patient is well controlled on current dose.	
4. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** ~~Approve for 12 months.~~Go to #5	**NO:** PASS TO RPH DENY (Medical Appropriateness). Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.
5. Is the medication of Anoro Ellipta (umeclidinium/vilanterol)?	**Yes:** Got to #6	**No:** Approve for 12 months.
6. Has the patient: • failed or have contraindication to an inhaled corticosteroid OR • Is there a documentation of Stage 4 COPD	**Yes:** Approve for 12 months	**No:** PASS TO RPH DENY (Medical Appropriateness).

Roflumilast

Goal(s):

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior exacerbations.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

Appendix 4: Current PA Criteria

Asthma Controller Drugs

Goal(s):

- *The purpose of this prior authorization policy is to ensure that non-preferred asthma controller drugs are used for an above the line indication.*

Length of Authorization:
Up to 12 months

Requires PA :
- Non-preferred drugs

Covered alternatives:
Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. Is the requested drug montelukast (Singulair®)?	Yes: Go to Leukotriene Inhibitor Criteria	No: Go to #2
2. Is the request for a LABA/ICS combination product?	Yes: Go to LABA/ICS criteria	No: Go to #3
3. What is the diagnosis being treated?	Record ICD-9 Code	
4. Is this an OHP covered diagnosis?	Yes: Go to #5	NO: PASS TO RPH DENY (not covered by OHP)
5. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	Yes: Document prior therapy in PA record. Approve for 1 year.	No: Go to #6
6. Will the provider consider a change to a preferred product? Message: • Preferred products do not require a PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T Committee).	Yes: Inform provider of covered alternatives	No: Approve for 1 year or length of prescription, whichever is less.

Appendix 5: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

Karabis, A., Lindner, L., Mocarski, M., Huisman, E. & Greening, A. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis* **8,** 405–423 (2013).

BACKGROUND: Aclidinium bromide is a new long-acting muscarinic antagonist (LAMA) indicated for maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). The efficacy of aclidinium was compared with tiotropium and glycopyrronium, using a network meta-analysis (NMA) of randomized controlled trials (RCTs) in moderate-to-severe COPD patients.

METHODS: A systematic review was performed to identify RCTs evaluating aclidinium 400 µg twice daily (BID), glycopyrronium 50 µg once daily (OD), tiotropium 18 µg OD, or tiotropium 5 µg OD in adults with moderate-to-severe COPD. The outcomes of interest were: trough forced expiratory volume in 1 second (FEV1); St George's Respiratory Questionnaire (SGRQ) total score and proportion of patients achieving ≥4 unit change; Transition Dyspnea Index (TDI) focal score and proportion of patients achieving ≥1 point change. The results were synthesized by means of a Bayesian NMA.

RESULTS: Twenty-one studies (22,542 patients) were included: aclidinium 400 µg BID (three studies); tiotropium 5 µg OD (three studies); tiotropium 18 µg OD (13 studies); and glycopyrronium 50 µg OD (two studies). Regarding trough FEV1 at 24 weeks, aclidinium demonstrated comparable efficacy to tiotropium 5 µg (difference in change from baseline [CFB]), (0.02 L [95% credible interval CrI -0.05, 0.09]); tiotropium 18 µg (0.02 L [95% CrI -0.05, 0.08]); and glycopyrronium (0.00 L [95% CrI -0.07, 0.07]). Aclidinium resulted in higher improvement in SGRQ score at 24 weeks, compared to tiotropium 5 µg (difference in CFB, -2.44 [95% CrI -4.82, -0.05]); and comparable results to tiotropium 18 µg (-1.80 [95% CrI -4.52, 0.14]) and glycopyrronium (-1.52 [95% CrI -4.08, 1.03]). Improvements in TDI score were comparable for all treatments.

CONCLUSION: Maintenance treatment with aclidinium 400 µg BID is expected to produce similar improvements in lung function, health-related quality of life, and dyspnea compared to tiotropium 5 µg OD; tiotropium 18 µg OD; and glycopyrronium 50 µg OD.

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Abbreviated Class Update: Antidepressants (First and Second Generation)

Month/Year of Review: July 2014 **End date of literature search:** June 1, 2014

Current Status of Voluntary PDL Class:

- Preferred Agents: BUPROPION HCL TABLET/TABLET ER, CITALOPRAM TABLET/SOLUTION, FLUOXETINE CAPSULE/SOLUTION/TABLET, FLUVOXAMINE, MIRTAZEPINE TAB RAPDIS/TABLET, PAROXETINE TABLET, SERTRALINE ORAL CONC/TABLET, VENLAFAXINE TABLET, VENLAFAXINE ER
- Non Preferred Agents: BUPROPRION XL, DESVENLAFAXINE (PRISTIQ ER), DULOXETINE (CYMBALTA®), ESCITALOPRAM, FLUOXETINE DF (PROZAC® WEEKLY), NEFAZODONE, PAROXETINE HCL (PAXIL CR®), SELEGILINE PATCH (ENSAM®), VILAZODONE (VIIBRYD®), OLANZAPINE/FLUOXETINE (SYMBYAX®), VORTIOXETINE (BRINTELLIX®), LEVOMILNACIPRAN (FETZIMA®)

Research Questions:

- What is the comparative efficacy of first and second generation antidepressants in the treatment of major depressive disorder?
- How do first and second generation antidepressants differ in type and incidence of adverse events?

Conclusions:

- There is low quality evidence that shows there are minimal differences in efficacy between first and second generation antidepressants. While some meta-analyses show a trend towards greater improvement with TCAs compared to SSRIs, TCAs are no longer favored when only higher quality studies are considered.
- The safety profiles of antidepressants vary by class, and there is no comprehensive analysis that directly compares the rate and type of adverse events between first and second generation antidepressants. There is low quality evidence to show that SSRIs are more tolerable than TCAs, as a larger proportion of patients treated with TCAs withdrew treatment due to adverse events compared to those treated with SSRIs. MAOIs are associated with more drug-drug and food-drug interactions than any other class of antidepressants.

Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with treatment guidelines, first and second generation antidepressants should be accessible to patients, with the selection of the individual agent dependent on severity of condition, comorbidities, medication history, and tolerability of side effects for the individual patient.
- Recommend including first generation antidepressants to the voluntary PDL and evaluate costs in executive session. Consider a non-preferred status for MAOIs, given the known safety concerns including high risks of drug-drug and drug-food interactions, particularly nefazodone.

Reason for Review:
To understand where first generation antidepressants fit on the PDL. Currently, all antidepressants are available without restriction and are not subject to prior authorization. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs, such as prior authorization. Thus, the mental health PDL is strictly voluntary. Second generation antidepressants have been reviewed for clinical efficacy and safety and specific agents have been chosen as clinically preferred. The advantage of this is the elimination of a copay. Reviewing the first generation agents and adding clinically appropriate agents to the PDL would reduce the copay burden to the client, while improving access to these medications.

Previous P&T conclusions and recommendations (May 2014):
- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder.
- There is moderate quality evidence that vortioxetine is safe and effective for the treatment of major depressive disorder (MDD) based on short-term placebo-controlled trials. There is insufficient evidence to determine the most effective treatment dose.
- There is moderate quality evidence that vortioxetine is not superior to duloxetine 60 mg daily or venlafaxine XR 225 mg daily in efficacy.
- There is low quality evidence that levomilnacipran is safe and effective for the treatment of MDD based on short-term placebo-controlled trials.
- There is insufficient evidence to determine the effectiveness of either vortioxetine or levomilnacipran in the maintenance treatment of MDD, as well as in pediatric patients or patients with severe hepatic impairment.
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

Background:
The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines major depressive disorder (MDD) as having one or more major depressive episodes (MDE) and the lifetime absence of mania and hypomania. An MDE is defined as having five of nine symptoms during a two week period. To qualify as an MDE one of the following symptoms must be present (1) depressed mood or (2) loss of interest or pleasure in usual activities that lasts for ≥ 2 weeks. This coincides with other symptoms of MDD which include: significant weight loss when not dieting or weight gain, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation nearly every day, fatigue or loss of energy nearly every day, feelings of worthlessness or excessive or inappropriate guilt nearly every day, diminished ability to think or concentrate or indecisiveness nearly every day, or recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan for committing suicide. These symptoms must cause significant distress or impairment, not be attributable to a substance or medical condition, and cannot be better explained by a psychotic disorder.[1]

Depression is a very common disorder throughout the world with an estimated lifetime prevalence of 12%.[2] The lifetime prevalence in the US is estimated at 17%, which reflects the variation of the disease.[3] The average age of onset for MDD in the United States is 32 years old.[4] Women are 70% more likely to experience depression at some point in their life than men.[4] Before the late 1980s, the pharmacologic treatment of Axis I psychiatric disorders (such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual disorders) was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[5] Antidepressant medications are generally broken down in into two categories; first-generation and second generation. TCAs and MAOIs are

often referred to as traditional or first-generation antidepressants. While these medications often are effective they are associated with more side effects than the second-generations. Common side effects of TCAs include classic anticholinergic effects including dry mouth and eyes, urinary retention, and constipation. The original MAOIs are rarely used do to their potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine.[5] Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters.[5] In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then several other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, escitalopram, and vilazodone. The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine.[5] Other agents used for treatment of MDD include bupropion, levomilnacipran, mirtazapine, and nefazodone.

Due to the heterogeneity and unknown definitive cause of depression, determining successful treatment in clinical trials can be difficult. The FDA has accepted primary success as improvement between a baseline score and a post-treatment score using commonly used observer-administered depression rating scores. The most widely used observer-administered depression rating scales are the Hamilton Depression Rating Scale (HAMD), 24-item and 17-item versions (HAMD24 and HAMD17, respectively), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinician Global Impressions-Severity of Illness (CGI-S) scale. The The HAMD scores patients on a scale of 0-5 on 24 items associated with major depression. MADRS uses a range of 0-6 on 10 items associated with major depression. The CGI-S measures disease severity on a 7-point scale which scores the clinician's global assessment of the patient rather than individual aspects of the disease state. Clinically meaningful changes on these scales are not well defined, yet these scales are still considered the gold standard in clinical trials for antidepressants.

Defining consensus outcomes has been described in previous papers.[6,7] The term 'response' is used to describe a clinically significant degree of depressive symptom reduction following treatment initiation.[6,7] Those who no longer have depressive symptoms are considered to be in remission.[6] The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).[6] Trials have used various changes in depression scales to define response and remission, but the most widely accepted cutoffs for response is a ≥50% reduction from baseline (both MADRS and HAMD), and a specific threshold for remission. For the HAMD17 a score of ≤7 on the HAMD17 is widely accepted, while some argue a score of ≤5 be used, but there are differing recommendations for remission using MADRS.[7] A HAMD17 score of ≤7 corresponds to a MADRS score of ≤9, but others recommend a MADRS score of ≤5 to define remission, while most clinical trials use a score of ≤10.[7] This variance has led to disagreements in the scientific community but represents the best method for defining pharmacological treatment success.

Methods:

A Medline literature search ending June 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing first generation antipsychotics to second generation antipsychotics. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

1. Systematic Reviews/Meta-analyses:

The relative efficacy and safety of first and second generation antidepressants for the treatment of major depressive disorder were evaluated in a 2012 meta-analysis. The analysis included studies that were randomized, double-blind, placebo-controlled trials in adults with acute, apparently unipolar, major depressive episode, based on DSM-III, III-R, or –IV, ICD-9 or -10, or RDC diagnostic criteria, and had at least 20 subjects per arm.[8] Antidepressants must have been studied as a monotherapy. Trials were excluded from the review if they evaluated drugs that were not FDA-approved for the treatment of acute episodes of major depressive disorder. The primary outcome measure was 'response,' which was defined as ≥50% reduction in initial depression rating-scale scores. Ratings were typically based on the HAMD or MADRS Depression Rating Scales. When these measures were not available, scores were based on the CGI ratings.[8]

In total, 107 trials met the inclusion criteria with 27,127 total subjects (17,059 randomized to one of 19 different antidepressants, 9,925 randomized to placebo). The antidepressants studied were: imipramine, fluoxetine, venlafaxine, paroxetine, amitriptyline, duloxetine, bupropion, desvenlafaxine, sertraline, R,S-citalopram, S-citalopram, mirtazapine, selegiline, desipramine, clomipramine, nortriptyline, phenelzine, tranylcypromine, and trazodone. The frequency of studies by antidepressant types is as follows: SSRIs [52 trials (36.6%)], TCAs [38 (26.8%)], SNRIs [33 (23.2%)], atypical agents (bupropion, mirtazapine, trazodone) [14 (9.9%)], and MAOIs [5 (3.5%)].[8]

The pooled responder rate ratio (RR) for all agents was 1.42 (CI 1.38-1.48) compared to placebo. Overall, phenelzine ranked the highest in terms of efficacy, and trazodone the lowest. However in addition to tranylcypromine and clomipramine, these four drugs were ranked as outliers among the other antidepressants, as each drug only had one related study included in the meta-analysis. When only drugs with greater than one trial are considered, amitriptyline is ranked highest and bupropion the lowest. All confidence intervals overlap, indicating the need for cautious interpretation of trial data. Authors also compared classes of antidepressants using response rate ratios (RRs), and found TCAs to be the most effective, followed by SNRIs, MAOIs, SSRIs, and atypicals, in order of decreasing efficacy. For the outcome of responder rate differences, the classes were ranked in order of decreasing efficacy: TCAs, SNRIs, SSRIs, MAOIs, atypicals. Adverse events, discontinuation rates, and other safety outcomes were not included in this analysis.[8]

This comprehensive meta-analysis found that the differences between antidepressants and placebo were moderate, yet statistically significant, and that differences in efficacy among the different agents are minimal. These findings are similar to results from previous meta-analyses, but differ in that TCAs demonstrated clear statistical superiority over the other classes of antidepressants. The authors propose that this is a reflection of evolving clinical trial design that has occurred over the last three decades, including increasing size and complexity, greater heterogeneity in diagnostic and clinical assessments, inclusion of patients with less severe depression, and increasing trial length. These factors may have contributed to an increase in placebo-response rate or a decline in antidepressant-response rate, so further research is needed to determine the optimal trial design for evaluating antidepressants.

Two different meta-analyses evaluated TCAs and SSRI's for depression, specifically in the primary care setting. Each study included randomized, placebo-controlled trials using TCAs or SSRIs in adults who had a diagnosis of depression and received treatment in the primary care setting, but the studies differed in primary endpoints. In the meta-analysis by Arrol et al., the primary endpoint was the efficacy of TCAs and SSRIs in comparison with placebo, calculated using the weighted mean difference in studies where the same outcome scale was used. Where there were dichotomous outcomes, the relative risk was calculated. Patient-reported adverse events were evaluated as a secondary outcome.[9] In the meta-analysis by MacGillivray et al., the primary endpoint was the relative efficacy of TCAs compared to SSRIs, measured by the mean difference of final mean depression scores and relative risk of response using the CGI score.[10]

Arrol et al. found that both TCAs and SSRIs were statistically superior to placebo, for both continuous and dichotomous outcomes. In total, 12 studies with 2,753 participants (596 using TCAs, 890 using SSRIs, and 1,267 using placebo) were evaluated. The relative risk for improvement was 1.26 (95% CI 1.12-1.42) with TCAs

and 1.37 (95% CI 1.21-1.55) with SSRIs. The numbers needed to treat for one improved patient was 3-4 and 6, for TCAs and SSRIs, respectively. Comparative efficacy of TCAs and SSRIs was not evaluated in this analysis. The relative risk for withdrawal due to adverse events was 2.35 (95% CI 1.59-3.46) for TCAs and 2.01 (95% CI 1.1-3.7) for SSRIs with a number needed to harm range of 5-10 and 21-94, respectively. All the studies included were of short duration (6-8 weeks), and all of the SSRI studies had commercial involvement.[9]

The analysis conducted by MacGillivray et al. included 11 studies with 2,954 total participants (1,607 using an SSRI and 1,347 using a TCA). Six studies contributed to the overall efficacy analysis and found that the standardized weighted mean difference on depression rating scales was 0.07 (95% CI -0.02-0.15). Though TCAs and SSRIs were not statistically significantly different, the data trended in favor of TCAs. When evaluators only considered the three studies that were deemed to be higher quality, TCAs are no longer favored, with a standardized mean difference of -0.03 (95% CI -0.2- 0.14). There was also no difference between TCAs and SSRIs for the endpoint of CGI improvement [relative risk 1.11 (95%CI 0.86-1.43)]. Fewer patients treated with SSRIs withdrew treatment due to an adverse event [11.6% (9.9%-13.3%)] compared to those treated with TCAs [17% (14.8%-19.1%)]. The results of this trial indicate that there is no difference in efficacy between TCAs and SSRIs, and that SSRIs may be better tolerated than TCAs. This is consistent with meta-analyses that have conducted similar comparisons of efficacy in patients of all care settings, however data is conflicting on the relative tolerability of the two classes. It appears that SSRIs may be marginally more tolerable, however high quality, long-term trials are needed to confirm this assertion.[10]

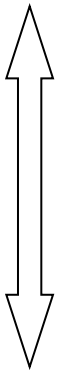
Table 1. Summary of meta-analysis comparing first and second generation antidepressants

<table>
<tr><th>Reference</th><th>Population</th><th>Primary Endpoint</th><th>Results</th></tr>
<tr><td>Underraga 2012[8]

Meta-analysis of all FDA-approved antidepressants</td><td>Adults with major depression

107 trials

Antidepressants: n=17,059

Placebo: n=9,925</td><td>Pooled rate ratios (RRs) of responder rates based on HDRS, MADRS, or CGI rating scales. Response: ≥ 50% reduction in rating-scale scores.</td><td>
<table>
<tr><td>Most effective</td><td></td><td>Relative response rates for drugs with >1 trial (95% CI, p-value)</td><td></td><td>Relative response rates for drugs by class (95% CI, p-value)</td></tr>
<tr><td rowspan="14">  </td><td>Amitriptyline</td><td>1.74 (1.5-2.01), p≤0.001</td><td rowspan="3">TCAs</td><td rowspan="3">1.62 (1.47-1.78), p=0.0001</td></tr>
<tr><td>Mirtazapine</td><td>1.73 (1.26-2.36), p≤0.001</td></tr>
<tr><td>Imipramine</td><td>1.58 (1.37-1.83), p≤0.001</td></tr>
<tr><td>Citalopram</td><td>1.48 (1.24-1.76), p≤0.001</td><td rowspan="3">SNRIs</td><td rowspan="3">1.40 (1.3-1.51), p=0.0001</td></tr>
<tr><td>Desipramine</td><td>1.45 (1.07-1.96), p≤0.001</td></tr>
<tr><td>Venlafaxine</td><td>1.45 (1.35-1.56), p≤0.001</td></tr>
<tr><td>Paroxetine</td><td>1.44(1.26-1.66), p≤0.001</td><td rowspan="2">MAOIs</td><td rowspan="2">1.39 (1.11-1.48), p=0.0001</td></tr>
<tr><td>Desvenlafaxine</td><td>1.41 (1.16-1.72), p≤0.001</td></tr>
<tr><td>Escitalopram</td><td>1.33 (1.2-1.48), p≤0.001</td><td rowspan="5">SSRIs</td><td rowspan="5">1.37 (1.27-1.48), p=0.0001</td></tr>
<tr><td>Sertraline</td><td>1.33 (1.2-1.47), p≤0.001</td></tr>
<tr><td>Selegiline</td><td>1.33 (1.07-1.65), p≤0.001</td></tr>
<tr><td>Fluoxetine</td><td>1.31 (1.07-1.60), p≤0.001</td></tr>
<tr><td>Duloxetine</td><td>1.29 (1.09-1.52), p≤0.001</td></tr>
<tr><td>Least effective</td><td>Bupropion</td><td>1.23 (1.14-1.33), p≤0.001</td><td>Atypicals</td><td>1.25 (1.15-1.35), p=0.0001</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Pooled</td><td>1.42 (1.38-1.48), p<0.0001</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Arroll 2005[9]

Meta-analysis comparing TCAs and SSRIs to</td><td>Adults with major depression, receiving care in the primary care setting

TCAs: n=596
SSRIs: n=890</td><td>Response, measured by HAMD, MADRS, or CGI rating scales</td><td>
<table>
<tr><th></th><th>Events (treatment)</th><th>Events (placebo)</th><th>Relative risk (95% CI)</th></tr>
<tr><td colspan="4">Efficacy endpoint: Response on depression rating scales (definition of response varied by scale)</td></tr>
<tr><td>TCAs vs. Placebo</td><td>323/535 (60.4%)</td><td>216/460 (47.0%)</td><td>1.26 (1.12-1.42)</td></tr>
<tr><td>SSRIs vs Placebo</td><td>310/552 (56.2%)</td><td>231/562 (41.1%)</td><td>1.37 (1.21-1.55)</td></tr>
<tr><td colspan="4">Safety endpoint: Adverse events leading to withdrawal</td></tr>
<tr><td>TCAs vs. Placebo</td><td>81/692 (11.7%)</td><td>30/578 (5.2%)</td><td>2.35 (1.69-3.46)</td></tr>
</table>
</td></tr>
</table>

placebo	Placebo: n=1,267		SSRIs vs Placebo: 30/576 (5.2%) vs 15/573 (2.6%), 2.01 (1.10-3.69)
MacGillivray 2003[10] Meta-analysis comparing TCAs to SSRIs	Adults with major depression, receiving care in the primary care setting TCAs: n=1,347 SSRIs: n=1,607	Standard mean difference of final mean depression scores	Standardized mean difference in final mean depression scores: 0.07 (-0.02, 0.15), in favor of TCAs. Relative risk of treatment withdrawal due to drug related adverse events: 0.73 (0.60, 0.88), in favor of SSRIs.

HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scales; CGI: Clinical Global Impression rating scale; HAMD: Hamilton Depression rating scale

2. Guidelines – Major Depressive Disorder:

The 3rd edition of the Practice Guideline for the Treatment of Patients with Major Depressive Disorder where released in 2010 by the American Psychiatric Association. Recommendations fell into one of three categories:[11]

[I] Recommended with substantial clinical confidence

[II] Recommended with moderate clinical confidence

[III] May be recommended on the basis of individual circumstances

For the acute phase of treatment, clinicians may use pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies to achieve a full return to the patient's baseline level of functioning. The guidelines recommend an antidepressant medication for the initial treatment for patients with mild to moderate major depressive disorder [I] and definitely should be used in severe major depressive disorder unless ECT is planned [I]. The guidelines state that because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g. half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [I]. The guideline's preferred agents for most patients are SSRIs, SNRIs, mirtazapine, or bupropion [I]. MAOIs should be restricted to patients who do not respond to other treatments [I], due to the necessity for dietary restrictions and drug-drug interactions. For patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) [III] or St. John's wort [III] might be considered although evidence of efficacy is modest at best.[8]

After starting a medication, the rate at which it is titrated to the full therapeutic dose depends on age, the treatment setting, the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [I]. During the early phase of treatment patients should be closely monitored on the response and to identify side effects [I]. The frequency of patient monitoring should be determined on patient factors including symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [II]. If side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [I].[11]

If at least moderate improvement in symptoms is not observed within 4-8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [I]. Therapeutic alliance and treatment adherence should also be addressed [I]. For antidepressant medications the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. For some TCAs a drug blood level can help with dose adjustments [I]. For patients who require a change in treatment plan, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to something within the same pharmacological class or to one from a different class [II]. Patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmacological class or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or second-generation antipsychotic [II]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a non-selective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline can also be considered [II].[11]

During the continuation phase patients should have systematic assessment of symptoms, side effects, adherence, and function status [I]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4-9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline.[11]

If it is decided to proceed to the maintenance phase of therapy, considerations including whether the patient has additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II].[11]

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks to minimize the likelihood of discontinuation symptoms [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II].[11]

A patient's co-occurring medical conditions can contribute to what therapy a patient should receive. In patients with preexisting hypertension or cardiac conditions, treatment with specific antidepressant agents may suggest a need for monitoring of vital signs or cardiac rhythm (e.g., ECG with TCA treatment; heart rate and blood pressure assessment with SNRIs and TCAs) [I]. When using antidepressant medications with anticholinergic side effects, it is important to consider the potential for increases in heart rate in individuals with cardiac disease, worsening cognition in individuals with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma [I]. Some antidepressant drugs reduce the seizure threshold and should be used with caution in individuals with preexisting seizure disorders [II]. Serotonergic agents can worsen Parkinson's disease symptoms [II] and selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents [I]. For patients being treated following a stroke, consideration should be given to potential interactions with anticoagulation medications [I]. The side effect of weight gain should be considered when choosing an agent. Patients who have undergone bariatric surgery should reconsider the pharmacokinetics and pharmacodynamics

of medications [I]. Drug interactions with HIV medications should be considered [I]. Interferon can exacerbate depressive symptoms, making close monitoring important [I]. Patients receiving tamoxifen who are going to be started on an antidepressive medication, should be treated with an agent that has minimal effect on the P450 2D6 isoenzyme [I]. When depression occurs in the context of chronic pain, SNRIs and TCAs may be preferable to other antidepressive agents [II].[11]

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

DOSE & AVAILABILITY

MEDICATIONS	USUAL DOSAGE	INDICATIONS
Tricyclic Antidepressants (TCAs)		
Amitriptyline, generic[12]	75-150 mg/day in divided doses	• Depression
Amoxapine, generic[13]	100-400 mg/day; Doses > 300mg should be divided	• Depression
Desipramine, generic[14]	100-200 mg/day	• Depression
Doxepin, generic[15]	25-300 mg/day	• Depression • Insomnia
Imipramine, generic[16]	50-150 mg/day	• Depression • Childhood enuresis
Maprotiline, generic[17]	25-225 mg/day (Max of 150mg in most patients)	• Depression
Nortriptyline, generic[18]	50-100 mg/day	• Depression
Protryptiline, generic[19]	15-60 mg/day in divided doses	• Depression
Trimipramine, generic[20]	50-150 mg/day	• Depression
Monoamine Oxidase Inhibitors		
Isocarboxazid, generic[21]	20-60 mg/day	• Depression
Phenelzine, generic[22]	15mg (every other day)-60 mg/day	• Depression
Selegiline patch, generic[23]	6-12mg/24 hours patches	• Depression
Tranylcypromine, generic[24]	30-60 mg/day	• Depression without melancholia
Selective Serotonin Reuptake Inhibitors		

Citalopram, generic[25]	20-40 mg/day	• Depression
Escitalopram, generic[26]	10-20 mg/day	• Depression • Generalized anxiety disorder
Fluoxetine, generic[27]	10-60 mg/day	• Depression • Acute and maintenance treatment of obsessive compulsive disorder age 7-17 • Treatment of Bulimia Nervosa in adult patients • Acute treatment of Panic Disorder in adult patients
Paroxetine, generic[28]	20-50 mg/day	• Depression • Panic disorder • Obsessive compulsive disorder • Social anxiety disorder • Generalized anxiety disorder • Post-traumatic stress disorder • Premenstrual dysphoric disorder
Sertraline, generic[29]	50-200 mg/day	• Depression • Obsessive compulsive disorder • Panic disorder • Post-traumatic stress disorder • Premenstrual dysphoric disorder • Social anxiety disorder
Vilazodone (Viibryd)[30]	10-40 mg/day	• Depression
Serotonin-norepinephrine reuptake inhibitors (SNRIs)		
Desvenlafaxine, generic[31]	50 mg/day	• Depression
Duloxetine, generic[32]	40-60 mg/day	• Depression • Generalized anxiety disorder • Diabetic peripheral neuropathic pain • Fibromyalgia • Chronic musculoskeletal pain
Levomilnacipran (Fetzima)[33]	40-120 mg/day	• Depression
Venlafaxine, generic[34]	37.5-225 mg/day	• Depression • Social anxiety disorder

Atypical antidepressants		
Bupropion, generic[35]	IR: 200-450 mg/day in divided doses SR: 150-400 mg/day in divided doses ER: 150-450 mg/day once daily	• Depression • Seasonal affective disorder • Adjunct in smoking cessation
Mirtazapine, generic[36]	15-45 mg/day	• Depression
Nefazodone, generic[37]	200-600 mg/day in two divided doses	• Depression
Trazadone, generic[38]	150-600 mg/day in divided doses Extended Release: 150mg once daily up to 375 mg/day	• Depression
Vortioxetine (Brintellix)[39]	5-20 mg/day	• Depression

SAFETY[12-40]

Black box warnings:

- All antidepressants
    - Suicidality/suicidal thoughts and behaviors – antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adults, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Nefazodone
-
    - Life threatening liver failure – Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000-300,000 patient-years of treatment. Treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases.

Contraindications:

- All antidepressants
    - Concomitant use of non-MAOIs with MAOIs
- TCAs: Nortriptyline, trimipramine, protryptiline, maprotiline
    - Acute recovery period after myocardial infarction
- TCAs: Doxepin
    - Urinary retention
    - Narrow-angle glaucoma
- MAOIs (all)
    - With pheochromocytoma
    - Congestive heart failure
    - Severe renal impairment or renal disease
    - History of liver disease or abnormal LFTs
    - With sympathomimetic drugs
    - Foods high in tyramine or dopamine/Food restrictions with high doses of selegilene patch
    - Do not use in combination with dextromethorphan or CNS depressants. Do not use with meperidine. Do not use multiple MAOIs together
    - Do not use in combination with buspirone
    - General anesthesia, spinal anesthesia. MAOIs should be stopped at least 10 days prior to procedure
    - Drug interactions – all medications should be checked before starting an MAOI or adding a new medication
- SSRIs – citalopram, escitalopram, fluoxetine, paroxetine, sertraline
    - Do not use with pimozide
- SSRIs –fluoxetine, paroxetine (sertraline, escitalopram, citalopram – double check PI),
    - Do not use with thioridazine
- SNRIs – duloxetine
    - Use in patients with uncontrolled narrow-angle glaucoma
- Atypicals – bupropion
    - Seizure disorders
    - Current or prior diagnosis of bulimia or anorexia
    - If undergoing abrupt discontinuation of alcohol or sedatives
- Atypicals – nefazodone
    - If previous use has caused liver injury
    - Avoid combining with triaozlam in most patients
    - Coadministration of terfenadine, astemizole, cisapride, pimozide, or carbamazepine
    - In the recovery phase of an MI

DOSE ADJUSTMENTS

MEDICATIONS	RENAL ADJ	HEPATIC ADJ	Pediatric	Elderly	OTHER DOSING CONSIDERATIONS

			Dose	Dose	
Tricyclic Antidepressants (TCAs)					
Amitriptyline, generic[12]	None specified	None specified	Not recommended in under 12 years of age	50 mg/day in divided doses	Sedative effect may be apparent before the antidepressant effect is noted, but therapeutic effect may take up to 30 days to develop.
Amoxapine, generic[13]	None specified	None specified	Not discussed	50-300 mg/day	Hospitalized patients refractory to antidepressant therapy may be cautiously titrated to 600 mg/day in divided doses
Desipramine, generic[14]	None specified	None specified	20-100 mg/day	20-100 mg/day	Higher doses should be initiated administered in hospitals
Doxepin, generic[15]	None specified	Use a lower dose and adjust gradually.	Not discussed	10-75 mg/day	A single dose should not exceed 150mg, select patients may respond to 25-50 mg/day.
Imipramine, generic[16]	None specified	None specified	Not to exceed 100 mg/day	Not to exceed 100 mg/day	If hospitalized, max dose is 250-300mg/day
Maprotiline, generic[17]	None specified	None specified	Not discussed	50-75 mg/day	Long half-life so initial doses should be maintained for 2 weeks.
Nortryptiline, generic[18]	None specified	None specified	No data on its use	30-50 mg/day	
Protriptyline, generic[19]	None specified	None specified	Adolescents: 15-20 mg/day	15-20 mg/day	
Trimipramine, generic[20]	None specified	None specified	Not discussed	50-100 mg/day	Hospitalized patients may receive 100 mg/day up to 200 mg/day in a few days up to a maximum of 300 mg/day
Monoamine Oxidase Inhibitors					
Isocarboxazid, generic[21]	Contraindicated in renal dysfunction	Contraindicated in liver disease	Not discussed	See adult dosing	Many drug and food interactions Doses of the selegiline patch <9 mg/24 hours do not have dietary restrictions.
Phenelzine, generic[22]	None specified but use caution	None specified but use caution	Not discussed	Use doses on the lower end	
Selegiline patch, generic[29]	No adjustment	No adjustment	Not discussed	6mg/24 hour patch	
Tranylcypromine,	None specified	None specified	Not discussed	See adult dosing	

generic[24]					
Selective Serotonin Reuptake Inhibitors					
Citalopram, generic[25]	No change for moderate renal impairment; use with caution in severe renal impairment.	Maximum 20 mg/day	10-40 mg/day for obsessive-compulsive disorder	Maximum recommended dose is 20 mg/day.	Doses greater than 40 mg/day are not recommended due to risk of QT prolongation and failure to show additional efficacy.
Escitalopram, generic[26]	Use with caution in severe renal impairment	10 mg/day	Age ≥12 10-20 mg/day	5-10 mg/day	
Fluoxetine, generic[27]	No adjustment	Lower and less frequent dosage should be used in patients with hepatic impairment	10-20 mg/day	Use adult dosing	
Paroxetine, generic[28]	10-40 mg/day	10-40 mg/day	Not discussed	10-40 mg/day	
Sertraline, generic[29]	No adjustment	Lower dose and less frequent dosing should be used	25-50 mg/day (for OCD)	25-100 mg/day	
Vilazodone (Viibryd)[30]	No adjustment	No adjustment	Not approved for pediatric use	No adjustment	Reduce dose if co-administered with a strong inhibitor of CYP3A4
Serotonin and norepinephrine reuptake inhibitors					
Desvenlafaxine, generic[31]	CrCl 30-50 mL/min – max dose 50 mg/day End-stage renal disease – 50 mg every other day	Max dose 50 mg/day	Safety and effectiveness not established	Increased incidence of orthostatic hypotension	No additional benefit was seen at doses greater than 50 mg/day and increased adverse reactions.
Duloxetine, generic[32]	Not recommended for patients with end-stage renal disease or severe renal impairment (CrCl <30 ml/min)	Avoid use	Efficacy not demonstrated Not studied in age <7	No adjustment	
Levomilnacipran	Do not exceed 80	No adjustment	Not studied	No adjustment	

(Fetzima)[33]	mg/day for moderate impairment. Max 40 mg/day for severe impairment.				
Venlafaxine, generic[34]	Reduce dose by 25-50% Reduce by 50% in hemodialysis	Reduce dose by 50% in mild to moderate impairment.	Not approved for pediatric use	No adjustment	
Other Antidepressants					
Bupropion, generic[35]	Use with caution, elimination is reduced, consider lowering frequency in IR formulations	Use with extreme caution in sever hepatic cirrhosis, low doses only	Not studied for depression	IR: 75-300 mg/day in divided doses	Doses given are for hydrochloride salt formulation. See package insert for dose conversions to hydrobromide salt.
Mirtazepine, generic[36]	Be aware that plasma levels increase in renal impairment	Be aware that plasma levels increase in hepatic impairment	Not studied	Use with caution due to decreased clearance in the elderly.	Do to the long half-life, dose changes should only be done every 1-2 weeks.
Nefazodone, generic[40]	Non provided, however it is partially cleared by the kidney	Contraindicated in patients with hepatic impairment	No information given	Initial dose of 100 mg/day in two divided doses	
Trazadone, generic[38]	None specified	None specified	Age 6-12: Initial 1.5-2 mg/kg/day in divided doses with maximum of 6 mg/kg/day in 3 divided doses	Short acting: 25-150 mg/day ER: Use caution	
Vortioxetine (Brintellix)[39]	None specified	None specified	Not studied	Not addressed	Maximum recommended dose is 10 mg/day for known CYP2D6 poor metabolizers. Reduce dose in half if strong CYP2D6 strong inhibitor is started.

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Abbreviated Class Update: Newer Drugs for Insomnia

Month/Year of Review: July 2014
End date of literature search: Week 5, April 2014
New drug(s): Tasimelteon (Hetlioz™)
Manufacturer: Vanda Pharmaceuticals Inc.

Current Status of PDL Class:

- Preferred Agents: ZOLPIDEM TABLET
- Non Preferred Agents: ZALEPLON CAPSULE, ZOLPIDEM EXTENDED-RELEASE TABLET, ZOLPIMIST™, LUNESTA™, ROZEREM™, SILENOR™, EDULAR™, INTERMEZZO™

PA Criteria: Treatment of sleep disorders without sleep apnea is not funded by Oregon Health Plan (OHP) diagnosis (Line 636). Treatment of insomnia contributing to a covered comorbid condition is funded. A quantity limit is in place to prevent chronic daily use of all sedatives (Appendix 2) and to determine if the diagnosis is funded. Electronic step edits are be incorporated into the PA process as recommended at the March 2014 P&T meeting to streamline this process. There is also a PA required to prevent a client from receiving two concurrent oral sedative medications.

Research Questions:

- Is there new comparative effectiveness or safety evidence since the last scan (literature search end date of Week 2, June 2013) of newer drugs for insomnia to warrant a change to the PDL?
- Is there evidence that tasimelteon is more effective or safer than currently available newer drugs for insomnia?
- Is there evidence that tasimelteon is more effective of safer for a sub-set of patients with insomnia?

Conclusions:

- There is no new comparative evidence for newer drugs for insomnia since the last scan.
- There is no comparative effectiveness or safety evidence for tasimelteon versus other newer drugs for insomnia.
- There is low level evidence from two small (n= 84, n=20), unpublished, randomized controlled trials (RCTs) in blind individuals that tasimelteon increases nighttime sleep on the worst 25% of nights by of 50 minutes and decreased daytime sleep on the worst 25% of days by 49 minutes.

Recommendations:

- As there is no new comparative evidence for the newer drugs for insomnia compare costs in executive session to determine potential changes to the preferred drug list (PDL)
- Make tasimelteon non-preferred in the newer insomnia drug class because there is insufficient evidence for insomnia treatment outside the narrow FDA approved indication and require a prior authorization for a funded OHP diagnosis.
- Consider a maximum dose of Lunesta of 1mg for all new prescriptions.

Reason for Review: Tasmelteon was approved by the Food and Drug Administration (FDA) in January 2014 for Non-24-Hour Sleep-Wake Disorder (Non-24).[1]

Previous P&T Conclusions (November 2013):[2,3]

- There is insufficient evidence of superiority or significant clinical advantage of Silenor™ and specialized zolpidem formulations (i.e. Edular™ and Zopimist™) over zolpidem tablets.
- There is good quality evidence that zolpidem and zaleplon are similarly effective for subjective sleep latency.
- There is fair quality evidence that there is no significant difference between zolpidem and eszopiclone on measured sleep outcomes.
- There is insufficient comparative evidence about long-term safety.

Background: The 2014 International Classification of Sleep Disorders classifies sleep disorders into seven categories; insomnia, sleep related breathing disorders, central disorders of hypersomnia, circadian rhythm sleep-wake disorders, parasomnias, sleep related movement disorders, and other sleep disorders.[4] Insomnia is a risk factor for many disorders including coronary heart disease, metabolic syndrome and depression. It is recommended that insomnia patients first get adequate treatment for conditions that may be exacerbating their sleep disturbance.[4,5]

Chronic insomniacs ($\geq$ 3 times per week for > 3 months) have an altered perception of sleep quality where subjective measures, such as self-reported sleep latency (time to fall asleep) or wakefulness after sleep onset (WASO) of more than 30 minutes do not correlate well with similar objective sleep measures derived from polysomnography.[6] The goals of treatment are to reduce the distress and anxiety associated with poor sleep, and to improve daytime function.[6] Behavioral approaches are recommended first-line for chronic insomnia.[4,5] There is moderate level evidence that both benzodiazepine and non-benzodiazepine sedatives moderately reduce the time to sleep onset and increase total sleep time.[5] However, the risks include complex sleep-related behaviors, increased risk of falls and abuse potential[5] Sedatives have not been adequately evaluated for risk versus benefit for long-term use.

Circadian rhythm disorders (i.e. Non-24) are characterized by patients falling asleep more than 2 hours later than conventional times.[7] These are thought to be caused by a disruption internal circadian system that is regulated by light signals to the suprachiasmatic nucleus which prevents the pineal gland from producing melatonin, a hormone that otherwise signals "biological night".[8] Common secondary causes of circadian rhythm disorders include shift work and jet lag. There is no consensus on the appropriate dose or timing of exogenous melatonin for circadian rhythm disorders and it is largely ineffective for shift-work or jet-lag caused insomnia.[7] Ramelteon was the first synthetic melatonin agonist approved but is indicated specifically for sleep onset insomnia and has not been evaluated for circadian rhythm disorders. Tasmelteon is a melatonin agonist at the MT1 and MT2 receptors. It is the only drug FDA approved for Non-24 in blind individuals and was granted orphan drug status.[10] Non-24 is a common complaint of blind patients who cannot receive light signals. Measurement of endogenous melatonin level entrainment is a proposed surrogate outcome for melatonin agonist efficacy for Non-24[9] but this has not been reliably correlated to accepted sleep measures (i.e. sleep latency or WASO). [10]

Medical therapy for the treatment of sleep disorders without sleep apnea falls below the funding line (i.e. Line 636) on the OHP list of prioritized services and is only covered as treatment of co-morbid conditions (i.e. depression) Medical treatment of circadian rhythm sleep disorders also falls on Line 636.

Methods:
A Medline literature search ending April 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing non-benzodiazepine sedatives for the treatment of insomnia was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches,

Systematic Reviews:
None identified.

New Guidelines:
None identified.

Randomized Controlled Trials:
No head to head comparisons were identified.

New Safety Alerts, Indications:
May 2014 – Ambien™, Ambien CR™ & Edular™

> "The U.S. Food and Drug Administration (FDA) is notifying the public that FDA has approved label changes specifying new dosing recommendations for zolpidem products (Ambien, Ambien CR, and Edluar), which are widely prescribed sleep medications. FDA has approved these changes because of the known risk of next-morning impairment with these drugs.
>
> FDA is also warning that patients who take the sleep medication zolpidem extended-release (Ambien CR)—either 6.25 mg or 12.5 mg—should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities. This new recommendation has been added to the Warnings and Precautions section of the physician label and to the patient Medication Guide for zolpidem extended-release (Ambien CR)"

May 2014 - Lunesta™

> "The U.S. Food and Drug Administration (FDA) is warning that the insomnia drug Lunesta (eszopiclone) can cause next-day impairment of driving and other activities that require alertness. As a result, we have decreased the recommended starting dose of Lunesta to 1 mg at bedtime. Health care professionals should follow the new dosing recommendations when starting patients on Lunesta. Patients should continue taking their prescribed dose of Lunesta and contact their health care professionals to ask about the most appropriate dose for them."

February 2014 - Lunesta™

"6 ADVERSE REACTIONS

6.2 Post-Marketing Experience..added paragraph

In addition to the adverse reactions observed during clinical trials, dysosmia, an olfactory dysfunction that is characterized by distortion of the sense of smell, has been reported during post-marketing surveillance with LUNESTA. Because this event is reported spontaneously from a population of unknown size, it is not possible to estimate the frequency of this event."

New Drug Evaluation: Tasimelteon (Hetlioz™)

FDA approved indications: Non-24-Hour Sleep-Wake Disorder (Non-24).

Potential Off-label Use: Chronic insomnia, other circadian rhythm sleep disorders and depression.

Clinical Efficacy Data: There are 5 completed, placebo-controlled, phase 3 studies (1 for Major Depressive Disorder, 2 for Non-24, 1 for adult primary insomnia, 1 for model of insomnia in health volunteers) and one completed phase 2 study for circadian rhythm disorders in health adult volunteers registered at www.clinicaltrials.gov. No results are posted for any trial. The depression trial (NCT01428661, n=507) was not published, but it was reported that it did not meet its primary endpoint of change in the Hamilton Depression Scale after 8 weeks.[9]

The two trials (NCT01163032 and NCT01430754) submitted to the FDA are published as abstracts only and cannot be evaluated for quality. What follows is a summary of the FDA review.[10] NCT01163032 (FDA ID 3201) was a placebo-controlled, double-blind trial of 84 totally blind patients randomized to tasimelteon 20mg or placebo for 6 months and at a time each day when the patient's circadian rhythm was thought to be coming into alignment based upon urinary melatonin. NCT01430754 (FDA ID 3203) was a randomized withdrawal placebo-controlled study designed to evaluated the long-term maintenance effect of tasimelteon versus placebo. After 11 weeks of treatment, 20 patients were randomized to receive tasimelteon 20mg or placebo. The primary endpoint in both studies was an un-validated surrogate of proportion of patients meeting melatonin entrainment. The FDA did not accept the surrogate and based their determinations on the secondary clinical endpoints of the change from baseline of the nighttime sleep duration on the 25% of nights with the least nighttime sleep and the 25% of days with the most daytime sleep. The baseline was a mean of 195 minutes of nighttime sleep and 137 minutes of daytime sleep. The change was nominally significant for the clinical endpoints of interest in both studies. There was a mean increase of 50 minutes of nighttime sleep on the worst 25% of nights and a mean decrease of 49 minutes of daytime sleep on the worst days.

NCT00490945 and NCT00291187 were published together in Lancet.[11] NCT0049045 was a fair quality, phase II study of 39 healthy volunteers. Subjects were randomized to placebo or tasimelteon 10mg, 20mg, 50mg or 100mg. After 2 weeks of a strict 8 hour sleep schedule they were admitted to a sleep facility where external cues to day and night were eliminated and then a 5-hour phase shift was induced using the study drug 1 hour before bedtime for 3 nights. Tasimelteon 50mg and 100mg increased the primary outcome of mean sleep efficiency by 14.6 – 18.4% over placebo. There was not a statistical difference in WASO, a secondary outcome. NCT00291187 was a good quality, phase III study of 411 health volunteers. Patients were maintained on a regular 8-hour sleep

schedule for 1 week and then admitted for inpatient study where bedtime was advanced by 5 hours for 1 night. Tasimelteon 50mg and 100mg reduced the primary outcome of mean latency to persistent sleep by 22.6 -26.1 minutes more than placebo and the secondary outcome of WASO by 24.1 – 34 minutes. While these studies both indicate the ability of tasimelton 50mg and 100mg to improve adjustment to an induced, 1 time 5-hour phase shift of sleep in a controlled setting in healthy, young volunteers they are difficult to extrapolate to shift-workers and frequent travelers who may be older, less healthy and need to phase shift more routinely. Of note, only the 20mg dose was approved by the FDA and significant findings were produced by the higher 50mg and 100mg doses.

Clinical Safety: Safety was evaluated by the FDA using a database of 1346 subjects that received at least one dose of tasimelteon, 621 of which got the 20mg dose and 111 were treated 6 months. Only 44 were treated for one year. It was judged adequate for an "orphan indication" and overall there were no safety concerns noted.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Sleep Latency as measured by polysomnography
2) Wakefulness after sleep onset as measured by polysomnography

Primary Study Endpoint:

1) Sleep Latency as measured by polysomnography
2) Mean sleep efficiency as measured by polysomnography

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	Safety Results (CI, p-values)	Quality Rating; Internal Validity Risk o Bias/ External Validity Concerns
NCT00490945[11] R-PCT, DB, Phase II 7/14/2004-4/1/2005	-Patients maintained on a regular 8-hour sleep schedule x 2 weeks ther admitted for inpatient study at 2 US sites -single-bed suites free of time cues and had controlled light intensity where induced a 5-hour sleep phase shift x 3 days. Dose of tasimelton varied from 10-100mg	Demographics: 18-50 yrs old mean age: 30's BMI 23-25 Inclusion Criteria: volunteers Exclusion Criteria: -no major sleep disorder - individuals who were adapted to early sleep schedules -good health	ITT: 45 (6 withdrew after the run-in) pbo: 8 t10mg: 9 t20mg: 8 t50mg: 7 t100mg: 7 Attrition: pbo: n=0 (0.00%) t: n=1 (0.03%)	<u>Mean Sleep efficiency Day1 (% of total sleep time asleep as scored by polysomnography):</u> Baseline: 90% pbo: 70.9% p<0.01 vs baseline t10mg: 79.9% t20mg: 82.5% t50mg: 85.5%* t100mg: 89.3%* *p<0.05 vs pbo AD Range: 14.6% - 18.4%) <u>Mean WASO (in minute):</u> Baseline: 34.5 pbo: 106.7 p<0.01 vs baseline t10mg: 79.8 t20mg: 71.9 t50mg: 56.6 t100mg: 41.8	No ADE significantly greater than pcb	**Quality Rating: Fair** **Internal Validity: RoB** <u>Selection:</u> MOD - unclear process & allocation concealment; stratified by sex <u>Performance:</u> MOD - matched placebo; who was blinded not described <u>Detection:</u> LOW- polysomnography scored by blinded, experienced scorers using standard criteria. <u>Attrition:</u> LOW **External Validity:** <u>Recruitment:</u> volunteers through advertising <u>Patient Characteristics:</u> very young, healthy cohort; probably unrepresentative of shift-workers <u>Setting:</u> model of phase-shift disorder <u>Outcomes:</u> objective polysomnography; a definition of clinically meaningful responders would have been helpful. One night evaluation; unclear if effects would last. **Analysis:** Potentially internally valid, but unclear clinical relevance.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	Safety Results (CI, p-values)	Quality Rating; Internal Validity Risk o Bias/ External Validity Concerns
NCT00291187[11] R-PCT, DB, Phase III 2/9/2006 – 8/21/2006	Patients maintained on a regular 8-hour sleep schedule x 1 weeks -admitted for inpatient study at 20 US sites, 19 of which did assessments. Bedtime advanced 5 hours x 1 night. Dose of tasimelton varied from 10-100mg	Demographics: 21-50 yrs old Inclusion Criteria: volunteers Exclusion Criteria: -no major sleep disorder - people who had previously slept in a sleep clinic -good health	ITT: 411 pbo:103 t20mg: 100 t50mg: 102 t100mg: 106 Attrition: 0	Mean Latency to Persistent Sleep (in minutes): pbo: 44.6 t20mg: 23.1 t50mg: 18.5* t100mg: 22.0* *p<0.01 vs pbo AD range: 22.6 -26.1 minutes Mean WASO (in minutes) pbo: 140.3 t20mg: 116.2* t50mg: 106.3^ t100mg: 122.3 *p<0.05 vs pbo ^p<0.01 vs pbo AD range: 24.1 – 34 minutes	No ADE significantly greater than pcb	**Quality Rating: Good** **Internal Validity: RoB** Selection: LOW – IVR used Performance: MOD: matched placebo; who was blinded not described Detection: LOW- polysomnography scored by blinded, experienced scorers using standard criteria. Attrition: LOW **External Validity:** Recruitment: volunteers through advertising Patient Characteristics: very young, healthy cohort; probably unrepresentative of shift-workers Setting: model of phase-shift disorder Outcomes: objective polysomnography; a definition of clinically meaningful responders would have been helpful. One night evaluation; unclear if effects would last. **Analysis: I**nternally valid, but unclear clinical relevance.

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Appendix 1: Specific Drug Information[1]

CLINICAL PHARMACOLOGY

Tasimelteon is a melatonin MT1 and MT2 receptor agonist. These receptors are thought to regulate circadian rhythms.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	NR
Protein Binding	90%
Elimination	80% recovered via metabolites in urine 4% recovered via metabolites in feces
Half-Life	1.3 hours
Metabolism	Extensively metabolized. CYP1A2 and CYP3A4 are the primary isoenzymes involved

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
20mg	Oral	Before bedtime	Tablet		Not studied in patients with severe hepatic impairment (Child-Pugh Class C)	Not established	2x increase in levels	C	-Take without food; -Drug effect may not occur for weeks or months -Smokers metabolize it quicker.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions: None

Look-alike / Sound-alike (LA/SA) Error Risk Potential: Halcion, Haldol, Healon, tramadol, trazadone

Author: Ketchum Date: 6/30/2014 12:53 PM

Central Nervous System (CNS) Sedatives –Quantity Limit

Goal(s):

- Approve only for covered OHP diagnoses.
- Treatment of uncomplicated insomnia is not covered, but insomnia contributing to covered comorbid conditions is.
- Prevent adverse events associated with long-term sedative use.
- Clients coming onto the plan on chronic sedative therapy are grandfathered.(refer to criteria). Also see related Sedative Therapy Duplication edit. The safety and effectiveness of chronic sedative use is not established in the medical literature.

Length of Authorization:

- 6 to 12 months (criteria specific)

Requires PA:

- All CNS sedatives in Standard Therapeutic Class 47 that exceed 15 doses per 30 days.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Trazodone, mirtazapine, diphenhydramine or tricyclic antidepressants may be alternatives for some clients.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does client have diagnosis of insomnia with sleep apnea, ICD9: 780.51?	Yes: Go to #3.	No: Go to #4.
3. Is client on CPAP?	Yes: Approve for up to 1 year. The use of CPAP essentially negates the sedative contraindication and they are often prescribed to help clients cope with the mask.	No: Pass to RPH, Deny, (Medical appropriateness). Due to the depressant effects of sedative/ hypnotics, sedative/hypnotics are contraindicated for this diagnosis and are not approvable.

Approval Criteria		
4. Is the client being treated for co-morbid depression,/ bipolar disorder (296.xx) OR anxiety / panic disorder (300.0x) AND Is there an existing claim history of antidepressants, lithium, antipsychotics, or other appropriate mental health drugs?	Yes: Approve for up to 1 year.	No: Pass to RPH; Go to #5.
5. RPH only: Is diagnosis being treated a covered indication on the OHP and is there medical evidence of benefit of the prescribed sedative? All indications need to be evaluated as to whether they are above the line or below the line.	Above: Document supporting literature and approve up to 6 months with subsequent approvals dependent on f/u and documented response.	Below: Go to #6.
6. RPH only: Is this a request for continuation therapy for client with history of chronic use where discontinuation would be difficult or unadvisable? NOTE: Clients coming onto the plan on chronic sedative therapy are “grandfathered.”	Yes: Document length of treatment and last follow-up date. Approve for up to 1 year.	No: Deny, (Medical Appropriateness)

P&T / DUR Action: *3/27/14, 11/21/13, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Revision(s): *??/??/14; 1/1/07, 7/1/06, 11/15/05*
Initiated: *11/15/02*

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Month/Year of Review: July 2014
PDL Classes: Insulin

Date of Last Review: May 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: HUM INSULIN NPH/REG INSULIN HM VIAL, HUM INSULIN NPH/REG INSULIN HM INSULN PEN (PA required), INSULIN ASPART VIAL, INSULIN ASPART CARTRIDGE (PA required), INSULIN ASPART INSULN PEN (PA required), INSULIN GLARGINE (LANTUS®) VIAL, INSULIN GLARGINE (LANTUS®) INSULN PEN (PA required), INSULIN LISPRO VIAL, INSULIN LISPRO CARTRIDGE (PA required), INSULIN NPL/INSULIN LISPRO VIAL, INSULIN REGULAR, HUMAN VIAL, INSULIN ZINC HUMAN REC VIAL, INSULN ASP PRT/INSULIN ASPART VIAL, INSULN ASP PRT/INSULIN ASPART INSULN PEN (PA required), NPH, HUMAN INSULIN ISOPHANE VIAL , NPH, HUMAN INSULIN ISOPHANE INSULIN PEN (PA required)
- Non-Preferred Agents: INSULIN DETEMIR VIAL AND PEN (LEVEMIR), INSULIN GLULISINE VIAL AND PEN (APIDRA, APIDRA SOLOSTAR), INSULIN LISPRO PEN, INSULIN NPL/INSULIN LISPRO PEN, INSULIN NPH PEN, HUM INSULIN NPH/REG INSULIN CARTRIDGE

PA criteria: Prior authorization criteria is currently in place for insulin to ensure appropriate drug use and safety of hypoglycemic agents by authorizing utilization in specific patient population (Appendix 1).

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend inclusion of at least one agent from each subgroup:
    - Short acting
    - Rapid acting
    - Rapid/intermediate acting combination products
    - Intermediate acting
    - Long acting
- Clinical criteria to approve insulin pens/cartridges

Conclusions and Recommendations:

- There is low quality evidence of no significant differences in change in HbA1C or overall and severe hypoglycemia between insulin determir and insulin glargine and high quality evidence that insulin determir is associated with less weight gain and low quality evidence of more injection site reactions compared to insulin glargine.[1] With no clinically relevant difference in efficacy or safety of the two long acting agents, evaluate comparative costs.
- There is no significant new comparative evidence on the efficacy and safety of other agents on the PDL.
- Bring back full review of inhaled Afrezza once available on the market.
- Continue to include at least one agent from each subgroup (short acting, rapid acting, etc.) as preferred on the PDL and evaluate comparative costs in executive session.

Methods:

A Medline OVID search was conducted with the following search terms: NPH insulin, regular insulin, human insulin, insulin aspart, insulin lispro, insulin glargine, insulin glulisine, insulin determir, insulin isophane, short acting insulin, long acting insulin, rapid acting insulin, diabetes, diabetes mellitus, insulin dependent diabetes, diabetes type 1, diabetes

type 2, and gestational diabetes. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to April week two 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

Rys et al. conducted a systematic review and meta-analysis to compare the efficacy of insulin aspart and regular human insulin in diabetic patients. Randomized controlled trials with either type 1 or 2 diabetics were eligible; individual trial duration was 4 weeks or longer for inclusion. A total of 28 trials were included; ten trials focused on type 2 diabetes, 17 on type 1 diabetes, and one study included both. The proposed primary endpoints for the analysis were morbidity and mortality; however, the authors were unable to find any trials with these types of outcomes. Instead, secondary outcomes were used such as change in glucose levels (measured by A1c, fasting glucose, or post-prandial glucose), weight loss, and quality of life from baseline. For type 1 diabetes, patients on insulin aspart experienced a significantly greater average decrease in A1c from baseline than the human insulin cohort (mean difference in change from baseline -0.11%; 95% CI: −0.16 to −0.06; N=13, n=4263). When looking at other outcomes for type 1 diabetics they found statistically significant differences in favor of treatment with insulin aspart for postprandial glucose (PPG) after breakfast (mean difference -1.43 mmol/L; 95% CI -1.75 to -1.11; N=5, n=2820), lunch (-1.11 mmol/L; 95% CI -1.61 to -0.61; N=5, n=2712)and (-0.97 mmol/L; 95% CI -1.25 to -0.69; N=6, n=3138) dinner, but not for fasting glucose (0.15 mmol/L; 95% CI -0.55 to 0.86; N=5, n=2138. For quality of life metrics, the Diabetes Treatment Satisfaction Questionnaire showed greater improvement in perception of treatment flexibility with aspart rather than human insulin (mean difference in change from baseline 0.31; 95% CI: 0.15 to 0.47). No difference was seen in episodes of severe hypoglycemia between treatments in the three studies (n=2358) that tracked the outcome (RR 0.92; 95% CI 0.75 to 1.12). In trials with type 2 diabetics, no difference (-0.4%; 95% CI: −0.10 to 0.03) was seen in change from baseline in A1c between treatments (N=9, n=1274). Mean PPG was significantly lower in the aspart cohort group (mean difference in change from baseline −1.18 mmol/L; 95% CI: −1.88 to −0.47; N=3, n=134). No studies tracking treatment satisfaction or quality of life were identified. No difference was seen between treatments in occurrence of severe hypoglycemia (RR 0.67; 95% CI 0.17 to 2.53; N=2, n=206). Individual trial quality was assessed by looking for the presence of randomization, blinding, allocation concealment, patient withdrawal reporting and rates. The majority of trials were noted to have a lack reporting reasons for withdrawals and random allocation with appropriate randomization. Four trials reported double-blinding, but only one of these was judged as having an adequate blinding method. Overall heterogeneity of data was not analyzed. Trial quality was uniformly poor.[2]

The Cochrane Collaboration performed a systematic review and meta-analysis to evaluate the comparative efficacy of insulin glargine and detemir for treating type 2 diabetes. Four trials (n=2250) were included; individual trial durations were between 24 and 52 weeks. The primary endpoint measured was glycemic control defined as an A1c of $\leq$7% with or without hypoglycemia. Weight gain and hypoglycemia rates by study end were secondary outcomes. The mean difference in change in A1c from baseline was not significantly different between treatment groups (0.08%; 95% CI -0.1 to 0.27). Insulin glargine was associated with a significantly lower fasting glucose by study end when compared with insulin detemir (mean difference 0.34 mmol/L; 95% CI 0.01 to 0.67). There was no difference between treatments in rates of overall hypoglycemia (RR 1.00; 95% CI 0.90 to 1.11) or severe hypoglycemia (RR 0.88; 95% CI 0.59 to 1.30). Treatment with insulin detemir was associated with less weight gain than glargine (mean difference in weight change -0.91 kg; 95% CI -1.201 to -0.61). Individual study quality was evaluated for randomization, allocation concealment, blinding, selective reporting, incomplete outcome data and other bias. Although randomization and allocation concealment descriptions were found to have a low risk of bias, all other metrics were rated as having an unclear to high rate of bias. The authors deemed the overall quality of data as having a high risk of bias and only weight gain results were graded as being high quality. All other reported results were graded as low quality.[1]

Szypowska et al assessed the comparative efficacy of insulin detemir with neutral protamine Hagedom (NPH) in type 1 diabetics. This systematic review and meta-analysis included ten studies with 3825 patients; trial duration was ≥12 weeks. The primary endpoint was difference in mean change in A1c at study end from baseline. Secondary outcomes included number of hypoglycemic episodes and weight gain. Patients in the detemir cohort had a significantly greater reduction in A1c compared with NPH (mean difference -0.073; 95% CI -0.135 to -0.011). Detemir patients were less likely to experience hypoglycemia during the day (RR 0.978; 95% CI 0.961 to 0.996) and at night (RR 0.877; 95% CI 0.816 to 0.942). They also had less incidence of severe hypoglycemia (RR 0.665; 95% CI 0.547 to 0.810). Weight gain was also lower for the detemir population compared with the NPH group (mean difference –0.779 kg; 95% CI –0.992 to –0.567). Individual trial quality was tracked by analyzing the study's presence of allocation concealment, blinding, randomization and whether if present these were adequate. No trials were blinded, but the majority of the studies included had adequate randomization and/or allocation concealment. Trial quality was not given a grade or rating, but the authors acknowledged that the individual trial quality was poor overall.[3]

Esposito et al compared the efficacy of insulin lispro protamine suspension with insulin glargine and insulin detemir in patients with type 2 diabetes. This systematic review and meta-analysis included four trials with a total of 1336 subjects; trial duration was between 24 and 36 weeks. The primary outcome of interest was mean difference in change in A1c from baseline to end of treatment. Three studies compared insulin lispro protamine with insulin glargine and one study with insulin detemir. When pooled, no significant difference between insulin lispro protamine versus insulin glargine or determir was seen in change in A1c (0.0%; 95% CI -0.24 to 0.24%). No difference in treatment groups was seen in the proportion of subjects achieving an A1c ≤7% (RR 0.99; 95% CI 0.87 to 1.12), in weight gain (mean difference 0.223 kg; 95% CI -0.81 to 1.26), or in overall hypoglycemia (mean difference 0.17 events/patient/30 days; 95% CI -0.14 to 0.48) by study's end. Individual trial quality was not assessed.[4]

Guidelines:

In 2010, the Department of Veteran Affairs and the Department of Defense published updated guidelines regarding the management of diabetes mellitus. These guidelines provided recommendations regarding the use of insulin. Recommendations were graded for the strength of the evidence source. An A grade indicates a strong recommendation that clinicians provide the intervention to patients. It was based on good evidence which showed that benefits substantially outweighed harms. Grade B recommendations were based on fair evidence that showed the benefit outweighed any harms. Grade C interventions are neither recommended nor opposed. Evidence for this grade was judged to be fair and to show some improved outcomes; however benefits and potential harms were judged to be too close to justify an endorsement. Grade D recommendations recommend not performing the intervention and were based of fair evidence showing harms outweigh potential benefits. Finally, grade I recommendations indicate the evidence was insufficient to recommend for or against an intervention. In these instances, a grade I is given when the evidence is poor, conflicting or the balance of benefits and harms cannot be determined.[5]

- Use of insulin therapy should be individualized, and managed by a healthcare team experienced in managing complex insulin therapy for patients with type 1 DM. **Grade I recommendation**
- Use intermediate- or long-acting insulin to provide basal insulin coverage. **Grade B recommendation**
- Insulin glargine or detemir may be considered in the NPH insulin-treated patient with frequent or severe nocturnal hypoglycemia. **Grade B recommendation**
- Use regular insulin or short-acting insulin analogues for patients who require mealtime coverage.
- Alternatives to regular insulin (aspart, lispro, or glulisine) should be considered in the following settings: **Grade B recommendation**
    - Demonstrated requirement for pre-meal insulin coverage due to postprandial hyperglycemia AND concurrent frequent hypoglycemia
    - Patients using insulin pump.

The American Diabetes Association (ADA) issued updated guidelines in 2014 for diabetes care. Topics included recommendations for treatment. A grading system (A, B, C, or E) developed by the ADA was used to explain and categorize the evidence used for the recommendations. Grade A recommendations were based on clear evidence from

well-conducted, generalizable RCTs that were adequately powered. Recommendations given a B grade were derived from supportive evidence from well-conducted cohort studies. Grade C recommendations were based on evidence from poorly controlled or uncontrolled trials, while grade E recommendations were taken from expert consensus or experience.[6]

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. **Grade A recommendation**
- In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. **Grade E recommendation**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin. **Grade A recommendation**
- A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. **Grade E recommendation**
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. **Grade B recommendation**

In 2011, the American Association of Clinical Endocrinologists published updated clinical practice guidelines for diabetes comprehensive care. Recommendations were graded for the strength of the evidence source: an A grade was based on randomized clinical trials, a B on well-conducted but not randomized clinical trials, and a C grade was made despite the absence of directly applicable clinical studies. Recommendations were further classified by quality of evidence. Recommendations derived from evidence from a meta-analysis or at least one randomized control trial was rated as level 1. Level 2 recommendations were based on evidence from well-designed nonrandomized clinical trials, prospective cohort studies or retrospective case-control studies. Level 3 recommendations were based on cross-sectional or surveillance studies and case reports; level 4 recommendations were based on no clinical evidence.[7]

- Insulin is required in all patients with type 1 diabetes mellitus (T1DM), and it should be considered for patient with type 2 diabetes mellitus (T2DM) when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia (**Recommendation Grade A; Level of Evidence 1**).
- When insulin therapy is indicated in patients with T2DM to target fasting plasma glucose (FPG), therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia (**Recommendation Grade A; Level of Evidence 1**).
- When postprandial hyperglycemia is present, glinides and/or a-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered (**Recommendation Grade A; Level of Evidence 1**).
- When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia (**Recommendation Grade A; Level of Evidence 1**).
- Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight (**Recommendation Grade A; Level of Evidence 1**).
- Premixed insulin (fixed combination of shorter- and longer-acting components) analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin (**Recommendation Grade D; Level of Evidence 4**).
- Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy (**Recommendation Grade B; Level of Evidence 3**).
- Physiologic insulin regimens, which provide both basal and prandial insulin, are recommended for most patients with T1DM (**Recommendation Grade A; Level of Evidence 1**).

- These regimens include (a) use of multiple daily injections (MDI), which usually provide 1 or 2 injections daily of basal insulin to control glycemia between meals and overnight and injections of prandial insulin before each meal to control meal-related glycemia; (b) the use of continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia; and (c) for other patients (especially if hypoglycemia is a problem), the use of insulin analogues (**Recommendation Grade A; Level of Evidence 1**).
- All women with preexisting diabetes mellitus (T1DM, T2DM, or previous gestational diabetes) should have access to preconception care to ensure adequate nutrition and glucose control before conception, during pregnancy, and in the postpartum period (**Recommendation Grade B; Level of Evidence 2**).
- Regular or rapid-acting insulin analogues are the preferred treatment for postprandial hyperglycemia in pregnant women. Basal insulin needs can be provided by using rapid-acting insulin via CSII or by using long-acting insulin (e.g., NPH; US Food and Drug Administration [FDA] pregnancy category B) (**Recommendation Grade B; Level of Evidence 2**).

The International Diabetes Federation updated its practice guidelines for type 2 diabetes care in 2011. Recommendations were divided into categories labeled “recommended care”,”limited care”, or “comprehensive care”. Recommended care recommendations were considered cost-effective, evidence-based care and should be available to all people with diabetes and the aim of any health-care system should be to achieve this level of care. Limited care recommendations were labeled the lowest level of care that anyone with diabetes should receive.[8]

Recommended Care recommendations:

- For second-line therapy, when glucose control targets are not being achieved, add a sulfonylurea.
- A rapid-acting insulin secretagogue is an alternative option to sulfonylureas.
- For third-line therapy, when glucose control targets are no longer being achieved, start insulin or add a third oral agent.
- If starting insulin, add basal insulin or use premix insulin.
- For fourth-line therapy, begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 RA) and lifestyle interventions are unable to maintain target glucose control.
- Intensify insulin therapy is already using insulin.
- Do not unduly delay the commencement of insulin.
- Maintain lifestyle measures, support for work and activities of daily living and after introduction of insulin.
- Consider every initiation or dose increase of insulin as a trial, monitoring the response.
- Explain to the person with diabetes from the time of diagnosis that insulin is one of the options available to manage their diabetes, and that it may turn out to be the best, and eventually necessary, way of maintaining glucose control, especially in the longer term.
- Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30-100 units/day.
- Continue metformin. Other oral agents may also be continued.
- Begin with:
    - A basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine or insulin determir;
    - Once or twice daily premix insulin (biphasic insulin).
    - Initiate insulin using a self-titration regimen (dose increases of two units every 3 days) or with biweekly or more frequent contact with a health-care professional.
    - Aim for pre-meal glucose levels of < 6.5 mmol/l (< 115 mg/dl).
- Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.

Limited Care recommendations:

- Less expensive human insulin can give most of the health care gains achievable with insulin therapy.
- Insulin supplies should be assured and be of consistent quality and type.

Comprehensive Care recommendations:

- Metformin remains the first-line therapy choice, unless contraindicated. More expensive therapies, and insulin, may be considered earlier in the treatment sequence.
- Insulin pump therapy is an additional option.

New drugs:
Afrezza (insulin human) Inhalation Powder was approved by the FDA in June 2014. Afrezza is a rapid acting inhaled insulin indicated to improve glycemic control in adults with diabetes mellitus. It is administered at the beginning of each meal, or within 20 minutes after starting a meal. Afrezza is not yet available on the market.[9]

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 1536 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, 20 relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

Forst et al conducted an open label pilot study to compare the effect of adding a long-acting insulin to metformin on postprandial release of proinsulin. Intact proinsulin (IP) is a marker for *β*-cell dysfunction in patients with type 2 diabetes. Patients (n=28) with type 2 diabetes were randomized to receive either insulin glargine or NPH insulin once daily at bedtime for three months. All patients were previously treated with metformin and a sulfonylurea prior to study start. At baseline and at three months, patients were required to eat standardized meals and have their pre- and post-prandial blood sampling to measure plasma proinsulin, total insulin, and blood glucose. Both glargine and NPH patients significantly reduced fasting blood glucose levels from baseline levels (glargine 158 vs. 121 mg/dL; NPH 156 vs. 119 mg/dL; both $p<0.01$). Fasting and postprandial glucose levels did not differ between groups. IP levels decreased in both groups ($p < 0.05$ at all timepoints). In direct comparison, both insulin had similar levels of proinulsin with the exception of glargine after diner which was significantly higher ($p=0.04$). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.[10]

Swinnen et al performed a study to determine whether insulin glargine was noninferior to insulin detemir in lowering A1c in patients with type 2 diabetes. Patients (n=973) were randomized to either glargine once daily or determir twice daily for six months. Patients were all insulin naïve but were allowed to be on oral agents during and prior to study initiation. The primary outcome was percent of patients to reach an A1c of $\leq$7%. Similar percentages of patients in both treatment groups reached the target A1c (27.5% of glargine and 25.6% of determir patients; $p=0.254$). Predetermined noninferiority margin was set at -7.68%; the difference between treatments was 1.85% (95% CI -3.78 to 7.48%), demonstrating noninferiority of glargine to detemir. Overall population improvements in A1c were also similar between treatments (1.46% A1c for glargine vs. 1.54% A1c for detemir; $p =0.149$). Significantly more detemir patients achieved an A1c $\leq$6.5% (22.7 vs. 16.5%; $p=0.017$). Incidence of hypoglycemia was similar between groups. Weight gain was higher in the glargine group: difference 0.77 kg, $p\leq0.001$. More patients on glargine than on detemir completed the study (95.4 and 89.9%, respectively, $p\leq 0.001$). This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.[11]

Chacra et al conducted a study to determine the comparative efficacy of insulin lispro protamine with insulin detemir in patients with type 1 diabetes. Patients (n=397) were randomized to receive lispro protamine or detemir twice daily; all patients received prandial insulin lispro three times daily. The primary outcome was change in A1c from baseline after

32 weeks. The change in A1c was similar between groups (least squares mean for protamine lispro 0.69%, detemir 0.59%; between treatment difference 0.1%; 95% CI -0.29 to 0.10). Predetermined noninferiority margin was set at 0.4% meaning lispro protamine is noninferior to detemir. Lispro protamine patients gained more weight than their detemir counterpoints (difference between groups 1.5 kg; 95% CI 0.34 to 1.60 kg). Severe hypoglycemia was similar between groups (p=0.37). This was a poor quality trail. Blinding, randomization and allocation concealment methodology were not described.[12]

Fogelfeld et al compared the efficacy of insulin detemir and insulin lispro protamine suspension in insulin naïve type 2 diabetics. Patients (n=442) were randomized to take one of the two insulin once daily at bedtime for 24 weeks; doses were titrated to target a fasting blood glucose below 7.2 mmol/L. For up to eight weeks, an additional prebreakfast dose was given. The primary outcome was comparative improvement from baseline in A1c. Both treatment groups saw an improvement an A1c from a baseline average of 8.8% to 7.3% for lispro protamine and 7.5% detemir (p=0.03). Predetermined noninferiority margin was set at 0.4%. The least squares mean difference between treatment A1c was -0.21% (95% CI -0.39 to 0.03%) demonstrating noninferiority. Clinical improvements in blood glucose were similar between groups. End-point mean fasting blood glucose was 7.0 vs. 6.9 mmol/L (p=0.85) for lispro protamine and detemir respectively. The percentage of patients achieving an A1c of $\leq$7.0% were 34.9% for lispro protamine and 31.2% detemir patients (p<0.001). Weight gain was a more significant issue for lispro protamine patients than those taking detemir (mean difference 1.52 kg; p <0.001). As were rates of patients' hypoglycemia adjusted per year: 24.2 episodes with lispro protamine vs. 16.2 episodes with detemir (p=0.001). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.[13]

Strojek et al examined the comparative efficacy of insulin glargine with insulin lispro protamine suspension in patients with type 2 diabetes. Insulin naïve patients (n= 471) were randomized to either lispro protamine or glargine for 24 weeks. Patients were allowed to continue pre-study oral diabetes medications; glargine patients were dosed one daily at bedtime, while lispro protamine patients could be dosed once or twice daily. The primary objective was comparative decrease in A1c from baseline. Decrease in baseline at endpoint was similar between groups (lispro protamine -1.46% and glargine -1.41%; least square mean difference -.0.05%, 95% CI -0.21 to 0.11%). Predetermined noninferiority margin was set at 0.4% meaning lispro protamine is noninferior to glargine. Difference in weight gain was not significant (difference between treatments -0.01kg, 95% CI -0.61 to 0.59 kg). Overall hypoglycemia rates (episodes/patient/year) were similar for lispro protamine and glargine (24.2 vs. 23.0). However, severe hypoglycemia was higher for lispro protamine than glargine patients (9 vs.2 patients; p = 0.04). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.[14]

Philotheou et al conducted an open label study in type 1 diabetics to compare the efficacy of insulin glulisine with insulin lispro. Children (n= 572) under 18 years old were randomized to either glulisine or lispro taken up to 15 minutes before a meal. The primary endpoint was comparative change in A1c from baseline after 26 weeks. Mean difference in A1c change from baseline was similar between the two groups: 0.10% glulisine vs. 0.16% lispro (difference 0.06%, 95% CI -0.24 to 0.12). Predetermined noninferiority margin was set at 0.4% meaning glulisine is noninferior to lispro. When stratified by age groups, the percentage of patients reaching their American Diabetes Association age specific A1c target by week 26 was significantly higher for glulisine (38.4%) than lispro (32%) patients (p=0.039). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.[15]

Hsia et al compared the efficacy of adding basal insulin to poorly controlled inner city type 2 diabetics. In this small open label trial, 85 insulin naïve patients were randomized to receive once daily bedtime NPH insulin, bedtime glargine, or morning glargine. The primary outcome was comparative change in A1c from baseline to endpoint at 26 weeks. All three groups had similar decreases in A1c; the overall mean end A1c was 7.8%, with no significant difference between treatment groups. There were also no differences in the proportions of subjects achieving HbA1c ≤ 7.0% by study end (23%, 23% and 28% for NPH, bedtime glargine, and morning glargine, respectively). There was no difference in weight gain between glargine groups: patients taking glargine at bedtime gained an average of 1.7 kg while those taking morning glargine also gained 1.7 kg. The NPH group lost an average of 0.2 kg, a significant improvement compared with

both glargine groups (p<0.05). Overall rates of hypoglycemia were not significantly different between treatment groups. This was a poor quality trial. It was a small study, ended early due to funding issues, with poorly outlined design methodology and incomplete outcome data reported.[16]

Van Bon et al performed a clinical trial to compare the efficacy of three rapid acting insulin (glulisine, aspart, or lispro) administered through continuous subcutaneous insulin infusion. This was an open label cross-over study; all subjects were treated with each insulin. Type 1 diabetics were randomized to one of three treatment orders: glulisine-aspart-lispro, aspart-lispro-glulisine, or lispro-glulisine-aspart. Each insulin was used for 13 weeks. The primary outcome was to establish the superiority of glulisine over aspart or lispro on unexplained hyperglycemia and perceived infusion set occlusion. A prespecified p value of 0.025 was considered significant to correct for multiple testing. Patients with a perceived infusion set occlusion and at least one unexplained episode of hyperglycemia were not significantly different between glulisine and aspart or glulisine and lispro: 68.4% of glulisine versus 62.1% aspart patients p=0.04; versus lispro patients 61.3% p=0.03. No differences were seen between insulin groups in A1c at endpoint. More patients experienced hypoglycemia in the glulisine group than in either the aspart or lispro cohorts (rates of hypoglycemia measured as episode per person per year); glulisine 73.84% versus aspart 65.01% p=0.008; versus lispro 62.69% p<0.001. This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.[17]

Sourij et al conducted a small, open-label, crossover trial to compare postprandial hyperglycemia with short-acting insulin aspart and regular human insulin. Thirteen adult type-2 diabetics were randomized for the study; all were on preexisting insulin therapy. Subjects were given either human insulin or insulin aspart before a standardized breakfast and again before a standardized lunch four hours later. Therapy was given on two separate days with three days separating treatments. All subjects were treated with both types of insulin. The primary outcome was whether postprandial hyperglycemia is reduced with an insulin analog as opposed to human insulin. Secondary outcomes included change in free fatty acids, triglycerides, c-peptide, and intact proinsulin levels. Blood was drawn for levels every 30 minutes with a fasting level drawn prior to the first meal and continued until four hours after the second meal. The mean increase in blood glucose was significantly lower with aspart use than with regular human insulin (24.1833 vs. 34.92 mg/dl, P=0.02). Free fatty acid reduction was also significantly higher with aspart use (0.47 vs 0.35 mmol/l, P<0.001). The mean increase in intact proinsulin was significantly lower after aspart use versus human insulin (10.53 vs 15.20 pmol/l, P=0.001). No differences were observed in the C-peptide levels between the two groups. This was a poor quality study. It was an open label design with a very small cohort. Randomization methodology was not defined. Although the primary outcome was postprandial hyperglycemia, secondary outcomes such as free fatty acid reduction and intact proinsulin levels were promoted as the primary importance. Overall, clinical significance of findings is unclear.[18]

Koivisto et al compared the efficacy and safety of lispro protamine insulin suspension versus insulin glargine. Type-2 diabetics (n=383) were randomized to either once daily lispro protamine suspension or glargine for 24 weeks. All subjects were also given bolus lispro insulin for meals. The primary outcome was mean change in A1c at study end. Secondary outcomes included HbA1c <7.0%, blood glucose profiles, insulin doses, hypoglycemic episodes, adverse events and vital signs. At 24 weeks mean change in percent A1c was -1.05% for lispro protamine and -1.20% for glargine. Predetermined noninferiority margin was set at 0.4%: least-square mean between-treatment difference was 0.1%, 95% CI −0.11 to 0.31. HbA1c <7.0% was achieved by 21.7% of lispro protamine versus 29.4% glargine of patients (p=0.01). Mean basal/mealtime insulin doses at week 24 were 29.6/36.2 IU/day (ILPS) versus 32.8/42.2IU/day (glargine); the difference was not statistically significant for total dose (p = 0.7). For adverse events, 39% of lispro protamine versus 43% of glargine patients reported at least one event (p = 0.4); 56.1% versus 63.6% of patients experienced hypoglycemia (p = 0.2). No relevant differences were noted in any other variables including vital signs, blood glucose profiles, or insulin doses. This was a poor quality trial. Trial design was open label and methods for randomization and subject selection was not described.[19]

Thalange et al examined the difference in safety and efficacy between insulin detemir and neutral protamine Hagedorn (NPH). Children with type-1 diabetes aged two to 16 (n=348) were randomized to one of the two long acting insulin in this multinational, open-labelled trial; only results for children aged two to five (n=82) was reported in this paper. Results for all ages were reported elsewhere.[20] All subjects were given mealtime insulin aspart. The trial duration was one year. The primary endpoint was decrease in hemoglobin A1c. After 52 weeks, subjects on detemir had a greater decrease from baseline in mean A1c than those on NPH: -0.1% vs. 0.2%; p>0.05. Mean fasting glucose levels also decreased greater for detemir than NPH subjects (−1.0 vs. −0.45 mmol/L) although this was also nonsignificant. Less patients receiving detemir reported an adverse event than with NPH (69.0 vs. 77.5%; this trend was also seen in serious adverse events (12% vs. 15%). A lower rate of hypoglycemia was observed with detemir compared with NPH (50.6 vs. 78.3 episodes per patient-year). No p value was reported for adverse events. This was a poor quality trial. It was an open label design and methodology for randomization was not discussed. Although the trail recruited children up to age 16, only data for subjects under 5 years old was reported. In addition, important patient baseline characteristics were not well balanced (gender percentages were not comparable) and statistical analysis was not performed for important safety outcomes.[21]

Aschner et al conducted a study to compare the efficacy and safety of insulin glargine with sitagliptin a dipeptidyl peptidase-4 (DPP-4) inhibitor in patients with uncontrolled diabetes. Adults with type-2 diabetes (n=515) were randomized to either 24 weeks insulin glargine (titrated to attain a fasting blood glucose of 4.0 to 5.5 mmol/L) or 100 mg oral sitagliptin once daily. The primary outcome was change from baseline in mean A1c after 24 weeks. At study end, adjusted mean reduction in HbA1c was greater for patients on insulin glargine (n=227; –1.72%) than for those on sitagliptin (n=253; –1.13%) with a mean difference of –0.59%; 95% CI –0.77 to –0.42. The rate of all hypoglycemic episodes was greater with insulin glargine than with sitagliptin (4.21 vs. 0.50 events per patient-year; p<0·0001). Severe hypoglycemia occurred in only three (1%) patients on insulin glargine and one (<1%) on sitagliptin. This was a fair quality trial. Although it was an open label design and the treatments were from different classes, the trial method and materials were well defined; as were the trial outcomes and results.[22]

Inagaki et al compared the efficacy of exenatide extended release with insulin glargine in lowering the hemoglobin A1c in patients with uncontrolled type-2 diabetes. Adults subjects (n=427) were randomized to either once daily insulin glargine or once weekly exenatide for 26 weeks. Subjects were able to continue their oral diabetic medications. The primary outcome studied was mean change in A1c from baseline at trial end with a predefined noninferiority margin of 0.4%. Secondary analyses included analysis of superiority for between-group comparisons of change in weight and the proportion of patients reaching HbA1c target levels of <7.0%. Exenatide was statistically noninferior to insulin glargine for the change in HbA1c from baseline to end point (least squares mean difference -0.43%, 95% CI -0.59 to -0.26%. In addition, subjects receiving exenatide had a significantly greater number of patients compared with insulin glargine achieve HbA1c target levels of <7.0% (42.2 vs 21.0%; p<0.001) at end point. Patient weight had a greater reduction with exenatide than with insulin glargine (least squares mean difference (-2.01 kg; 95% CI -2.46 to -1.56). This was a poor quality trial. Trial design was open label and methods for randomization and subject selection was not described.[23]

Mathieson et al conducted a trial to compare the efficacy of different long-acting insulin in pregnant patients with type-1 diabetes. Women (n= 310) were randomized to use either insulin detemir or neutral protamine Hagedorn (NPH) for up to 12 months prior to pregnancy or started at eight to 12 weeks gestation. All patients received supplemental bolus insulin aspart. The primary endpoint was mean change from baseline in A1c at 36 weeks gestation. The predetermined noninferiority margin was set at 0.4%. The estimated A1c at 36 weeks was 6.27% for insulin detemir and 6.33% for NPH. Insulin detemir was determined to be noninferior to NPH (mean difference –0.06%; 95% CI –0.21 to 0.08). Secondary outcome fasting plasma glucose (FPG) was significantly lower with insulin detemir rather than NPH: at 36 gestation weeks 85.7 versus 97.4 mg/dL, p=0.017. Hypoglycemic episodes were statistically similar between the two group: 16% of the detemir subjects versus 21% in the NPH group. There was no difference between groups in weight gain during pregnancy (11.5 kg in the detemir group and 11.0 kg in the NPH group). This was a poor quality trial. The study design was open label which can increase the risk of bias. In addition the length of time for the treatment was not fixed and not well explained.[24]

Thalange et al examined the difference in safety and efficacy between insulin detemir and neutral protamine Hagedorn (NPH). Children with type-1 diabetes aged two to 16 (n=348) were randomized to one of the two long acting insulin in this multinational, open-labelled trial. The primary outcome was change in A1c from baseline after 52 weeks. Secondary outcomes included weight change and rate of hypoglycemia. At 52 weeks, insulin detemir was determined to be non-inferior to NPH insulin with regard to HbA1c (mean difference 0.13%, 95% CI –0.12 to 0.37). Hypoglycemic events per subject-year were significantly lower with insulin detemir than with NPH insulin (rate ratio 0.76; 95% CI 0.60 to 0.97. Weight standard deviation (SD) scores (body weight standardized by age and gender) decreased with insulin detemir, but increased slightly with NPH insulin (change: –0.12 vs. 0.04, P < 0.001). This was a poor quality study. Trial design was open label and methods for randomization and subject selection was not described.[20]

Hickman et al compared the safety and tolerability of metformin to insulin for glycemic control among women with preexisting type 2 and early A2 gestational diabetes. Pregnant women (n=28) were randomized to receive either oral metformin or long-acting insulin. The primary outcome was glycemic control compared between the two groups as defined as >50% capillary blood glucose within target range. Mean study outcome was 11.5 weeks. No significant difference was apparent when evaluated over the entire course of study enrollment or at any of the 2-week intervals chosen for evaluation Secondary outcomes included adverse events and weight gain. Women treated with metformin had significantly fewer subjective episodes of hypoglycemia compared with those using insulin (0% versus 36%; p= 0.04) as well as reported glucose values < 60 mg/dL (7.1% versus 50%; p= 0.03). All metformin subjects continued using metformin after delivery and 43% required supplemental insulin to achieve glycemic control. This was a poor quality, very small study. There were differences in patient baseline demographics and the primary outcome was not well defined.[25]

Davies et al looked at the difference in efficacy and safety of exenatide extended release compared with insulin detemir. Adults with type-2 diabetes (n=216) were randomized to receive either exenatide 2 mg once weekly or detemir once or twice daily (titrated to a fasting blood glucose of 5.5mmol/mol). The primary outcome was the amount of patients achieving an A1c of <7.0% and weight loss of >1 kg after 26 weeks. Patients treated with exenatide were significantly more likely to achieve the primary outcome than insulin detemir patients (44.1% vs. 11.4%; P= 0.0001). Individually, exenatide use resulted in significantly greater reductions than detemir in A1C (least-square mean -1.30% vs. -0.88%; P=0.0001) and weight (-2.7 kg vs. +0.8 kg; P=0.0001). Gastrointestinal-related and injection site–related adverse events occurred more frequently with exenatide than with detemir. Five (6%) exenatide patients and six (7%) detemir patients experienced minor hypoglycemia; no serious hypoglycemia events were reported. This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.[26]

Spaulonci et al evaluated metformin versus neutral protamine Hagedorn (NPH) insulin for glycemic control in women with gestational diabetes. Subjects (n=92) with gestational diabetes who failed to achieve glycemic goals through nonpharmacological means (diet and exercise) were randomized to receive metformin (titrated to a goal dose of 850 three times daily) or NPH insulin (0.4 units per kg in three divided doses). The primary outcomes were rates of preeclampsia, prematurity and neonatal outcomes including hypoglycemia, macrosomia, and hyperbilirubinemia. Mean glucose levels were also tracked. There was no difference between groups in rates of preeclampsia (p=0.420), or prematurity (p>0.99). In neonatal outcomes there were no significant differences between the two groups In frequency of macrosomia (p=0.242). There were more occurrences of neonatal hypoglycemia in the insulin group compared with newborns from the metformin group (p=0.032). Hyperbilirubinemia frequency was not reported. Subjects on metformin had lower mean glucose levels (p=0.020), and less weight gain (p=.0.002) than insulin subjects. This was a poor quality study. Study design was not specified although it was most likely open label design; study methodology (randomization, blinding, etc.) was also not described. The primary outcomes described in the body of the paper were not all reported and a secondary outcome was reported as the primary endpoint in the abstract. Study duration was not reported.[27]

Karagianni et al. examined the difference in efficacy between exenatide and insulin glargine in diabetes. Adults (n=47) with type two diabetes were given either exenatide twice daily or glargine once daily for 26 weeks. The primary outcome was change in hemoglobin A1c; secondary outcomes included change in body mass index (BMI), lipid profile and blood pressure. Adverse events, including episodes of hypoglycemia and gastrointestinal symptoms, were recorded. There was not a statistically significant difference in the decrease in A1c after week 26 (-1.3% in the exenatide vs. -0.5% in the glargine group; p=0.131). However, nine exenatide and six glargine patients achieved HbA1c ≤ 7% by the 26th week (50% vs. 21%; p=0.036). There was a significant decrease in BMI by study end for exenatide subjects but not for the insulin group (-2.5 kg/m^2 vs. 0.1 kg/m^2; p<0.001). Exenatide subjects also had a larger decrease in triglycerides than the insulin cohort (-37 mg/dL vs. -10 mg/dL; p=0.022). There was no significant difference in blood pressure, LDL or HDL levels between treatment groups. Six patients in the insulin glargine group experienced hypoglycemia compared with no patients in the exenatide group (33.3% vs. 0%; p=0.039). Gastrointestinal adverse events were higher in the exenatide group (p=0.114). This was a poor quality study with multiple opportunities for bias. The study was a very small open label study, subjects were not randomized, and treatment groups were not equal. Patient characteristics at baseline were not provided.[28]

Meneghini et al. performed an open label study to assess the comparative efficacy of basal insulin initiation added to existing metformin in type 2 diabetics. Adults (n=457) were randomized to either insulin detemir or insulin glargine once daily for 26 weeks. The primary efficacy endpoint was comparison of change in A1c from baseline. Secondary endpoints included the proportion of subjects achieving HbA1c levels ≤7% at 26 weeks, and the proportions achieving this without symptomatic hypoglycemia during the last month of treatment. At study end, there was no significant difference in mean change in A1c from baseline for either treatment group (-0.48% for detemir vs. -0.74% for glargine; p=0.30). More patients achieved an A1c of 7% or less by 26 weeks in the glargine group compared with the detemir cohort (53% vs. 38%; p=0.026). Hypoglycemia occurred less frequently with detemir rather than glargine treatment (rate ratio 0.73; 95% CI 0.54–0.98). Rates of hypoglycemia in patients who achieved an A1c of $\leq$7% were not different between treatments. Weight decreased in detemir and increased in glargine subjects (-0.49 kg vs. 1.0 kg; 95% CI −2.17 to −0.89 kg). This was a fair quality trial. Although it was an open label design, the trial method and materials were well defined as were the trial outcomes and results.[29]

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Insulins

Goal(s):

- To ensure appropriate drug use and safety of hypoglycemic agents by authorization utilization in specified patient population

Initiative:

- Initiative

Length of Authorization:

Up to 12 months

Requires PA: Non-Preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPh; Deny, (Not covered by the OHP)
3. Is the request for an Insulin Pen or Cartridge?	Yes: Go to #4	No: Go to #5
4. Is the insulin being administered by the patient or a non-professional caregiver AND any of the following criteria apply: • Does the patient have physical dexterity problems/vision impairment • Comprehension related issues • Dosing errors with use of vials • The patient is on a low dose of insulin (≤40 units/day) • Is the request for a child < 18 years old? •	Yes: Go to #5	No: Pass to RPh; go to #6

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. • Yes: Inform provider of covered alternatives in class. www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. For insulin pens approve for 1 year (other preferred products covered without a PA) • No: Approve for 1 year		
6. RPh only • Requests for insulin pens and cartridges on a client-specific basis • Refer to the PDL for the preferred pens. AND/OR • If the above criteria are met and the request is NOT for convenience issues alone then approve insulin pen or cartridge use.		

P&T / DUR Action: 9/16/10 (KS)
Revision(s): 12/16/10
Initiated: 1/1/11

Appendix 2: Abstracts of Randomized Control Trials

Forst T, Larbig M, Hohberg C, et al. Adding insulin glargine vs. NPH insulin to metformin results in a more efficient postprandial beta-cell protection in individuals with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(5):437-441. doi:10.1111/j.1463-1326.2010.01209.x.

Aim: Postprandial release of intact proinsulin (IP) is an independent marker for β-cell dysfunction in patients with type 2 diabetes. This open-label, parallel-group, two-arm, pilot study compared the β-cell protective effect of adding insulin glargine (GLA) vs. NPH insulin to ongoing metformin.

Material and methods: Overall, 28 insulin-naive type 2 diabetes subjects (mean ± SD age, 61.5 ± 6.7 years; diabetes duration, 9.8 ± 6.5 years; HbA1c, 7.1 ± 0.5%; BMI, 30.7 ± 4.3 kg/m2) treated with metformin and sulfonylurea were randomized to add once-daily GLA or NPH at bedtime. At baseline and after 3 months, subjects received a standardized breakfast, lunch and dinner, with pre- and postprandial blood sampling to measure plasma IP, total insulin and blood glucose (BG).

Results: Insulin dose after 3 months was comparable in both groups (GLA vs. NPH: 23.6 ± 13.4 vs. 23.3 ± 12.7; p = NS). Both treatments significantly reduced fasting BG levels (GLA: 158 ± 19 to 121 ± 23 mg/dl; NPH: 156 ± 34 to 119 ± 29 mg/dl; both p < 0.01 vs. baseline). Fasting and postprandial BG levels did not differ between groups. IP levels decreased in both groups (p < 0.05 at all timepoints). Although IP release after breakfast did not differ between treatments, GLA induced a greater reduction in IP release after lunch (p = 0.08) and dinner (p = 0.04). Total plasma insulin levels did not differ between groups.

Conclusions: Adding basal insulin to metformin reduces postprandial β-cell load. While GLA and NPH had comparable effects at breakfast, GLA reduces β-cell stress more effectively at dinner, and with a trend at lunch, most probably because of its longer lasting pharmacodynamic profile.

Swinnen SG, Dain M-P, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care*. 2010;33(6):1176-1178. doi:10.2337/dc09-2294.

OBJECTIVE— To determine whether glargine is noninferior to detemir regarding the percentage of patients reaching A1C _7% without symptomatic hypoglycemia _3.1 mmol/l.

RESEARCH DESIGN AND METHODS— In this 24-week trial, 973 insulin-naive type 2 diabetic patients on stable oral glucose-lowering drugs with A1C 7.0–10.5% were randomized to glargine once daily or detemir twice daily. Insulin doses were systematically titrated.

RESULTS— 27.5 and 25.6% of patients reached the primary outcome with glargine and detemir, respectively, demonstrating the noninferiority of glargine. Improvements in A1C were _1.46 _ 1.09% for glargine and _1.54 _ 1.11% for detemir (*P* _ 0.149), with similar proportions of patients achieving A1C _7% (*P* _ 0.254) but more detemir-treated patients reaching A1C _6.5% (*P* _ 0.017). Hypoglycemia risk was similar. Weight gain was higher for glargine (difference: 0.77 kg, *P*_0.001). Glargine doses were lower than detemir doses: 43.5_ 29.0 vs. 76.5 _ 50.5 units/day (*P* _ 0.001).

CONCLUSIONS— In insulin-naive type 2 diabetic patients, glargine reached similar control as detemir, with more weight gain, but required significantly lower doses.

Chacra AR, Kipnes M, Ilag LL, Sarwat S, Giaconia J, Chan J. Comparison of insulin lispro protamine suspension and insulin detemir in basal-bolus therapy in patients with Type 1 diabetes. *Diabetic Medicine*. 2010;27(5):563-569. doi:10.1111/j.1464-5491.2010.02986.x.

Aims The efficacy of two basal insulins, insulin lispro protamine suspension (ILPS) and insulin detemir, was compared in basal bolus regimens in Type 1 diabetes.

Methods In this 32-week, multinational, parallel-group, randomized, controlled trial, adult patients with Type 1 diabetes received ILPS or insulin detemir, injected twice daily (before breakfast and bedtime) and prandial insulin lispro three times daily. The primary outcome was change in glycated haemoglobin (HbA1c) from baseline to endpoint.

Results Least squares mean (_se) changes in HbA1c were similar between groups, meeting non-inferiority (margin, 0.4%):)0.69 _ 0.07% for ILPS and)0.59 _ 0.07% for insulin detemir [between-treatment difference)0.10%; 95% confidence interval (CI))0.29, 0.10]. Standard deviation of fasting blood glucose was similar (non-inferiority margin 0.8 mmol ⁄ l): 2.74 _ 0.14 mmol⁄ l for ILPS and 2.38 _ 0.14 mmol⁄ l for insulin detemir (CI)0.03, 0.75). Patients on ILPS gained more weight (1.59 _ 0.23 kg vs. 0.62 _ 0.24 kg; CI 0.34, 1.60; margin 1.5 kg). Weight-adjusted daily total and prandial insulin doses were lower for ILPS (prandial insulin, 0.38 _ 0.01 U⁄ kg ⁄ day for ILPS, 0.44 _ 0.01 U⁄ kg ⁄ day for insulin detemir; P = 0.004); daily basal insulin dose was similar. All hypoglycaemia incidence and rate and nocturnal hypoglycaemia incidence were similar between groups; nocturnal hypoglycaemia rate was lower for insulin detemir (mean _ sd 0.79 _ 1.23 for ILPS, 0.49 _ 0.85 for insulin detemir; P = 0.001). Severe hypoglycaemia rate was 0.03 _ 0.11 for ILPS and 0.02 _ 0.10 for insulin detemir (P = 0.37).

Conclusions ILPS-treated patients with Type 1 diabetes achieved similar glycaemic control as insulin detemir-treated patients after 32 weeks. Glucose variability was similar. While weight gain and nocturnal hypoglycaemia rate were statistically higher with ILPS, the clinical relevance is unclear.

Fogelfeld L, Dharmalingam M, Robling K, Jones C, Swanson D, Jacober S. A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naive patients with Type 2 diabetes. *Diabetic Medicine*. 2010;27(2):181-188. doi:10.1111/j.1464-5491.2009.02899.x.

Aims Insulin lispro protamine suspension (ILPS) and insulin detemir were compared in insulin-naive patients with Type 2 diabetes poorly controlled by oral glucose-lowering agents (OGLAs) to demonstrate non-inferior overall glycaemic control.

Methods This was a 24-week, multinational, open-label, parallel-group, treat-to-target trial. Adults taking two or more OGLAs were randomized to ILPS (n = 223) or detemir (n = 219) once daily at bedtime. Doses were titrated to target fasting blood glucose (FBG) 5.0–7.2 mmol⁄ l. A pre-breakfast dose was added up to week 8 per prespecified criteria. The primary objective was comparison of glycated haemoglobin (HbA1c) change from baseline (non-inferiority margin 0.4%).

Results At end-point, HbA1c decreased from 8.8 _ 0.7% in both groups to 7.3 _ 0.9% (ILPS) and 7.5 _ 1.1% (detemir). Least-squares mean difference (95% confidence interval) for HbA1c [)0.21% ()0.39,)0.03)] and glycaemic variability [0.10 mmol ⁄ l ()0.02, 0.23)] demonstrated non-inferiority. End-

point mean FBG was 7.0 vs. 6.9 mmol⁄l (P = 0.85), and percentages of patients achieving H < 7.0%were 34.9% vs. 31.2% for ILPS vs. detemir. More ILPS patients used twice-daily dosing (59% vs. 49%). Mean daily insulin dose was 0.39 vs. 0.46 U⁄ kg (P = 0.005) and weight gain was 1.88 vs. 0.36 kg (P < 0.001) for ILPS vs. detemir. Overall hypoglycaemia (episodes•patient-1•year-1) (24.2 _ 33.0 vs. 16.2 _ 26.1, P = 0.001) and nocturnal (6.3 _ 12.1 vs. 3.8 _ 13.2, P < 0.001) rates were higher for ILPS.
Conclusions At end-point, ILPS was non-inferior to detemir in HbA1c change from baseline. Patients using ILPS achieved lower end-point HbA1c with lower insulin doses but greater hypoglycaemia and weight gain.

Strojek K, Shi C, Carey MA, Jacober SJ. Addition of insulin lispro protamine suspension or insulin glargine to oral type 2 diabetes regimens: a randomized trial. *Diabetes Obes Metab*. 2010;12(10):916-922. doi:10.1111/j.1463-1326.2010.01257.x.
Aims: The addition of basal insulin to existing oral therapy can help patients with type 2 diabetes (T2D) achieve glycaemic targets. This study compares the efficacy and safety of insulin lispro protamine suspension (ILPS) and insulin glargine in insulin-naive patients with T2D and inadequate control on oral antihyperglycaemic medication (OAM).
Materials and Methods: An open-label, randomized, multicentre, multinational 24-week study of 471 patients receiving ≥2 OAMs for ≥3 months with a body mass index between 25 and 45 kg/m2 and HbA1c 7.5–10.0% was conducted. ILPS was injected once or twice daily vs. glargine injected once daily plus prestudy OAMs. Primary objective compared the HbA1c change from baseline.
Results: HbA1c change from baseline to endpoint was similar in both groups [−1.46% (ILPS) and −1.41% (glargine)]. Least-squares mean difference (95% CI) for HbA1c (−0.05 [−0.21, 0.11]%), glycaemic variability (0.06 [−0.06, 0.19] mmol/l) and weight change (−0.01 [−0.61, 0.59] kg) showed non-inferiority (margins of 0.4%, 0.8 mmol/l and 1.5 kg, respectively). Percentages of patients achieving HbA1c <7.0% were 43.8% ILPS and 41.2% glargine. Mean daily insulin dose was 0.39 vs. 0.35 U/kg (p = 0.02) and weight gain was 1.04 vs. 1.07 kg for ILPS vs. glargine (p = 0.98). Overall hypoglycaemia (episodes/patient/year) was similar for ILPS and glargine (24.2 ± 28.8 vs. 23.0 ± 30.9); nocturnal (6.1 ± 10.6 vs. 4.1 ± 9.4, p < 0.001) rates were higher for ILPS. Severe hypoglycaemia was higher for ILPS vs. glargine (n = 9 vs. n = 2; p = 0.04).
Conclusions: At endpoint, ILPS was non-inferior to glargine in HbA1c change from baseline, but associated with increased risk of hypoglycaemia

Philotheou A, Arslanian S, Blatniczky L, Peterkova V, Souhami E, Danne T. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. *Diabetes Technol Ther*. 2011;13(3):327-334. doi:10.1089/dia.2010.0072.
Background: We compared the efficacy and safety of insulin glulisine with insulin lispro as part of a basal–bolus regimen in children and adolescents with type 1 diabetes.
Methods: Overall, 572 children and adolescents (4–17 years old) using insulin glargine or neutral protamine Hagedorn insulin as basal insulin were enrolled in a 26-week, multicenter, open, centrally randomized, parallel group, noninferiority study. Subjects were randomized to receive glulisine (n¼277) or lispro (n¼295) 0–15 min premeal.
Results: Baseline-to-endpoint hemoglobin A1c changes were similar between the two insulins: adjusted mean change (glulisine vs. lispro), 0.10% versus 0.16%; between-treatment difference (glulisine–lispro), &minsu;0.06, 95% confidence interval (_0.24; 0.12); and prespecified noninferiority margin, 0.4%. Overall, for all age groups together, the percentage of patients achieving American Diabetes Association age-specific A1c targets at endpoint was significantly higher (P¼0.039) with glulisine (38.4%) versus lispro (32.0%). From Month 4 to endpoint, both ''all'' and ''severe'' symptomatic hypoglycemia rates were similar (3.10 vs. 2.91 and 0.06 vs. 0.07 events/patient-month, respectively). Frequency and type of adverse events, serious adverse events, or hypoglycemia reported as serious adverse events were similar between both groups.
Conclusions: Glulisine was as effective as lispro in baseline-to-endpoint A1c change, and both treatments were similarly well tolerated.

Hsia SH. Insulin glargine compared to NPH among insulin-naïve, U.S. inner city, ethnic minority type 2 diabetic patients. *Diabetes Res Clin Pract*. 2011;91(3):293-299. doi:10.1016/j.diabres.2010.11.028.
Aims—We compared basal regimens of glargine or NPH among insulin-naïve, U.S. inner city, ethnic minority type 2 diabetic patients who were sub-optimally controlled on maximally tolerated doses of combination oral agents.
Methods—Eighty-five subjects were randomized to 26 weeks of open-label, add-on therapy using single doses of bedtime NPH, bedtime glargine, or morning glargine; initially through an 8- week dose titration phase, followed by a 16-week maintenance phase during which insulin doses were adjusted only to avoid symptomatic hypoglycemia.
Results—All 3 groups were comparable at baseline (mean HbA1c 9.3 ± 1.4%), and improved their HbA1c (to 7.8 ± 1.3%), fasting, and pre-supper glucose readings, with no significant between-group differences. Weight gain was greater with either glargine regimen (+3.1 ± 4.1 kg and +1.7 ± 4.2 kg) compared to NPH (−0.2 ± 3.9 kg), despite comparable total insulin doses. Presupper hypoglycemia occurred more frequently with morning glargine, but nocturnal hypoglycemia and improvements in treatment satisfaction did not differ among groups.
Conclusions—Among inner city ethnic minority type 2 diabetic patients in the U.S., we found no differences in basal glycemic control or nocturnal hypoglycemia between glargine and NPH, although glargine precipitated greater weight gain.

Van Bon AC, Bode BW, Sert-Langeron C, DeVries JH, Charpentier G. Insulin Glulisine Compared to Insulin Aspart and to Insulin Lispro Administered by Continuous Subcutaneous Insulin Infusion in Patients with Type 1 Diabetes: A Randomized Controlled Trial. *Diabetes Technology & Therapeutics*. 2011;13(6):607-614. doi:10.1089/dia.2010.0224.
Background: In a previous pilot study comparing insulin glulisine (GLU) with insulin aspart (ASP) administered by continuous subcutaneous insulin infusion (CSII), GLU-treated patients did show a trend toward fewer catheter occlusions compared with ASP-treated patients. Here we performed a randomized open-label, three-way crossover, controlled multicenter study comparing GLU with ASP and insulin lispro (LIS).

Methods: Subjects with type 1 diabetes were allocated to one of three treatment orders—GLU-ASP-LIS, ASP-LISGLU, or LIS-GLU-ASP—with each insulin used for 13 weeks. The study was designed to demonstrate the superiority of GLU over ASP and LIS on unexplained hyperglycemia and/or perceived infusion set occlusion. A prespecified P value of 0.025 was considered significant to correct for multiple testing.
Results: Percentages of subjects with at least one unexplained hyperglycemia and/or infusion set occlusion were not significantly different between GLU and ASP (68.4% [62.7–74.1%] vs. 62.1% [56.2–68.1%], P¼0.04) and GLU and LIS (68.4% [62.7–74.1%] vs. 61.3% [55.4–67.3%], P¼0.03). No differences were seen in hemoglobin A1c at end point, most points of the seven-point glucose curves, severe hypoglycemia, and symptomatic ketoacidosis. The overall rate of hypoglycemia with a plasma glucose level below 70 mg/dL per patient-year was significantly
different between GLU and ASP (73.84 vs. 65.01, P¼0.008) and GLU and LIS (73.84 vs. 62.69, P<0.001). Insulin doses remained unchanged during the trial.
Conclusions: GLU was not superior to ASP and LIS with no significant difference seen among GLU, ASP, and LIS in CSII use with respect to unexplained hyperglycemia and/or perceived catheter set occlusion. GLU was associated with a higher frequency of symptomatic hypoglycemia, possibly because of slight overdosing, as previous trials suggested lower insulin requirements when GLU is initiated in type 1 diabetes.

Sourij H, Schmoelzer I, de Campo A, et al. Non-glycemic effects of insulin therapy: a comparison between insulin aspart and regular human insulin during two consecutive meals in patients with type 2 diabetes. *European Journal of Endocrinology*. 2011;165(2):269-274. doi:10.1530/EJE-11-0061
Objective: To control postprandial hyperglycemia in insulin-treated type 2 diabetic patients, prandial therapy with regular human insulin (HI) or fast acting insulin analogs is used. Postprandial hyperglycemia seems to be reduced more effectively with insulin analogs than with normal insulin, but there are no data concerning the effect on lipolysis or pancreatic insulin and proinsulin secretion of normal insulin in comparison to insulin analogs.
Design and methods: We included 13 patients with type 2 diabetes mellitus (age 62.2G10.3 years) with preexisting insulin therapy in this crossover, prospective, open-labeled, randomized trial comparing regular HI with insulin aspart (IA) in the setting of a standardized breakfast and a standardized lunch 4 h later. Blood samples for determination of glucose, free fatty acids (FFA), triglycerides, C-peptide, and intact proinsulin were drawn during fasting and every 30 min until 4 h after the second test meal. Statistical analysis was performed with ANOVA for repeated measurements and paired Student's t-test.
Results: The mean increase in blood glucose was significantly lower after IA (24.18G16.33 vs 34.92G29.07 mg/dl, PZ0.02) compared with HI. Both therapies reduced FFA; however, the mean reduction was significantly higher after IA than after HI (K0.47G0.16 vs K0.35G0.15 mmol/l, P!0.001). The mean increase in intact proinsulin was significantly lower after IA than after HI (10.53G5 vs 15.20G6.83 pmol/l, P!0.001). No differences were observed in the C-peptide levels between the two groups.
Conclusion: In the setting of two consecutive meals, IA reduces lipolysis and proinsulin secretion more effectively than HI.

Koivisto V, Cleall S, Pontiroli AE, Giugliano D. Comparison of insulin lispro protamine suspension versus insulin glargine once daily in basal-bolus therapies with insulin lispro in type 2 diabetes patients: a prospective randomized open-label trial. *Diabetes Obes Metab*. 2011;13(12):1149-1157. doi:10.1111/j.1463-1326.2011.01484.x.
Aims: To compare the efficacy and safety of insulin lispro protamine suspension (ILPS) versus insulin glargine once daily in a basal-bolus regimen in type 2 diabetes mellitus (T2DM) patients.
Methods: Three hundred eighty-three insulin-treated patients were randomized to either ILPS plus lispro or glargine plus lispro in this open-label 24-week European study. Insulin doses were titrated to predefined blood glucose (BG) targets. Non-inferiority of ILPS versus glargine was assessed by comparing the upper limit of the 95% confidence interval (CI) for the change of HbA1c from baseline to week 24 (adjusted for country and baseline HbA1c) with the non-inferiority margin of 0.4%. Secondary endpoints included HbA1c categories, BG profiles, insulin doses, hypoglycaemic episodes, adverse events and vital signs.
Results: Non-inferiority of ILPS versus glargine in the change of HbA1c from baseline was shown: least-square mean between-treatment difference (95% CI) was 0.1% (−0.11; 0.31). Mean changes at week 24 were −1.05% (ILPS) and −1.20% (glargine). HbA1c <7.0% was achieved by 21.7 versus 29.4% of patients. Mean basal/mealtime insulin doses at week 24 were 29.6/36.2 IU/day (ILPS) versus 32.8/42.2 IU/day (glargine); the difference was not statistically significant for total dose (p = 0.7). In both groups, 56.1/25.7% versus 63.6/19.3% of patients experienced any/nocturnal hypoglycaemia (p = 0.2 for both). No relevant differences were noted in any other variables.
Conclusions: A basal-bolus regimen with ILPS once daily resulted in non-inferior glycaemic control compared to a similar regimen with glargine, without statistically significant or clinically relevant differences in hypoglycaemia. ILPS-based regimens can be considered an alternative to basal-bolus regimens with glargine for T2DM patients.

Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. *Pediatr Diabetes*. 2011;12(7):632-641. doi:10.1111/j.1399-5448.2010.00750.x.
This randomised (1:1), multinational, open-labelled, parallel group trial compared insulin detemir (IDet) with neutral protamine Hagedorn (NPH) insulin, in combination with mealtime insulin aspart, over 1 yr in subjects aged 2–16 yr with type 1 diabetes mellitus. Of 348 randomised subjects, 82 (23.6%) were 2–5 yr (IDet: 42, NPH: 40). This article is a descriptive subgroup analysis of these young children. Baseline characteristics (IDet vs. NPH) were similar: mean age, 4.3 vs. 4.5 yr; diabetes duration, 2.2 vs. 2.1 yr; males, 42.9 vs. 52.5%. Mean haemoglobin A1c (HbA1c) was similar between groups at baseline (8.2 vs. 8.1%), and changed little over 1 yr (8.1 vs. 8.3%). Fasting plasma glucose (FPG) was similar at baseline (8.44 vs. 8.56 mmol/L) and decreased during the study (−1.0 vs. −0.45 mmol/L). A lower rate of hypoglycaemia was observed with IDet compared with NPH (24-h; 50.6 vs. 78.3 episodes per patient-year; nocturnal hypoglycaemia, 8.0 vs. 17.4 episodes per patient-year). No severe hypoglycaemic episodes occurred with IDet, while 3 subjects reported 6 episodes with NPH. Change in weight standard deviation score standardised by age and gender was −0.17 with IDet and +0.03 with NPH. A slightly lower proportion of subjects in this age group reported adverse events with IDet than with NPH (69.0 vs. 77.5%). Serious adverse events were few (5 with IDet, 7 with NPH). In conclusion, long-term treatment with IDet in children aged 2–5 yr

suggested similar glycaemic control, greater reduction in FPG, lower rates of hypoglycaemia, no inappropriate weight gain, and fewer adverse events compared with NPH.

Aschner P, Chan J, Owens DR, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. *The Lancet*. 2012;379(9833):2262-2269. doi:10.1016/S0140-6736(12)60439-5.
Background In people with type 2 diabetes, a dipeptidyl peptidase-4 (DPP-4) inhibitor is one choice as second-line treatment after metformin, with basal insulin recommended as an alternative. We aimed to compare the efficacy, tolerability, and safety of insulin glargine and sitagliptin, a DPP-4 inhibitor, in patients whose disease was uncontrolled with metformin.
Methods In this comparative, parallel, randomised, open-label trial, metformin-treated people aged 35–70 years with glycated haemoglobin A1c (HbA1c) of 7–11%, diagnosis of type 2 diabetes for at least 6 months, and body-mass index of 25–45 kg/m² were recruited from 17 countries. Participants were randomly assigned (1:1) to 24-week treatment with insulin glargine (titrated from an initial subcutaneous dose of 0·2 units per kg bodyweight to attain fasting plasma glucose of 4·0–5·5 mmol/L) or sitagliptin (oral dose of 100 mg daily). Randomisation (via a central interactive voice response system) was by random sequence generation and was stratified by centre. Patients and investigators were not masked to treatment assignment. The primary outcome was change in HbA1c from baseline to study end. Efficacy analysis included all randomly assigned participants who had received at least one dose of study drug and had at least one on-treatment assessment of any primary or secondary efficacy variable. This trial is registered at ClinicalTrials.gov, NCT00751114.
Findings 732 people were screened and 515 were randomly assigned to insulin glargine (n=250) or sitagliptin (n=265). At study end, adjusted mean reduction in HbA1c was greater for patients on insulin glargine (n=227; –1·72%, SE 0·06) than for those on sitagliptin (n=253; –1·13%, SE 0·06) with a mean difference of –0·59% (95% CI –0·77 to –0·42, p<0·0001). The estimated rate of all symptomatic hypoglycaemic episodes was greater with insulin glargine than with sitagliptin (4·21 [SE 0·54] *vs* 0·50 [SE 0·09] events per patient-year; p<0·0001). Severe hypoglycaemia occurred in only three (1%) patients on insulin glargine and one (<1%) on sitagliptin. 15 (6%) of patients on insulin glargine versus eight (3%) on sitagliptin had at least one serious treatment-emergent adverse event.
Interpretation Our results support the option of addition of basal insulin in patients with type 2 diabetes inadequately controlled by metformin. Long-term benefits might be expected from the achievement of optimum glycaemic control early in the course of the disease.

Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther*. 2012;34(9):1892-1908.e1. doi:10.1016/j.clinthera.2012.07.007.
Background: Exenatide once weekly (QW) is an extended-release formulation of exenatide, a glucagon- like peptide-1 receptor agonist that reportedly improves glycemic control in patients with type 2 diabetes.
Objective: The goal of this study was to test the hypothesis that exenatide QW is noninferior to insulin glargine, as measured by change in glycosylated hemoglobin (HbA1c) from baseline to end point (week 26 [primary end point]) in Japanese patients with type 2 diabetes who have inadequate glycemic control with oral antidiabetes drugs.
Methods: In this open-label, parallel-group, multicenter, noninferiority registration study, patients were randomized (1:1) to add exenatide QW(2 mg) or once daily insulin glargine (starting dose, 4 U) to their current oral antidiabetes drug treatment. The primary analysis was change in HbA1c from baseline to end point, evaluated by using a last-observation-carried forward ANCOVA model, with a predefined noninferiority margin of 0.4%. Secondary analyses (a priori) included analysis of superiority for between-group comparisons of change in weight and the proportion of patients reaching HbA1c target levels of _7.0% or _6.5%.
Results: The baseline characteristics of the exenatide QW (215 patients) and insulin glargine (212 patients) treatment groups were similar: mean (SD) age, 57 (10) years and 56 (11) years, respectively; 66.0% and 69.8% male; mean HbA1c, 8.5% (0.82%) and 8.5% (0.79%); and mean weight, 69.9 (13.2) kg and 71.0 (13.9) kg. Exenatide QW was statistically noninferior to insulin glargine for the change in HbA1c from baseline to end point (least squares mean difference, _0.43% [95% CI,_0.59 to_0.26]; *P*_0.001), with the 95% CI upper limit less than the predefined noninferiority margin (0.4%). A significantly greater proportion of patients receiving exenatide QW compared with insulin glargine achieved HbA1c target levels of _7.0% (89 of 211 [42.2%] vs 44 of 210 [21.0%]) or _6.5% (44 of 214 [20.6%] vs 9 of 212 [4.2%]) at end point (*P* _ 0.001 for both). Patient weight was reduced with exenatide QW compared with insulin glargine at end point (least squares mean difference, _2.01 kg [95% CI, _2.46 to _1.56]; *P* _ 0.001). Exenatide QW was well tolerated, with a lower risk of hypoglycemia compared with insulin glargine but a higher incidence of injection-site induration.
Conclusions: Exenatide QW was statistically noninferior to insulin glargine for the change in HbA1c from baseline to end point; these results suggest that exenatide QW may provide an effective alternative treatment for Japanese patients who require additional therapy to control their diabetes.

Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal Efficacy and Safety Outcomes in a Randomized, Controlled Trial Comparing Insulin Detemir With NPH Insulin in 310 Pregnant Women With Type 1 Diabetes. *Diabetes Care*. 2012;35(10):2012-2017. doi:10.2337/dc11-2264.
OBJECTIVEdThis randomized, controlled noninferiority trial aimed to compare the efficacy and safety of insulin detemir (IDet) versus neutral protamine Hagedorn (NPH) (both with prandial insulin aspart) in pregnant women with type 1 diabetes.
RESEARCH DESIGNANDMETHODSdPatients were randomized and exposed to IDet or NPH up to 12 months before pregnancy or at 8–12 weeks gestation. The primary analysis aimed to demonstrate noninferiority of IDet to NPH with respect to A1C at 36 gestational weeks (GWs) (margin of 0.4%). The data were analyzed using linear regression, taking several baseline factors and covariates into account.
RESULTSdA total of 310 type 1 diabetic women were randomized and exposed to IDet (n = 152) or NPH (n = 158) up to 12 months before pregnancy (48%) or during pregnancy at 8–12 weeks (52%). The estimated A1C at 36 GWs was 6.27% for IDet and 6.33% for NPH in the full analysis set (FAS). IDet was declared noninferior to NPH (FAS, –0.06% [95% CI –0.21 to 0.08]; per protocol, –0.15%[–0.34 to 0.04]). Fasting plasma glucose (FPG) was

significantly lower with IDet versus NPH at both 24 GWs (96.8 vs. 113.8 mg/dL, P = 0.012) and 36 GWs (85.7 vs. 97.4 mg/dL, P = 0.017). Major and minor hypoglycemia rates during pregnancy were similar between groups.
CONCLUSIONSdTreatment with IDet resulted in lower FPG and noninferior A1C in late pregnancy compared with NPH insulin. Rates of hypoglycemia were comparable.

Hickman M, McBride R, Boggess K, Strauss R. Metformin Compared with Insulin in the Treatment of Pregnant Women with Overt Diabetes: A Randomized Controlled Trial. *American Journal of Perinatology*. 2012;30(06):483-490. doi:10.1055/s-0032-1326994.
Study Design Women with preexisting type 2 diabetes and those diagnosed with gestational diabetes who required medical management prior to 20 weeks were randomly assigned to metformin or insulin. Glycemic control, defined as >50% capillary blood glucose within target range, was compared between groups. Other outcomes included patient tolerance, neonatal and obstetric complications, maternal weight gain, neonatal cord blood C-peptide, and patient satisfaction with therapy.
Results Twenty-eight women completed the study, with 14 in each group. Of the 15 women assigned to metformin, 100% continued to receive metformin until delivery, although 43% required supplemental insulin to achieve glycemic control. Glucose measures did not differ between the groups, and the proportion who met fasting and postprandial glycemic target values did not differ between the groups. Women treated with metformin had significantly fewer subjective episodes of hypoglycemia compared with those using insulin (0% versus 36%; p ¼ 0.04) as well as reported glucose values < 60 mg/dL (7.1% versus 50%; p ¼ 0.03).
Conclusion Metformin should be considered for treatment of overt diabetes and early A2 gestational diabetes in pregnancy.

Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with Type 1 diabetes: a 52-week randomized clinical trial. *Diabetic Medicine*. 2013;30(2):216-225. doi:10.1111/dme.12041.
Aims This 52-week, randomized, multinational, open-label, parallel-group, non-inferiority trial investigated the efficacy and safety of basal–bolus treatment with insulin detemir vs. NPH (neutral protamine Hagedorn) insulin, in combination with insulin aspart, in subjects aged 2–16 years with Type 1 diabetes mellitus.
Methods Of the 347 randomized and exposed subjects, 177 received insulin detemir and 170 NPH insulin, both administered once or twice daily in combination with mealtime insulin aspart. Glycaemic measurements and weight were followed over 52 weeks.
Results After 52 weeks, insulin detemir was shown to be non-inferior to NPH insulin with regard to HbA1c [mean difference insulin detemir–NPH: 1.30 mmol/mol, 95% CI –1.32 to 3.92 (0.12%, 95% CI –0.12 to 0.36) in the full analysis set and 1.41 mmol/mol, 95% CI –1.26 to 4.08 (0.13%, 95% CI –0.12 to 0.37) in the per protocol analysis set]. Hypoglycaemic events per subject-year of exposure of 24-h and nocturnal hypoglycaemia were significantly lower with insulin detemir than with NPH insulin (rate ratio 0.76, 95% CI 0.60–0.97, P = 0.028 and 0.62, 95% CI 0.47–0.84, P = 0.002, respectively). Weight standard deviation (SD) scores (body weight standardized by age and gender) decreased with insulin detemir, but increased slightly with NPH insulin (change: –0.12 vs. 0.04, P < 0.001). At end of the trial, median insulin doses were similar in both treatment groups.
Conclusions Insulin detemir was non-inferior to NPH insulin after 52 weeks' treatment of children and adolescents aged 2–16 years, and was associated with a significantly lower risk of hypoglycaemia, together with significantly lower weight SD score when compared with NPH insulin.

Davies M, Heller S, Sreenan S, et al. Once-Weekly Exenatide Versus Once- or Twice-Daily Insulin Detemir: Randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. *Diabetes Care*. 2013;36(5):1368-1376. doi:10.2337/dc12-1333.
OBJECTIVEdThis multicenter, open-label, parallel-arm study compared the efficacy and safety of exenatide once weekly (EQW) with titrated insulin detemir in patients with type 2 diabetes inadequately controlled with metformin (with or without sulfonylureas).
RESEARCH DESIGN AND METHODSdPatients were randomized to EQW (2 mg) or detemir (once or twice daily, titrated to achieve fasting plasma glucose #5.5 mmol/L) for 26 weeks. The primary outcome was proportion of patients achieving A1C #7.0% and weight loss $1.0 kg at end point, analyzed by means of logistic regression. Secondary outcomes included measures of glycemic control, cardiovascular risk factors, and safety and tolerability.
RESULTSdOf 216 patients (intent-to-treat population), 111 received EQWand 105 received detemir. Overall, 44.1% (95% CI, 34.7–53.9) of EQW-treated patients compared with 11.4% (6.0–19.1) of detemir-treated patients achieved the primary outcome (P , 0.0001). Treatment with EQWresulted in significantly greater reductions than detemir in A1C (least-square mean6 SE,21.3060.08%vs.20.8860.08%; P,0.0001) and weight (22.760.3 kg vs. +0.860.4 kg; P,0.0001). Gastrointestinal-related and injection site–related adverse events occurred more frequently with EQWthan with detemir. There was no major hypoglycemia in either group. Five (6%) patients in the EQW group and six (7%) patients in the detemir group experienced minor hypoglycemia; only one event occurred without concomitant sulfonylureas (detemir group).
CONCLUSIONSdTreatment with EQW resulted in a significantly greater proportion of patients achieving target A1C and weight loss than treatment with detemir, with a low risk of hypoglycemia. These results suggest that EQWis a viable alternative to insulin detemir treatment in patients with type 2 diabetes with inadequate glycemic control using oral antidiabetes drugs.

Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RPV. Randomized trial of metformin vs insulin in the management of gestational diabetes. *American Journal of Obstetrics and Gynecology*. 2013;209(1):34.e1-34.e7. doi:10.1016/j.ajog.2013.03.022.
OBJECTIVE: To evaluate glycemic control in women receiving metformin or insulin for gestational diabetes, and to identify factors predicting the need for supplemental insulin in women initially treated with metformin.
STUDY DESIGN: Women with gestational diabetes who failed to achieve glycemic control with diet and exercise were randomized to receive metformin (n ¼ 47) or insulin (n ¼ 47). Criteria for inclusion were singleton pregnancy, diet, and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus. Patients who were lost to prenatal followup were excluded.

RESULTS: Comparison of mean pretreatment glucose levels showed no significant difference between groups (P ¼ .790). After introduction of the drug, lower mean glucose levels were observed in the metformin group (P ¼ .020), mainly because of lower levels after dinner (P ¼ .042). Women using metformin presented less weight gain (P¼.002) and a lower frequency of neonatal hypoglycemia (P¼ .032). Twelve women in the metformin group (26.08%) required supplemental insulin for glycemic control. Early gestational age at diagnosis (odds ratio, 0.71; 95% confidence interval, 0.52e0.97; P ¼ .032) and mean pretreatment glucose level (odds ratio, 1.061; 95% confidence interval, 1.001e1.124; P ¼.046) were identified as predictors of the need for insulin.
CONCLUSION: Metformin was found to provide adequate glycemic control with lower mean glucose levels throughout the day, less weight gain and a lower frequency of neonatal hypoglycemia. Logistic regression analysis showed that gestational age at diagnosis and mean pretreatment glucose level were predictors of the need for supplemental insulin therapy in women initially treated with metformin.

Karagianni P, Polyzos S, Kartali N, Zografou I, Sambanis C. Comparative efficacy of exenatide versus insulin glargine on glycemic control in type 2 diabetes mellitus patients inadequately treated with metformin monotherapy. *Advances in Medical Sciences*. 2013;58(1):38-43. doi:10.2478/v10039-012-0078-7.
Purpose: Comparative efficacy of exenatide versus insulin glargine primarily on glucemic control, and secondarily on body mass index (BMI), lipid profile and blood pressure, in type 2 diabetes mellitus (T2DM) patients suboptimally treated with metformin monotherapy.
Material/Methods: Forty-seven inadequately treated T2DM patients on metformin assigned to exenatide (n=18) or insulin glargine (n=29) for 26 weeks. Glycosylated hemoglobin (HbA1c), serum lipids, BMI, systolic and diastolic blood pressure, and adverse events, including episodes of hypoglycemia and gastrointestinal symptoms, were recorded.
Results: Either treatment had a similar favorable mean reduction in HbA1c. However, more patients in exenatide group achieved HbA1c ≤ 7% at the 26th week compared with insulin glargine group (p=0.036). Insulin glargine group had significantly more episodes of hypoglycemia compared with exenatide group (p=0.039). Gastrointestinal adverse events were non-significantly higher in the exenatide group. A significantly greater BMI reduction was observed in exenatide group, whereas BMI was not altered in insulin glargine group. Total and LDL cholesterol (p=0.012), and triglycerides (p=0.016) significantly decreased, whereas HDL cholesterol increased (p=0.021) in the exenatide group, whereas only total cholesterol decreased in insulin glargine group. Changes in systolic and diastolic blood pressure were insignificant in both groups.
Conclusions: Exenatide provided similar reduction in HbA1c, but fewer episodes of hypoglycemia, compared with insulin glargine. Exenatide had also a favorable effect on weight loss, although more gastrointestinal adverse events. Exenatide may provide a justified alternative in second line treatment of T2DM, but more trials are required to elucidate its long-term safety and cost-effectiveness.

Meneghini L, Kesavadev J, Demissie M, Nazeri A, Hollander P. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15(8):729-736. doi:10.1111/dom.12083.
Aims: This study assessed the efficacy and safety of once-daily insulin initiation using insulin detemir (detemir) or insulin glargine (glargine) added to existing metformin in type 2 diabetes (T2D).
Methods: This 26-week, multinational, randomized, treat-to-target trial involved 457 insulin-naıve adults with T2D (HbA1c 7–9%). Detemir or glargine was added to current metformin therapy [any second oral antidiabetic drug (OAD) discontinued] and titrated to a target fasting plasma glucose (FPG) ≤90 mg/dl (≤5.0 mmol/l). Primary efficacy endpoint was change in HbA1c.
Results: Mean (s.d.) HbA1c decreased with detemir and glargine by 0.48 and 0.74%-points, respectively, to 7.48% (0.91%) and 7.13% (0.72%) [estimated between-treatment difference, 0.30 (95% CI: 0.14–0.46)]. Non-inferiority for detemir at the a priori level of 0.4%-points was not established. The proportions of patients reaching HbA1c≤7% at 26 weeks were 38% and 53% (p=0.026) with detemir and glargine, respectively. FPG decreased ∼43.2mg/dl (∼2.4 mmol/l) in both groups [non-significant (NS)]. Treatment satisfaction was good for both insulins. Hypoglycaemia, which occurred infrequently, was observed less with detemir than glargine [rate ratio 0.73 (95% CI 0.54–0.98)]. The proportions of patients reaching HbA1c≤7% without hypoglycaemia in the detemir and glargine groups were 32% and 38% (NS), respectively. Weight decreased with detemir [−0.49 (3.3) kg] and increased with glargine [+1.0 (3.1) kg] (95% CI for difference: −2.17 to −0.89 kg).
Conclusion: While both detemir and glargine, when added to metformin therapy, improved glycaemic control, glargine resulted in greater reductions in HbA1c, while detemir demonstrated less weight gain and hypoglycaemia.

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Month/Year of Review: July 2014 **Date of Last Review:** August 2013
PDL Classes: Skeletal Muscle Relaxants **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: BACLOFEN, CYCLOBENZAPRINE HCL, TIZANDINE HCL
- Non-Preferred Agents: CHLORZOXAZONE, METAXALONE, METHOCARBAMOL, DANTROLENE SODIUM, ORPHENADRINE CITRATE, CARISOPRODOL , CYCLOBENZARPINE ER (AMRIX®)

Previous Conclusions and Recommendation:

- The evidence does not support any conclusions about the comparative effectiveness between baclofen, tizanidine, or dantrolene for spasticity. All are effective and equivalent to diazepam. Dantrolene is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions for the comparative efficacy or safety between skeletal muscle relaxants for musculoskeletal conditions.
- Cyclobenzaprine had the largest body of evidence to support its efficacy compared to placebo.
- Chlorzoxazone is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions about the comparative efficacy or adverse effects for different subpopulations of patients such as race, gender, or age.

PA Criteria: Prior authorization is in place to support preferred PDL skeletal muscle relaxants and to cover for OHP above the line diagnoses only. A quantity limit restricts carisoprodol products to less than 56 tablets within 90 days unless the patient has a terminal illness. (Appendix 1).

Conclusions and Recommendations:

- There is limited new evidence since the last review on skeletal muscle relaxants; no further review or research needed.
- Evaluate comparative costs in executive session.

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

References:

1. Holzhammer, B. Drug Effectiveness Review Project: Drug Class Review on Skeletal Muscle Relaxants. Preliminary Scan Report #6. May 2014.

Appendix 1: PA Criteria

Skeletal Muscle Relaxants

Goal(s):

- Cover non-preferred drugs only for above the line diagnoses.
- Restrict carisoprodol to short-term use per medical evidence.
    a. There are no long-term studies of efficacy or safety for carisoprodol.
    b. Case reports suggest it is often abused and can be fatal when used in association with opioids, benzodiazepeines, alcohol, or illicit drugs.
    c. Carisoprodol is metabolized to meprobamate.

Length of Authorization: Up to 6 months

Requires PA:

- Non-preferred NSAIDs

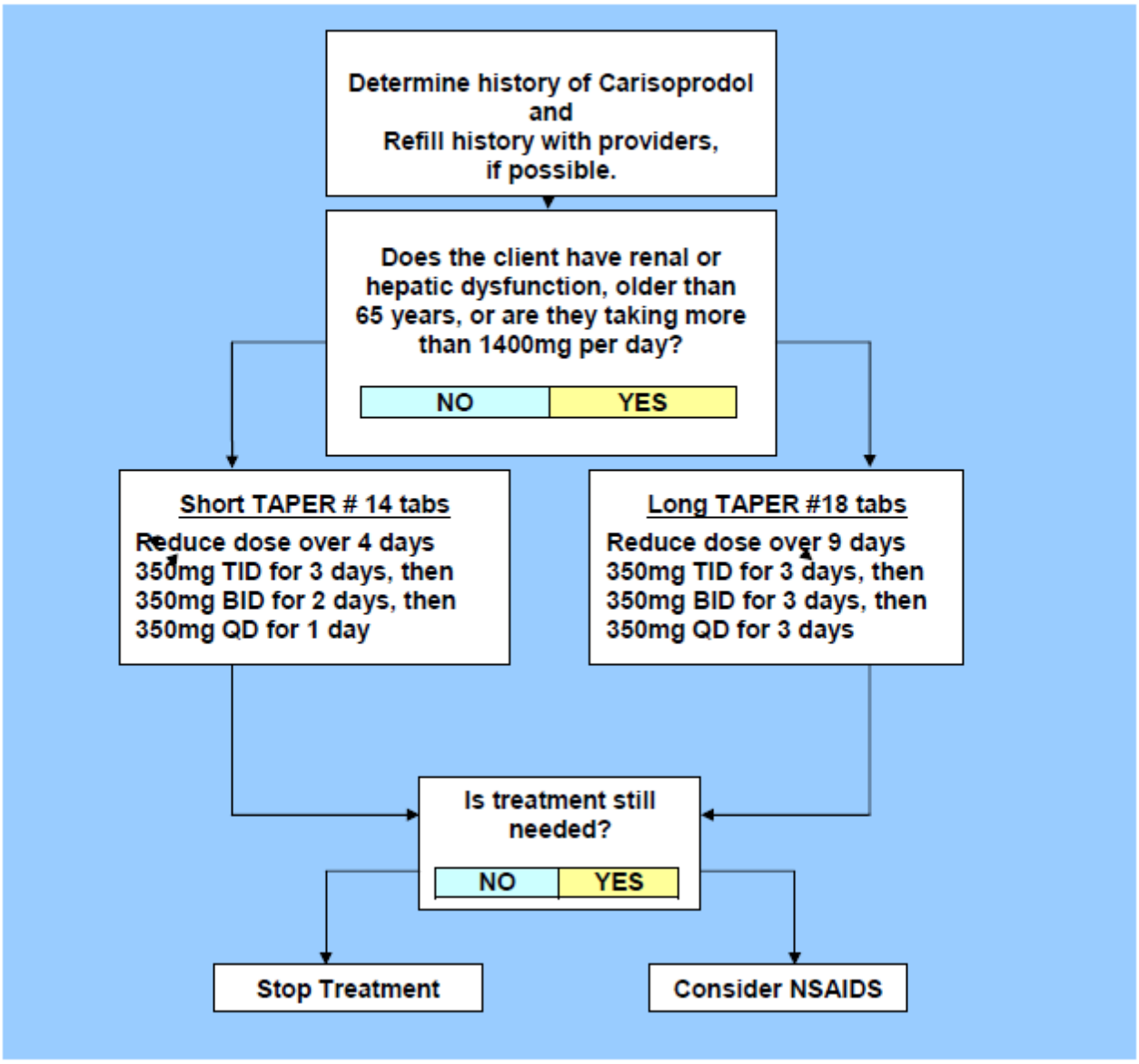
Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/
Cyclobenzaprine has the largest body of evidence supporting long-term use and is the preferred product in the muscle relaxant class. For patients that have contraindications to TCAs, NSAIDs, benzodiazepeines or opioids are other alternatives. OHP does not cover pain clinic treatment.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is diagnosis covered by the Oregon Health Plan?	Yes: Go to #3.	No: Pass to RPH; Deny, (Not Covered by the OHP)
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC).	Yes: Inform provider of covered alternatives in class	No. Go to #4
4. Is drug requested carisoprodol (Soma®)?	Yes: Go to #5	No. Approve for up to 6 months

5. Does total quantity of carisoprodol (Soma®) products exceed 56 tablets within 90 days? From claims, document product, dose, directions, and amount used during last 90 days:	Yes: Go to #6	No: Approve for up to 6 months
6. Does patient have a terminal illness (e.g. metastatic CA, end stage HIV, ALS)?	Yes: Approve for 6 months.	No: Pass to RPH. Go to #7

7. Pharmacist's Statement:
 	
• Carisoprodol cannot be approved for long term usage.
• Patients are limited to 56 tablets in a 90 day period.
• It is recommended that the patient undergo a "taper" of the Soma (Carisoprodol) product of which a supply may be authorized for this to occur.
• The amount and length of taper depends upon the patient's condition. Does the patient meet one or more of the following?:
  ○ >65 years old
  ○ Renal Failure
  ○ Hepatic failure
 	
Take > 1400mg per day (>3.5 tablets)
	Yes: Document reason and approve long taper:
	
	• Authorize 18 tablets
	• Reduce dose over 9 days
	• 350mg TID X 3 days, then
	• 350mg BID X 3 days, then
	• 350mg QD x 3 days then evaluate
		No: Approve short taper:
		
		• Authorize 10 tablets
		• Reduce dose over 4 days
		• 350 mg tid x 1 day, then
		• 350 mg bid x 2 days, then
		• 350 mg QD x 1 day, then evaluate

Tapering Carisoprodol



Drug Class Review
on
Skeletal Muscle Relaxants

Preliminary Scan Report #6

May 2014

Last Report: Update 2 (May 2005)

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
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OBJECTIVE

The purpose of the preliminary updated literature scan process is to provide the Drug Effectiveness Review Project participants with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with consideration of allocating resources. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last scan. Other important studies could exist.

Date of Last Update Report

Original Report: September 2003
Update #1: January 2004
Update#2: May 2005 (searches through November 2004)

Date of Last Preliminary Update Scan Report

Update #3 Preliminary Scan #1: February 2007
Update #3 Preliminary Scan #2: March 2008
Update #3 Preliminary Scan #3: June 2009
Update #3 Preliminary Scan #4: September 2010
Update #3 Preliminary Scan #5: May 2013 (searches through April Week 3 2013)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

- Adult or pediatric patients with spasticity or a musculoskeletal condition. We defined spasticity as muscle spasms associated with an upper motor neuron syndrome. Musculoskeletal conditions were defined as peripheral conditions resulting in muscle or soft tissue pain or spasms.
- We included patients with nocturnal leg cramps however, excluded patients with restless legs syndrome or nocturnal myoclonus.
- Obstetric and dialysis patients were also excluded.

Interventions

Table 1. Included interventions*

Active Ingredient	Brand name	Forms
Baclofen	Generic	Oral tablet
Carisoprodol	Soma®	Oral tablet
Chlorzoxazone	Parafon Forte® DSC	Oral tablet
Cyclobenzaprine hydrochloride	Amrix®	Extended release oral capsule
Cyclobenzaprine hydrochloride	Generic	Oral tablet
Dantrolene	Dantrium®	Oral capsule
Metaxalone	Skelaxin®	Oral tablet
Methocarbamol	Robaxin®, Robaxin-750	Oral tablet
Orphenadrine	Generic	Extended release oral tablet
Tizanidine	Zanaflex®	Oral tablet and oral capsule

Study designs

- Controlled clinical trials/randomized controlled trials
- Comparative effectiveness reviews

Comparators: Effectiveness and harms of individual skeletal muscle relaxants

- Benzodiazepines were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with any of the skeletal muscle relaxants listed above.
- Other medications used for spasticity but considered to be in another drug class, such as gabapentin (a neuroleptic) and clonidine (an antihypertensive), were also only reviewed when they were directly compared to an included skeletal muscle relaxant.
- Quinine was only included if it was compared to a skeletal muscle relaxant.

Effectiveness outcomes

- Relief of muscle spasms or pain, functional status, quality of life
- Non-clinical outcomes such as electromyogram measurements or spring tension measurements were excluded.

Harms outcomes

- Somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction
- Withdrawal rates and adverse events
- We also paid special attention to reports of serious hepatic injury.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2013 through May 14, 2014 using terms for included drugs and limited to humans, English language, controlled clinical trials and randomized clinical trials. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm).

Study Selection

The reviewer assessed abstracts of citations identified from literature searches for inclusion using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan
None

New drugs identified in previous Preliminary Update Scan(s)
Amrix® (cyclobenzaprine hydrochloride, 15 mg and 30 mg extended-release oral tablet): indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions in adult patients (02/11/2007).

Soma® (carisoprodol, 250 mg oral capsule): indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults (9/13/2007).

New Indications

New indications identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
None

New Safety Alerts

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
Dantrium (dantrolene sodium) Oral Capsule: July 2012

BOXED WARNING

- Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving Dantrium. However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
None

Reviews identified in previous Preliminary Update Scan(s)
None

Randomized Controlled Trials

Trials identified since the most recent scan
Medline searches resulted in 10 citations, none of which were relevant to the key questions and populations of interest in this scan. Table 2 includes all placebo-controlled trials that were identified in previous preliminary update scans. Appendix A includes the abstracts for each relevant trial identified in previous preliminary update scans.

Table 2. Previously identified potentially relevant trials

Author Year	Drugs/Comparisons	Focus
Placebo-Controlled Trials		
Malanga, 2009	Cyclobenzaprine ER vs. placebo (report of two trials)	Low back and neck pain
Serfer, 2010	Carisoprodol vs. placebo	Low back spasm
Mathew 2005	Diazepam vs. placebo	Motor function in children with cerebral palsy

Ketenci 2005	Thiocolchicoside vs. Tizanidine vs. placebo	Low back pain associated with muscle spasm

Summary

There is no new evidence on skeletal muscle relaxants since the last preliminary update scan. No new head-to-head trials, placebo controlled trials, or comparative effectiveness reviews pertaining to existing drugs were identified in this preliminary update scan.

Appendix A. Abstracts of relevant trials and systematic reviews of skeletal muscle relaxants identified in previous scans (N=5)

Placebo-Controlled Trials (N=4)

Ketenci, A., E. Ozcan, et al. (2005). "Assessment of efficacy and psychomotor performances of thiocolchicoside and tizanidine in patients with acute low back pain." International Journal of Clinical Practice 59(7): 764-70.

> Objectives of this study were to assess efficacy and effects on psychomotor performances of thiocolchicoside (TCC) and tizanidine (TZ) compared to placebo. Patients complaining of acute low back pain (LBP) associated with muscle spasm were enrolled in this randomised, double-blind clinical trial, comparing the effects of oral TCC, TZ and placebo on psychomotor performances assessed by a visual analogue scale of tiredness, drowsiness, dizziness and alertness and by psychometric tests after 2 and 5-7 days of treatment. The efficacy assessments, both TCC and TZ, were more effective than placebo in improving pain at rest, hand-to-floor distance, Schober test and decreased paracetamol consumption. There were significant differences among the treatment groups in favour of TCC compared to TZ in visual analog scale-parameters. TZ-induced reduction of psychomotor performances of the patients was confirmed by psychometric tests, which showed significant differences among groups. This study showed that TCC is at least as effective as TZ in the treatment of acute LBP, while it appears devoid of any sedative effect in contrast to TZ.

Malanga, G.A., G. E. Ruoff, et al. (2009). “Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design.” Current Medical Research & Opinion **25**(5): 1179-96.

> OBJECTIVE: To evaluate efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15- and 30-mg capsules in patients with muscle spasm associated with acute, painful musculoskeletal conditions. METHODS: Two identically designed, randomized, double-blind, placebo- and active-controlled, parallel-group studies in patients aged 18-75 years with muscle spasm associated with neck or back pain. Patients received CER 15 or 30 mg once daily, cyclobenzaprine immediate release (CIR) 10 mg three times daily, or placebo for 14 days. Primary efficacy measures were patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. Secondary measures were patient's rating of medication helpfulness and physician's clinical global assessment of response (days 8 and 14), relief from local pain, global impression of change, restriction in activities of daily living, restriction of movement, daytime drowsiness, quality of nighttime sleep (days 4, 8, and 14), and quality of life (days 8 and 14). RESULTS: A total of 156/254 randomized patients in study 1 and 174/250 in study 2 completed 14 days of treatment. Significant improvements in patient's rating of medication helpfulness were reported with CER versus placebo (CER 30 mg, study 1, p = 0.007; CER 15 mg, study 2, p = 0.018) at day 4. Significant improvements with CER 30 mg versus placebo were also seen at day 4 in study 1 for patient-rated global impression of change (p = 0.008), relief of local pain (p =

0.004), and restriction of movement (p = 0.002). Neither study reported differences between study groups on the physician's clinical global assessment. Improvements with CER were comparable to that of CIR. In both studies, daytime drowsiness was reported more frequently in active treatment groups than in the placebo group; however, reports of drowsiness decreased over time in all groups. In general, daytime drowsiness was reported more frequently in CIR groups than in CER groups. More adverse events were reported in the active treatment groups versus placebo and were similar in the CER and CIR groups, except somnolence, which occurred more frequently with CIR. CONCLUSIONS: Once-daily CER 15 mg (study 2) and CER 30 mg (study 1) were effective in treating muscle spasm associated with painful musculoskeletal conditions after 4 days of treatment. Differences between CER and placebo groups did not reach statistical significance on all efficacy measures, and the protocols were not powered to detect differences between active treatment arms. CER was generally safe and well tolerated, with low rates of somnolence.

Mathew, A., M. C. Mathew, et al. (2005). "The efficacy of diazepam in enhancing motor function in children with spastic cerebral palsy." Journal of Tropical Pediatrics 51(2): 109-13.

Muscle spasm and hypertonia limit mobility in children with spastic cerebral palsy. This double-blind, placebo-controlled, randomized controlled clinical trial studies the clinical efficacy of a low dose of diazepam in enhancing movement in children with spastic cerebral palsy. One hundred and eighty children fulfilled the criteria and were randomly allocated to receive one of two doses of diazepam or placebo at bedtime; 173 completed the study. There was a significant reduction of hypertonia, improvement in the range of passive movement, and an increase in spontaneous movement in the children who received diazepam. There was no report of daytime drowsiness. In developing countries, where cost factors often determine choice of drug, diazepam is a cheap and effective way of relieving spasm and stiffness, optimizing physical therapy and facilitating movement in children with spasticity.

Serfer, G.T., W. J. Wheeler, et al. (2010). “Randomized, double-blind trials of carisoprodol 250 mg compared with placebo and carisoprodol 350 mg for the treatment of low back spasm.” Current Medical Research & Opinion 26(1): 91-9.

BACKGROUND: Carisoprodol, a centrally active skeletal muscle relaxant, is widely used for the treatment of acute, painful musculoskeletal disorders. When administered at a dose of 350 mg four times daily, carisoprodol demonstrated significant clinical benefit in its early clinical development trials; however, some unfavorable side effects, such as drowsiness and dizziness, were reported. Recently, research was conducted to determine if a lower dose of carisoprodol would retain efficacy but improve tolerability compared to the higher 350-mg dose. OBJECTIVE: The purpose of this multicenter study was to compare the efficacy and safety of carisoprodol 250-mg tablets four times daily to 350-mg tablets four times daily and to placebo in patients with acute, painful musculoskeletal spasm of the lower back. RESEARCH DESIGN AND METHODS: In this 1-week double-blind, placebo-controlled, parallel-group multicenter trial, patients 18 to 65 years of age with moderate to severe back spasm were randomly assigned to treatment with

carisoprodol 250-mg tablets (n = 264), 350-mg tablets (n = 273), or matching placebo tablets (n = 269) three times daily and at bedtime. RESULTS: The carisoprodol 250-mg regimen was significantly more effective than placebo as assessed by both patient-rated relief from starting backache (p = 0.0001) and patient-rated global impression of change (p = 0.0046). There were no significant differences between the 250-mg and 350-mg dosages for the coprimary efficacy endpoints, and patients improved with or without sedation. Fewer than 1% of patients in the carisoprodol 250-mg group discontinued prematurely because of treatment-emergent adverse events, and no patient discontinued because of drowsiness. CONCLUSIONS: When administered three times daily and at bedtime, carisoprodol 250 mg was as effective as 350 mg three times daily and at bedtime with a lower incidence of adverse events and fewer discontinuations of therapy due to adverse events. Patients improved whether or not they reported sedation as an adverse event.

Systematic Reviews (N=1)

Taricco, M., M. C. Pagliacci, et al. (2006). "Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review." Europa Medicophysica 42(1): 5-15.

The aim of this paper was to assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in spinal cord injury (SCI) patients, as well as the effectiveness and safety of different routes of administration of baclofen. A systematic review of randomised controlled trials (RCTs), within the Cochrane Collaboration Injuries Group, was carried out. The Cochrane Injuries Group Specialised Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE and CINAHL were searched up to July 2006 without language restriction. Drug companies and experts active in the area were also contacted to find other relevant studies. Two investigators independently identified relevant studies, extracted data and assessed methodological quality of studies resolving disagreement by consensus. Nine out of 55 studies met the inclusion criteria. The heterogeneity among studies did not allow quantitative combination of RESULTS: Study designs were: 8 crossover, 1 parallel-group trial. Two studies (14 SCI patients) showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth score and activities of daily living [ADL] performances), compared to placebo, without any adverse effect. The study comparing tizanidine to placebo (118 SCI patients) showed a significant effect of tizanidine in improving Ashworth score but not in ADL performances. The tizanidine group reported significant rates of adverse effects (drowsiness, xerostomia). For the other drugs (gabapentine, clonidine, diazepam, amytal and oral baclofen) the results do not provide evidence for a clinical significant effectiveness. This systematic review indicates that there is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care. [References: 66]

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Month/Year of Review: July 2014 **Date of Last Review:** August 2013
PDL Classes: Nonsteroidal Anti-inflammatory Drugs (NSAIDS) **Source Document:** DERP

Current Status of PDL Class:

- Preferred Agents: DICLOFENAC POTASSIUM, DICLOFENAC SODIUM DR, ETODOLAC TABLET, FLURBIPROFEN, IBUPROFEN CAPSULE/DROPS/ORAL SUSP/CHEWABLE/TABLET, INDOMETHASONE CAPSULE, KETOPROFEN, MELOXICAM, NABUMETONE, NAPROXEN TABLET, NAPROXEN DR, NAPROXEN SODIUM, OXAPROZIN, SALSALATE, SULINDAC
- Non-Preferred Agents: CELECOXIB (CELEBREX®), DICLOFENAC TAB ER 24H, DIFLUNISAL, ETODOLAC CAPSULE, ETODOLAC TABLET ER 24H, FENOPROFEN, INDOMETHASONE ORAL SUSPENSION/CAPSULE ER, KETOPROFEN CAPSULE 24H, KETOROLAC TALET, KETOROLAC NASAL SPRAY (SPRIX®), MECLOFENAMATE SODIUM, MEFENAMIC ACID, NAPROXEN CAPSULE, PIROXICAM ,TOLMETIN SODIUM, NAPROXEN AND ESOMEPRAZOLE (VIMOVO®)

Previous Conclusions and Recommendation:

- For pain relief, no significant short-term (< 6 months) differences were found among oral NSAIDs.
- For serious harms, celecoxib did not appear to be associated with higher risk of cardiovascular (CV) events and is gastroprotective in the short term compared with nonselective NSAIDs.
- Findings vary by subgroup, depending on age, recent history of gastrointestinal bleeding, and concomitant use of antiulcer medication.
- Nonselective NSAIDs were associated with similar increased risks of serious GI events, and all but naproxen were associated with similar increased risk of serious CV events, but eh partially selective NSAID nabumetone was gastroprotective compared with nonselective NSAIDs.
- A meta-analysis of randomized controlled trials showed diclofenac to be associated with an increased incidence of major vascular events (driven by coronary events) and death due to vascular causes, similar to those seen with selective COX-2 inhibitors, such as celecoxib. Naproxen was shown to confer less cardiovascular (CV) risk.
- A meta-analyses of observational data showed diclofenac to have a higher risk of acute myocardial infarction (MI) than other commonly used NSAIDS.2
- Gastrointestinal (GI) risks were similar for diclofenac compared to other NSAIDS.
- Overall, there is limited evidence on safety data associated with diclofenac therapy and the inherent risks associated with all NSAIDs.

PA Criteria: Prior authorization is in place to ensure that non-preferred NSAIDs are used for above the line conditions and to restrict ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning (Appendix 1).

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

Conclusions and Recommendations:

- No further review or research needed.
- Evaluate comparative costs in executive session.

References:

1. Peterson, Kim. Drug Effectiveness Review Project: Drug Class Review Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Preliminary Scan Report #2, May 2014.

Appendix 1: PA Criteria

Analgesics, Non-Steroidal Anti-Inflammatory Drugs

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred NSAIDs are used for an above the line condition and restrict ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning.

WARNING - Ketorolac is indicated for the short-term (up to 5 days) management of moderately severe acute pain that requires analgesia at the opioid level. It is not indicated for minor or chronic painful conditions. Ketorolac is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac is indicated, especially when the drug is used inappropriately. Increasing the dose beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Length of Authorization: Up to 12 months

Requires PA:

- Non-preferred NSAIDs
- Ketorolac: Maximum of one claim per 60 days. That claim can be a maximum of 20tablets/5 days, i.e. there is a 5 day maximum per 60 days.

Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis covered by the Oregon Health Plan? All indications need to be evaluated as to whether they are above the line or below the line.	**Yes:** Go to #3	**No**: Pass to RPH; Deny, (Not covered by the OPH)
3. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	**Yes:** Document prior therapy in PA record. Go to #4	**No**: Go to #5
4. Is request for ketorolac greater than a 5 day supply within 60 days (200mg total over 5 days for tablets, 630mg total over 5 days for the nasal spray)?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness). Review FDA warnings	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message:	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.

• Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.		

P&T/DUR Action: 2/23/12 (TW). 9/24/09 (DO/KK), 2/23/06
Revision(s): 5/14/12, 1/1/10
Initiated: ?

Drug Class Review

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Preliminary Scan Report #2

May 2014

Last Report: Update #4 (November 2010)
Last Preliminary Scan: July 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #4, November 2010 (searches through June 2010)

Date of Last Preliminary Update Scan Report

July 2013

Scope and Key Questions

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
2. Are there clinically important differences in short-term harms (< 6 months) between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
3. Are there clinically important differences in long-term harms (≥ 6 months) between NSAIDs, with or without antiulcer medication, when used chronically in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one

medication is more effective or associated with fewer harms?

Inclusion Criteria

Populations

Adults with:

- Chronic pain from osteoarthritis
- Rheumatoid arthritis
- Soft-tissue pain
- Back pain
- Ankylosing spondylitis

Interventions

- Oral drugs: celecoxib, diclofenac potassium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketoprofen extended release, ketoprofen sustained release, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen delayed release, naproxen sustained release, naproxen sodium, oxaprozin, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid, and tolmetin
- Topical drugs: diclofenac epolamine 1.3% topical patch, diclofenac sodium 1% topical gel, diclofenac sodium 1.5% topical solution, diclofenac sodium 3% topical gel, and topical diclofenac diethylamine 1.16%.

Comparisons

Celecoxib compared with NSAIDs
NSAIDs compared with NSAIDs

Outcomes

Effectiveness outcomes

- Pain
- Functional status
- Discontinuations due to lack of effectiveness.

Harms

- Serious gastrointestinal events (gastrointestinal bleeding, symptomatic ulcer disease, perforation of the gastrointestinal tract, and death)
- Serious cardiovascular events (myocardial infarction, angina, stroke, transient ischemic

attack, cardiovascular death, hypertension, congestive heart failure, and related measures)
- Tolerability and adverse event (discontinuation due to any adverse event; any serious adverse event; the overall rate of adverse events; the rate of gastrointestinal adverse events; the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, edema, hypertension, or congestive heart failure; and the frequency of, and discontinuations due to, abnormal laboratory tests—primarily elevated transaminases).

Timing

Inclusion of randomized controlled trials were limited to only those of at least 4 weeks' duration

Study Designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews
- For harms, controlled clinical trials, good-quality systematic reviews and observational studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2013 through May 13, 2014 using terms for included drugs and conditions. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

Pennsaid (diclofenac sodium 2% topical). Approved on 1/16/14 for the treatment of osteoarthritis of the knee.

New drugs identified in previous Preliminary Update Scan

Vimovo (naproxen and esomeprazole magnesium fixed-dose combination tablet): Approved on 4/30/10 to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis

New Indications

New indications identified in this Preliminary Update Scan

None.

New indications identified in previous Preliminary Update Scan

None.

New Safety Alerts

New Safety Alerts Identified in this Preliminary Update Scan

None.

New Safety Alerts Identified in previous Preliminary Update Scan

None.

Comparative Effectiveness Reviews

We identified two new comparative effectiveness reviews. The abstracts of these reviews are attached in Appendix A, and links to the full reports are listed below.

Reviews identified in this Preliminary Update Scan

From CADTH:

Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Safety. August 2013. http://www.cadth.ca/en/publication/3919

Reviews identified in previous Preliminary Update Scans

Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm
.

Randomized Controlled Trials Identified since the most recent Full Report

Medline searches for this scan resulted in 96 citations. Of those, there was only one new companion publication (shaded row in Table 1).

From the previous scan, there were six potentially relevant new randomized controlled trials and one new companion publication (Table 1).

Among the new randomized controlled trials, five involved head-to-head comparisons and one was placebo-controlled. Among the head-to-head trials, two involved the new naproxen/esomeprazole magnesium fixed-dose combination product, which has not been included in any previous full update DERP report.

The two companion publications pertained to the CONDOR trial (Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis), which we included in our DERP Update #4 report from November 2010.

Abstracts of all of these trials are attached in Appendix B.

Table 1. New potentially relevant randomized controlled trials

Author Year	Comparison	Focus
Head-to-head trials		
Cryer 2013 (GI-REASONS)	Celecoxib vs NSAIDs	Osteoarthritis
Essex 2012	Celecoxib vs naproxen	Knee osteoarthritis

Kellner 2012 *(companion to CONDOR, Chan 2010)*	Celecoxib vs diclofenac plus omeprazole	Subgroup analysis of elderly patients
Kellner 2013 *(companion to CONDOR, Chan 2010)*	Celecoxib vs diclofenac plus omeprazole	Improvement in arthritic signs and symptoms
Schmitt 1999	Diclofenac sodium dual release capsule vs standard release	Activated osteoarthritis
Cryer 2011/Hochberg 2011	Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib	Knee osteoarthritis
Goldstein 2010	Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib vs naproxen alone	Patients with a history of ulcer
Placebo-controlled trials		
Baraf 2010	Diclofenac sodium topical gel 1% vs placebo	Knee osteoarthritis

Appendix A. Abstracts of potentially relevant new comparative effectiveness reviews of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

CADTH: Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Saftey

Context
Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in pain management for clinical conditions such as headaches, menstrual disorders, post-operative pain, spinal and soft tissue pain, rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Technology
NSAIDs reduce pain by blocking cyclooxygenase (COX) enzymes needed to produce prostaglandin. There are two forms of the enzyme: COX-1 and COX-2. Traditional NSAIDs, called "non-selective NSAIDs," block both forms. NSAIDs that target only the COX-2 form are called "COX-2 selective NSAIDs" or "COX-2 inhibitors."

Celecoxib (Celebrex) is the only COX-2 inhibitor currently available in Canada.

Issue
Based on their mechanism of action, COX-2 inhibitors are thought to be safer than non-selective NSAIDs in terms of gastrointestinal (GI) bleeding. However, COX-2 inhibitors are associated with an increased risk of major cardiovascular events such as heart attacks and strokes. The COX-2 inhibitor rofecoxib (Vioxx) was removed from the Canadian market in 2004 for this reason. Generic versions of celecoxib will soon be available in Canada.

A review of the comparative safety of NSAIDs will help inform decisions on their use for the management of pain.

Methods
A limited literature search was conducted of key resources, and titles and abstracts of the retrieved publications were reviewed. Full-text publications were evaluated for final article selection according to predetermined selection criteria (population, intervention, comparator, outcomes, and study designs).

Key Messages

- The COX-2 inhibitor, celecoxib, appears to be associated with:
  - a cardiovascular risk similar to diclofenac and ibuprofen, and a higher risk than naproxen
  - a GI bleeding risk similar to diclofenac, and a lower risk than ibuprofen and naproxen.
- Among non-selective NSAIDs:
  - diclofenac may be associated with a higher cardiovascular risk than ibuprofen or naproxen

  - naproxen may be associated with a lower cardiovascular risk than diclofenac, ibuprofen, or indomethacin.
- Interpret these results with caution as:
  - study durations were short (generally less than three months)
  - studies used different NSAID doses.

Results
The literature search identified 275 citations, with an additional 8 articles identified from other sources. Of these, 13 were deemed potentially relevant and 6 met the criteria for inclusion in this review — 5 systematic reviews and 1 health technology assessment.

Abstracts for comparative reviews from previous update:

Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Structured Abstract

Objectives:
To update a previous report on the comparative benefits and harms of oral non-steroidal anti-inflammatory drugs (NSAIDs) , acetaminophen, over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Data Sources:
Ovid MEDLINE (1996–January 2011), the Cochrane database (through fourth quarter 2010), and reference lists.

Review Methods:
We included randomized trials, cohort studies, case-control studies, and systematic reviews that met predefined inclusion criteria. For each study, investigators abstracted details about the study population, study design, data analysis, followup, and results, and they assessed quality using predefined criteria. We assessed the overall strength of each body of evidence using predefined criteria, which included the type and number of studies; risk of bias; consistency; and precision of estimates. Meta-analyses were not performed, though pooled estimates from previously published studies were reported.

Results:
A total of 273 studies were included. Overall, we found no clear differences in efficacy for pain relief associated with different NSAIDs. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) compared to nonselective NSAIDs. Coprescribing of proton pump inhibitors, misoprostol, and H2-antagonists reduce the risk of endoscopically detected gastroduodenal ulcers compared to placebo in persons prescribed NSAIDs. Celecoxib

and most nonselective, nonaspirin NSAIDs appeared to be associated with an increased risk of serious cardiovascular (CV) harms. There was no clear association between longer duration of NSAID use or higher doses and increased risk of serious CV harms. There were no clear differences between glucosamine or chondroitin and oral NSAIDs for pain or function, though evidence from a systematic review of higher-quality trials suggests that glucosamine had some very small benefits over placebo for pain. Head-to-head trials showed no difference between topical and oral NSAIDs for efficacy in patients with localized osteoarthritis, lower risk of gastrointestinal (GI) adverse events, and higher risk of dermatological adverse events, but serious GI and CV harms were not evaluated. No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs.

Conclusions:
Each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. Choosing the optimal analgesic for an individual with osteoarthritis requires careful consideration and thorough discussion of the relevant tradeoffs.

Appendix B. Abstracts of potentially relevant new randomized controlled trials of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Head-to-Head Trials

Cryer, B., C. Li, et al. (2013). "GI-REASONS: a novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial." American Journal of Gastroenterology **108**(3): 392-400.

OBJECTIVES: Because of the limitations of randomized controlled trials (RCTs) and observational studies, a prospective, randomized, open-label, blinded endpoint (PROBE) study may be an appropriate alternative, as the design allows the assessment of clinical outcomes in clinical practice settings. The Gastrointestinal (GI) Randomized Event and Safety Open-Label Nonsteroidal Anti-inflammatory Drug (NSAID) Study (GI-REASONS) was designed to reflect standard clinical practice while including endpoints rigorously evaluated by a blinded adjudication committee. The objective of this study was to assess if celecoxib is associated with a lower incidence of clinically significant upper and/or lower GI events than nonselective NSAIDs (nsNSAIDs) in standard clinical practice.

METHODS: This was a PROBE study carried out at 783 centers in the United States, where a total of 8,067 individuals aged >= 55 years, requiring daily NSAIDs to treat osteoarthritis, participated. The participants were randomized to celecoxib or nsNSAIDs (1:1) for 6 months and stratified by Helicobacter pylori status. Treatment doses could be adjusted as per the United States prescribing information; patients randomized to nsNSAIDs could switch between nsNSAIDs; crossover between treatment arms was not allowed, and patients requiring aspirin at baseline were excluded. The primary outcome was the incidence of clinically significant upper and/or lower GI events.

RESULTS: Significantly more nsNSAID users met the primary endpoint (2.4% (98/4,032) nsNSAID patients and 1.3% (54/4,035) celecoxib patients; odds ratio, 1.82 (95% confidence interval, 1.31-2.55); P = 0.0003). Moderate to severe abdominal symptoms were experienced by 94 (2.3%) celecoxib and 138 (3.4%) nsNSAID patients (P=0.0035). Other non-GI adverse events were similar between treatment groups. One limitation is the open-label design, which presents the possibility of interpretive bias.

CONCLUSIONS: Celecoxib was associated with a lower risk of clinically significant upper and/or lower GI events than nsNSAIDs. Furthermore, this trial represents a successful execution of a PROBE study, where therapeutic options and management strategies available in clinical practice were incorporated into the rigor of a prospective RCT.

Essex, M. N., P. Bhadra, et al. (2012). "Efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis of the knee: a randomized, double-blind, double-dummy trial." Journal of International Medical Research **40**(4): 1357-70.

OBJECTIVE: To assess the efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis (OA) of the knee.

METHODS: This 6-month, randomized, double-blind, double-dummy trial was conducted at 47 centres in the USA. Patients with OA of the knee were randomized to receive 200 mg

celecoxib orally once daily or 500 mg naproxen orally twice daily. The primary endpoint was defined as a 20% improvement from baseline to 6 months in Western Ontario and McMaster Universities (WOMAC) OA total score.

RESULTS: A total of 586 out of 589 randomized patients received at least one dose of celecoxib (n=294) or naproxen (n=292). The primary endpoint (6-month response rate) was achieved by 52.7% and 49.7% of patients in the celecoxib and naproxen treatment groups, respectively. Significantly fewer discontinuations due to gastrointestinal adverse events occurred in patients receiving celecoxib than in those receiving naproxen (4.1% versus 15.1%, respectively).

CONCLUSIONS: Over the 6month study period, celecoxib provided similar improvements in OA symptoms to naproxen. In addition, celecoxib provided better upper gastrointestinal tolerability than naproxen.

Kellner, H. L., C. Li, et al. (2012). "Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial." Current Medical Research & Opinion **28**(9): 1537-45.

OBJECTIVE: To compare the safety and efficacy of celecoxib versus diclofenac slow release (SR) plus omeprazole in elderly arthritis patients.

RESEARCH DESIGN AND METHODS: Patients aged>=65 years, with osteoarthritis and/or rheumatoid arthritis, at high gastrointestinal (GI) risk who participated in the CONDOR trial (Celecoxib vs. Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) were included in this subanalysis. CONDOR was a 6-month prospective, double-blind, randomized, parallel-group, multicenter, international study comparing treatment with celecoxib 200mg twice daily (BID) versus diclofenac SR 75mg BID plus omeprazole 20mg daily.

MAIN OUTCOME MEASURES: The primary end point was a composite of Clinically Significant Upper and Lower GI Events adjudicated by an independent blinded expert committee. Efficacy was determined by the Patient's Global Assessment of Arthritis.

RESULTS: A total of 2446 patients aged>=65 years were included in the intent-to-treat (ITT) population (n=1219 celecoxib; n=1227 diclofenac). Eight patients in the celecoxib group and 52 in the diclofenac group were adjudicated as having Clinically Significant Upper and Lower GI events (adjusted odds ratio: 6.27; p<0.0001). Clinically significant reductions in hemoglobin (>=2g/dL) and/or hematocrit (>=10%) were observed in 23 patients in the celecoxib group and in 76 in the diclofenac group (relative risk: 3.22 [95% confidence interval: 2.04-5.07]; p<0.0001). Incidence of moderate-to-severe abdominal symptoms and discontinuation of treatment due to GI adverse events (AEs) were lower in the celecoxib group. The Patient's Global Assessment of Arthritis score least squares mean change from baseline to final visit and percentage of patients rating treatment efficacy as good/very good at baseline and final visit were similar in both groups.

LIMITATIONS: The dose of celecoxib used is consistent with the European label for the management of osteoarthritis and may not reflect what is commonly prescribed in current clinical practice in the United States. The data were obtained in a clinical trial setting where patients were enrolled based on specific inclusion and exclusion criteria;

as such, the patients may not be broadly representative of the patient population in a general practice setting.

CONCLUSIONS: Efficacy was comparable in the two treatment groups. There were fewer endpoints as well as fewer GI AEs reported in patients treated with celecoxib compared with diclofenac. These data may help physicians in their treatment decisions for elderly patients with arthritis.

Kellner, H. L., C. Li, et al. (2013). "Celecoxib and Diclofenac Plus Omeprazole are Similarly Effective in the Treatment of Arthritis in Patients at High GI Risk in the CONDOR Trial." The open rheumatology journal **7**: 96-100.

OBJECTIVE: Compare effectiveness of celecoxib versus diclofenac plus omeprazole in improving arthritis signs and symptoms in patients at high gastrointestinal (GI) risk who were enrolled in the CONDOR (Celecoxib vs Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) trial.

METHODS: CONDOR was a 6-month, prospective, double-blind, triple-dummy, parallel-group, randomized, multicenter trial comparing celecoxib 200 mg twice daily versus diclofenac slow release (SR) 75 mg twice daily plus omeprazole 20 mg daily. Patients were Helicobacter pylori negative, had osteoarthritis (OA) or rheumatoid arthritis (RA), were aged >60 years, were with or without a history of gastroduodenal ulceration, or were >18 years with previous gastroduodenal ulceration. Patients' Global Assessment of Arthritis was determined at each study visit.

RESULTS: A total of 4484 patients were randomized to treatment (2238 celecoxib, 2246 diclofenac SR) and included in the intention-to-treat analyses. Least squares mean (LSM) (standard error [SE]) for Patients' Global Assessment of Arthritis was 3.219 (0.017) and 3.221 (0.017) at baseline for celecoxib and diclofenac SR (p=0.90). Improvement in both groups was similar in months 2, 4, and 6; at month 1 the LSM (SE) was 2.647 (0.017) and 2.586 (0.017) for celecoxib and diclofenac (p=0.0025). LSM difference (SE) from baseline to final visit demonstrated an improvement of 0.75 (0.02) in celecoxib-treated patients and 0.77 (0.02) in diclofenac SR-treated patients (p=0.42).

CONCLUSIONS: Celecoxib and diclofenac plus omeprazole were shown to have similar efficacy in patients with OA and/or RA at increased GI risk who were enrolled in the CONDOR trial.

TRIAL REGISTRY: Trial was registered under ClinicalTrials.gov identifier NCT00141102.

Schmitt, W., K. Walter, et al. (1999). "Clinical trial on the efficacy and safety of different diclofenac formulations: multiple-unit formulations compared to enteric coated tablets in patients with activated osteoarthritis." Inflammopharmacology **7**(4): 363-75.

This double-blind, randomised, multicentre study investigated the efficacy and safety of two different dosages of a diclofenac sodium dual release capsule (150 mg or 75 mg once daily) in comparison to a standard treatment with enteric coated tablets (50 mg t.i.d.) and placebo in patients with activated osteoarthritis. Pain relief as the main efficacy variable was measured through 24 hours by means of a Visual Analogue Scale at baseline and on five assessment days during the 12 weeks of treatment. Efficacy was

observed in all treatment groups with a statistically significant difference between the verum groups and placebo. The overall safety and tolerability of the active treatments was good. For the 75 mg group, a lower incidence of liver and biliary system-related side effects was reported. Considering efficacy, safety, and compliance aspects, the once daily administration of diclofenac sodium 75 mg dual release capsule is the appropriate dosage regimen for mid- and long-term treatment of osteoarthritis.

Cryer, B. L., M. B. Sostek, et al. (2011). "A fixed-dose combination of naproxen and esomeprazole magnesium has comparable upper gastrointestinal tolerability to celecoxib in patients with osteoarthritis of the knee: results from two randomized, parallel-group, placebo-controlled trials." Annals of Medicine **43**(8): 594-605.

BACKGROUND. Non-steroidal anti-inflammatory drugs are associated with poor upper gastrointestinal (UGI) tolerability and increased ulcer risk, but patient adherence to gastroprotective co-therapy is frequently inadequate. A fixed-dose combination of enteric-coated naproxen 500 mg and immediate-release esomeprazole magnesium 20 mg was evaluated: efficacy is reported by Hochberg et al. (Curr Med Res Opin 2011;27:1243-53); tolerability findings are reported here. PATIENTS AND METHODS. In two 12-week double-blind, placebo-controlled, multicenter, phase III studies (PN400-307 and PN400-309), patients aged >= 50 years with symptomatic knee osteoarthritis randomly (2:2:1) received naproxen/esomeprazole magnesium BID, celecoxib 200 mg QD, or placebo. Tolerability end-points included: modified Severity of Dyspepsia Assessment (mSODA); heartburn severity; and UGI adverse events (AEs). RESULTS. Overall, 619 (PN400-307) and 615 (PN400-309) patients were randomized; mSODA scores improved (baseline to week 12) in each group, with no significant treatment differences between naproxen/esomeprazole magnesium and celecoxib (95% CIs: PN400-307: -0.4, 1.9; PN400-309: -1.8, 0.6). Naproxen/esomeprazole magnesium-treated patients reported significantly more heartburn-free days versus celecoxib (95% CIs: PN400-307: 2.1, 12.7; PN400-309: 2.5, 13.4). UGI AE incidence (PN400-307: 17.3%; PN400-309: 20.3%) was similar between treatment groups. UGI AEs resulted in few discontinuations (< 4%, either study). CONCLUSIONS. Naproxen/esomeprazole magnesium has comparable UGI tolerability to celecoxib in patients with osteoarthritis.

Hochberg, M. C., J. G. Fort, et al. (2011). "Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials." Current Medical Research & Opinion **27**(6): 1243-53.

OBJECTIVE: To demonstrate that a fixed-dose combination of enteric-coated naproxen 500mg and immediate-release esomeprazole magnesium 20mg has comparable efficacy to celecoxib for knee osteoarthritis.

RESEARCH DESIGN AND METHODS: Two randomized, double-blind, parallel-group, placebo-controlled, multicenter phase III studies (PN400-307 and PN400-309) enrolled patients aged >=50 years with symptomatic knee osteoarthritis. Following an osteoarthritis flare, patients received naproxen/esomeprazole magnesium twice daily, celecoxib 200mg once daily, or placebo for 12 weeks.

CLINICAL TRIAL REGISTRATION: NCT00664560 and NCT00665431.

MAIN OUTCOME MEASURES: Three co-primary efficacy endpoints were mean change from baseline to week 12 in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain and function subscales, and Patient Global Assessment of osteoarthritis using a visual analog scale (PGA-VAS).

RESULTS: In Study 307, 619 patients were randomized and 614 treated. In Study 309, 615 patients were randomized and 610 treated. Both naproxen/esomeprazole magnesium and celecoxib were associated with improvements (least squares mean change from baseline to week 12) in WOMAC pain (Study 307: -42.0 and -41.8, respectively; Study 309: -44.2 and -42.9, respectively), WOMAC function (Study 307: -36.4 and -36.3, respectively; Study 309: -38.9 and -36.8, respectively), and PGA-VAS (Study 307: 21.2 and 21.6, respectively; Study 309: 29.0 and 25.6, respectively). A prespecified non-inferiority margin of 10mm between naproxen/esomeprazole magnesium and celecoxib was satisfied for each co-primary endpoint at week 12 in both studies. Significant improvements were observed with naproxen/esomeprazole magnesium versus placebo in both studies ($p<0.05$). Celecoxib was significantly different from placebo in Study 307 ($p<0.05$); however, the improvements were not significant in Study 309. Acetaminophen use and patient expectation of receiving active treatment (80% probability) may have contributed to a high placebo response observed.

CONCLUSIONS: Naproxen/esomeprazole magnesium has comparable efficacy to celecoxib for the management of pain associated with osteoarthritis of the knee over 12 weeks.

Goldstein, J. L., M. C. Hochberg, et al. (2010). "Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone." Alimentary Pharmacology & Therapeutics **32**(3): 401-13.

BACKGROUND: Gastroprotective co-therapy may reduce the risk of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, but adherence is suboptimal.

AIM: To compare the incidence of gastric ulcers with PN 400 [enteric-coated (EC) naproxen 500 mg and immediate-release esomeprazole 20 mg], or EC naproxen.

METHODS: Two randomized, double-blind, multicentre studies (PN400-301, PN400-302). Patients [stratified by low-dose aspirin (< or =325 mg) use] aged > or =50 years or 18-49 years with a history of ulcer, received PN 400 BID (301, n = 218; 302, n = 210) or EC naproxen 500 mg BID (301, n = 216; 302, n = 210) for 6 months. The primary endpoint was the cumulative incidence of endoscopic gastric ulcers.

RESULTS: The cumulative incidence of gastric ulcers was significantly lower with PN 400 vs. EC naproxen (301: 4.1% vs. 23.1%, $P < 0.001$; 302: 7.1% vs. 24.3%, $P < 0.001$). PN 400 was associated with a lower combined incidence of gastric ulcers vs. EC naproxen in low-dose aspirin users (n = 201) (3.0% vs. 28.4%, $P < 0.001$) and non-users (n = 653) (6.4% vs. 22.2%, $P < 0.001$). The incidence of, and discontinuations due to, upper gastrointestinal (UGI) AEs was significantly lower with PN 400 relative to EC naproxen ($P < 0.01$, both studies).

CONCLUSIONS: PN 400 significantly reduces the incidence of gastric ulcers, regardless of low-dose aspirin use, in at-risk patients, and is associated with improved UGI tolerability relative to EC naproxen (ClinicalTrials.gov, NCT00527782).

Placebo-Controlled Trials

Baraf, H. S., M. S. Gold, et al. (2010). "Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial." Physician & Sportsmedicine **38**(2): 19-28.

Background Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may provide an alternative to oral NSAIDs to relieve pain from osteoarthritis (OA), reducing systemic exposure. This 12-week, randomized, double-blind, parallel-group, multicenter trial examined the efficacy and safety of topical diclofenac sodium 1% gel (DSG) for symptomatic knee OA. Methods Eligible patients were aged >/= 35 years with symptomatic Kellgren-Lawrence grade (KLG) 1 to 3 OA in 1 or both knees for >/= 6 months. Patients meeting entry criteria applied DSG 4 g or vehicle 4 times daily to the symptomatic knee(s). Primary endpoints were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and global rating of benefit at week 12. Pain on movement at week 4 was an additional primary endpoint for European regulatory purposes. Secondary endpoints included primary outcomes at weeks 1, 4, and 8; WOMAC stiffness subscale; spontaneous pain; global rating of disease; and global evaluation of treatment. Subanalyses were performed according to KLG, the number of knees treated, and age. Results Four hundred twenty patients were randomly assigned to DSG (n = 208) or vehicle (n = 212). At week 12, DSG provided significantly greater reductions in WOMAC pain (52.6% vs 43.1%; P = 0.008) and physical function (49.7% vs 39.4%; P = 0.004) versus vehicle and provided significant improvements in most secondary endpoints. Treatment-related adverse events (AEs) were infrequent (DSG, 7.7%; vehicle, 4.2%), with application site dermatitis being the most common AE (DSG, 4.8%; vehicle, 0%). No treatment-related gastrointestinal or serious AEs occurred with DSG. Conclusion Topical DSG treatment provided effective pain relief and functional improvement of OA in 1 or both knees and was well tolerated, irrespective of disease severity or patient age.

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Month/Year of Review: July 2014 **Date of Last Review:** April 2012
PDL Classes: Oral Hypoglycemics **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: GLIMEPIRIDE, GLIPIZIDE, GLYBURIDE, METFORMIN, METFORMIN ER
- Non-Preferred Agents: ACARBOSE, CHLORPROPAMIDE, GLIPIZIDE ER, GLIPIZIDE XL, GLIPIZIDE/METFORMIN, GLYBURIDE/METFORMIN, METFORMIN TAB ER GR 24 H (GLUMETZA), GLYBURIDE MICRONIZED, MIGLITOL, REPAGLINIDE, NATEGLINIDE, RAPAGLINIDE/METFORMIN, TOLAZAMIDE, TOLBUTAMIDE

Previous Conclusions and Recommendation:

- There is no clinically significant difference between any of the agents in these two drug classes (oral sulfonylureas and non-sulfonylurea secretagogues) in their ability to lower hemoglobin HbAlc.
- There is no statistically significant difference between glyburide and chlorpropamide in the progression or occurrence of clinically relevant outcomes with the exception of retinopathy. Patients on glyburide had greater risk reduction of progression of retinopathy than those on chlorpropamide.
- There is insufficient evidence on other sulfonylureas and nonsulfonylureas secretagogues to identify a difference in progression or occurrence of clinically relevant outcomes.
- Chlorpropamide has a less favorable adverse effect profile compared to glyburide. There is no difference in safety or adverse effect profiles for other oral sulfonylureas and non-sulfonylureas secretagogues. Glimepiride, glipizide, glyburide, micronized glyburide and repaglinide do not differ in safety or adverse effect profile. No evidence exists for evaluation of tolbutamide, tolazamide or nateglinide.

Conclusions and Recommendations:

- There is limited new evidence since the last review; no further review or research needed.
- Evaluate comparative costs in executive session.

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

References:

1. Thakurta, S. Drug Effectiveness Review Project: Drug Class Review on Oral Hypoglycemics. Preliminary Scan Report #6. May 2014.

Drug Class Review
on
Oral Hypoglycemics

Preliminary Scan Report #6: Last Report Update 2

May 2014

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
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Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations rule in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update:

Update #2 Final Report was completed in May of 2005.

Date of Last Preliminary Update Scan Report

Preliminary Update Scan #1: January 2007
Preliminary Update Scan #2: February 2008
Preliminary Update Scan #3: May 2009
Preliminary Update Scan #4 September 2010
Preliminary Update Scan #5 May 2013

SCOPE AND KEY QUESTIONS:

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

Key Question 1. For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in the progression or occurrence of clinically relevant outcomes?

Key Question 2. For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in the ability to reduce HbA1C levels?

Key Question 3. For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in safety or adverse effects?

Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one oral hypoglycemic (sulfonylureas and short-acting secretagogues) is more effective or associated with fewer adverse effects?

Inclusion Criteria

Population

Adult patients with Type 2 diabetes. Subgroups of interest will include, but are not limited to differences by race, age (older adult versus younger adult), gender and patients with chronic stable angina.

Intervention

- Sulfonylureas: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide (both immediate and extended release formulations included)
- Short-acting secretagogues: repaglinide and nateglinide

Effectiveness outcomes

- Lowering of HbA1c
- Clinically relevant outcomes:
  - Time to requiring insulin
  - Progression or occurrence of long-term microvascular disease (nephropathy as evidenced by proteinuria/dialysis/transplant/end-stage renal disease, retinopathy including proliferative retinopathy and blindness, and neuropathy)
  - Progression or occurrence of macrovascular disease (cardiovascular disease and mortality, myocardial infarction, stroke, coronary disease, angioplasty/CABG, amputation)
  - Exercise tolerance
  - Complications of diabetes
  - All-cause mortality
  - Quality of life

Safety outcomes**:**

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (e.g., hypoglycemia, weight gain, or effects on lipids)

Study designs

1. For effectiveness, study is a double-blind, randomized controlled trial in an outpatient setting (including emergency department) or good quality systematic reviews. Crossover trials will be included.
2. For safety, controlled clinical trial, observational study, or drug-drug interaction study.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from April 2013 to April Week 4, 2014 using terms for the included drugs. We limited the search to randomized controlled published in English. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and boxed warnings. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm)

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

None

New drugs identified in this Preliminary Update Scan

None

New drugs identified in previous Preliminary Update Scan(s)

None

New Indications

New indications identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scan(s)

None

New Boxed Warnings

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
None

Comparative Effectiveness Reviews
Reviews identified in this Preliminary Update Scan
None

Reviews identified in previous Preliminary Update Scan(s)

An Update of the 2007 Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes was prepared for the Agency for Healthcare Research and Quality in March, 2011. The Title of the review is "Oral Diabetes Medications for Adults with Type 2 Diabetes: An Update, available at http://www.effectivehealthcare.ahrq.gov/ehc/products/155/644/type-2-diabetes-medications-report-130911.pdf. The abstract and key questions are included in Appendix A

A rapid response Report by the Canadian Agency for Drugs and Technologies in Health was produced in June 15, 2011. The title of the review is "Glyburide, Gliclazide or Glimepiride in the Elderly with Type 2 Diabetes: A Review of the Clinical Effectiveness and Safety", available at http://www.cadth.ca/media/pdf//htis/june-2011/RC0285_Glyb_Glic_Glim_for_Eld_with_T2DM_Final.pdf.
Key questions from the rapid response report are included in Appendix A.

Head to head trials

We were not able to find any head to head trial from our current Medline search. We found 2 placebo control trials, one of which compared TAK-875 (falsiglifam) to placebo. Glimepiride was used as a non-blinded active control. The second trial compared glucokinase activator AZD 1656 to placebo and glipizide. Both focus on glycemic control and no clinically relevant outcomes (listed above). There are a total of 17 head-to-head trials identified in the previous preliminary update scans, none of which reported any 'clinically relevant outcomes' that would likely be added in a full update of this review. See Appendix B. for abstracts of potentially relevant head to head trials.

Table 1. Head-to-head trials

Author Year	Comparison
Anwar 2006	Glimepiride vs repaglinide
Dimic 2009	Glimepiride vs repaglinide
Rizzo 2005	Glimepiride vs repaglinide
Li 2010	Glimepiride vs repaglinide
Sari 2004	Glimepiride vs repaglinide
Gonzalez-Ortiz	Glimepiride vs glibenclamide, both in combination with

2009	metformin
Cesur 2007	Glimepiride vs repaglinide vs insulin glargine
Go 2004	Glipizide GITS vs glibenclamide
DeRosa 2007	Nateglinide vs glibenclamide
Derosa 2009	Nateglinide vs glibenclamide, both in combination with metformin
Bellomo Damato 2011	Nateglinide vs glyburide
Schwartz 2008	Nateglinide vs glyburide, both in combination with metformin
Li 2007	Nateglinide vs repaglinide
Li 2009	Nateglinide vs repaglinide
Stephens, 2011	Repaglinide vs glibenclamide
Papa 2006	Repaglinide vs glibenclamide
Rosenstock 2004	Repaglinide vs nateglinide

Appendix A. Relevant Comparative Effectiveness Reviews

1.. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update

Structured Abstract

Objectives. Given the number of medications available for type 2 diabetes mellitus, clinicians and patients need information about their effectiveness and safety to make informed choices. The objective of this review was to summarize the benefits and harms of medications (metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, and glucagon-like peptide-1 [GLP-1] receptor agonists), as monotherapy and incombination, for the treatment of adults with type 2 diabetes.

Data Sources. We searched the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases from inception through April 2010 for original English-language articles and sought unpublished data from the Food and Drug Administration and others.

Review Methods. Two reviewers independently screened titles to identify studies that assessed intermediate outcomes (e.g., hemoglobin A1c [HbA1c]), long-term clinical outcomes (e.g., mortality), and harms (e.g., hypoglycemia) in head-to-head monotherapy or combination therapy
comparisons. Two reviewers serially extracted data for each article using standardized protocols,
assessed applicability, and independently evaluated study quality.

Results. The review included 140 randomized controlled trials and 26 observational studies. We graded evidence as low or insufficient for long-term clinical outcomes of all-cause mortality, cardiovascular disease, nephropathy, and neuropathy. Most medications lowered HbA1c on average by 1 absolute percentage point, but metformin was more efficacious than the DPP-4 inhibitors. Two-drug combinations had similar HbA1c reduction. Compared with metformin, thiazolidinediones and sulfonylureas had a more unfavorable effect on weight (mean difference of +2.6 kg). Metformin decreased low density lipoprotein cholesterol relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors. Sulfonylureas had a fourfold higher risk of mild/moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a fivefold increased risk compared with metformin plus thiazolidinediones. Thiazolidinediones had an increased risk of congestive heart failure relative to sulfonylureas and
bone fractures relative to metformin. Diarrhea occurred more often for metformin compared with
thiazolidinedione users.

Conclusions. Comprehensive information comparing benefits and harms of diabetes medications
can facilitate personalized treatment choices for patients. Although the long-term benefits and harms of diabetes medications remain unclear, the evidence supports use of metformin as a firstline
agent. Comparisons of two-drug combinations showed little to no difference in HbA1c reduction, but some combinations increased risk for hypoglycemia and other adverse events.

Key Question 1. In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (Table 2 and Appendix A) for the intermediate outcomes
of glycemic control (in terms of HbA1c), weight, or lipids?

Key Question 2. In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (Table 2) in terms of the following long-term clinical outcomes?
- All-cause mortality
- Cardiovascular mortality
- Cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke)
- Retinopathy
- Nephropathy
- Neuropathy

Key Question 3. In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the following treatment options (Table 2) in terms of the following adverse events and side effects?
- Hypoglycemia
- Liver injury
- Congestive heart failure
- Severe lactic acidosis
- Cancer
- Severe allergic reactions
- Hip and non-hip fractures
- Pancreatitis
- Cholecystitis
- Macular edema or decreased vision
- Gastrointestinal side effects

Key Question 4. Do safety and effectiveness of these treatment options (Table 2) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, and cardiovascular and cerebrovascular outcomes?

2. Glyburide, Gliclazide or Glimepiride in the Elderly with Type 2 Diabetes: A Review of the Clinical Effectiveness and Safety

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of glyburide versus gliclazide or glimepiride in elderly patients with type 2 diabetes?

2. What is the clinical evidence on the patient safety associated with glyburide, gliclazide or glimepiride in elderly patients with type 2 diabetes?

Appendix B. Abstracts of potentially relevant new head to head trials found in previous scans

Anwar, A., K. N. Azmi, et al. (2006). "An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan." Medical Journal of Malaysia **61**(1): 28-35.

This study was conducted to compare the treatment efficacy between a prandial glucose regulator, repaglinide and a new sulphonylurea, glimepiride in Muslim Type 2 diabetic patients who practice Ramadan fasting. Forty-one patients, previously treated with a sulphonylurea or metformin, were divided to receive either repaglinide (n=20, preprandially three-times daily) or glimepiride (n=21, preprandially once daily) 3 months before the month of Ramadan. During Ramadan, patients modified their eating pattern to two meals daily, and the triple doses of repaglinide were redistributed to two preprandial doses. Four point blood glucose monitoring were performed weekly during the month of Ramadan and the subsequent month. Measurements of the 4-point blood glucose were significantly lower in the glimepiride group compared to the repaglinide group both during and after Ramadan. The glycaemic excursion was better in the morning for the repaglinide group and better in the afternoon and evening for the glimepiride group during the Ramadan period. There was no statistically significant difference in the incidence of hypoglycaemia between the two groups during and after Ramadan. There was no difference in the glycaemic excursion post-Ramadan. The longer duration of action of glimepiride may offer an advantage over repaglinide during the 13.5 hours of fast in Ramadan for diabetic patients.

Bellomo Damato, A., G. Stefanelli, et al. (2011). "Nateglinide provides tighter glycaemic control than glyburide in patients with Type 2 diabetes with prevalent postprandial hyperglycaemia." Diabetic Medicine 28(5): 560-566.

AIMS: Postprandial hyperglycaemia in patients with Type 2 diabetes mellitus has been linked to the development of cardiovascular disease. This study compared the effects of mealtime (thrice-daily) nateglinide with once-daily glyburide on postprandial glucose levels in patients with Type 2 diabetes and postprandial hyperglycaemia.
METHODS: Patients with Type 2 diabetes aged >= 21 years with 2-h postprandial glucose levels >= 11.1 mmol/l, HbA(1c) of 6.5-8.5% (48-69 mmol/mol) and BMI of 22-30 kg/m(2) were randomized to 6 weeks' double-blind treatment with nateglinide 120 mg three times daily prior to meals, or glyburide 5 mg once daily before breakfast. The primary endpoint was the baseline-adjusted change in plasma glucose from preprandial (fasting plasma glucose) to 2-h postprandial glucose levels (2-h postprandial glucose excursion) at 6 weeks.
RESULTS: Patients were randomized to nateglinide (n = 122) or glyburide (n = 110). The treatment groups were similar in terms of age, gender, BMI, fasting plasma glucose, 2-h postprandial glucose and HbA(1c). At endpoint, nateglinide recipients had significantly greater reductions than those receiving glyburide in both the 2-h (-2.4 vs. -1.6 mmol/l; P

= 0.02) and 1-h (-1.7 vs. -0.9 mmol/l; P = 0.016) postprandial glucose excursions. Adverse events, most commonly symptomatic hypoglycaemia, were reported in 26% of recipients of glyburide and 22% of recipients of nateglinide. Episodes of suspected mild hypoglycaemia were reported in 24% of recipients of glyburide and 10% of recipients of nateglinide.
CONCLUSIONS: Nateglinide leads to greater reductions in postprandial glucose excursions and is associated with a lower risk of hypoglycaemia than glyburide in this selected population of patients with Type 2 diabetes.

Cesur, M., D. Corapcioglu, et al. (2007). "A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting." Diabetes Research & Clinical Practice **75**(2): 141-7.

Although diabetics may be exempted from Ramadan fasting, many patients still insist on this worship. Aim of the present study is to compare the effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetics during Ramadan fasting on the glucose metabolism. Patients, who were willing to fast, were treated with glimepiride (n=21), repaglinide (n=18), and insulin glargine (n=10). Sixteen non-fasting control type 2 diabetics matched for age, sex, and body mass index were also included. Fasting blood glucose (FBG), post-prandial blood glucose (PBG), HbA1c, and fructosamine as well as lipid metabolism were evaluated in pre-Ramadan, post-Ramadan, and 1-month post-Ramadan time points. There was no significant change from pre-Ramadan in FBG, PBG, and HbA1c variables in fasting diabetics at post-Ramadan and 1-month post-Ramadan. However, PBG was found higher in non-fasting control diabetics at post-Ramadan and 1-month post-Ramadan ($p<0.05$ and $p<0.001$, respectively). In fructosamine levels, a significant increase was noted both in fasting group and non-fasting group at 1-month post-Ramadan ($p<0.01$ for all). However, no significant difference was found in the comparison of the changes in fructosamine levels between fasting group and non-fasting group. Risk of hypoglycemia did not significantly differ between fasting and non-fasting diabetics. There was no significant difference between three drug therapies regarding glucose metabolism and rate of hypoglycemia. No adverse effects on plasma lipids were noted in fasting diabetics. In this fasting sample of patients with type 2 diabetes, glimepiride, repaglinide, and insulin glargine did not produce significant changes in glucose and lipid parameters.

Derosa, G., A. D'Angelo, et al. (2007). "Effects of nateglinide and glibenclamide on prothrombotic factors in naive type 2 diabetic patients treated with metformin: a 1-year, double-blind, randomized clinical trial." Internal Medicine **46**(22): 1837-46.

OBJECTIVE: To evaluate the effect on coagulation and fibrinolysis parameters and on non-conventional cardiovascular risk factors of metformin plus nateglinide or glibenclamide in naive type 2 diabetes patients. PATIENTS AND METHODS: A total of 248 type 2 diabetic patients were enrolled and randomly assigned to receive nateglinide or glibenclamide, and metformin for 12 months. We assessed body mass index (BMI),

glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), homeostasis model assessment index (HOMA index), lipid profile with lipoprotein (a) [Lp(a)], fibrinogen (Fg), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), homocysteine (Hcy), systolic blood pressure (SBP), diastolic blood pressure (DBP). RESULTS: After 9 months of treatment, both tested drug combinations were similarly associated with a significant reduction in FPG (nateglinide, -17.2%; glibenclamide, -16.9%, both $p<0.05$) compared to the baseline, while HbA1c (-17.3%, $p<0.05$) and PPG (-15.2%, $p<0.05$) significantly decreased only in the nateglinide group. After one year of treatment, compared to the baseline the nateglinide group showed a significant reduction in HbA1c (-21%, $p<0.01$), FPG (-20.7%), $p<0.01$, PPG (-21.5%, $p<0.05$), HOMA index (-25.4%, $p<0.05$); the glibenclamide group, showed a significant reduction in HbA1c (-11%, $p<0.05$), FPG (-23.2%, $p<0.05$), PPG (-11.2%, $p<0.05$), and HOMA index (-23.9%, $p<0.05$) but to a minor extent. Moreover, the HbA1c difference value from baseline observed in the nateglinide-treated group was significantly higher than that observed in the glibenclamide group. Therefore the nateglinide-treated patients showed a significant reduction in some prothrombotic parameters (PAI-1=-19%, Lp(a)=-31%, and Hcy=-32.3%, all $p<0.05$), whereas the glibenclamide-treated patients did not. CONCLUSION: Nateglinide appears to improve glycemic control as well as the levels of some prothrombotic parameters compared to glibenclamide when administered in combination with metformin.

Derosa, G., A. D'Angelo, et al. (2009). "Nateglinide and glibenclamide metabolic effects in naive type 2 diabetic patients treated with metformin." Journal of Clinical Pharmacy & Therapeutics **34**(1): 13-23.

BACKGROUND AND OBJECTIVE: Most antidiabetic agents target only one of several underlying causes of diabetes. The complementary actions of the glinides and the biguanides may give optimal glycemic control in patients with type 2 diabetes mellitus. The aim of the present study was to compare the effects of nateglinide plus metformin with glibenclamide plus metformin on glucose and lipid metabolism, and haemodynamic parameters in patients with type 2 diabetes mellitus. METHODS: We enrolled 248 type 2 diabetic patients. Patients were randomly assigned to receive nateglinide (n = 124) or glibenclamide (n = 124), after 6 months of run-in, in which we titrated nateglinide (starting dose 180 mg/day), glibenclamide (starting dose 7.5 mg/day), and metformin (starting dose 1500 mg/day). The final doses were (mean +/- standard deviation), 300 +/- 60, 12.5 +/- 2.5, and 2500 +/- 500 mg/day, respectively. We followed these patients for 1 year after titration. We assessed body mass index (BMI), fasting (FPG) and post-prandial (PPG) plasma glucose, glycosylated haemoglobin (HbA(1c)), fasting (FPI) and post-prandial (PPI) plasma insulin, homeostasis model assessment (HOMA) index, and lipid profile [total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B)], systolic blood pressure (SBP), and diastolic blood pressure (DBP). All variables were evaluated at

baseline and after 3 and 6 months in the run-in period, and at baseline, and after 3, 6, 9 and 12 months for both treatment groups. RESULTS AND DISCUSSION: Body mass index did not show any significant change during the study. We observed a significant improvement from baseline to 1 year on HbA(1c) (P < 0.01 vs. baseline and vs. glibenclamide group, respectively), FPG (P < 0.01 vs. baseline), PPG (P < 0.01 vs. baseline), and on HOMA index (P < 0.05 vs. baseline) in the nateglinide group. In the glibenclamide group, we found significant changes in HbA(1c) (P < 0.05 vs. baseline), FPG (P < 0.01 vs. baseline), PPG (P < 0.05 vs. baseline), and HOMA index (P < 0.05 vs. baseline). No significant change was observed in TC, LDL-C, HDL-C, Tg, Apo A-I, Apo B, SBP, DBP and HR in either group after 3, 6, 9 and 12 months. These effects of nateglinide and glibenclamide on insulin-resistance parameters are in agreement with previous reports. Contrarily to previous reports, we did not observe any significant BP change in patients treated with glibenclamide. Although both nateglinide and glibenclamide attenuated PPG and HOMA index, they did not have significant effects on lipid metabolism, as already shown in subjects with type 2 diabetes and good glycemic control. CONCLUSION: Nateglinide improved glycemic control better than glibenclamide in combination with metformin.

Dimic, D., M. Velojic Golubovic, et al. (2009). "Evaluation of the repaglinide efficiency in comparison to the glimepiride in the type 2 diabetes patients poorly regulated by the metformin administration." Bratislavske Lekarske Listy 110(6): 335-9.

OBJECTIVES: An impaired early phase of insulin secretion in the type 2 diabetes mellitus (DM) is very important for the postprandial hyperglycemia. The aim of the study was to compare the efficacy of metformin/repaglinide and metformin/glimepiride regimes in type 2 diabetics uncontrolled with metformin monotherapy. METHODS: Totally, 60 type 2 diabetics with haemoglobin A1c > or = 7.5% and 2000 mg of metformin monotherapy for at least three months were divided in the following groups: A-30 patients with metformin+repaglinid (2 mg for each meal) and B metformin+glimepirid (3 mg in the morning). Assessment of the regimes efficacy comprised of haemoglobin A1c, fasting blood glucose (FBG) and postprandial blood glucose (PBG). Assessment of the safety was performed on the basis of recorded hypoglycemia (<4.0 mmol/l). RESULTS: In both groups, FBG was significantly lower at the end of the study. In the group A it decreased from 9.03 +/- 1.00 to 7.32 +/- 0.65 (p < 0.001), in the group B from 8.94 +/- 1.01 to 7.23 +/- 0.70 (p < 0.001). There was no statistical difference between the groups. PBG was significantly lower after 12 weeks in both groups. CONCLUSION: Metformin/repaglinid is an efficient and safe therapeutic regime in the treatment of the type 2 DM that ensure a better control of PBG levels (Tab. 4, Ref. 18).

Go, E. H., M. Kyriakidou-Himonas, et al. (2004). "Effects of glipizide GITS and glibenclamide on metabolic control, hepatic glucose production, and insulin secretion in patients with type 2 diabetes." Diabetes/Metabolism Research Reviews **20**(3): 225-31.

OBJECTIVE: Evaluation of effects of glipizide gastrointestinal therapeutic system (GITS) administered once daily (AM or PM) and glibenclamide on glycemic control, insulin secretory response, and hepatic glucose production (HGP) in patients with type 2 diabetes. METHODS: In a randomized, double-blind, and placebo-controlled study, subjects (HbA(1c) between 8.6 and 10.0%) received a titrated daily dose (5-20 mg) of either glipizide GITS AM (n = 11), glipizide GITS PM (n = 10), glibenclamide (n = 11), or placebo (n = 10) for eight weeks. Fasting and 24-h glucose and insulin, HGP, fructosamine, and HbA(1c) were measured at baseline and at study conclusion; glucose and insulin were also evaluated after Sustacal challenge. RESULTS: Fasting and 24-h glucose were significantly reduced by glipizide GITS AM (33%, $p < 0.001$; 39%, $p < 0.0001$), glipizide GITS PM (33%, $p < 0.0001$; 32%, $p < 0.0001$), and glibenclamide (37%, $p < 0.05$; 37%, $p < 0.0001$). Fasting insulin was not significantly increased by any treatment; 24-h insulin was not increased by glipizide GITS AM, but was elevated by glipizide GITS PM (39%, $p < 0.05$) and glibenclamide (23%, $p < 0.05$). Fructosamine and HbA(1c) were significantly reduced by glipizide GITS AM (28%, $p < 0.001$; 22%, $p < 0.0001$), glipizide GITS PM (25%, $p < 0.005$; 24%, $p < 0.005$), and glibenclamide (17%, $p < 0.001$; 14%, $p < 0.05$). Glipizide GITS AM and glibenclamide significantly reduced HGP by approximately 19% ($p < 0.05$) and 17% ($p < 0.01$) respectively. Glipizide GITS and glibenclamide significantly ($p < 0.0001$) decreased the glucose excursion after Sustacal challenge. The reductions in glucose excursions were accompanied by significant ($p < 0.05$) increases in the insulin response, suggesting an improvement in meal-related insulin secretion. CONCLUSIONS: Glipizide GITS and glibenclamide treatment are effective agents for improving fasting plasma glucose and HbA(1c). Each possessed a suppressive effect on basal HGP and improved postprandial glycemia, but only glipizide GITS AM was effective without causing a persistent elevation in insulin. This profile of glipizide GITS AM is therapeutically attractive, as it is consistent with the potential for a reduced risk of hypoglycemia. Copyright 2004 John Wiley & Sons, Ltd.

Gonzalez-Ortiz, M., J. F. Guerrero-Romero, et al. (2009). "Efficacy of glimepiride/metformin combination versus glibenclamide/metformin in patients with uncontrolled type 2 diabetes mellitus." Journal of Diabetes & its Complications 23(6): 376-9.

AIM: The aim of this study was to compare the efficacy of glimepiride/metformin combination versus glibenclamide/metformin for reaching glycemic control in patients with uncontrolled type 2 diabetes mellitus. PATIENTS AND METHODS: A randomized, double-blind, multicenter clinical trial was performed in 152 uncontrolled type 2 diabetic patients. Serum fasting and postprandial glucose, hemoglobin A1c (A1C), high-density lipoprotein cholesterol, and triglycerides were measured. After random allocation, all patients received two pills of glimepiride (1 mg)/metformin (500 mg) or glibenclamide (5 mg)/metformin (500 mg) po once a day. Dosage was increased to a maximum of four pills in order to reach the glycemic control goals (fasting glucose <or=7.2 mmol/l, postprandial glucose <10.0 mmol/l, A1C <7%, or an A1C >or=1% reduction). Statistical analyses were carried out using chi-square, ANOVA, or Student's t test. The protocol was approved by an ethics committee and met all requirements needed to perform research in human subjects; all patients gave written informed

consent. RESULTS: Each study group included 76 patients. No significant differences in basal clinical and laboratory characteristics between groups were found. At the end of the study, A1C concentration was significantly lower in the glimepiride/metformin group (P=.025). A higher proportion of patients from the glimepiride group (44.6% vs. 26.8%, P<.05) reached the goal of A1C <7% at 12 months of treatment. A higher proportion of hypoglycemic events were observed in the glibenclamide group (28.9% vs. 17.1%, P<.047). CONCLUSION: Glimepiride/metformin demonstrated being more efficacious than glibenclamide/metformin at reaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus.

Li, J., H. Tian, et al. (2007). "Improvement of insulin sensitivity and beta-cell function by nateglinide and repaglinide in type 2 diabetic patients - a randomized controlled double-blind and double-dummy multicentre clinical trial." Diabetes, Obesity & Metabolism **9**(4): 558-65.

AIM: To evaluate the efficacy of nateglinide vs. repaglinide in blood glucose (BG) control and the effect on insulin resistance and beta-Cell function in patients with type 2 diabetes. METHODS: A randomized controlled double-blind and double-dummy multicentre clinical trial was conducted. A total of 230 Chinese patients with type 2 diabetes were enrolled in five clinical centres. The patients were divided randomly into group A [repaglinide 1.0 mg three times daily (t.i.d.), n = 115] or group B (nateglinide 90 mg t.i.d., n = 115). At baseline and end of the 12-week clinical trial, standard mixed meal tolerance tests were performed. RESULTS: A total of 223 patients (96.9%) completed the trial. There was no significant difference between repaglinide and nateglinide groups in the effects of reducing fasting blood glucose (FBG), 30-, 60- and 120-min BG during 12 weeks ($p > 0.05$). At week 12, no significant difference was shown between the two groups in BG or haemoglobin A(1c) (HbA(1c)) ($p > 0.05$). However, the effect on HbA(1c) in repaglinide group was stronger than that in nateglinide group ($p < 0.05$). After 12-week treatment, area under the curve (AUC) of BG decreased ($p < 0.05$), and AUC of insulin and C-peptide (CP) increased in both groups ($p < 0.05$). The effects of nateglinide on AUC of BG, insulin and CP were similar to that of repaglinide ($p > 0.05$). There was no significant difference between the two groups in AUC of BG, insulin or CP in week 12 ($p > 0.05$). Furthermore, homeostasis model assessment of insulin resistance (HOMA-IR) and beta-cell function indexes measured by HOMA-beta, DeltaI(30)/DeltaG(30) and (DeltaI(30)/DeltaG(30))/HOMA-IR were improved significantly in both groups during 12 weeks ($p < 0.05$). The effects of improving HOMA-IR and beta-cell function indexes in nateglinide group were comparable with that of repaglinide group ($p > 0.05$). CONCLUSIONS: The efficacy of repaglinide and nateglinide in FBG, postprandial glucose excursion and early-phase insulin secretion is similar. But the effect of repaglinide 1.0 mg t.i.d. on HbA(1c) is stronger than that of nateglinide 90 mg t.i.d.. This trial had shown that nateglinide and repaglinide could comparably improve insulin sensitivity and beta-cell function.

Li, C., J. Xia, et al. (2009). "Nateglinide versus repaglinide for type 2 diabetes mellitus in China." Acta Diabetologica 46(4): 325-33.

Li, Y., L. Xu, et al. (2010). "Effects of short-term therapy with different insulin secretagogues on glucose metabolism, lipid parameters and oxidative stress in newly diagnosed Type 2 Diabetes Mellitus." Diabetes Research & Clinical Practice 88(1): 42-7.

AIM: To compare effects of three different insulin secretagogues on early-phase insulin secretion, metabolism of glucose and lipids, and lipid peroxidation in newly diagnosed Type 2 Diabetes Mellitus (T2DM). METHODS: Totally 60 newly diagnosed T2DM outpatients were randomized to three groups with 1-month monotherapy of repaglinide (Rg), glimepiride (Gm) or gliclazide MR (Gli), respectively. Some indexes of early-phase insulin secretion, glucose, lipids, and lipid peroxidation were inspected. RESULTS: Fasting plasma glucose (FPG), glycosylated hemoglobin (HbA(1c)) and fructosamine (FA) were improved in all groups similarly (p>0.05). Rg group was with the highest early-phase insulin secretion index (DeltaI30/DeltaG30) (p=0.026), lower mean amplitude of glycaemic excursion (MAGE) (p<0.05), lowest mean peak value of post-lunch glucose (p=0.043), and lowest postprandial triglyceride (TG) (p=0.039). Postprandial free fatty acid (FFA) was lower after Rg and Gli treatment (p<0.05). Serum 8-iso prostaglandin F(2alpha) (8-iso PGF(2alpha)) was improved in all groups, but the improvement showed statistically significant only in Rg group (p=0.04). CONCLUSION: Rg, Gm and Gli can all decrease blood glucose effectively in newly diagnosed T2DM patients, while Rg performs outstandingly in the aspects of improving early-phase insulin secretion, glucose excursion, postprandial lipids and 8-iso PGF(2alpha).

Papa, G., V. Fedele, et al. (2006). "Safety of type 2 diabetes treatment with repaglinide compared with glibenclamide in elderly people: A randomized, open-label, two-period, cross-over trial." Diabetes Care **29**(8): 1918-20.

Rizzo, M. R., M. Barbieri, et al. (2005). "Repaglinide has more beneficial effect on cardiovascular risk factors than glimepiride: data from meal-test study." Diabetes & Metabolism **31**(3 Pt 1): 255-60.

Aim our study is to compare the effects of repaglinide vs glimepiride administration on cardiovascular risk factors after meal test. Thus, after 2 weeks washout period, a 3-month randomised, cross-over parallel group trial of repaglinide (1 mg x 2/day) vs glimepiride (2 mg/day) in 14 patients with type 2 diabetes "naive" on diet treatment was made. Both treatments significantly declined plasma glucose, total-cholesterol, LDL-cholesterol, triglycerides, PAI-1, PAP levels and increased HDL-cholesterol. Lowering in plasma PAI-1 and PAP levels was significantly greater in repaglinide group. Furthermore, repaglinide administration resulted in a significant decrease in fasting plasma free fatty acids, fibrinogen, thrombin-antithrombin complex and reaction product of malondialdehyde with thiobarbituric acid (TBARS) levels, in absence of significant difference in fasting plasma insulin levels. Decrease in plasma TBARS levels correlated

with the decrease in Plasminogen Activator Inhibitor-1 (r = 0.72; P < 0.003) and free fatty acids concentrations (r = 0.62; P < 0.01). Analysis of the insulin and glucose concentrations throughout the meal test revealed that AUC for glucose (758 +/- 19 vs 780 +/- 28 mg/Lxmin; P = 0.02) was significantly lower after repaglinide than glimepiride administration despite similar AUC for insulin (2327 +/- 269 vs 2148 +/- 292 mU/Lxmin; P = 0.105). At time 120' of meal test, repaglinide vs glimepiride administration was associated with a significant decline in plasma triglycerides, free fatty acids, fibrinogen, Plasminogen Activator Inhibitor-1, plasmin-alpha(2)-antiplasmin complex, thrombin-antithrombin complex, TBARS levels and increase in plasma HDL-cholesterol levels. In repaglinide group a negative correlation between insulin secretion during 1st phase of meal-test and plasma TBARS levels (r = -0.55; P < 0.03) at time 120' was found. Such correlation was lost after adjusting for changes in postprandial hyperglycaemia (r = -0.48; P < 0.09). In conclusion, our results support the hypothesis that repaglinide is more efficient than glimepiride on controlling for postprandial glucose excursion and may have beneficial effect on reducing cardiovascular risk factors.

Rosenstock, J., D. R. Hassman, et al. (2004). "Repaglinide versus nateglinide monotherapy: a randomized, multicenter study." Diabetes Care **27**(6): 1265-70.

OBJECTIVE: A randomized, parallel-group, open-label, multicenter 16-week clinical trial compared efficacy and safety of repaglinide monotherapy and nateglinide monotherapy in type 2 diabetic patients previously treated with diet and exercise. RESEARCH DESIGN AND METHODS: Enrolled patients (n = 150) had received treatment with diet and exercise in the previous 3 months with HbA(1c) >7 and < or =12%. Patients were randomized to receive monotherapy with repaglinide (n = 76) (0.5 mg/meal, maximum dose 4 mg/meal) or nateglinide (n = 74) (60 mg/meal, maximum dose 120 mg/meal) for 16 weeks. Primary and secondary efficacy end points were changes in HbA(1c) and fasting plasma glucose (FPG) values from baseline, respectively. Postprandial glucose, insulin, and glucagon were assessed after a liquid test meal (baseline, week 16). Safety was assessed by incidence of adverse events or hypoglycemia. RESULTS: Mean baseline HbA(1c) values were similar in both groups (8.9%). Final HbA(1c) values were lower for repaglinide monotherapy than nateglinide monotherapy (7.3 vs. 7.9%). Mean final reductions of HbA(1c) were significantly greater for repaglinide monotherapy than nateglinide monotherapy (-1.57 vs. -1.04%; P = 0.002). Mean changes in FPG also demonstrated significantly greater efficacy for repaglinide than nateglinide (-57 vs. -18 mg/dl; P < 0.001). HbA(1c) values <7% were achieved by 54% of repaglinide-treated patients versus 42% for nateglinide. Median final doses were 6.0 mg/day for repaglinide and 360 mg/day for nateglinide. There were 7% of subjects treated with repaglinide (five subjects with one episode each) who had minor hypoglycemic episodes (blood glucose <50 mg/dl) versus 0 patients for nateglinide. Mean weight gain at the end of the study was 1.8 kg in the repaglinide group as compared with 0.7 kg for the nateglinide group. CONCLUSIONS: In patients previously treated with diet and exercise, repaglinide and nateglinide had similar postprandial glycemic effects, but repaglinide monotherapy

was significantly more effective than nateglinide monotherapy in reducing HbA(1c) and FPG values after 16 weeks of therapy.

Sari, R., M. K. Balci, et al. (2004). "The effects of diet, sulfonylurea, and Repaglinide therapy on clinical and metabolic parameters in type 2 diabetic patients during Ramadan." Endocrine Research **30**(2): 169-77.

BACKGROUND AND AIM: Diabetes and its treatment can cause problems for the Muslim population. The aim of this study was to evaluate the effect of different therapy models on clinical and metabolic status in type 2 diabetic patients during Ramadan. MATERIAL AND METHODS: Fifty-two type 2 diabetic patients were included to this study. Twelve of patients were on diabetic diet only before and during Ramadan (Group 1). Forty of patients had had sulfonylurea (Glimepiride 23 patients, gliclazide 17 patients) before Ramadan. Thirteen of these patients were on a single dose sulfonylurea (Glimepiride 8 patients, gliclazide 5 patients) (Group 2) and 27 were on Repaglinide 2 x 2 mg (Group 3) during Ramadan. Beta-hydroxybutyric acid, glucose, fructosamine, HbA1c, lipid levels and body weight were measured before and after Ramadan. RESULTS: Body weight, fasting plasma glucose, fructosamine, HbA1c, total cholesterol were not changed in groups during the study. Triglyceride level decreased after Ramadan in groups 2 ($p = 0.002$) and 3 ($p = 0.024$). HDL-cholesterol level increased in group 3 ($p = 0.022$). Fasting capillary beta-hydroxybutyric acid level increased in group 1 ($p = 0.034$) and didn't change in groups 2 and 3 during the Ramadan. Only one hypoglycemic event occurred at day 6 of Ramadan in patients in group 2 (the patient was on 3 mg glimepiride). CONCLUSION: Our results conclude that Ramadan fasting affects metabolic parameters in type 2 diabetes and hypoglycemia should be kept in mind especially in patients using sulfonylurea treatment. Ramadan fasting is not advised for type 2 diabetics while taking medical therapy. If the patient wants Ramadan fasting, these patients using Repaglinide can reduce the frequency of hypoglycemia.

Schwarz, S. L., J. E. Gerich, et al. (2008). "Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naive elderly patients with type 2 diabetes." Diabetes, Obesity & Metabolism **10**(8): 652-60.

AIM: The aim of this work was to assess the efficacy and tolerability of nateglinide alone or in combination with metformin in elderly patients with type 2 diabetes (T2DM). METHODS: Study 1 was a 12-week, multicentre, randomized, double blind and placebo-controlled study of nateglinide monotherapy (120 mg, before meals) in 66 drug-naive patients with T2DM aged >or=65 years. Study 2 was a 104-week, multicentre, randomized, double blind and active-controlled study of nateglinide (120 mg, before meals) or glyburide (up to 5 mg bid) in combination with metformin (up to 1000 mg bid) in 69 treatment-naive patients with T2DM aged >or=65 years. HbA(1c), fasting and postprandial glucose levels, and safety assessments were made. RESULTS: In Study 1, nateglinide significantly reduced HbA(1c) from baseline (7.6 +/- 0.1% to 6.9 +/- 0.1%; Delta = -0.7 +/- 0.1%, $p < 0.001$) and compared with placebo (between-group difference

= -0.5%, p = 0.004 vs. nateglinide). No hypoglycaemia was reported. In Study 2, combination therapy with nateglinide/metformin significantly reduced HbA(1c) from baseline (7.8 +/- 0.2% to 6.6 +/- 0.1%; Delta = -1.2 +/- 0.2%, p < 0.001), as did glyburide/metformin (7.7 +/- 0.1% to 6.5 +/- 0.1%; Delta = -1.2 +/- 0.1%, p < 0.001). There was no difference between treatments (p = 0.310). One nateglinide/metformin-treated patient experienced a mild hypoglycaemic episode compared with eight episodes in eight patients on glyburide/metformin; one severe episode led to discontinuation. Target HbA(1c) (<7.0%) was achieved by 60% of patients receiving nateglinide (Study 1) and 70% of nateglinide/metformin-treated patients (Study 2). CONCLUSION: Initial drug treatment with nateglinide, alone or in combination with metformin, is well tolerated and produces clinically meaningful improvements in glycaemic control in elderly patients with T2DM.

Stephens, J. W., T. B. Bodvarsdottir, et al. (2011). "Effects of short-term therapy with glibenclamide and repaglinide on incretin hormones and oxidative damage associated with postprandial hyperglycaemia in people with type 2 diabetes mellitus." Diabetes Research & Clinical Practice 94(2): 199-206.

AIM: To examine the effects of glibenclamide and repaglinide on glucose stimulated insulin release, incretins, oxidative stress and cell adhesion molecules in patients with type 2 diabetes suboptimally treated with metformin.

METHODS: A randomized clinical trial was performed recruiting 27 subjects (HbA(1c) between 7.5 and 10.5%) free from cardiovascular and renal disease. Glucose, insulin, C-peptide, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), total antioxidant status, F(2)-isoprostane, interleukin-6 and cell adhesion molecules were measured during an oral glucose load at baseline and after eight weeks of treatment. The areas under the curve were analysed at 45, 60 and 120 min (AUC(45), AUC(60), AUC(120)).

RESULTS: Significant improvements in glucose were observed with repaglinide (HBA(1c): -1.5%, fasting glucose: -2.8 mmol/L, 2-h glucose: -3.7 mmol/L, AUC(120): -18.9%) and glibenclamide (-1.0%, -2.2 mmol/L, -2.5 mmol/L, -17.5%). Repaglinide was also associated with an increase in the AUC(60) and AUC(120) for insulin (+56%, +61%) and C-peptide (+41%, +36%). GLP-1, GIP, IL-6, ICAM-1 and E-selectin levels did not change in either group. No association was observed between GLP-1, GIP-1 and plasma markers of oxidative stress.

CONCLUSION: Repaglinide is associated with improved postprandial glycaemic control via insulin and C-peptide release. We observed no direct effects of glibenclamide or repaglinide on plasma levels of GLP-1 or GIP. We observed no associations of GLP-1 and GIP with plasma markers of oxidative stress. Copyright 2011 Elsevier Ireland Ltd. All rights reserved.

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Month/Year of Review: July 2014 **Date of Last Review:** August 2013
PDL Classes: Antiemetics, Newer **Source Document:** DERP

Current Status of PDL Class:

- Preferred Agents: ONDANSETRON TAB RAPDIS/SOLUTION/TABLET
- Non-Preferred Agents: APREPITANT/FOSAPREPITANT (EMEND®), DOXYLAMINE SUCCINATE/PYRIDOXINE HCL (DICLEGIS®), DOLASETRON (ANZEMET®), GRANISETRON HCL, GRANISETRON TRANSDERMAL PATCH (SANCUSO®), ONDANSETRON ORAL FILM (ZUPLENZ®), PALONOSETRON (ALOXI®)

Previous Conclusions and Recommendation:

- In patients with post-operative nausea and vomiting (PONV) and chemotherapy induced nausea and vomiting (CINV):
  - Dolasetron, granisetron and ondansetron are equally effective in preventing nausea or vomiting.
  - There is evidence that palonsetron may be superior to other 5HT3 antagonists in the treatment of chemotherapy induced nausea and vomiting for moderately emetogenic chemotherapy and that ondansetron, dolasetron, and granisetron are equally effective.
- In patients with radiotherapy-induced nausea and vomiting (RINV):
  - Granisetron and ondansetron showed no difference in efficacy.
- In pregnant patients:
  - Ondansetron was not superior to promethazine for effectiveness, but was less sedating.
  - Long term studies show no difference in number of live births, proportion of infant deformities, and birth weight between ondansetron and the active control groups.
- Ondansetron is superior to granisetron for complete response rates in subpopulations based on a predisposition to nausea/vomiting such as motion sickness or previous treatment with emetogenic chemotherapy.
- There is low quality evidence that the combination of doxylamine/pyridoxine led to significantly greater improvement in nausea vomiting symptoms as compared with placebo (-4.8 PUQE score vs. -3.9; p=0.006) but insufficient comparative evidence compared to other available agents.

PA Criteria: Prior authorization is in place to: promote preferred drugs, reserve costly antiemetics for appropriate indications, restrict chronic use (> 3 days per week), and if chemotherapy is more frequent than once weekly, approve a quantity sufficient for three days beyond the duration of chemotherapy (Appendix 1).

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

Conclusions and Recommendations:

- No further review or research needed.
- Evaluate comparative costs in executive session.

References:

1. Peterson, Kim. Drug Effectiveness Review Project: Drug Class Review on Newer Antiemtics. Preliminary Scan Report, May 2014.

Appendix 1

Antiemetics, New

Goal(s):

- Promote Preferred drugs.
- Reserve costly antiemetics for appropriate indications.
- Restrict chronic use (> 3 days per week).
- If chemotherapy is more frequent than once weekly, approve a quantity sufficient for three days beyond the duration of chemotherapy.

Length of Authorization: 3 days to 6 months (criteria specific)

Requires PA:

- Non-preferred drugs.

Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/

Check the Reason for PA:

- Non-preferred drugs will deny on itiation
- Preferred drugs will deny only when maximum dose exceeded (www.orpdl.org)

HICL	Generic	Brand	Quantity Limit
025058	Aprepitant	Emend	3 doses/ 7 days
016576	Dolasetron	Anzemet	9 doses/ 7 days
007611	Granisetron	Kytril Tablets Kytril solution	6 doses / 7 days (30 ml liquid)

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the drug requested preferred?	**Yes:** Go to #4	**No**: Go to #3
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA for <4 days/week. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class and dose limits. If dose > limits, continue to #4.	**No:** Go to #4

4. Is client currently diagnosed with cancer AND receiving chemotherapy or radiation therapy more frequently than every 7 days?	**Yes:** Approve for 3 days past length of therapy (Chemo regimen more frequently than weekly)	**No:** Go to #5
5. Does client have refractory nausea that would require hospitalization or ER visits?	**Yes:** Go to #6	**No:** go to #8
6. Has client tried and failed two conventional antiemetics, listed below? Generic Name / Brand Name Metoclopramide / Reglan Prochlorperazine / Compazine Promethazine / Phenergan	**Yes:** Approve up to 6 months.	**No:** Go to #7
7. Does client have contraindications to conventional antiemetics, e.g. Allergy; or cannot tolerate?	**Yes:** Document reason and approve up to 6 months. (Contraindications to required alternative medications)	**No:** Pass to RPH; Go to #8
8. RPH only: All other indications need to be evaluated as to whether they are above the line or below the line. • Above: Deny, (Medical Appropriateness) • Below: Deny, (Not Covered by the OHP)		

P&T/DUR Action: 9/24/09 (DO/KK), 2/23/06, 2/24/04, 11/18/03, 9/9/03, 5/13/03, 2/11/03
Revision(s): 1/1/10, 7/1/06, 3/20/06, 6/30/04 (added aprepitant), 3/1/04 (removed injectables), 6/19/03
Initiated: ?

Drug Class Review
On
Newer Antiemetics

Preliminary Scan Report

May 2014

Last Report: Update #1 January 2009

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #1 Final Report: January 2009 (searches through October 2008)

Date of Last Preliminary Update Scan Report

The last preliminary update scan was conducted in April 2013.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?

2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?

3. Are there subgroups of patients based on demographics (age, race, and gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adults or children at risk for or with nausea, vomiting (including retching), or both related to the following therapies and conditions:

- Chemotherapy of various emetogenicity
- Radiation therapy
- Surgical procedure
- Pregnancy

In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999(1, 2) to clarify the level of emetogenicity of the chemotherapeutic regimen with which the cancer population of the study is being treated. This scale rates the emetic potential of the chemotherapeutic agent (or combination of agents) given to a cancer patient as if the patient would not be receiving any antiemetic drugs; that is, it classifies the chemotherapeutic agents by the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as "1" on this scale have a low emetic potential, while agents rated as "5" are considered to be severely emetic (a >90% chance of emesis in patients).

Interventions

Included interventions are listed in Table 1.

Table 1. Included interventions

Drug	Trade name	Formulations
Aprepitant/fosaprepitant	Emend®	injectable, oral
Doxylamine Succinate; Pyridoxine Hydrochloride	Diclegis	Tablet, oral, delayed release
Dolasetron	Anzemet®	injectable, oral
Granisetron	Generics, Sancuso®	injectable, oral, transdermal patch
Ondansetron	Zofran®, generics Zuplenz®	injectable, oral, orally disintegrating tablet, oral film
Palonosetron[a]	Aloxi®	injectable

Shading = new since last full report update

Effectiveness outcomes

Treatment of established postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient
    - Early: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Early: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in the postoperative period
    - Acute: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the postoperative period
    - Acute: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of nausea and/or vomiting related to chemotherapy

- Success: Absence of vomiting and/or retching
    - Acute: During the first 24 hours of chemotherapy administration
        - Vomiting and/or retching induced by highly emetic chemotherapy
        - Vomiting and/or retching induced by moderately emetic chemotherapy
    - Late: After the first 24 hours of chemotherapy administration
        - Vomiting and/or retching induced by highly emetic chemotherapy
        - Vomiting and/or retching induced by moderately emetic chemotherapy
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Acute: During the first 24 hours of chemotherapy administration
        - Emetic event induced by highly emetic chemotherapy
        - Emetic event induced by moderately emetic chemotherapy
    - Late: After the first 24 hours of chemotherapy administration
        - Emetic event induced by highly emetic chemotherapy
        - Emetic event induced by moderately emetic chemotherapy
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention of radiation-induced nausea and/or vomiting

- Success: Absence of vomiting and/or retching
    - Acute: During the first 24 hours of onset of radiation therapy
    - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Acute: During the first 24 hours of onset of radiation therapy
    - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, or need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Treatment of nausea and/or vomiting associated with pregnancy (including hyperemesis gravidarum)

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman
- Success: Absence of any emetic event (nausea, vomiting, retching)
- Change in Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes per period of time, need for rescue medications, serious emetic sequelae, number of emesis-free days, number of episodes and duration of hospitalization

  Wherever possible, data on effective dose range, dose response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.ert text

Harms

- Overall adverse events
- Specific adverse events (headache, constipation, dizziness, sedation, etc)
- Withdrawals due to adverse events
- Serious adverse events reported

Study designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews.
- For safety, controlled clinical trials and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE from January 2013 to May 2014. We used terms for included drugs and limits for humans, English and controlled clinical trials. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm). We also

searched FDA websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

No new drugs were identified.

New drugs identified in previous Preliminary Update Scan(s)

Doxylamine succinate/pyridoxine hydrochloride (Diclegis®) – FDA-approved April 2013 for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.
Granisetron transdermal patch (Sancuso®) – FDA-approved on 9/12/2008
Ondansetron oral film (Zuplenz®) – FDA-approved on 7/2/2010

New Indications

Identified in this Preliminary Update Scan
No new indications were identified.

Identified in previous Preliminary Update Scan(s)
None.

New Safety Alerts

Identified in this Preliminary Update Scan

No new safety alerts were identified.

Identified in previous Preliminary Update Scan(s)

On 12/17/2010, FDA notified healthcare professionals that the injection form of dolasetron should no longer be used to prevent nausea and vomiting associated with chemotherapy in pediatric and adult patients, due to risk of developing torsade de pointes, which in some cases can be fatal (Appendix A).

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

No new comparative effectiveness reviews were identified.

Reviews identified in previous Preliminary Update Scan(s)

On 12/4/2012 the FDA notified health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm (Appendix A).

In September of 2011 the FDA approved a safety labeling change warning for Anzemet (dolasetron mesylate) tablet and injection indicating that it has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients for which it should be used with caution certain patients (Appendix A).

An updated practice guideline for antiemetics in Oncology was published by the American Society of Clinical Oncology in November 2011. Abstract is included in Appendix B. A rapid response review on Ondansetron for the management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients was produced by CADTH in February 2013. See appendix B for the research questions on this topic.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches conducted for this scan resulted in 73 citations. Of those, there were 13 potentially relevant new trials, including 5 head-to-head trials and 8 placebo-controlled trials (see Appendix C for abstracts). We found no new trials of the fixed dose combination product doxylamine succinate and pyridoxine hydrochloride.

Including the 18 head-to-head trials and 13 placebo-controlled trials identified in the previous scans from April 2013, March 2011 and December 2009 (Appendix D), there are now cumulative totals of 23 head-to-head trials and 21 placebo-controlled trials. Characteristics of the head to head trials are shown in Table 2, below. Shading indicates trials identified in this scan; others were identified in previous scans. Placebo controlled trials are listed in Table 3. There are two placebo controlled trials on the new fixed dose combination product doxylamine succinate and pyridoxine hydrochloride.

Table 2. New head-to-head trials

Trial	Drugs	Indication
Habib 2011	Ondansetron vs aprepitant	PONV in adults
Grover 2009	Ondansetron orally disintegrating tablet vs IV ondansetron	PONV in adults
Kim 2004	Dolasetron vs ondansetron	Chemotherapy in adults

Mandanas 2005	Dolasetron vs ondansetron	Chemotherapy in adults
Maru 2013	Fosaprepitant vs aprepitant	Chemotherapy in adults
Boccia 2011	Granisetron transdermal vs Granisetron oral	Chemotherapy in adults
Metaxari 2011	Granisetron vs ondansetron	PONV in adults
Siddique 2011	Granisetron vs ondansetron	Chemotherapy in children
Dabbous 2010	Granisetron vs ondansetron	PONV in adults
Jain 2009	Granisetron vs ondansetron	PONV in adults
Tan 2010	Granisetron vs ondansetron	PONV in adults
Basu 2011	Palonosetron vs ondansetron vs granisetron	PONV in adults
Moon 2012	Palonosetron vs ondansetron	PONV in adults
Park 2011	Palonosetron vs ondansetron	PONV in adults
Kim 2013	Palonosetron vs ondansetron	PONV in adults
Kim 2013	Palonosetron vs ondansetron	PONV in adults
Laha 2013	Palonosetron vs ondansetron	PONV in adults
Kaushal 2010	Palonosetron vs ondansetron	Chemotherapy in adults
Mattiuzzi 2010	Palonosetron vs ondansetron	Chemotherapy in adults
Wenzell 2013	Palonosetron vs ondansetron	Chemotherapy in adults
Saito 2009	Palonosetron vs granisetron	Chemotherapy in adults
Tian 2011	Palonosetron vs granisetron	Chemotherapy in Chinese adults
Yu 2009	Palonosetron vs granisetron	Chemotherapy in adults

*Shading indicates trials identified in this scan; others were identified in previous scans.

Table 3. Placebo-Controlled Trials

Placebo-controlled trials of 5-HT3 antagonists		
Albany 2012	Aprepitant	PONV in adults
Jung 2013	Aprepitant	PONV in adults
Lim 2013	Aprepitant	PONV in adults
Sinha 2014	Aprepitant	PONV in adults
Tanioka 2013	Aprepitant	Chemotherapy in adults
Saito 2013	Fosaprepitant	Chemotherapy in adults
Barrett 2011	Ondansetron	PONV in adults
de Orange 2012	Ondansetron	PONV in children
Ebrahim Soltani, 2011	Ondansetron	PONV in adults
Zhang 2013	Ondansetron	PONV in adults
Chun 2014	Palonosetron	PONV in adults
Hesketh, 2012	Palonosetron	PONV in adults
Wagner 2007	Ondansetron orally disintegrating tablet	PONV in children
Vallejo 2012	aprepitant	PONV in adults
Trials of Aprepitant triple-therapy (aprepitant + 5-HT3 antagonist + corticosteroid) vs 5-HT3		

antagonist + corticosteroid		
Hu 2014	Granisetron	Chemotherapy in Chinese adults
Takahashi 2010	Granisetron	Chemotherapy in Japanese adults
Gore 2009	Ondansetron	Chemotherapy in adolescents
Rapoport 2010	Ondansetron	Chemotherapy in adults
Yeo 2009	Ondansetron	Chemotherapy in Chinese adults
Other		
Koren, 2010	Doxylamine succinate and pyridoxine hydrochloride	PONV in pregnancy
Reeve, 2005	Doxylamine succinate and pyridoxine hydrochloride	PONV in women undergoing laparoscopic tubal ligation

*Shading indicates trials identified in this scan; others were identified in previous scans.

PONV=post-operative nausea and vomiting, 5-HT3 Antagonists = ondansetron, granisetron, dolasetron and palonosetron

1. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. Journal of Clinical Oncology. [C]. 1997;15(1):103-9.
2. Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice. Oncologist. 1999;4(3):191-6.

APPENDIX A. NEW FDA WARNINGS AND PRECAUTIONS

Ondansetron (Zofran) 32 mg, Single Intravenous (IV) Dose: Updated Safety Communication – Product Removal due to Potential For Serious Cardiac Risks
[Posted: 12/4/2012]
ISSUE: FDA is notifying health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of the potential for serious cardiac risks.
BACKGROUND: The 32 mg, single IV dose of Zofran had been used to prevent chemotherapy-induced nausea and vomiting. A previous Drug Safety Communication (DSC), issued on June 29, 2012, communicated that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm. These drugs are sold pre-mixed in solutions of either dextrose or sodium chloride in plastic containers.
FDA anticipates these products will be removed from the market through early 2013. FDA does not anticipate that removal of the 32 mg intravenous dose of ondansetron currently sold as pre-mixed injections will contribute to a drug shortage of IV ondansetron, as the 32 mg dose makes up a very small percentage of the current market
RECOMMENDATION: FDA continues to recommend the intravenous regimen of 0.15 mg/kg administered every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. Oral dosing of Ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting. At this time, there is not enough information available for FDA to recommend an alternative single IV dose regimen.
Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

Anzemet (dolasetron mesylate) tablet and injection-labeling revision
September 2011
Anzemet prolongs the QT interval in a dose dependent fashion. Torsade de Pointes has been reported during post-marketing experience. Avoid Anzemet in patients with congenital long QT syndrome, hypomagnesemia, or hypokalemia. Hypokalemia and hypomagnesemia must be corrected prior to Anzemet administration. Monitor these electrolytes after administration as clinically indicated. Use ECG monitoring in patients with congestive heart failure, bradycardia, renal impairment, and elderly patients.
PR and QRS Interval Prolongation
Anzemet has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients. At particular risk are patients with underlying structural heart disease and preexisting conduction system abnormalities, elderly, patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia or patients receiving drugs known to prolong the PR interval (such as verapamil) and QRS interval (e.g., flecainide or quinidine). Anzemet should be used with caution and with ECG monitoring in these patients. Anzemet should be avoided in patients with complete heart block or at risk for complete heart block, unless they have an implanted pacemaker.

Anzemet (dolasetron mesylate): Drug Safety Communication - Reports of Abnormal Heart Rhythms
[Posted 12/17/2010]
AUDIENCE: Oncology, Cardiology

ISSUE: FDA notified healthcare professionals that a contraindication is being added to the prescribing information advising that the injection form of Anzemet (dolasetron mesylate) should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric and adult patients. New data demonstrate that Anzemet injection can increase the risk of developing torsade de pointes, an abnormal heart rhythm, which in some cases can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Anzemet causes a dose-dependant prolongation in the QT, PR, and QRS intervals on an electrocardiogram.

BACKGROUND: FDA previously noted cardiovascular safety concerns which suggested Anzemet could cause QT prolongation. However, limitations of the previous data did not clearly establish the degree to which Anzemet may cause QT prolongation. FDA recommended that the drug sponsor conduct a thorough QT study in adults in order to determine the degree of the prolongation. A pediatric study was not recommended due to the wide variability in heart rate and, thus, QTc interval in the pediatric population. See the Data Summary section of the Drug Safety Communication (DSC) for information that supports this change in the prescribing information.

RECOMMENDATION: Anzemet should not be used in patients with congenital long-QT syndrome. Hypokalemia and hypomagnesemia should be corrected before administering Anzemet. These electrolytes should be monitored after administration as clinically indicated. Use electrocardiogram monitoring in patients with congestive heart failure, patients with bradycardia, patients with underlying heart disease, the elderly and in patients who are renally impaired who are taking Anzemet. Anzemet injection may still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used are less likely to affect the electrical activity of the heart and result in abnormal heart rhythms.

Anzemet tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this drug is less than that seen with the injection form. However, a stronger warning about this potential risk is being added to the Warnings and Precautions sections of the Anzemet tablet label.

See the DSC for additional recommendations for healthcare professionals and for patients.

APPENDIX B. NEW COMPARATIVE EFFECTIVENESS REVIEWS AND GUIDELINES

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

Purpose
To update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology.
Methods
A systematic review of the medical literature was completed to inform this update. MEDLINE, the Cochrane Collaboration Library, and meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer were all searched. Primary outcomes of interest were complete response and rates of any vomiting or nausea.
Results
Thirty-seven trials met prespecified inclusion and exclusion criteria for this systematic review. Two systematic reviews from the Cochrane Collaboration were identified; one surveyed the pediatric literature. The other compared the relative efficacy of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists.
Recommendations
Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5. The Update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.

J Clin Oncol 29:4189-4198.

Ondansetron for the Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients: A Review of the Clinical Effectiveness, Safety and Guidelines
http://www.cadth.ca/media/pdf/htis/apr-2013/RC0424-Ondansetron-Final.pdf

RESEARCH QUESTIONS

1. What is the clinical effectiveness of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients?

2. What is the clinical evidence on the safety and harms of ondansetron for the management of CINV in pediatric patients?

3. What are the evidence-based guidelines regarding the use of ondansetron for the management of CINV in pediatric patients?

Appendix C. Abstracts of new randomized controlled trials from current scan

Head-to-head trials

Kim, S.-H., J.-Y. Hong, et al. (2013). "Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a prospective, randomized, double-blinded study." Korean Journal of Anesthesiology **64**(6): 517-523.

BACKGROUND: Postoperative nausea and vomiting (PONV) continues to be a major problem, because PONV is associated with delayed recovery and prolonged hospital stay. Although the PONV guidelines recommended the use of 5-hydroxy-tryptamine (5-HT3) receptor antagonists as the first-line prophylactic agents in patients categorized as high-risk, there are few studies comparing the efficacies of ondansetron, ramosetron, and palonosetron. The aim of present study was to compare the prophylactic antiemetic efficacies of three 5HT3 receptor antagonists in high-risk patients after laparoscopic surgery.

METHODS: In this prospective, randomized, double-blinded trial, 109 female nonsmokers scheduled for elective laparoscopic surgery were randomized to receive intravenous 4 mg ondansetron (n = 35), 0.3 mg ramosetron (n = 38), or 75 g palonosetron (n = 36) before anesthesia. Fentanyl-based intravenous patient-controlled analgesia was administered for 48 h after surgery. Primary antiemetic efficacy variables were the incidence and severity of nausea, the frequency of emetic episodes during the first 48 h after surgery, and the need to use a rescue antiemetic medication.

RESULTS: The overall incidence of nausea/retching/vomiting was lower in the palonosetron (22.2%/11.1%/5.6%) than in the ondansetron (77.1%/48.6%/28.6%) and ramosetron (60.5%/28.9%/18.4%) groups. The rescue antiemetic therapy was required less frequently in the palonosetron group than the other groups ($P < 0.001$). Kaplan-Meier analysis showed that the order of prophylactic efficacy in delaying the interval to use of a rescue emetic was palonosetron, ramosetron, and ondansetron.

CONCLUSIONS: Single-dose palonosetron is the prophylactic antiemetics of choice in high-risk patients undergoing laparoscopic surgery.

Kim, Y. Y., S. Y. Moon, et al. (2013). "Comparison of palonosetron with ondansetron in prevention of postoperative nausea and vomiting in patients receiving intravenous patient-controlled analgesia after gynecological laparoscopic surgery." Korean Journal of Anesthesiology **64**(2): 122-126.

BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after anesthesia and surgery. This study was designed to compare the effects of palonosetron and ondansetron in preventing PONV in high-risk patients receiving intravenous opioid-based patient-controlled analgesia (IV-PCA) after gynecological laparoscopic surgery.

METHODS: One hundred non-smoking female patients scheduled for gynecological laparoscopic surgery were randomly assigned into the palonosetron group (n = 50) or the ondansetron group (n = 50). Palonosetron 0.075 mg was injected as a bolus in the palonosetron group. Ondansetron 8 mg was injected as a bolus and 16 mg was added to

the IV-PCA in the ondansetron group. The incidences of nausea, vomiting and side effects was recorded at 2 h, 24 h, 48 h and 72 h, postoperatively.

RESULTS: There were no significant differences between the groups in the incidence of PONV during 72 h after operation. However, the incidence of vomiting was lower in the palonosetron group than in the ondansetron group (18% vs. 4%, P = 0.025). No differences were observed in use of antiemetics and the side effects between the groups.

CONCLUSIONS: The effects of palonosetron and ondansetron in preventing PONV were similar in high-risk patients undergoing gynecological laparoscopic surgery and receiving opioid-based IV-PCA.

Laha, B., A. Hazra, et al. (2013). "Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: a randomized controlled trial." Indian Journal of Pharmacology **45**(1): 24-29.

OBJECTIVES: Incidence of postoperative nausea and vomiting (PONV), without active intervention, following laparoscopic cholecystectomy is unacceptably high. We evaluated the effectiveness of intravenous (IV) palonosetron in counteracting PONV during the first 24 hrs following laparoscopic cholecystectomy, using ondansetron as the comparator drug.

MATERIALS AND METHODS: In a randomized, controlled, single blind, parallel group trial, single pre-induction IV doses of palonosetron (75 mcg) or ondansetron (4 mg) were administered to adult patients of either sex undergoing elective laparoscopic cholecystectomy. There were 49 subjects per group. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary effectiveness measure was total number of PONV episodes in the 24 hrs period following end of surgery. The frequencies of individual nausea, retching and vomiting episodes, visual analog scale (VAS) score for nausea at 2, 6 and 24 hrs, use of rescue antiemetic (metoclopramide), number of complete responders (no PONV or use of rescue in 24 hrs) and adverse events were secondary measures.

RESULTS: There was no statistically significant difference between the groups in primary outcome. Similarly, the frequencies of nausea, retching and vomiting episodes, when considered individually, did not show significant difference. Nausea score was comparable at all time points. With palonosetron, 14 subjects (28.6%) required rescue medication while 13 (26.5%) did so with ondansetron. The number of complete responders was 14 (28.6%) and 16 (32.7%), respectively. Adverse events were few and mild. QTc prolongation was not encountered.

CONCLUSION: Palonosetron is comparable to ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.

Maru, A., V. P. Gangadharan, et al. (2013). "A Phase 3, randomized, double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting: Results of an Indian population subanalysis." Indian Journal of Cancer **50**(4): 285-291.

Context: Currently, there is limited data on the prevention of chemotherapy-induced nausea and vomiting (CINV) in Indian patients. Aims: This post hoc study assessed the efficacy and safety of fosaprepitant compared with aprepitant for prevention of CINV in the Indian population. A subgroup analysis was performed from data collected in a phase 3 study of intravenous (IV) fosaprepitant or oral aprepitant, plus the 5-HT 3 antagonist ondansetron and the

corticosteroid dexamethasone, in cisplatin-nave patients with solid malignancies. Materials and Methods: Patients scheduled to receive cisplatin (>70 mg/m 2) were administered a single IV dose of fosaprepitant dimeglumine (150 mg) on day 1 or a 3-day dosing regimen of oral aprepitant (day 1:125 mg, days 2 and 3:80 mg) with standard doses of ondansetron and dexamethasone. Patients recorded nausea and/or vomiting episodes and their use of rescue medication and were monitored for adverse events (AEs) and tolerability. Statistical Analysis Used: Differences in response rates between fosaprepitant and aprepitant were calculated using the Miettinen and Nurminen method. Results: In the Indian subpopulation (n = 372), efficacy was similar for patients in both the fosaprepitant or aprepitant groups; complete response in the overall, acute, and delayed phases and no vomiting in all phases were approximately 4 percentage points higher in the fosaprepitant group compared with the aprepitant group. Fosaprepitant was generally well-tolerated; common AEs were similar to oral aprepitant. Conclusions: IV fosaprepitant is as safe and effective as oral aprepitant in the Indian subpopulation and offers an alternative to the oral formulation.

Wenzell, C. M., M. J. Berger, et al. (2013). "Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy." Supportive Care in Cancer **21**(10): 2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

Placebo-controlled trials

Chun, H. R., I. S. Jeon, et al. (2014). "Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial." British Journal of Anaesthesia **112**(3): 485-490.

BACKGROUND: The aim of this study was to evaluate the efficacy of palonosetron, the latest 5-HT3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) during the first 72 h after operation.

METHODS: In this randomized, double-blinded, placebo-controlled study, 204 healthy inpatients who were undergoing elective surgery with general anaesthesia were enrolled. Patients were divided into two groups: the palonosetron group (palonosetron 0.075 mg i.v.; n=102) and the placebo group (normal saline i.v.; n=102). The treatments were given after the induction of anaesthesia. The incidence of nausea, vomiting, severity of nausea, and the use of rescue anti-emetics during the first 72 h after surgery were evaluated.
RESULTS: The incidence of PONV was lower in the palonosetron group compared with the placebo group during the 0-24 h (33% vs 47%) and 0-72 h period (33% vs 52%) ($P<0.05$), but not during the 24-72 h postoperative period (6% vs 11%). The incidence of nausea was also significantly lower in the palonosetron group than in the placebo group during the 0-24 and 0-72 h period ($P<0.05$), but not during the 24-72 h postoperative period. However, there were no significant differences in the incidence of vomiting, and the use of rescue anti-emetics between the groups.
CONCLUSIONS: Palonosetron 0.075 mg i.v. effectively reduced the incidence of PONV during the first 72 h after operation, with most of the reduction occurring in the first 24 h.

Hu, Z., Y. Cheng, et al. (2014). "Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial." Supportive Care in Cancer **22**(4): 979-987.
PURPOSE: Aprepitant, an oral neurokinin-1 receptor antagonist, has demonstrated improved control of chemotherapy-induced nausea and vomiting (CINV) in previous studies. This is the first phase III study to evaluate the efficacy and tolerability of aprepitant in patients receiving highly emetogenic chemotherapy (HEC) in Asian countries.
METHODS: This multicenter, double-blind, placebo-controlled trial assessed the prevention of CINV during the acute phase (AP), delayed phase (DP), and overall phase (OP). Patients receiving HEC were randomized to either an aprepitant group (day 1, aprepitant 125 mg; days 2-3, aprepitant 80 mg) or a standard therapy group (days 1-3, placebo). Both groups received intravenous granisetron and oral dexamethasone. The primary end point was complete response (CR; no emesis and no use of rescue therapy) during the OP.
RESULTS: Of the 421 randomized patients, 411 (98%) were assessable for efficacy; 69.6% (142/204) and 57.0% (118/207) of patients reported CR during the OP in the aprepitant and standard therapy groups, respectively ($P = 0.007$). CR rates in the aprepitant group were higher during the DP (74.0% vs. 59.4%, $P = 0.001$) but were similar during the AP (79.4% vs. 79.3%, $P = 0.942$). Toxicity and adverse events were comparable in both groups.
CONCLUSIONS: The addition of aprepitant to standard antiemetic treatment regimens for Chinese patients undergoing HEC provided superior CINV prevention and was well tolerated.

Jung, W. S., Y. B. Kim, et al. (2013). "Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy." Journal of Anesthesia **27**(3): 396-401.
PURPOSE: The use of opioids following surgery is associated with a high incidence of postoperative nausea and vomiting (PONV). We conducted a prospective, randomized, double-blind, placebo-controlled study to investigate the effect of orally administered

aprepitant, a neurokinin-1 receptor antagonist, for reducing PONV in patients with fentanyl-based, patient-controlled analgesia (PCA) given intravenously after gynecological laparoscopy.

METHODS: One hundred and twenty female patients (ages 21-60) undergoing laparoscopic hysterectomy were randomly allocated to receive 80 mg (A80 group, n = 40) or 125 mg aprepitant (A125 group, n = 40) or placebo (control group, n = 40) orally 2 h before anesthesia induction. Anesthesia was maintained with isoflurane and remifentanil, and PCA IV using fentanyl and ketorolac were provided for 48 h after surgery. Incidences of nausea, vomiting/retching, and use of rescue antiemetics were recorded at 2, 24, and 48 h after surgery. Complete response was defined as no PONV and no need for rescue treatment.

RESULTS: The incidence of complete response was significantly lower in the A80 and A125 groups than in controls, 56 % and 63 %, vs. 28 %, respectively, P = 0.007 and P = 0.003, respectively, during the first 48 h, and 65 % and 65 % vs. 38 %, respectively, both P = 0.025, during the first 2 h. However, there were no statistically significant differences between A80 and A125 groups in the incidences of complete response and PONV during the study period.

CONCLUSIONS: Aprepitant 80 mg orally was effective in lowering the incidence of PONV in the first 48 h after anesthesia in patients receiving fentanyl-based PCA after gynecological laparoscopy.

Lim, C. S., Y.-K. Ko, et al. (2013). "Efficacy of the oral neurokinin-1 receptor antagonist aprepitant administered with ondansetron for the prevention of postoperative nausea and vomiting." Korean Journal of Anesthesiology **64**(3): 212-217.

BACKGROUND: 5-HT3 receptor antagonist, dexamethasone and droperidol were used for the prevention of postoperative nausea and vomiting (PONV). Recently, neurokinin-1 (NK1) antagonist has been used for PONV. We evaluated the effect of oral aprepitant premedication in addition to ondansetron.

METHODS: A total 90 patients scheduled for elective rhinolaryngological surgery were allocated to three groups (Control, Ap80, Ap125), each of 30 at random. Ondansetron 4 mg was injected intravenously to all patients just before the end of surgery. On the morning of surgery, 80 mg and 125 mg aprepitant were additionally administered into the Ap80 group and Ap125 group, respectively. The rhodes index of nausea, vomiting and retching (RINVR) was checked at 6 hr and 24 hr after surgery.

RESULTS: Twelve patients who used steroids unexpectedly were excluded. Finally 78 patients (control : Ap80 : Ap125 = 24 : 28 : 26) were enrolled. Overall PONV occurrence rate of Ap125 group (1/26, 3.9%) was lower (P = 0.015) than the control group (7/24, 29.2%) at 6 hr after surgery. The nausea distress score of Ap125 group (0.04 + 0.20) was lower (P = 0.032) than the control group (0.67 + 1.24) at 6 hr after surgery. No evident side effect of aprepitant was observed.

CONCLUSIONS: Oral aprepitant 125 mg can be used as combination therapy for the prevention of PONV.

Saito, H., H. Yoshizawa, et al. (2013). "Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose

cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial." Annals of Oncology **24**(4): 1067-1073.

BACKGROUND: We evaluated the efficacy and safety of single-dose fosaprepitant in combination with intravenous granisetron and dexamethasone.

PATIENTS AND METHODS: Patients receiving chemotherapy including cisplatin (>70 mg/m(2)) were eligible. A total of 347 patients (21% had received cisplatin with vomiting) were enrolled in this trial to receive the fosaprepitant regimen (fosaprepitant 150 mg, intravenous, on day 1 in combination with granisetron, 40 mug/kg, intravenous, on day 1 and dexamethasone, intravenous, on days 1-3) or the control regimen (placebo plus intravenous granisetron and dexamethasone). The primary end point was the percentage of patients who had a complete response (no emesis and no rescue therapy) over the entire treatment course (0-120 h).

RESULTS: The percentage of patients with a complete response was significantly higher in the fosaprepitant group than in the control group (64% versus 47%, P = 0.0015). The fosaprepitant regimen was more effective than the control regimen in both the acute (0-24 h postchemotherapy) phase (94% versus 81%, P = 0.0006) and the delayed (24-120 h postchemotherapy) phase (65% versus 49%, P = 0.0025).

CONCLUSIONS: Single-dose fosaprepitant used in combination with granisetron and dexamethasone was well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Sinha, A. C., P. M. Singh, et al. (2014). "Aprepitant's prophylactic efficacy in decreasing postoperative nausea and vomiting in morbidly obese patients undergoing bariatric surgery." Obesity Surgery **24**(2): 225-231.

BACKGROUND: Postoperative nausea and vomiting is a major cause of patient dissatisfaction towards surgery. For bariatric surgery, increased vomiting/retching is detrimental to surgical anastomosis. The present study evaluated the efficacy of aprepitant (neurokinin-1 inhibitor) as a prophylactic antiemetic in morbidly obese patients for laparoscopic bariatric surgery.

METHODS: After institutional review board approval, 125 morbidly obese patients were recruited into this double-blind placebo-controlled trial. On random division, the patients received a tablet of aprepitant (80 mg) in group A, or a similar-appearing placebo in group P, an hour prior to surgery. All patients received intravenous ondansetron (4 mg) intraoperatively. Postoperatively, the patients were evaluated for nausea and vomiting by a blinded evaluator at 30 min, 1, 2, 6, 24, 48, and 72 h.

RESULTS: Both groups were evenly distributed for age, body mass index, type, and length of surgery. Cumulative incidence of vomiting at 72 h was significantly lower in group A (3%) compared to group P (15%; p=0.021). Odds ratio for vomiting in group P compared to group A was 5.47 times. On Kaplan-Meier plot, time to first vomiting was also significantly delayed in group A (p=0.019). A higher number of patients showed complete absence of nausea or vomiting in group A compared to group P (42.18 vs. 36.67%). On the other hand, nausea scores were unaffected by aprepitant, and no significant difference between groups was found at any of the measured time points.

CONCLUSIONS: In morbidly obese patients undergoing laparoscopic bariatric surgery, addition of aprepitant to ondansetron can significantly delay vomiting episodes simultaneously lowering the incidence of postoperative vomiting.

Tanioka, M., A. Kitao, et al. (2013). "A randomised, placebo-controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy." British Journal of Cancer **109**(4): 859-865.

BACKGROUND: We evaluated the efficacy of aprepitant plus granisetron and an increased dose of dexamethasone in selected patients undergoing moderately emetogenic chemotherapy (MEC).

METHODS: Nondrinking women <70 years undergoing MEC were randomly assigned to aprepitant (day 1, 125 mg; days 2 and 3, 80 mg) or placebo. Dexamethasone on days 1-3 was 12, 4, and 4 mg with aprepitant and 20, 8, and 8 mg with placebo. The primary end point was complete response (CR; no emesis or rescue therapy) during 120 h of the first cycle. Logistic regression analysis was performed to identify predictors of overall CR.

RESULTS: Of the 94 patients enrolled, 91 were assessable. Most received carboplatin-based chemotherapy. In the aprepitant (n=45) and placebo (n=46) groups, the overall, acute (day 1), and delayed (days 2-5) CR rates were 62% and 52%, 98% and 96%, and 62% and 52%, respectively. Although not statistically significant, the overall CR rate was 10% higher in the aprepitant group. Both regimens were well tolerated. On multivariate analysis, advanced ovarian cancer (OR, 0.26 (0.10-0.72)) was independently associated with a lower CR.

CONCLUSION: Even with an increased dose of dexamethasone, aprepitant seemed more effective than placebo in these selected patients undergoing MEC; however, delayed phase management remains a significant problem.

Zhang, D., Z. Shen, et al. (2013). "Effect of ondansetron in preventing postoperative nausea and vomiting under different conditions of general anesthesia: a preliminary, randomized, controlled study." Upsala Journal of Medical Sciences **118**(2): 87-90.

METHODS: Two hundred and forty patients were randomly allocated into six groups: Group I, anesthesia was maintained with sevoflurane; Group II, anesthesia was maintained with sevoflurane and 8 mg of ondansetron; Group III, anesthesia was maintained with propofol; Group IV, anesthesia was maintained with propofol and 8 mg of ondansetron; Group V, anesthesia was maintained with sevoflurane and propofol; Group VI, anesthesia was maintained with sevoflurane combined with propofol and 8 mg of ondansetron.

RESULTS: We found that the incidence of vomiting was lower in group II (17.5%), group IV (7.5%), and group VI (10%) compared with group I (55%), group III (27.5%), and group V (30%), respectively ($P < 0.05$). The incidence of vomiting was also lower in group III (27.5%) and group V (30%) when compared with group I (55%) ($P < 0.05$). The incidence of nausea was 55% in group I, 42.5% in group II, 30% in group III, 27.5% in group IV, 30% in group V, and 30% in group VI. Groups III and V had a lower incidence of nausea than group I ($P < 0.05$).

CONCLUSIONS: We conclude that compared with sevoflurane anesthesia alone, anesthesia with either propofol alone or propofol combined with sevoflurane resulted in a reduced incidence of vomiting and nausea during the first 24 h after surgery. Administration of

ondansetron effectively reduced the incidence of vomiting but not that of nausea for all three types of general anesthesia.

Wenzell, C. M., M. J. Berger, et al. (2013). "Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy." Supportive Care in Cancer **21**(10): 2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

APPENDIX D. ABSTRACTS OF POTENTIALLY RELEVANT TRIALS FOUND IN PREVIOUS SCANS

Head to head trials

Basu, A., D. Saha, et al. (2011). "Comparison of palanosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery." Journal of the Indian Medical Association 109(5): 327-329.

The objective of the study was to compare the efficacy of palanosetron (0.25 mg), granisetron (3.0 mg) and ondansetron (8.0 mg) used as anti-emetics for the prevention of postoperative nausea/vomiting in patients undergoing middle ear surgery. The study was done among 75 adult patients (age group 30-45 years) of which 50 were males and rest (25) females, all of ASA I and ASA II. The patients were randomly allocated into 3 equal groups: Group I (n = 25) received injection palanosetron (0.25 mg) IV, group II (n = 25) received injection granisetron (3 mg) IV and group III (n = 25) received injection ondansetron (8.0 mg) IV at the end of the surgical procedure. A standard general anaesthesia technique was employed. Emetic episodes and safety assessments were performed during two periods of 0-6 hours in the postanaesthesia care unit and 6-24 hours in the ward after anaesthesia. The incidence of emesis-free patients during the 0-6 hours period was 100% for group I; 72% for group II and 56% for group III. During the 6-24 hours period incidence of emesis-free patients were 96% for group I; 56% for group II and 32% for group III. So to conclude, a single dose of palanosetron (0.25 mg) is a superior anti-emetic to granisetron (3.0 mg) or ondansetron (8.0 mg) in complete prevention of postoperative nausea and vomiting after middle ear surgery during the first 24 hours period.

Boccia, R. V., L. N. Gordan, et al. (2011). "Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study." Supportive Care in Cancer 19(10): 1609-1617.

PURPOSE: A novel transdermal formulation of granisetron (the granisetron transdermal delivery system (GTDS)) has been developed to deliver granisetron continuously over 7 days. This double-blind, phase III, non-inferiority study compared the efficacy and tolerability of the GTDS to daily oral granisetron for the control of chemotherapy-induced nausea and vomiting (CINV).

PATIENTS AND METHODS: Six hundred forty-one patients were randomized to oral (2 mg/day, 3-5 days) or transdermal granisetron (one GTDS patch, 7 days), before receiving multi-day chemotherapy. The primary endpoint was complete control of CINV (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final administration. The prespecified non-inferiority margin was 15%.

RESULTS: Five hundred eighty-two patients were included in the per protocol analysis. The GTDS displayed non-inferiority to oral granisetron: complete control was achieved by 60% of patients in the GTDS group, and 65% in the oral granisetron group (treatment

difference, -5%; 95% confidence interval, -13-3). Both treatments were well tolerated, the most common adverse event being constipation.

CONCLUSIONS: The GTDS provides effective, well-tolerated control of CINV associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron.

Dabbous, A. S., S. I. Jabbour-Khoury, et al. (2010). "Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery." Middle East Journal of Anesthesiology **20**(4): 565-70.

In a prospective randomized double-blind study, we compared the effectiveness of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery. Hundred ASA I and II patients scheduled for laparoscopic surgery were enrolled in the study and 84 patients completed it. Following induction of anesthesia, group I (n=42) received granisetron 1 mg and dexamethasone 8 mg, group II (n=42) received ondansetron 4 mg and dexamethasone 8 mg. Nausea and vomiting episodes, pain scores as well as side effects were recorded during the first hour and subsequently during the first 6 and 24 hours postoperatively. Satisfaction scores were obtained at discharge. There was no statistically significant difference between the 2 groups during the 1st 24 hours following surgery in regards to pain scores, satisfaction and side effects manifestations. At 0-1 hour interval, 100% of patients in group I and 97.6% in group II had no vomiting. Total response (no moderate or severe nausea and no rescue antiemetics) was 83.3% in group I and 80.95% in group II, and metoclopramide was used in 7.1% of patients in both groups. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II. At 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. In conclusion, the combination of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg following induction of anesthesia in patients undergoing laparoscopic surgery showed no statistically significant difference in antiemetic efficacy with minimal side effects and excellent patient satisfaction.

Grover, V. K., P. J. Mathew, et al. (2009). "Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study." Anaesthesia **64**(6): 595-600.

Peri-operative prophylactic anti-emetics are commonly used parenterally. Orally disintegrating ondansetron is efficacious during chemotherapy. Therefore, we aimed to study the efficacy of orally disintegrating ondansetron for postoperative nausea and vomiting. In a randomised, double-blind, placebo controlled trial on 109 patients scheduled for laparoscopic cholecystectomy, oral ondansetron was compared to intravenous ondansetron and placebo. The anaesthetic technique was standardised. Mean time (SD) to tolerating oral intake was delayed in the placebo group to 366.1 (77.6) min compared to oral 322.9 (63.7) min and intravenous 322.4 (65.2) min groups. This is corroborated by a higher incidence of nausea and vomiting in the control group during the first 6 h

postoperatively (control 44.4%, oral 17.7%, intravenous 18.2%). There was no significant difference between oral and intravenous groups. In conclusion, orally disintegrating ondansetron was as efficacious as intravenous ondansetron in the peri-operative phase and may be a viable option for prophylaxis of emesis in day care surgery

Habib, A. S., J. C. Keifer, et al. (2011). "A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy." Anesthesia & Analgesia 112(4): 813-818.

BACKGROUND: Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 hours. In addition to causing patient discomfort, the physical act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery, aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 hours postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia.

METHODS: Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 hours after surgery. Statistical analysis was performed using Wilcoxon's ranked sum test and (2) test. $P < 0.05$ was considered statistically significant.

RESULTS: One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($P = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% vs. 21%, $P = 0.0419$) and 24 hours (14% vs. 36%, $P = 0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs. 60%), nausea scores, need for rescue antiemetics (65% vs. 60%), complete response (no PONV and no rescue, 22% vs. 36%), or patient satisfaction with the management of PONV.

CONCLUSION: The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

Jain, V., J. K. Mitra, et al. (2009). "A randomized, double-blinded comparison of ondansetron, granisetron, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy." Journal of Neurosurgical Anesthesiology **21**(3): 226-30.

Postoperative nausea and vomiting (PONV) are frequent and distressing complications after neurosurgical procedures. We evaluated the efficacy of ondansetron and granisetron to prevent PONV after supratentorial craniotomy. In a randomized double-blind, placebo controlled trial, 90 adult American Society of Anesthesiologists I, II patients were included in the study. A standard anesthesia technique was followed. Patients were divided into 3 groups to receive either placebo (saline), ondansetron 4 mg, or granisetron 1 mg intravenously at the time of dural closure. After extubation, episodes of nausea and vomiting were noted for 24 hours postoperatively. Statistical analysis was performed using chi2 test and 1-way analysis of variance. Demographic data, duration of surgery, intraoperative fluids and analgesic requirement, and postoperative pain (visual analog scale) scores were comparable in all 3 groups. It was observed that the incidence of vomiting in 24 hours, severe emetic episodes, and requirement of rescue antiemetics were less in ondansetron and granisetron groups as compared with placebo ($P<0.001$). Both the study drugs had comparable effect on vomiting. However, the incidence of nausea was comparable in all 3 groups ($P=0.46$). A favorable influence on the patient satisfaction scores, and number needed to prevent emesis was seen in the 2 drug groups. No significant correlation was found between neurosurgical factors (presence of midline shift, mass effect, pathologic diagnosis of tumor, site of tumor) and the occurrence of PONV. We conclude that ondansetron 4 mg and granisetron 1 mg are comparably effective at preventing emesis after supratentorial craniotomy. However, neither drugs prevented nausea effectively.

Kaushal, J., M. C. Gupta, et al. (2010). "Clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer." Singapore Medical Journal **51**(11): 871-5.

INTRODUCTION: Palonosetron and ondansetron are two selective 5-hydroxytryptamine (5-HT3) receptor antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of moderately emetic anticancer chemotherapy. Their efficacy is enhanced by the concurrent administration of dexamethasone. In the present study, we aimed to compare the antiemetic efficacy of a palonosetron plus dexamethasone (PD) schedule versus an ondansetron plus dexamethasone (OD) schedule. METHODS: A randomised, crossover trial was conducted in 30 patients with head and neck cancer who were receiving moderately emetogenic chemotherapy. The patients were divided into two groups. In the first cycle, one group was given a PD schedule and the other, an OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases. RESULTS: Complete response in the acute phase was observed in 83.3 percent of the patients on the PD schedule and in 80 percent of those on the OD schedule. In the delayed phase, complete response was observed in 76.7 percent and 66.7 percent of the patients on the PD schedule and OD schedule, respectively. The overall rate of complete response was 66.7 percent in the PD group and 46.7 percent in the OD group. In the PD group, there were 73.3 percent of nausea-free patients as opposed to 66.7 percent in the OD group.

CONCLUSION: The results suggest that the PD schedule was superior to the OD schedule in controlling emesis in cancer chemotherapy, although this difference was not statistically significant.

Kim, J.-S., J. Y. Baek, et al. (2004). "Open-label, randomized comparison of the efficacy of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed cisplatin-induced emesis in cancer patients." Cancer Research & Treatment **36**(6): 372-6.

PURPOSE: The aim of this study is to compare the antiemetic efficacy and tolerability of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed emesis. MATERIAL AND METHODS: From April 2002 through October 2002, a total of 112 patients receiving cisplatin- based combination chemotherapy were randomized to receive a single i.v. dose of dolasetron 100 mg or ondansetron 8 mg, 30 minutes before the initiation of chemotherapy. In the ondansetron group, two additional doses of ondansetron 8 mg were given at intervals of 2 to 4 hours. To prevent delayed emesis, dolasetron 200 mg p.o. daily or ondansetron 8 mg p.o. bid was administered from the 2(nd) days to a maximum of 5 days. The primary end point was the proportion of patients that experienced no emetic episodes and required no rescue medication (complete response, CR) during the 24 hours (acute period) and during Day 2 to Day 5+/-2 days (delayed period), after chemotherapy. The secondary end points included the incidence and severity of emesis. RESULTS: 105 patients were evaluable for efficacy. CR rates during the acute period were 36.0% for a single dose of dolasetron 100 mg, and 43.6% for three doses of ondansetron 8 mg. CR rates during the delayed period were 8.0% and 10.9%, respectively. There was no significant difference in the efficacy between the two groups. Adverse effects were mostly mild to moderate and not related to study medication. CONCLUSIONS: A single i.v. dose of dolasetron 100 mg is as effective as three i.v. doses of ondansetron 8 mg in preventing acute and delayed emesis after cisplatin-based chemotherapy, with a comparable safety profile.

Mandanas, R. A., R. Beveridge, et al. (2005). "A randomized, multicenter, open-label comparison of the antiemetic efficacy of dolasetron versus ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy." Supportive Cancer Therapy **2**(2): 114-21.

This study assessed the efficacy and safety of dolasetron compared with ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy followed by peripheral blood stem cell support. Twenty centers randomized 197 patients to receive dolasetron 100 mg intravenously (I.V.) followed 8-12 hours later by a single oral dose of dolasetron 100 mg or ondansetron 32 mg I.V., followed 8-12 hours later by a single oral dose of ondansetron 8 mg during high-dose chemotherapy (HDC) regimens for breast cancer (n = 96; 48.7%), non-Hodgkin's lymphoma (n = 83; 42.1%), or Hodgkin's disease (n = 18; 9.1%). All patients received a daily I.V. bolus of dexamethasone 10 mg with study antiemetic agents and a continuous infusion of diphenhydramine, lorazepam, and dexamethasone (ie, BAD pump) throughout the course of the study, with patient-controlled on-demand bolus doses as needed. After completing a daily diary of emetic episodes and rescue medication use, 164 of 197 patients were evaluable. Total plus complete responses (no emesis, no nausea, no rescue) over the entire study period were achieved in 45.7% and 46.9% of patients on the dolasetron and

ondansetron arms, respectively. Dolasetron and ondansetron were well-tolerated. This study demonstrates that dolasetron and ondansetron are equally safe and effective in the prevention of nausea and vomiting associated with HDC (P = 0.955).

Mattiuzzi, G. N., J. E. Cortes, et al. (2010). "Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia." Cancer **116**(24): 5659-66.

BACKGROUND: Nausea and vomiting in patients with acute myelogenous leukemia (AML) can be from various causes, including the use of high-dose cytarabine.
METHODS: The authors compared 2 schedules of palonosetron versus ondansetron in the treatment of chemotherapy-induced nausea and vomiting (CINV) in patients with AML receiving high-dose cytarabine. Patients were randomized to: 1) ondansetron, 8 mg intravenously (IV), followed by 24 mg continuous infusion 30 minutes before high-dose cytarabine and until 12 hours after the high-dose cytarabine infusion ended; 2) palonosetron, 0.25 mg IV 30 minutes before chemotherapy, daily from Day 1 of high-dose cytarabine up to Day 5; or 3) palonosetron, 0.25 mg IV 30 minutes before high-dose cytarabine on Days 1, 3, and 5. RESULTS: Forty-seven patients on ondansetron and 48 patients on each of the palonosetron arms were evaluable for efficacy. Patients in the palonosetron arms achieved higher complete response rates (no emetic episodes plus no rescue medication), but the difference was not statistically significant (ondansetron, 21%; palonosetron on Days 1-5, 31%; palonosetron on Days 1, 3, and 5, 35%; P = .32). Greater than 77% of patients in each arm were free of nausea on Day 1; however, on Days 2 through 5, the proportion of patients without nausea declined similarly in all 3 groups. On Days 6 and 7, significantly more patients receiving palonosetron on Days 1 to 5 were free of nausea (P = .001 and P = .0247, respectively). CONCLUSIONS: The daily assessments of emesis did not show significant differences between the study arms. Patients receiving palonosetron on Days 1 to 5 had significantly less severe nausea and experienced significantly less impact of CINV on daily activities on Days 6 and 7. Cancer 2010. Copyright 2010 American Cancer Society.

Metaxari, M., A. Papaioannou, et al. (2011). "Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents." Journal of Anesthesia 25(3): 356-362.

PURPOSE: The aim of this double-blind randomized study was to compare the antiemetic efficacy of three 5-hydroxytryptamine type 3 antagonists in terms of the incidence and intensity of postoperative nausea and vomiting (PONV) in a homogenous group of female patients undergoing thyroidectomy.
METHODS: The study cohort consisted of 203 American Society of Anesthesiologists PS I-II female patients randomized into four groups to receive at induction of anesthesia an intravenous (IV) bolus of 5 ml solution of one of the following: normal saline (placebo), granisetron 3 mg, ondansetron 4 mg, or tropisetron 5 mg. Nausea and vomiting were evaluated at five time points: during the first hour in the postanesthesia care unit (PACU) and 6, 12, 18, and 24 h postoperatively. Nausea intensity was measured using a visual analogue scale score (0-10).
RESULTS: Patients in the placebo group displayed a high incidence of nausea in the PACU and at 6, 12, and 18 h postoperatively (44, 60, 50, and 34%, respectively) and of

vomiting (26, 42, 30 and 10%). The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 h (26, 18, and 2%, respectively) and vomiting at 6 and 12 h (10 and 6%, respectively). Ondansetron reduced significantly the incidence of nausea and vomiting only at 6 h postoperatively (28 and 12%, respectively). The administration of tropisetron did not affect the incidence of PONV compared to placebo. CONCLUSION: Among the female patients of this study undergoing thyroid surgery, granisetron 3 mg provided the best prophylaxis from PONV. Ondansetron 4 mg was equally effective, but its action lasted only 6 h, whereas tropisetron 5 mg was found ineffective.

Moon, Y. E., J. Joo, et al. (2012). "Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study.[Erratum appears in Br J Anaesth. 2012 Jun;108(6):1047-8]." British Journal of Anaesthesia 108(3): 417-422.

BACKGROUND: Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking. This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy.
METHODS: A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue anti-emetics, and adverse effects were evaluated during 0-2 and 2-24 h.
RESULTS: The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, P=0.045). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2-24 h. The only difference in the use of rescue anti-emetics was at 2-24 h (10% with palonosetron compared with 28% with ondansetron, P=0.02).
CONCLUSIONS: Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2-24 h after surgery.

Park, S. K. and E. J. Cho (2011). "A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery." Journal of International Medical Research 39(2): 399-407.

This randomized, double-blind study evaluated the relative efficacy of palonosetron (a new, selective 5-hydroxytryptamine type 3 [5-HT(3)] receptor antagonist) and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 45) or ondansetron 8 mg (n = 45), intravenously, immediately before induction of general anaesthesia. The occurrence of nausea and vomiting and the severity of nausea according to a visual analogue scale were monitored immediately after the end of surgery and during the following 24 h. The incidence of PONV was significantly

lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale for nausea. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.

Saito, M., K. Aogi, et al. (2009). "Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial.[see comment]." Lancet Oncology **10**(2): 115-24.

BACKGROUND: Palonosetron is a second-generation 5-hydroxytryptamine 3 (5-HT(3))-receptor antagonist that has shown better efficacy than ondansetron and dolasetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy, and similar efficacy to ondansetron in preventing CINV in patients receiving highly emetogenic chemotherapy. In this phase III, multicentre, randomised, double-blind, double-dummy, stratified, parallel-group, active-comparator trial, we assessed the efficacy and safety of palonosetron versus granisetron for chemotherapy-induced nausea and vomiting, both of which were administered with dexamethasone in patients receiving highly emetogenic chemotherapy. METHODS: Between July 5, 2006, and May 31, 2007, 1143 patients with cancer who were receiving highly emetogenic chemotherapy (ie, cisplatin, or an anthracycline and cyclophosphamide combination [AC/EC]) were recruited from 75 institutions in Japan, and randomly assigned to either single-dose palonosetron (0.75 mg), or granisetron (40 microg/kg) 30 min before chemotherapy on day 1, both with dexamethasone (16 mg intravenously) on day 1 followed by additional doses (8 mg intravenously for patients receiving cisplatin or 4 mg orally for patients receiving AC/EC) on days 2 and 3. A non-deterministic minimisation method with a stochastic-biased coin was applied to the randomisation of patients. Covariates known to effect emetic risk, such as sex, age, and type of highly emetogenic chemotherapy, were used as stratification factors of minimisation to ensure balance between the treatment groups. Primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute phase (0-24 h postchemotherapy; non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24-120 h postchemotherapy; superiority comparison with granisetron). The non-inferiority margin was predefined in the study protocol as a 10% difference between groups in the proportion of patients with complete response. The palonosetron dose of 0.75 mg was chosen on the basis of two dose-determining trials in Japanese patients. All patients who received study treatment and highly emetogenic chemotherapy were included in the efficacy analyses (modified intention to treat). This trial is registered with ClinicalTrials.gov, number NCT00359567. FINDINGS: 1114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. 418 of 555 patients (75.3%) in the palonosetron group had complete response during the acute phase compared with 410 of 559 patients (73.3%) in the granisetron group (mean difference 2.9% [95% CI -2.70 to 7.27]). During the delayed phase, 315 of 555 patients (56.8%) had complete response in the palonosetron group compared with 249 of 559 patients (44.5%) in the granisetron group ($p<0.0001$). The main treatment-related adverse events were constipation (97 of 557

patients [17.4%] in the palonosetron group vs 88 of 562 [15.7%] in the granisetron group) and raised concentrations of serum aminotransferases (aspartate aminotransferase: 24 of 557 [4.3%] vs 34 of 562 [6.0%]; alanine aminotransferase: 16 of 557 [2.9%] vs 33 of 562 [5.9%]); no grade 4 main treatment-related adverse events were reported. INTERPRETATION: When administered with dexamethasone before highly emetogenic chemotherapy, palonosetron exerts efficacy against chemotherapy-induced nausea and vomiting which is non-inferior to that of granisetron in the acute phase and better than that of granisetron in the delayed phase, with a comparable safety profile for the two treatments. FUNDING: Taiho Pharmaceutical (Tokyo, Japan).

Siddique, R., M. G. Hafiz, et al. (2011). "Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia." Mymensingh Medical Journal: MMJ 20(4): 680-688.

Effect of ondansetron and granisetron were evaluated in sixty (60) children (age 4-11 years) irrespective of sex, diagnosed case of acute lymphoblastic leukemia (ALL) who received high dose methotrexate and did not receive any antiemetic 24 hours prior to HDMTX. This was a prospective, randomized, double-blind, single center study. Of 60 children, 30 received oral ondansetron (4mg) and rest 30 granisetron (1mg) half an hour before therapy. Drugs were randomly allocated with appropriate code. The patients were followed up from day 1 to day 5 of therapy. Episodes of nausea and vomiting were recorded and scorings was done every 24 hours following chemotherapy. No significant difference was found between two groups according to acute emesis (Day-1) ($p=0.053$). In day two and day three it was significant ($p<0.05$). In day four it was significant ($p=0.002$). Early chemotherapy induced nausea and vomiting (CINV) were controlled 90% in children who received granisetron and 70% in children who received ondansetron. Delayed (Day 2-4) CINV were controlled in 80% of children who received granisetron and 43.4% who received ondansetron ($p<0.05$). Granisetron group required additional doses only 3.3% cases and ondanseton group 30% cases on the second day ($p<0.05$). Result was significant between two groups. About 36.7% patients had episodes of nausea on day four of chemotherapy in ondansetron group and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself ($p=0.001$). Maximum episodes of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% ($p=0.003$). Though adverse effects like headache, constipation, abdominal pain and loose motion were common in both group of children but their number was much less in children who received granisetron. On second day of therapy score of nausea and vomiting was maximum in ondansetron and minimum in granisetron treated on day 4 and the result was significant. So, to prevent acute and delayed CINV in children with ALL, oral graniseteron can be considered as more effective and well tolerated with minimum adverse effects compared with ondansetrons.

Tan, T., R. Ojo, et al. (2010). "Reduction of severity of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine: a randomised comparison of prophylactic granisetron and ondansetron." International Journal of Obstetric Anesthesia **19**(1): 56-60.

BACKGROUND: The incidence of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine may be 60-100%, and is a common cause of maternal dissatisfaction. Ondansetron has been shown to reduce pruritus but the effect is

short-lived. The objective of this randomized double-blind trial was to evaluate the anti-pruritic efficacy of granisetron compared with ondansetron. METHODS: Eighty ASA I or II women undergoing elective caesarean section received spinal anaesthesia with 0.5% hyperbaric bupivacaine 10 mg, fentanyl 25 microg and preservative-free morphine 150 microg. After delivery of the baby and clamping of the umbilical cord, they were randomised to receive granisetron 3mg i.v. (group G) or ondansetron 8 mg i.v. (group O). RESULTS: The two groups were similar for age, gestational age, height and weight. According to visual analogue pruritus scores, patients in group G experienced less pruritus at 8h (P=0.003) and 24h (P=0.01). Fewer patients in group G (n=8) than group O (n=18) required rescue anti-pruritic medication (P=0.03). Satisfaction scores were also higher in group G than in group O (P=0.03). There was no difference in overall incidence of pruritus, nausea and vomiting, and visual analogue pain scores between the two groups. CONCLUSIONS: Administration of granisetron 3mg i.v. reduces the severity of pruritus and the use of rescue anti-pruritic medication, and improves satisfaction but does not reduce the overall incidence of pruritus in women who have received subarachnoid morphine 150 microg compared to ondansetron 8 mg i.v. Copyright 2009 Elsevier Ltd. All rights reserved.

Tian, W., Z. Wang, et al. (2011). "Randomized, double-blind, crossover study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population." Medical Oncology **28**(1): 71-8.

The objective of this study was to compare the efficacy and tolerability of palonosetron and granisetron in a Chinese population receiving highly emetogenic cisplatin-based chemotherapy or moderately emetogenic chemotherapy. Patients were stratified by chemotherapy with cisplatin (yes/no) and then randomly assigned to receive either palonosetron (0.25mg i.v.) in the first cycle followed by granisetron (3mg i.v.) in the second cycle or vice versa. The primary efficacy endpoint was the proportion of patients with complete response 0-24h post-chemotherapy administration. The proportions of patients with complete response 24-120 and 0-120h following chemotherapy were also compared. Of the 144 patients randomized, 36 (25%) received 60-80mg/m(2) cisplatin; 66 of 72 patients in the palonosetron to granisetron group and 56 of 72 patients in the granisetron to palonosetron group completed treatment with both antiemetics. The efficacy and safety analyses included 128 palonosetron treatments and 138 granisetron treatments. Palonosetron consistently produced numerically higher complete response rates than granisetron in the acute phase (0-24h, 71.09 vs. 65.22%), the delayed phase (24-120h, 60.16 vs. 55.80%), and overall (0-120h, 53.13 vs. 50.00%) though the differences were not significant. Both palonosetron and granisetron were well tolerated. Palonosetron was well tolerated and effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in a Chinese population. When used as monotherapy, 0.25-mg palonosetron was not inferior to 3-mg granisetron for preventing vomiting following highly or moderately emetogenic chemotherapy.

Yu, Z., W. Liu, et al. (2009). "The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicenter, randomized, double-blind, parallel, comparative clinical trial." Supportive Care in Cancer **17**(1): 99-102.

PURPOSE: This clinical trial was conducted to evaluate the efficacy and safety of Palonosetron in preventing chemotherapy-induced vomiting (CIV) among the Chinese cancer patients. PATIENTS AND METHODS: Two hundred and forty patients were scheduled to be enrolled and randomized to receive a single intravenous dose of palonosetron 0.25 mg, or granisetron 3 mg, 30 min before receiving highly emetogenic chemotherapy. The primary efficacy endpoint was the complete response (CR) rate for acute CIV (during the 0-24-h interval after chemotherapy). Secondary endpoints included the CR rates for delayed CIV (more than 24 h after chemotherapy). RESULTS: Two hundred and eight patients were accrued and received study medication. CR rates for acute CIV were 82.69% for palonosetron and 72.12% for granisetron, which demonstrated that palonosetron was not inferior to granisetron in preventing acute CIV. Comparisons of CR rates for delayed CIV yielded no statistical difference between palonosetron and granisetron groups and did not reveal non-inferiority of palonosetron to granisetron. Adverse events were mostly mild to moderate, with quite low rates among the two groups. CONCLUSIONS: A single dose (0.25 mg) of palonosetron is not inferior to a single dose (3 mg) of granisetron in preventing CIV and possesses an acceptable safety profile in the Chinese population.

Placebo-controlled trials

Albany, C., M. J. Brames, et al. (2012). "Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study." Journal of Clinical Oncology 30(32): 3998-4003.

PURPOSE: Aprepitant, a 5-HT3 receptor antagonist (5HT3-RA), and dexamethasone are standard antiemetic therapy for prevention of single-day, cisplatin-induced nausea and vomiting. We conducted a double-blind, placebo-controlled phase III cross-over study that compared aprepitant to placebo combined with standard antiemetic prophylaxis (a 5HT3-RA and dexamethasone) in patients receiving 5 days of cisplatin combination chemotherapy for testicular cancer.

PATIENTS AND METHODS: Patients receiving two consecutive identical courses of a 5-day cisplatin-based chemotherapy were randomly assigned to aprepitant 125 mg on day 3 and 80 mg per day on days 4 through 7 or to placebo with the initial course and crossover to the opposite treatment with the second course. The primary objective was complete response (CR). Secondary end points were emetic episodes (acute and delayed), nausea measurement based on a visual analog scale (VAS), and patient-stated preference after the second study cycle.

RESULTS: In all, 71 patients were screened for the study and 69 were evaluable. Thirty-five patients were randomly assigned to receive aprepitant and 34 to receive placebo for the first course. Forty-two percent achieved CR with aprepitant compared with 13% with placebo ($P < .001$). Eleven patients (16.2%) had at least one emetic episode during the aprepitant cycle versus 32 patients (47.1%) with placebo. Thirty-eight patients preferred the aprepitant cycle whereas 11 preferred placebo ($P < .001$). There was no statistical difference in VAS for nausea, but it was numerically superior with aprepitant. There was no toxicity with aprepitant compared with placebo.

CONCLUSION: There was a significant improvement in CR rate with aprepitant combined with a 5HT3-RA and dexamethasone. Patient preference strongly favored the aprepitant cycle.

Barrett, T. W., D. M. DiPersio, et al. (2011). "A randomized, placebo-controlled trial of ondansetron, metoclopramide, and promethazine in adults." American Journal of Emergency Medicine 29(3): 247-255.

OBJECTIVES: The objective of the study was to assess whether ondansetron has superior nausea reduction compared with metoclopramide, promethazine, or saline placebo in emergency department (ED) adults.

METHODS: This randomized, placebo-controlled, double-blinded superiority trial was intended to enroll a convenience sample of 600 patients. Nausea was evaluated on a 100-mm visual analog scale (VAS) at baseline and 30 minutes after treatment. Patients with a minimum preenrollment VAS of 40 mm were randomized to intravenous ondansetron 4 mg, metoclopramide 10 mg, promethazine 12.5 mg, or saline placebo. A 12-mm VAS improvement in nausea severity was deemed clinically important. We measured potential drug adverse effects at baseline and 30 minutes. Patients received approximately 500 mL of saline hydration during the initial 30 minutes.

RESULTS: Of 180 subjects who consented, 163 completed the study. The median age was 32 years (interquartile range, 23-47), and 68% were female. The median 30-minute VAS reductions (95% confidence intervals) and saline volume given for ondansetron, metoclopramide, promethazine, and saline were -22 (-32 to -15), -30 (-38 to -25.5), -29 (-40 to -21), and -16 (-25 to -3), and 500, 500, 500, and 450, respectively. The median 30-minute VAS differences (95% confidence intervals) between ondansetron and metoclopramide, promethazine, and saline were -8 (-18.5 to 3), -7 (-21 to -5.5), and 6 (-7 to 20), respectively. We compared the antiemetic efficacy across all treatments with the Kruskal-Wallis test (P = .16).
CONCLUSIONS: Our study shows no evidence that ondansetron is superior to metoclopramide and promethazine in reducing nausea in ED adults. Early study termination may have limited detection of ondansetron's superior nausea reduction over saline.

de Orange, F. A., J. Marques, et al. (2012). "Dexamethasone versus ondansetron in combination with dexamethasone for the prophylaxis of postoperative vomiting in pediatric outpatients: a double-blind, randomized, placebo-controlled clinical trial." Paediatric Anaesthesia 22(9): 890-896.

OBJECTIVES: To determine the frequency of postoperative vomiting (POV) in children submitted to outpatient surgery and to compare the efficacy of antiemetic drugs in preventing this complication.
BACKGROUND: Nausea and vomiting are common in the immediate postoperative period following anesthetic and surgical procedures. Compared to adults, pediatric patients are more likely to develop postoperative nausea and vomiting, the incidence of which ranges from 8.9% to 42%.
METHODS: This double-blind, randomized, placebo-controlled clinical trial included 129 children. The participants were randomized into three prophylactic treatment groups: dexamethasone (n = 43), ondansetron in combination with dexamethasone (n = 44), and placebo (n = 42). The variables studied were the frequency of POV and the incidence of vomiting after the patient had been discharged from hospital, the need for antiemetic rescue therapy in the postanesthesia care unit (PACU), need for hospitalization, and the time the patient remained in the PACU. A significance level of 5% was adopted.
RESULTS: Postoperative vomiting occurred in 12.4% of the children, with no statistically significant difference between the groups: 6.8% in the group receiving ondansetron combined with dexamethasone, 14.3% in the placebo group, and 14% in the group that received dexamethasone alone (P = 0.47). Furthermore, no significant difference was found between the groups with respect to the time the children remained in the PACU, and only five patients reported having vomited following discharge from hospital.
CONCLUSIONS: The prophylactic use of antiemetic drugs failed to reduce the incidence of POV in pediatric outpatient surgery with a low emetic potential; therefore, routine prophylaxis may be unnecessary.

Ebrahim Soltani, A. R., H. Mohammadinasab, et al. (2011). "Comparing the efficacy of prophylactic p6 acupressure, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery." Acta Medica Iranica 49(4): 208-212.

To compare the efficacy of acupressure wrist bands, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery. Two hundred patients, ASA physical status I or II, aged between 10 and 60 years, undergoing strabismus surgery in Farabi Hospital in 2007-2008 years, were included in this randomized, prospective, double-blind and placebo-controlled study. Group I was the Control, group II received metoclopramide 0.2 mg/kg, group III received ondansetron 0.15 mg/kg iv just before induction, in Group IV acupressure wristbands were applied at the P6 points. Acupressure wrist bands were placed inappropriately in Groups I, II and III. The acupressure wrist bands were applied 30 min prior to the induction of anesthesia and removed six hours after surgery. Postoperative nausea and vomiting (PONV) was evaluated within 0-2 hours and 2-24 hours after surgery by a blinded observer. Results were analyzed by X(2) test. A P value of < 0.05 was taken as significant. The incidence of PONV was not significantly different in acupressure, metoclopramide and ondansetron during the 24 hours. Acupressure at P6 causes a significant reduction in the incidence of PONV 24 hours after strabismus surgery as well as metoclopramide 0.2 mg/kg and ondansetron 0.15 mg/kg iv for patients aged 10 or more.

Gore, L., S. Chawla, et al. (2009). "Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability." Pediatric Blood & Cancer **52**(2): 242-7.

BACKGROUND: The neurokinin-1 receptor antagonist aprepitant, plus a 5HT3 antagonist and corticosteroid is well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in adults but has not been formally assessed in adolescents. PROCEDURE: Patients age 11-19 years old receiving emetogenic chemotherapy were randomized 2:1 to aprepitant triple therapy (aprepitant [A] 125 mg p.o., dexamethasone [D] 8 mg p.o., and ondansetron [O] 0.15 mg/kg i.v. t.i.d. day 1; A 80 mg, D 4 mg, and O 0.15 mg/kg t.i.d. day 2; A 80 mg and D 4 mg day 3; and D 4 mg day 4) or a control regimen (D 16 mg and O 0.15 mg/kg t.i.d. day 1; D 8 mg and O 0.15 mg/kg t.i.d. day 2; and D 8 mg days 3 and 4). The primary endpoint was the difference in drug-related adverse events during and for 14 days following treatment. Efficacy and aprepitant pharmacokinetics were assessed. RESULTS: Baseline characteristics were similar between aprepitant (N = 28) and control (N = 18) groups. Febrile neutropenia was more frequent in the aprepitant group (25% vs. 11.1%). Complete response (CR) rates were 35.7% for aprepitant triple therapy versus 5.6% for the control group. Mean plasma aprepitant AUC(0-24 hr) and C(max) on day 1 and mean trough concentrations on days 2 and 3 were consistently lower compared to historical data obtained from healthy adults; however, the differences were not clinically significant. CONCLUSION: Aprepitant triple therapy was generally well tolerated; CR were greater with aprepitant, although not statistically significant. Pharmacokinetics suggest that the adult dosing regimen is appropriate for adolescents. (c) 2008 Wiley-Liss, Inc.

Hesketh, P. J., G. Morrow, et al. (2012). "Efficacy and safety of palonosetron as salvage treatment in the prevention of chemotherapy-induced nausea and vomiting in patients receiving low emetogenic chemotherapy (LEC)." Supportive Care in Cancer **20**(10): 2633-2637.

PURPOSE: The purpose of this study is to evaluate the efficacy and safety of intravenous (IV) palonosetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients with cancer who had incomplete control of CINV during their previous cycle of low emetogenic chemotherapy (LEC).

METHODS: Patients with histologically or cytologically confirmed cancer, >=18 years of age, with a Karnofsky Performance Scale score of >=50% who had received LEC that induced vomiting and/or at least moderate nausea during their previous treatment cycle received palonosetron 0.25 mg IV 30 min before chemotherapy. Outcomes were recorded in patient diaries over 120 h and at an end-of-study visit on days 6, 7, or 8 after LEC administration. The primary efficacy variable was the complete response rate, defined as no emetic episodes and no rescue medication at 0-24 h (acute post-chemotherapy phase), 24-120 h (delayed phase), and 0-120 h (overall).

RESULTS: Complete responses among the intent-to-treat study population (n = 34) were recorded for 88.2 % of patients in the acute phase, 67.6% in the delayed phase, and 67.6% overall. No emetic episodes occurred in 91.2 and 79.4% of patients during the acute and delayed phases, respectively, and no nausea in 73.5 and 52.9%, respectively. Palonosetron was well tolerated; only two patients experienced treatment-related adverse events.

CONCLUSIONS: Among the patients with cancer who had a history of CINV with LEC, palonosetron was effective in preventing CINV in both the acute and delayed post-chemotherapy phases, and was well tolerated. Randomized comparative studies in larger populations of patients receiving LEC are needed to confirm these findings.

Koren, G., S. Clark, et al. (2010). "Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial." American Journal of Obstetrics & Gynecology 203(6): 571.e571-577.

OBJECTIVE: To evaluate the effectiveness of Diclectin (doxylamine succinate 10 mg-pyridoxine hydrochloride 10 mg, delayed-release preparation) as compared with placebo for nausea and vomiting of pregnancy.

STUDY DESIGN: A randomized, double-blind, multicenter placebo controlled trial studying pregnant women suffering from nausea and vomiting of pregnancy, analyzed by intention to treat. Women received Diclectin (n = 131) or placebo (n = 125) for 14 days. Nausea and vomiting of pregnancy symptoms were evaluated daily using the pregnancy unique quantification of emesis scale.

RESULTS: Diclectin use resulted in a significantly larger improvement in symptoms of nausea and vomiting of pregnancy compared with placebo based on both the pregnancy unique quantification of emesis score (-4.8 +/- 2.7 vs -3.9 +/- 2.6; P = .006) and quality of life. After the trial, 64 (48.9%) women receiving Diclectin asked to continue compassionate use of their medication, as compared with 41 (32.8%) of placebo-treated women (P = .009).

CONCLUSION: Diclectin delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating nausea and vomiting of pregnancy.

Rapoport, B. L., K. Jordan, et al. (2010). "Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study." Supportive Care in Cancer **18**(4): 423-31.

PURPOSE: Aprepitant was shown previously to be effective for prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately emetogenic chemotherapy (MEC) in breast cancer patients receiving an anthracycline and cyclophosphamide (AC)-based regimen. This study assessed aprepitant in patients receiving a broad range of MEC regimens with a variety of tumor types. METHODS: This phase III, randomized, gender-stratified, double-blind trial enrolled patients with confirmed malignancies, naive to MEC or highly emetogenic chemotherapy, who were scheduled to receive a single dose of at least one MEC agent. Patients received an aprepitant triple-therapy regimen (aprepitant, ondansetron, and dexamethasone) or a control regimen (ondansetron and dexamethasone) administered orally. Primary and key secondary efficacy endpoints were proportions of patients with no vomiting and complete response (no vomiting and no rescue medication), respectively, during the 120 h post-chemotherapy. RESULTS: Of 848 randomized patients, 77% were female, and 52% received non-AC-based antineoplastic regimens. Significantly, more patients in the aprepitant group achieved no vomiting and complete response, regardless of whether they received AC or non-AC regimens, in the 120 h after chemotherapy. Overall, the incidences of adverse events were generally similar in the aprepitant (62.8%) and control groups (67.2%). CONCLUSIONS: The aprepitant regimen provided superior efficacy in the treatment of CINV in a broad range of patients receiving MEC (non-AC or AC) in both no vomiting and complete response endpoints. Aprepitant was generally well tolerated. These results show the benefit of including aprepitant as part of the standard antiemetic regimen for cancer patients receiving MEC.

Reeve, B. K., D. J. Cook, et al. (2005). "Prophylactic Diclectin reduces the incidence of postoperative vomiting." Canadian Journal of Anaesthesia 52(1): 55-61.

BACKGROUND: Diclectin(R) (DCL) is an effective antiemetic used for relief of nausea and vomiting in pregnancy. It is unknown whether DCL is effective in the prevention of postoperative nausea and vomiting (PONV).

METHODS: We conducted a randomized, stratified, double-blind placebo-controlled trial to examine the incidence of PONV in women undergoing elective laparoscopic tubal ligation in the day surgery setting. DCL (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) was administered orally the night before surgery, the morning of surgery, and upon hospital discharge.

RESULTS: We enrolled 146 women in the trial, 127 of whom were included in the effectiveness analysis and 102 of whom were included in the efficacy analysis. We did not detect a difference in the incidence of nausea and vomiting in the first six hours postoperatively after adjusting for additional antiemetics administered. Patients receiving DCL as compared with placebo were significantly less likely to experience vomiting six to 24 hr

postoperatively [5/59 (8.5%) vs 14/55 (25.4%), P < 0.017]. Treated patients tended to return to work earlier than those who received placebo (1.74 vs 3.7 days P = NS). CONCLUSION: Perioperative oral DCL reduces the incidence of postoperative vomiting in women undergoing elective laparoscopic tubal ligation, and may accelerate return to work.

Takahashi, T., E. Hoshi, et al. (2010). "Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin." Cancer Science **101**(11): 2455-61.

Aprepitant is a new neurokinin-1 (NK(1)) receptor antagonist developed as a treatment for chemotherapy-induced nausea and vomiting (CINV). To evaluate the efficacy and safety of aprepitant used in combination with standard therapy (granisetron and dexamethasone), we conducted a multicenter, phase II, placebo-controlled, double-blind, randomized study in Japanese cancer patients who received cancer chemotherapy including cisplatin (>=70mg/m(2)). Aprepitant was administered for 5days. A total of 453 patients were enrolled. In the three study groups, (i) standard therapy, (ii) aprepitant 40/25mg (40mg on day 1 and 25mg on days 2-5) and (iii) aprepitant 125/80mg (125mg on day 1 and 80mg on days 2-5), the percentage of patients with complete response (no emesis and no rescue therapy) was 50.3% (75/149 subjects), 66.4% (95/143 subjects) and 70.5% (103/146 subjects), respectively. This shows that efficacy was significantly higher in the aprepitant 40/25mg and 125/80mg groups than in the standard therapy group ((2) test [closed testing procedure]: P=0.0053 and P=0.0004, respectively) and highest in the aprepitant 125/80mg group. The delayed phase efficacy (days 2-5) was similar to the overall phase efficacy (days 1-5), indicating that aprepitant is effective in the delayed phase when standard therapy is not very effective. In terms of safety, aprepitant was generally well tolerated in Japanese cancer patients. (ClinicalTrials.gov number, NCT00212602.) Copyright 2010 Japanese Cancer Association.

Vallejo, M. C., A. L. Phelps, et al. (2012). "Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery." Plastic & Reconstructive Surgery 129(2): 519-526.

BACKGROUND: Postoperative nausea and vomiting is a major challenge in the perioperative setting. The incidence can be as high as 80 percent, and the majority of the symptoms among outpatients occur after discharge. This study evaluated the efficacy of a neurokinin-1 receptor antagonist (aprepitant) in reducing postoperative symptoms for up to 48 hours in patients undergoing outpatient plastic surgery.
METHODS: A prospective, double-blinded, randomized, two-arm evaluation of 150 ambulatory plastic surgery patients receiving a standardized general anesthetic, including postoperative nausea and vomiting prophylaxis with ondansetron and either aprepitant or placebo, was performed. The main outcome measures were the occurrence of vomiting and the severity of nausea for up to 48 hours postoperatively.
RESULTS: Overall, 9.3 percent of patients who received aprepitant versus 29.7 percent in group B had vomiting, with the majority of vomiting episodes occurring after hospital discharge. The Kaplan-Meier plot of the hazards of vomiting revealed an increased incidence of emesis in patients receiving ondansetron alone compared with the combination of ondansetron and aprepitant (p = 0.006). The incidence of nausea was not significantly different in the two groups. Severity of nausea, however, was significantly higher in those receiving ondansetron alone compared with those receiving ondansetron

and aprepitant, as measured by a peak nausea score (p = 0.014) and by multivariate analysis of variance results comparing repeated verbal rating scale scores over 48 hours after surgery (p = 0.024).
CONCLUSION: In patients undergoing plastic surgery, the addition of aprepitant to ondansetron significantly decreases postoperative vomiting rates and nausea severity for up to 48 hours postoperatively.
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Wagner, D. S., V. Gauger, et al. (2007). "Ondansetron oral disintegrating tablets for the prevention of postoperative vomiting in children undergoing strabismus surgery." Therapeutics & Clinical Risk Management **3**(4): 691-4.

Strabismus surgery in pediatric patients is associated with a high incidence of postoperative nausea and vomiting (PONV). Ondansetron disintegrating tablets (ODT), an oral freeze-dried formulation of the 5-HT(3) antagonist, are well-tolerated and have been shown to reduce chemotherapy-induced vomiting. The purpose of this study was to assess the efficacy of the ODT in preventing postoperative vomiting (POV) in children undergoing strabismus repair. Healthy children aged 4-12 years of age were administered a 4 mg ODT 30 minutes prior to the induction of general anesthesia. Induction and maintenance of anesthesia were standardized; each child received acetaminophen and ketorolac pre-emptively for analgesia. This study group was compared with a historical control group who received a placebo in previously conducted identical trials of POV. The 35 children included in this study were compared with 31 controls. The incidence and severity of POV and use of rescue antiemetics were significantly lower in children who received ODT compared with placebo (p </= 0.001). The acute complete response (ie, no emesis and no rescue antiemetics in 24 hours) was 76% in the ODT group compared with 16% in the controls (p </= 0.001). Results suggest that ODT given preoperatively reduces the incidence and severity of POV in children undergoing strabismus surgery.

Yeo, W., F. K. F. Mo, et al. (2009). "A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy." Breast Cancer Research & Treatment **113**(3): 529-35.

OBJECTIVES: This is a single center, randomized, double-blind placebo-controlled study to evaluate the NK(1)-receptor antagonist, aprepitant, in Chinese breast cancer patients. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy. The secondary objective was to compare the patient-reported quality of life in these two groups of patients. PATIENTS AND METHODS: Eligible breast cancer patients were chemotherapy-naive and treated with adjuvant AC chemotherapy (i.e. doxorubicin 60 mg/m(2) and cyclophosphamide 600 mg/m(2)). Patients were randomly assigned to either an aprepitant-based regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, aprepitant 80 qd) or a control arm which consisted of standard regimen (day 1, ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and

ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary, patients quality of life were assessed by self-administered Functional Living Index-Emesis (FLIE). RESULTS: Of 127 patients randomized, 124 were assessable. For CINV in Cycle 1 AC, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea'. The requirement of rescue medication appears to be lesser in patients treated with the aprepitant-based regimen compared to those with the standard regimen (11% vs. 20%; P = 0.06). Assessment of FLIE revealed that while there was no difference in the nausea domain and the total score between the two groups; however, patients receiving standard antiemetic regimen had significantly worse quality of life in the vomiting domain (mean score [SD] = 23.99 [30.79]) when compared with those who received the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) (P = 0.0002). Both treatments were generally well tolerated. Patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (53.2% vs. 35.5%, P = 0.0468), grade >or= 3 neutropenia (21.0% vs. 45.2, P = 0.0042) and delay in subsequent cycle of chemotherapy (8.1% vs. 27.4%, P = 0.0048). CONCLUSION: The aprepitant regimen appears to reduce the requirement of rescue medication when compared with the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide, and is associated with a better quality of life during adjuvant AC chemotherapy.