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, May 28, 2015 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 — R. Citron (OSU)
- B. Conflict of Interest Declaration — R. Citron (OSU)
- C. Approval of Agenda and Minutes — T. Klein (Vice Chair)
- D. Department Update — L. Saris (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. Evaluation of High Dose SSRI Initiation in Pediatrics
  2. The Opioid Epidemic: Are Abuse-deterrent Formulations the Answer?

III. DUR OLD BUSINESS
- A. PDL Status of Simeprevir — M. Herink (OSU)
  1. Clarification
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- B. Pediatric SSRI High Dose DUE Clarification — T. Williams (OSU)
  1. Maximum Initial Dose for Children < 5 yo
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- C. Tapering Clarification for PPI PA Criteria — A. Gibler (OSU)
  1. PA Criteria Update
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS
- A. Ivacaftor Drug/Policy Update — M. Herink (OSU)
  1. Drug Update
  2. Policy Update
  3. Public Comment
  4. Discussion of Clinical Recommendations to OHA

B. Oral Anticoagulants Class Update / Policy Evaluation K. Sentena / K. Ketchum (OSU)
1. Class Update
2. Policy Evaluation
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

C. Leuprolide Drug/Policy Update A. Meeker (OSU)
1. Drug Update
2. Policy Update
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

A. Otic Antibiotics Class Update A. Gibler (OSU)
1. Class Update
2. Public comment
3. Discussion of Clinical Recommendations to OHA

B. Oxazolidinone Antibiotic Class Review K. Ketchum (OSU)
1. Class Review
2. Public comment
3. Discussion of Clinical Recommendations to OHA

C. Rifaximin New Drug Evaluation A. Gibler (OSU)
1. New Drug Evaluation
2. Public comment
3. Discussion of Clinical Recommendations to OHA

D. Drug Class Literature Scans A. Gibler / M. Herink / A. Meeker / T. Williams (OSU)
1. Antibiotics for *Clostridium difficile* infection
2. Fluoroquinolones
3. Ophthalmic Anti-inflammatory Drugs
4. Inhaled Cystic Fibrosis Drugs
5. Gout Agents
6. Short-acting Opioids
7. Tetracyclines
8. DERP Scan Summaries
    a. Second-generation Antihistamines
    b. Beta-blockers
    c. Overactive Bladder Drugs
9. Public Comment
10. Discussion of Clinical Recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

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Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Corvallis	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Albany	December 2016
Kathryn Lueken, M.D., M.M.M.	Physician	Medical Director	Salem	December 2016
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2015
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2015
Vacant	Physician			December 2015

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 26, 2015 1:00-5:00 PM
Wilsonville 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: Cathy Zehrung, RPh; Phillip Levine, PhD; William Origer, MD; Caryn Mickelson, PharmD; Tracey Klein, PhD., FNP;

Members Present by Phone: Kathryn Lueken, MD; James Slater, PharmD;

Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Shannon Jasper; Amanda Meeker, PharmD; Andrew Gibler, PharmD; Dee Weston, Trevor Douglas, Walter Shaffer, MD

Staff Present by Phone:

Audience: Barry Benson (BMS), Michelle Bice (Gilead), Stuart O'Brochta (Gilead)*, Dean Haxby (OSU), Kim Blood (WVCH), Desiree Allen (Abbvie), Laurie Hill (Abbvie)*, Tom Horton (Lumara Health), Tina Patel (Pacific Source), Allen Hammagren (Abbvie), Catherine Datto (AstraZeneca)*, Randy Legg (AstraZeneca), Patrick Moty (Supernus), Dan Benson (Abbvie), Jim Graves (BMS), Roy Palmer (Pfizer)*, Richard McLeod (Pfizer), Steve Faloon (Otsuka), Henry Washington (Abbott), China Katt (Abbott), James McAdams (Orexo), David Barhoum (Genentech), Gabriela Schneider (GNE), Molly Meekin (Hyperian Therapeutics), Kerrie Fowler (Umpqua Health Alliance)

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:00 pm. Introductions were made by 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 Dr. Origer. (pages 4 – 9)

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

d. No current department updates for OHA.

II. PREFERRED DRUG LIST NEW BUSINESS

a. Viekira Pak New Drug Evaluation (pages 10 – 31)
Dr. Herink presented the following new drug evaluation:

1. Update Hepatitis C Direct-Acting Antivirals PA criteria. The Committee recommended amending questions #19 and #21 of the proposed PA criteria to permit for appropriate discontinuation of contraindicated medications.

2. *After executive session, accept supplemental rebate for Viekira Pak™

3. *After executive session, make Viekira Pak™ preferred as soon as SR is available.

Public Comment:
Laura Hill from Abbvie.
Stuart O'Brochta from Gilead.

***ACTION:** After executive session. All in favor. Approved.

b. Long-acting Opioids Class Update (pages 32 – 48)
Dr. Meeker presented the following class update:

1. *After executive session, maintain hydrocodone ER (Hysingla™) and morphine sulfate / naltrexone (Embeda™) as non-preferred.

2. *After executive session, make oxycodone / naloxone ER (Targiniq™) non-preferred when it becomes available.

Public Comment:
Dr. Roy Palmer from Pfizer.

***ACTION:** After executive session. All in favor. Approved.

c. Drugs for Constipation Review (pages 49 – 81)
Dr. Gibler presented the following class review.

1. Implement PA criteria for linaclotide, lubiprostone, alvimopan, methylnaltrexone and naloxegol.

2. Establish a Laxatives drug class on the PDL.

3. Make polyethylene glycol 3350, lactulose and senna products preferred.

4. *After executive session, make bulk forming laxatives less than $1/unit PDL = Y, all other bulk forming laxatives PDL = N.

5. *After executive session, make osmotic laxatives (inc. PEG 3350 & lactulose) less than $1/unit PDL = Y, all other osmotic laxatives PDL = N.

6. *After executive session, make all lubricant laxatives PDL = N.

7. *After executive session, make all surfactant, stimulant, and saline laxatives PDL = Y.

Public Comment:
Catherine Datto from Astra Zeneca.

***ACTION:** After executive session. All in favor. Approved.

d. Drug Class Scans

1. Antiepileptic Drugs (pages 82 – 98)
   Dr. Gibler presented the following class scan.

   a. Discontinuing PA criteria for pregabalin.

   b. Include pregabalin the PA criteria "Drugs Used for Non-Funded Pain Conditions" as presented at this meeting.

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

   d. *After executive session, remove PA criteria for preferred topiramate products due to cost effectiveness.

***ACTION:** After executive session. All in favor. Approved.

2. Topical Corticosteroids (pages 99 – 105)
   Dr. Herink presented the following class scan.

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

   b. *After executive session, no changes recommended at this time.

***ACTION:** After executive session. All in favor. Approved.

III. DUR NEW BUSINESS

a. Fibromyalgia Drug Use Evaluation (pages 106 – 121)
   Ms. Ketchum presented the following new drug evaluation:

   1. Adopt the PA criteria "Drugs Used for Non-Funded Pain Conditions" as presented at this meeting and apply it to the following medications:
      - Pregabalin
      - Milnacipran

   2. Retire milnacipran-specific PA criteria and adopt the proposed comprehensive drug use criteria for high cost drugs used for fibromyalgia, chronic low back pain and chronic pain syndrome.

   3. Allow automatic approvals for pregablin based on prior claims for epilepsy.

   4. The committee declined recommending applying new criteria to duloxetine due to recent change in price and asked to review generic pricing at the May P&T meeting.

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

b. PPI/H2RA Class updates and Drug Use Evaluation (pages 122 – 143)

Dr. Gibler and Ms. Ketchum presented the following updates and evaluation:

1. *After executive session, maintain open access of preferred H2RAs.

2. *After executive session, continue open access of preferred PPIs for up to 60 days to allow for short-term treatment of GERD and *H. pylori.*

3. *After executive session, establish new PA criteria as discussed in this meeting.

4. *After executive session, implement broad education outreach to prescribers before applying new criteria and to grandfather current long-term PPI users to phase-in implementation.

5. *After executive session, re-evaluating policy 1 year after implementation.

***ACTION:** After executive session. All in favor. Approved.

c. High Dose Opioid Policy Evaluation (pages 144 – 160)
Dr. Williams presented the following policy evaluation:

1. Maintain high-dose opioid PA policy.

2. Collaborate with the Prescription Drug Monitoring Program to determine if high dose opioid therapy was continued in patients who did not have a Prior Authorization approved.

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

IV. EXECUTIVE SESSION

V. RECONVENE for PUBLIC RECOMMENDATIONS

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Pharmacy Utilization Summary Report: October 2013 - September 2014

Eligibility	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Total Members (FFS & Encounter)	621,935	622,966	613,155	819,426	852,414	899,321	933,189	961,855	969,341	980,871	996,544	1,007,305	856,527
FFS Members	75,036	76,075	79,453	140,103	133,822	155,785	137,326	138,745	136,943	132,379	140,158	134,462	123,357
OHP Basic with Medicare	27,177	27,343	27,371	27,575	27,629	27,787	27,903	28,145	28,393	28,468	28,659	28,804	27,938
OHP Basic without Medicare	25,347	25,569	27,446	26,374	24,867	24,408	24,179	24,696	24,989	24,836	24,911	24,494	25,176
ACA	22,100	22,925	23,945	83,884	79,176	99,440	82,228	82,479	80,139	76,302	82,901	77,853	67,781
Encounter Members	546,899	546,891	533,702	679,323	718,592	743,536	795,863	823,110	832,398	848,492	856,386	872,843	733,170
OHP Basic with Medicare	37,420	37,665	37,741	37,758	37,903	38,017	38,134	38,244	38,302	38,419	38,620	38,770	38,083
OHP Basic without Medicare	230,687	228,678	222,953	227,448	228,120	227,677	226,830	224,805	222,503	220,955	219,511	215,256	224,619
ACA	278,211	279,977	272,459	413,355	450,189	474,533	524,688	552,052	562,718	578,698	587,284	606,217	465,032

Gross Cost Figures for Drugs	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	YTD Sum
Total Amount Paid (FFS & Encounter)	$34,989,069	$33,786,664	$32,572,219	$40,814,777	$40,396,459	$45,057,635	$43,007,870	$46,687,895	$49,487,453	$48,664,970	$46,417,807	$48,605,863	$510,488,682
Mental Health Carve-Out Drugs	$8,228,070	$7,434,555	$7,908,255	$8,909,345	$8,431,666	$9,406,072	$9,878,415	$10,180,519	$10,280,352	$10,912,213	$10,583,208	$11,065,347	$113,218,017
OHP Basic with Medicare	$21,032	$13,060	$11,010	$9,185	$12,723	$13,217	$10,812	$13,664	$9,967	$4,554	$5,429	$2,439	$127,092
OHP Basic without Medicare	$6,207,813	$5,634,325	$5,987,747	$6,296,032	$5,682,105	$6,124,056	$6,222,231	$6,157,026	$6,157,731	$6,343,678	$6,055,784	$6,185,055	$73,053,583
ACA	$1,938,459	$1,737,438	$1,849,527	$2,579,847	$2,714,893	$3,247,513	$3,623,543	$3,945,707	$4,026,390	$4,465,257	$4,437,024	$4,783,489	$39,349,086
FFS Physical Health Drugs	$2,336,245	$2,205,473	$2,411,354	$3,591,111	$3,477,027	$3,425,829	$3,325,103	$3,272,659	$3,345,673	$3,389,017	$3,204,229	$3,469,631	$37,453,352
OHP Basic with Medicare	$275,323	$251,918	$272,014	$274,543	$247,826	$268,399	$265,822	$278,671	$269,178	$269,942	$238,961	$242,365	$3,154,961
OHP Basic without Medicare	$1,553,249	$1,457,756	$1,645,484	$1,692,317	$1,616,942	$1,524,786	$1,450,566	$1,430,476	$1,419,594	$1,360,621	$1,242,468	$1,443,862	$17,838,121
ACA	$392,983	$386,911	$377,623	$1,558,343	$1,535,123	$1,562,221	$1,522,838	$1,476,174	$1,569,183	$1,662,062	$1,635,440	$1,701,500	$15,380,402
FFS Physician Administered Drugs	$1,175,394	$1,025,838	$839,384	$1,637,395	$1,239,927	$1,399,193	$1,479,468	$1,433,816	$1,558,845	$1,332,397	$1,465,874	$1,737,354	$16,324,886
OHP Basic with Medicare	$160,967	$156,020	$126,724	$166,564	$123,633	$172,532	$199,609	$130,719	$190,627	$175,086	$145,306	$150,519	$1,898,305
OHP Basic without Medicare	$605,503	$421,141	$427,158	$568,065	$471,715	$419,892	$634,467	$441,678	$556,472	$420,667	$438,046	$489,081	$5,893,884
ACA	$123,621	$162,720	$64,444	$572,136	$373,147	$590,348	$429,263	$635,807	$586,935	$536,620	$651,380	$888,847	$5,615,270
Encounter Physical Health Drugs	$18,864,117	$19,144,092	$17,421,121	$21,210,665	$22,207,060	$25,883,793	$22,780,833	$25,823,801	$28,469,672	$26,306,441	$25,429,131	$26,340,006	$279,880,731
OHP Basic with Medicare	$230,974	$194,496	$243,784	$258,108	$223,819	$188,071	$155,957	$174,266	$195,036	$175,063	$173,705	$176,557	$2,389,836
OHP Basic without Medicare	$12,398,844	$12,485,718	$11,419,862	$12,265,529	$12,084,098	$13,310,839	$11,259,572	$12,234,209	$13,097,151	$12,015,504	$11,072,208	$11,157,680	$144,801,215
ACA	$6,074,397	$6,284,816	$5,627,659	$8,562,162	$9,811,837	$12,275,282	$11,187,009	$13,096,015	$14,827,671	$13,828,931	$13,927,625	$14,750,687	$130,254,092
Encounter Physician Administered Drugs	$4,385,244	$3,976,707	$3,992,106	$5,466,260	$5,040,779	$4,942,748	$5,544,051	$5,977,100	$5,832,910	$6,724,903	$5,735,365	$5,993,525	$63,611,697
OHP Basic with Medicare	$118,215	$85,537	$101,802	$240,738	$209,181	$179,585	$191,172	$220,737	$173,064	$171,693	$139,488	$84,300	$1,915,512
OHP Basic without Medicare	$2,596,096	$2,410,267	$2,386,240	$2,963,357	$2,369,751	$2,175,818	$2,346,217	$2,521,636	$2,463,930	$3,206,326	$2,378,323	$2,255,887	$30,073,850
ACA	$963,682	$853,257	$923,188	$1,584,409	$1,931,865	$2,217,377	$2,587,259	$2,895,037	$2,963,611	$3,136,528	$3,022,246	$3,413,340	$26,491,799

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion

Last Updated: April 24, 2015

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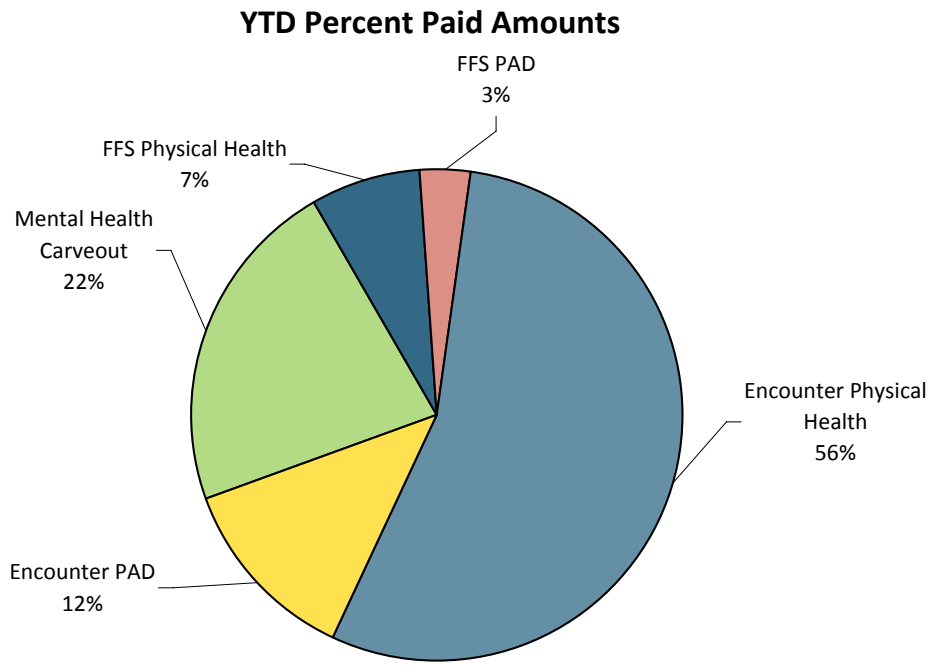
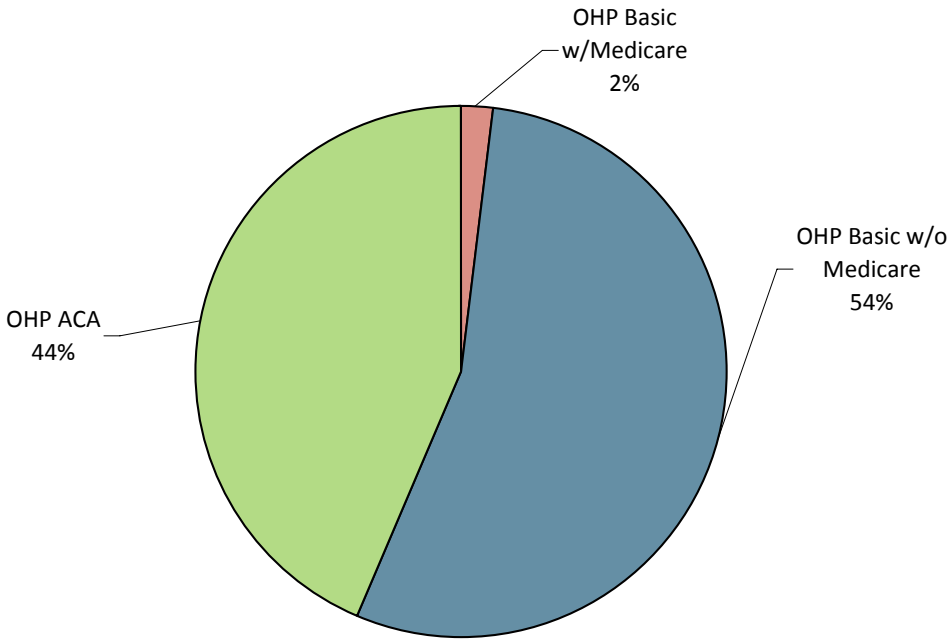
Pharmacy Utilization Summary Report: October 2013 - September 2014





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

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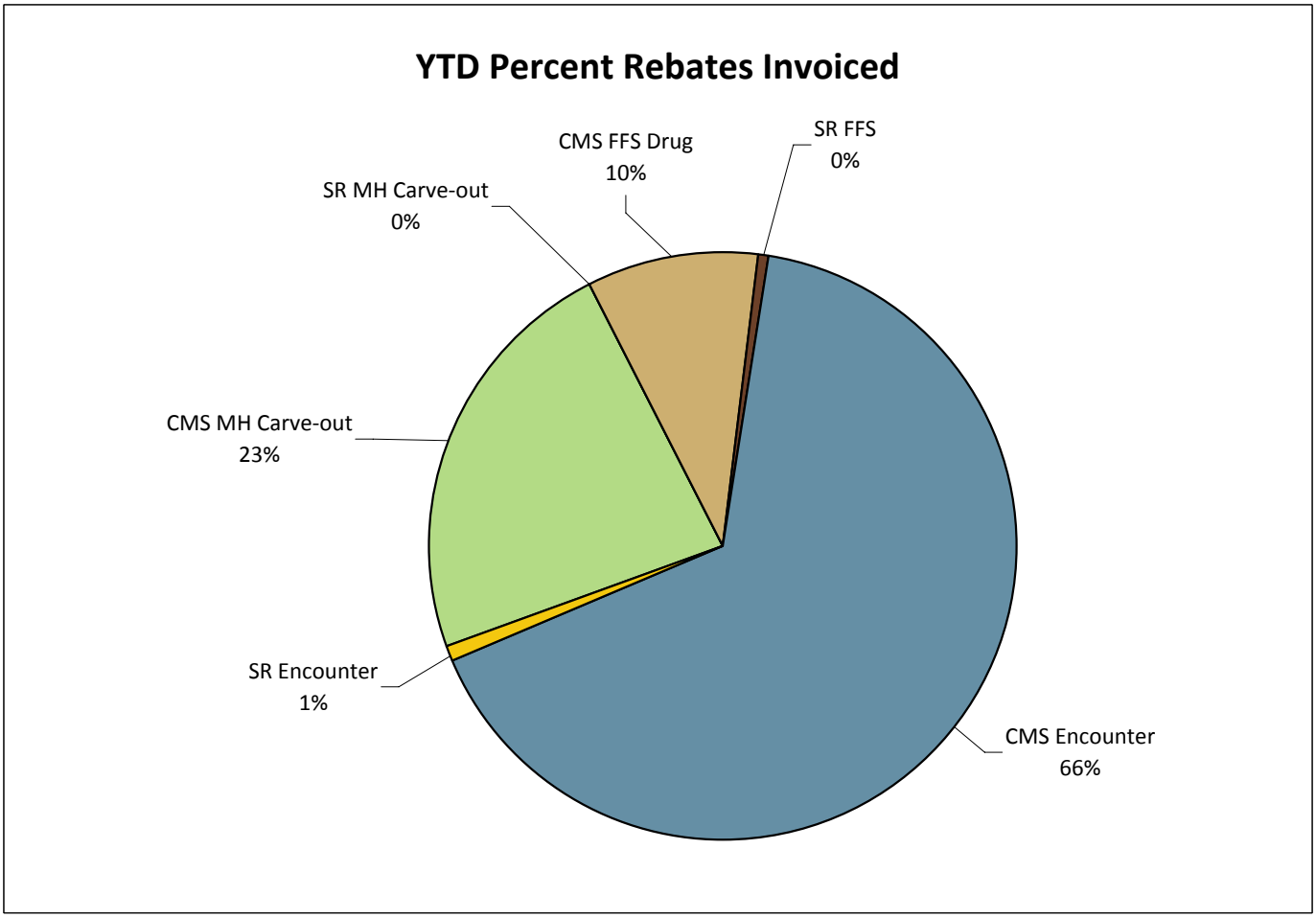
Pharmacy Utilization Summary Report: October 2013 - September 2014

Quarterly Rebates Invoiced	2013-Q4	2014-Q1	2014-Q2	2014-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$40,974,375	$54,275,882	$68,530,791	$72,424,461	$236,205,509
CMS MH Carve-out	$11,801,015	$12,860,015	$14,577,339	$15,224,248	$54,462,618
SR MH Carve-out			$62,707		$62,707
CMS FFS Drug	$4,206,159	$5,906,347	$6,079,980	$6,342,755	$22,535,240
SR FFS	$189,687	$479,375	$220,540	$206,805	$1,096,407
CMS Encounter	$24,496,481	$34,539,342	$46,913,964	$50,068,881	$156,018,667
SR Encounter	$281,034	$490,802	$676,262	$581,772	$2,029,870

Quaterly Net Drug Costs	2013-Q4	2014-Q1	2014-Q2	2014-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$60,373,578	$71,992,990	$70,652,427	$71,264,180	$274,283,174
Mental Health Carve-Out Drugs	$11,769,865	$13,887,068	$15,699,240	$17,336,519	$58,692,692
FFS Phys Health + PAD	$5,597,842	$8,384,761	$8,115,045	$8,048,943	$30,146,591
Encounter Phys Health + PAD	$43,005,871	$49,721,161	$46,838,141	$45,878,718	$185,443,891



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

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PMPM Drug Costs (Excludes Rebate)	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$56.26	$54.24	$53.12	$49.81	$47.39	$50.10	$46.09	$48.54	$51.05	$49.61	$46.58	$48.25	$50.09
Mental Health Carve-Out Drugs	$13.23	$11.93	$12.90	$10.87	$9.89	$10.46	$10.59	$10.58	$10.61	$11.13	$10.62	$10.99	$11.15
FFS Physical Health Drugs	$31.13	$28.99	$30.35	$25.63	$25.98	$21.99	$24.21	$23.59	$24.43	$25.60	$22.86	$25.80	$25.88
FFS Physician Administered Drugs	$15.66	$13.48	$10.56	$11.69	$9.27	$8.98	$10.77	$10.33	$11.38	$10.07	$10.46	$12.92	$11.30
Encounter Physical Health Drugs	$34.49	$35.01	$32.64	$31.22	$30.90	$34.81	$28.62	$31.37	$34.20	$31.00	$29.69	$30.18	$32.01
Encounter Physician Administered Drugs	$8.02	$7.27	$7.48	$8.05	$7.01	$6.65	$6.97	$7.26	$7.01	$7.93	$6.70	$6.87	$7.27

Claim Counts	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Total Claim Count (FFS & Encounter)	674,493	617,750	591,560	758,586	750,235	865,104	880,481	896,426	907,511	871,517	835,711	862,221	792,633
Mental Health Carve-Out Drugs	97,399	89,093	93,661	113,662	109,872	124,562	130,353	134,489	134,057	140,514	136,740	142,299	120,558
FFS Physical Health Drugs	63,980	57,440	60,745	77,608	71,057	78,835	77,238	79,600	79,563	78,059	76,258	78,616	73,250
FFS Physician Administered Drugs	7,993	7,465	7,541	18,150	14,803	15,078	15,214	14,079	13,249	12,771	12,574	11,408	12,527
Encounter Physical Health Drugs	462,603	425,398	391,809	488,571	498,641	581,583	583,334	592,721	606,714	565,660	540,585	560,516	524,845
Encounter Physician Administered Drugs	42,518	38,354	37,804	60,595	55,862	65,046	74,342	75,537	73,928	74,513	69,554	69,382	61,453

Amount Paid per Claim (Excludes Rebate)	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$51.87	$54.69	$55.06	$53.80	$53.85	$52.08	$48.85	$52.08	$54.53	$55.84	$55.54	$56.37	$53.71
Mental Health Carve-Out Drugs	$84.48	$83.45	$84.43	$78.38	$76.74	$75.51	$75.78	$75.70	$76.69	$77.66	$77.40	$77.76	$78.67
FFS Physical Health Drugs	$36.52	$38.40	$39.70	$46.27	$48.93	$43.46	$43.05	$41.11	$42.05	$43.42	$42.02	$44.13	$42.42
FFS Physician Administered Drugs	$147.05	$137.42	$111.31	$90.21	$83.76	$92.80	$97.24	$101.84	$117.66	$104.33	$116.58	$152.29	$112.71
Encounter Physical Health Drugs	$40.78	$45.00	$44.46	$43.41	$44.54	$44.51	$39.05	$43.57	$46.92	$46.51	$47.04	$46.99	$44.40
Encounter Physician Administered Drugs	$103.14	$103.68	$105.60	$90.21	$90.24	$75.99	$74.57	$79.13	$78.90	$90.25	$82.46	$86.38	$88.38

Amount Paid per Claim - Multi Source Drugs (Excludes Rebate)	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.76	$24.14	$23.69	$23.62	$23.58	$22.96	$21.13	$22.51	$22.81	$22.51	$22.82	$22.90	$22.95
Mental Health Carve-Out Drugs	$39.55	$39.28	$38.63	$38.21	$37.16	$36.93	$37.12	$37.30	$37.59	$38.89	$38.68	$39.25	$38.22
FFS Physical Health Drugs	$20.70	$20.92	$21.69	$22.26	$21.98	$21.42	$21.51	$21.74	$21.76	$21.82	$21.95	$21.86	$21.63
Encounter Physical Health Drugs	$19.60	$21.48	$20.52	$20.42	$20.82	$20.18	$17.51	$19.26	$19.67	$18.53	$18.92	$18.86	$19.65

Amount Paid per Claim - Single Source Drugs (Excludes Rebate)	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$314.94	$348.01	$358.16	$358.74	$394.07	$397.31	$367.50	$396.64	$427.17	$439.29	$433.30	$414.01	$387.43
Mental Health Carve-Out Drugs	$480.01	$480.56	$486.70	$586.34	$591.90	$586.72	$588.67	$587.92	$601.58	$604.29	$603.87	$597.73	$566.36
FFS Physical Health Drugs	$213.68	$241.05	$246.65	$308.52	$347.28	$297.45	$307.10	$281.26	$294.58	$308.01	$293.65	$307.61	$287.24
Encounter Physical Health Drugs	$284.91	$326.82	$335.07	$317.27	$357.73	$371.78	$326.46	$369.68	$407.56	$418.65	$412.29	$387.13	$359.61

Multi-Source Drug Use Percentage	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Multi-Source Drug Use Percentage	91.6%	91.9%	91.9%	92.3%	92.8%	93.0%	93.0%	93.0%	92.9%	93.0%	92.9%	92.5%	92.6%
Mental Health Carve-Out Drugs	89.8%	90.0%	89.8%	92.7%	92.9%	93.0%	93.0%	93.0%	93.1%	93.1%	93.1%	93.1%	92.2%
FFS Physical Health Drugs	91.8%	92.1%	92.0%	91.6%	91.7%	92.0%	92.5%	92.5%	92.6%	92.5%	92.6%	92.2%	92.2%
Encounter Physical Health Drugs	92.0%	92.3%	92.4%	92.3%	93.0%	93.1%	93.0%	93.1%	93.0%	93.0%	92.9%	92.4%	92.7%

Preferred Drug Use Percentage	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Avg Monthly
Preferred Drug Use Percentage	84.60%	84.51%	84.42%	85.97%	86.02%	86.28%	86.23%	85.91%	86.01%	86.09%	86.01%	86.38%	85.7%
Mental Health Carve-Out Drugs	70.92%	71.09%	71.12%	74.11%	74.36%	74.46%	74.46%	73.35%	73.24%	73.11%	73.04%	75.81%	73.3%
FFS Physical Health Drugs	91.47%	91.34%	91.46%	93.73%	93.56%	93.56%	93.57%	93.66%	93.87%	94.35%	94.55%	94.44%	93.3%
Encounter Physical Health Drugs	87.14%	86.99%	87.21%	87.97%	87.92%	88.21%	88.29%	88.16%	88.22%	88.36%	88.28%	88.14%	87.9%

Last Updated: April 24, 2015

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

Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2015

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$11,634,299	25.3%	12,729	$914	V
2	LATUDA	Antipsychotics, 2nd Gen	$1,912,130	4.2%	2,546	$751	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,786,099	3.9%	3,025	$590	V
4	STRATTERA	ADHD Carve Out Drugs	$1,539,699	3.3%	4,930	$312	Y
5	INVEGA SUSTENNA	Injectable Antipsychotics	$981,441	2.1%	701	$1,400	V
6	INTUNIV	ADHD Carve Out Drugs	$916,330	2.0%	3,034	$302	V
7	DULOXETINE HCL	Antidepressants	$878,362	1.9%	21,982	$40	V
8	BUPROPION XL	Antidepressants	$807,136	1.8%	15,013	$54	V
9	INVEGA	Antipsychotics, 2nd Gen	$796,335	1.7%	896	$889	V
10	GUANFACINE HCL ER	ADHD Carve Out Drugs	$703,889	1.5%	2,824	$249	V
11	DIVALPROEX SODIUM ER	Antiepileptics	$631,535	1.4%	4,070	$155	Y
12	FLUOXETINE HCL	Antidepressants	$485,921	1.1%	30,603	$16	Y
13	LAMOTRIGINE ER	Antiepileptics	$464,228	1.0%	912	$509	V
14	SERTRALINE HCL	Antidepressants	$432,345	0.9%	35,299	$12	Y
15	PRISTIQ ER	Antidepressants	$371,077	0.8%	1,522	$244	V
16	AMITRIPTYLINE HCL	Antidepressants	$366,774	0.8%	17,696	$21	Y
17	SAPHRIS	Antipsychotics, 2nd Gen	$363,888	0.8%	700	$520	V
18	Factor Viii Recombinant Nos	Physican Administered Drug	$350,108	0.8%	10	$35,011	
19	TRAZODONE HCL	STC 11 - Psychostimulants, Antidepressants	$345,811	0.8%	36,365	$10	
20	ZIPRASIDONE HCL	Antipsychotics, 2nd Gen	$320,816	0.7%	3,228	$99	V
21	ABILIFY MAINTENA	Injectable Antipsychotics	$305,188	0.7%	201	$1,518	V
22	HARVONI	Hepatitis C	$283,567	0.6%	9	$31,507	N
23	CITALOPRAM HBR	Antidepressants	$276,695	0.6%	31,465	$9	Y
24	LAMOTRIGINE	Antiepileptics	$271,714	0.6%	19,195	$14	Y
25	BUPROPION HCL SR	Antidepressants	$270,699	0.6%	12,034	$22	Y
26	MODAFINIL	ADHD Carve Out Drugs	$265,633	0.6%	728	$365	V
27	LANTUS	Insulins	$265,614	0.6%	837	$317	Y
28	HUMIRA	Targeted Immune Modulators	$261,325	0.6%	102	$2,562	Y
29	RISPERDAL CONSTA	Injectable Antipsychotics	$257,537	0.6%	367	$702	V
30	VIIBRYD	Antidepressants	$252,627	0.5%	1,286	$196	V
31	VENLAFAXINE HCL ER	Antidepressants	$249,836	0.5%	13,233	$19	Y
32	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$242,928	0.5%	11,326	$21	Y
33	Erwinaze Injection	Physican Administered Drug	$240,607	0.5%	17	$14,153	
34	VENLAFAXINE HCL ER	Antidepressants	$236,478	0.5%	1,606	$147	V
35	PROAIR HFA	Asthma Rescue	$224,242	0.5%	4,290	$52	Y
36	ESCITALOPRAM OXALATE	Antidepressants	$224,138	0.5%	15,940	$14	Y
37	CLOZAPINE	Antipsychotics, 2nd Gen	$207,167	0.5%	2,496	$83	Y
38	SOVALDI	Hepatitis C	$205,188	0.4%	9	$22,799	Y
39	LORAZEPAM	Benzodiazepine Anxiolytics	$204,831	0.4%	21,068	$10	
40	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$201,032	0.4%	11,260	$18	
		Top 40 Aggregate:	**$31,035,268**		**345,554**	**$2,916**	
		All FFS Drugs Totals:	**$46,001,401**		**689,632**	**$350**	

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

Last updated: April 24, 2015

ProDUR Report for January through March 2015

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	40	10	0	30	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,960	457	0	1,502	1.67%
DD (Drug/Drug Interaction)	Set alert/Pay claim	265	52	0	213	0.20%
ER (Early Refill)	Set alert/Deny claim	77,463	13,559	81	63,821	68.30%
ID (Ingredient Duplication)	Set alert/Pay claim	20,524	5,005	3	15,499	18.07%
LD (Low Dose)	Set alert/Pay claim	932	177	0	753	0.77%
LR (Late Refill/Underutilization)	Set alert/Pay claim	80	54	1	25	0.00%
MC (Drug/Disease Interaction)	Set alert/Pay claim	1,338	620	0	716	1.13%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,100	274	1	823	0.90%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	2,480	1,504	5	969	2.13%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,128	1,941	0	5,168	6.27%
	Totals	**113,310**	**23,653**	**91**	**89,519**	**99.43%**

ProDUR Report for January through March 2015											
Top Drugs in Early Refill											
DUR Alert	**Drug Name**	**# Alerts**	**# Overrides**	**# Claims Screened**	**% Overrides**	**% Claims Screened Override ER**	**CC-3 Vacation Supply**	**CC-4 Lost Rx**	**CC-5 Therapy Change**	**CC-6 Starter Dose**	**CC-7 Medically Necessary**
ER	Alprazolam	1,489	209	21,662	14.04%	0.96%	10	11	94	0	74
	Amitriptyline	2,034	287	22,009	14.11%	1.30%	11	19	117	2	75
	Aripiprazole (Abilify)	2,323	411	19,364	17.69%	2.12%	11	19	103	4	149
	Atomoxetine (Straterra)	773	93	7,003	12.03%	1.33%	2	6	17	1	45
	Bupropion (Wellbutrin)	3,741	495	39,511	13.23%	1.25%	28	46	110	2	180
	Buspirone (Buspar)	1,494	228	14,339	15.26%	1.59%	9	19	78	1	74
	Citalopram (Celexa)	3,459	407	37,807	11.77%	1.08%	9	18	134	2	166
	Diazepam	814	177	12,016	21.74%	1.47%	5	8	71	1	54
	Divalproex Sodium (Depakote)	1,535	264	13,956	17.20%	1.89%	15	14	86	2	131
	Duloxetine (Cymbalta)	2,936	437	28,157	14.88%	1.55%	14	33	140	2	153
	Escitaloprim (Lexapro)	2,112	257	20,751	12.17%	1.24%	8	22	73	3	88
	Fluoxetine (Prozac)	3,757	538	39,276	14.32%	1.37%	26	40	168	1	191
	Gabapentin	437	104	3,550	23.80%	2.93%	5	2	50	1	40
	Hydrocodone Bit/APAP	281	85	8,312	30.25%	1.02%	2	1	31	0	27
	Lamotrigine (Lamictal)	3,485	588	27,708	16.87%	2.12%	25	24	241	0	231
	Lithium Carbonate	1,158	218	8,307	18.83%	2.62%	7	2	72	2	82
	Lorazepam	1,676	368	25,756	21.96%	1.43%	15	12	140	0	141
	Mirtazapine (Remeron)	1,050	144	8,585	13.71%	1.68%	7	8	45	1	72
	Olanzapine (Zyprexa)	1,744	264	13,800	15.14%	1.91%	8	9	63	1	162
	Oxycodone HCl	300	110	6,187	36.67%	1.78%	1	2	38	0	43
	Paroxetine (Paxil)	1,291	128	14,150	9.91%	0.90%	6	11	43	1	44
	Quetiapine (Seroquel)	2,957	464	20,678	15.69%	2.24%	21	42	133	1	210
	Risperidone (Risperdal)	2,068	337	15,707	16.30%	2.15%	10	19	112	1	157
	Sertraline (Zoloft)	4,819	820	44,685	17.02%	1.84%	30	41	327	5	268
	Trazodone	4,989	751	44,964	15.05%	1.67%	22	40	249	5	300
	Venlafaxine (Effexor)	2,034	252	23,569	12.39%	1.07%	13	24	75	1	90
	Ziprasidone (Geodon)	661	111	4,572	16.79%	2.43%	9	7	31	0	57

Clarification Code & Description	# of Paid Claims	# of Recipients	# of Drugs
None	1,424	930	180
1 - No Override	2	2	2
2 - Other Override	50	47	29
3 - Vacation Supply	444	331	114
4 - Lost Prescription	647	483	133
5 - Therapy Change	3,874	3,362	345
6 - Starter Dose	71	52	48
7 - Medically Necessary	5,340	3,682	494
14 - Long Term Care Leave of Absence	3	2	3
17 - Long Term Care Emergency supply remainder	1	1	1
18 - Long Term Care Patient Admit/Readmit Indicator	19	15	18

Client	# of ER claims	Reason?	Notes
HJ	25	7 - Medically Necessary	OHSU Out-Pt
CB	17	7 - Medically Necessary	OHSU Out-Pt
HW	15	7 - Medically Necessary	Safeway-Portland
IP	13	7 - Medically Necessary	Walmart-Grants Pass (normally payless LTC)
BC	12	5 - Therapy Change	Walmart-Roseburg (normally payless LTC)
AH	11	7 - Medically Necessary	Genoa (mail order)
BR	11	7 - Medically Necessary	Genoa (mail order)
AC	8	7 - Medically Necessary	Care RX (nursing home)
BR	7	7 - Medically Necessary	OHSU Out-Pt
AB	6	7 - Medically Necessary	Central City Concern
AF	4	3 - Vacation Supply	Bend Pill Box
AP	3	4 - Lost Prescription	Rite Aid

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2014 - 2015

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	25	28		
		Profiles Sent	13	17		
		Responses Received	4	0		
		Response Rate	31%	0%		
		Information Useful or Will Change Practice	2	0		
		Patient Not With Office	1	0		
		Already Scheduled	3	0		
		Will Not Schedule	0	0		
		Requested No Future Notifications	0	0		
	Antipsychotic Metabolic Monitoring	Members Identified	639	0		
		Profiles Sent	637	0		
		Members With Response	125	0		
		Response Rate	20%	0		
		Newly Scheduled	38	0		
		Provider Contacted	265	0		
		Provider Responses	56	0		
		Provider Agreed with Recommendation	12	0		
		Patient Not With Office	17	0		
	Polypharmacy	Members Identified	0	254		
		Profiles Sent	0	252		
		Responses Received	0	23		
		Response Rate	0	9%		
		Information Useful or Will Change Practice	0	0		
		Patient Not With Office	0	0		

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500 Summer Street NE, E35, Salem, Oregon 97301-1079
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Retro-DUR Intervention History by Quarter FFY 2014 - 2015

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	158	134		
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	30	24		
	Children under age 18 on any psychotropic	Profiles Reviewed	128	113		
	Children under age 6 on any psychotropic	Profiles Reviewed	8	7		
	Lock-In	Profiles Reviewed	46	7		
		Letters Sent To Providers	3	0		
		Provider Responses	0	0		
		Provider Agreed / Found Info Useful	0	0		
		Locked In	19	2		
	Polypharmacy	Profiles Reviewed	10	56		
		Letters Sent To Providers	1	2		
		Provider Responses	0	0		
		Provider Agreed / Found Info Useful	0	0		

Oregon State University
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Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2014 - 2015

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	1,164	2,583	45%									
Five or more concurrent psychotropics	112	9,762	1%									
Three or more concurrent psychotropics	1,672	9,762	17%									
Two or More Concurrent Antipsychotics	93	9,762	1%									
Under 18 years old on any antipsychotic	2,590	9,762	27%									
Youth five years and younger on psychotropics	173	9,762	2%									

5/15/2015

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 these

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.

Oregon State University
College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

Pediatric Psychotropic Quarterly Report

Fee For Service

Fiscal Year 2014 - 2015

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	306	502	61%									
Five or more concurrent psychotropics	14	2,065	1%									
Three or more concurrent psychotropics	328	2,065	16%									
Two or More Concurrent Antipsychotics	11	2,065	1%									
Under 18 years old on any antipsychotic	503	2,065	24%									
Youth five years and younger on psychotropics	43	2,065	2%									

5/15/2015

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 these

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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Evaluation of High Dose SSRI Initiation in Pediatrics and Young Adults

Laura Davis Pharm.D. Candidate 2016, Megan Herink, Pharm.D., BCPS, Oregon State University College of Pharmacy

There is conflicting evidence in the literature regarding initiation of selective serotonin reuptake inhibitors (SSRIs) and the increase of new-onset of deliberate self-harm (DSH) thoughts and behaviors, or suicidality. In 2004, the Food and Drug Administration (FDA) added a black box warning to the labels of many antidepressants in response to case reports[1] describing increased risk of suicidal thinking and behavior among pediatric patients taking SSRIs.[2] However, other studies disagree with this claim, and the FDA warning led to fewer visits and prescriptions written for depression. A meta-analysis conducted by the FDA in 2006 and a more recent Cochrane systematic review further established this relationship, reporting a statistically significant, moderate increase in suicidality among users of SSRIs aged 24 years and younger.[3] However, until very recently, no study had been conducted to explore an association between DSH and antidepressant dose.[4] This newsletter will summarize recent literature describing dose-related effects of SSRIs in pediatric patients as well as a recent drug use evaluation in the Oregon Medicaid population. Recommendations for SSRIs in pediatric patients, approved by the Oregon Pharmacy and Therapeutics (P&T) Committee in response to these study results, will also be described.

Pediatrics and SSRIs

Miller et al. recently published the results of a large propensity score-matched, retrospective cohort study that examined how antidepressant dose at initiation of therapy affected resultant risk of DSH.[4] This study involved 162,625 patients aged 10-64 years who had been diagnosed with depression and were initiating one of three SSRIs (citalopram, fluoxetine, or sertraline). Doses were categorized as modal, lower than modal, or higher than modal relative to the overall distribution of doses prescribed for study participants. Modal doses for each SSRI included in this study are defined in Table 1. Analyses were limited to patients prescribed modal (n=32,504) or higher than modal doses (n=7117).

Table 1. Modal Doses of Antidepressants[4]

Citalopram	20 mg/day
Sertraline	50 mg/day
Fluoxetine	20 mg/day

Overall, 13.1% of patients aged 10-24 years were initiated on a higher than modal SSRI dose. A total of 142 of the 21,305 modal or high dose participants aged 10-24 years engaged in DSH in the year after starting treatment (68 of whom were prescribed a modal dose and 74 a higher than modal dose). Among patients in this age group, those initiated on higher than modal SSRI doses were significantly more likely to engage in DSH than were their counterparts initiated on modal doses (HR, 2.2; 95% CI, 1.6-3.0). For every 1,000 patients in this age group initiating high dose SSRIs, researchers found approximately 7 more instances of DSH over the first 90 days of treatment, as compared to those initiating with a modal dose (NNH=136). No statistically significant relationship between dose and DSH was noted for patients aged 25-64 years. Miller concluded that these results provide strong evidence against initiating high-dose antidepressant therapy in adolescents and young adults with depression.[4] In addition, very limited evidence exists to demonstrate that greater antidepressant doses produce greater relief of depressive symptoms.[5-8] For instance, one meta-analysis of 33 relevant studies reported that higher doses were not accompanied by increased efficacy, and that adverse events significantly increased with dose.[7]

Drug Use Evaluation

Due to the results of the Miller study, a drug use evaluation was subsequently undertaken to describe the frequency of high dose SSRI initiation in Oregon Medicaid patients under 25 years of age.[9] A cross-sectional study was performed; patients were included if they had a paid claim for a SSRI between April 1, 2013 and March 31, 2014. Patients younger than 5 years (n=19) or those on fluvoxamine (n=31) or paroxetine CR (n=10) were excluded due to small numbers coupled with the lack of definitive dosing recommendations for these treatments.

There were 4,879 patients newly-initiated on one of five SSRIs (citalopram, escitalopram, fluoxetine, immediate-release paroxetine, or sertraline). As in Miller's study, doses were categorized as modal, lower than modal, or higher than modal. However, unlike Miller's paper, which established a single modal dose for each SSRI, modal doses in this study were determined for multiple age groups (5-9, 10-15, 16-19, and 20-24 years). Age-specific and pooled modal doses for SSRIs included in this study are defined in Table 2.

Table 2. Drug Use Evaluation Modal Doses of Antidepressants[9]

SSRI	Age-specific modal dose (mg/day)				Pooled modal dose (mg)
	Age range (years)				
	5-9	10-15	16-19	20-24	
Citalopram	10	10	20	20	20
Escitalopram	5	10	10	10	10
Fluoxetine	10	10	10	20	10
Paroxetine (immediate release)	10	10	20	20	20
Sertraline	25	25	50	50	50

This drug use evaluation reported that 27.0% (n=1301) of patients under age 25 years were initiated on a SSRI above the modal dose, thus increasing these patients' risk of DSH without necessarily increasing therapeutic efficacy. Patients aged 10-15 years were most likely to have been initiated above a modal dose (53.8%), as were patients with a diagnosis of MDD or depression (35.0%). This is especially concerning, because the Miller study, which reported a dose-dependent increase in risk of DSH, focused specifically on MDD patients.

Fluoxetine, sertraline, and citalopram were the most frequent SSRIs initiated (86.9%). Fluoxetine was both the most commonly-prescribed SSRI (33.7%) and the most likely to have been initiated above modal dose (47.2%). There are several possible explanations for this finding; among them, that a lower pooled modal fluoxetine dose was used in this study than was used by Miller (10 mg, as compared to 20 mg, respectively), which could infer differences in our population compared to the population evaluated in the Miller study. Although a fluoxetine dose of 10 mg daily is on the lower side of the recommended starting dose range (Table 3), it is not uncommon for transition age adults (16-25 years) to be initiated on higher doses (20 mg), particularly those with severe depression, due the prolonged half-life of fluoxetine.[9] The use of the lower pooled modal dose in the adolescent age

groups could have led to an increased number of patients categorized as initiated above modal dose. In addition, fluoxetine is first line therapy for depression, has a longer history of use, is FDA approved for pediatric patients and has the most supporting evidence for treatment of MDD and additional indications. Therefore, practitioners may be more comfortable prescribing fluoxetine at higher doses.

It is also important to make note that paroxetine has no FDA approved pediatric uses and based on expert opinion, can cause significant agitation and suicidal ideation.[13] Cessation can also be very different due to withdrawal issues. It may be prudent for only experienced pediatric mental health providers to use initiate paroxetine in children and adolescents. Although rarely prescribed, fluvoxamine has similar safety concerns.

Table 3. Recommended Initial and Maximum Dose in Children and Adolescents[10-12]

	Recommended Initial Dose* (mg)	Recommended Maximum Dose* (mg)
Citalopram	10-20	40
Escitalopram	5-10	20
Fluoxetine	5-20	20-80
Paroxetine** (immediate release)	10-20	50
Sertraline	12.5-50	200

*Doses for MDD or depression were used if listed and other indication doses were used if no MDD or depression dose was available
**No FDA approved indication for pediatric use

Conclusion and Implications to practice

Results of this drug use evaluation identified 27% of Oregon Medicaid patients aged 5 to 24 years were initiated on high-dose SSRI therapy during the study period. The association between SSRI use and increased risk of DSH remains controversial, and the potential DSH risk is quite small compared to the risks of untreated MDD.[9] Recent meta-analyses, cited by Miller, have demonstrated that the antidepressant dose is generally not related to its therapeutic efficacy.[4-8] Therefore, Miller proposes that limiting antidepressant dose at initiation is a means by which MDD may be treated, while antidepressant-associated increases in DSH risk may be minimized.[4]

On the basis of the study results described above, and to avoid exposing pediatric, adolescent, and young adult patients to undue risk of self-harm, the Oregon P&T Committee has approved the following recommendations,[9] which will be implemented in April of this year.

1. Initiate a maximum dose prior authorization for patients less than 25 years starting SSRIs (i.e. no prior antidepressant claim in the previous 102 days). Set the dose at the age-specific modal doses used in the drug use evaluation study (Table 2) except increase the fluoxetine dose to 20 mg for 16-19 year olds.

2. Exclude child psychiatrists from the prior authorization requirement.

3. Consider age edit to restrict use of paroxetine and fluvoxamine to adults (>18 years) per expert opinion.

References

1. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry.* 1990; 147(2): 207-210. http://ajp.psychiatryonline.org.liboff.ohsu.edu/doi/pdf/10.1176/ajp.147.2.207. Accessed February 7, 2015.
2. United States Food and Drug Administration. Labeling Change Request Letter for Antidepressant Medications. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm. Accessed February 7, 2015.
3. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry.* 2006; 63(3): 332-339. doi: 10.1001/archpsyc.63.3.332.
4. Miller M, Swanson SA, Azrael D, Pate V, Stürmer T. Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Intern Med.* 2014; 174(6): 899-909. doi: 10.1001/jamainternmed.2014.1053.
5. Bech P, Tanghøj P, Andersen HF, Overø K. Citalopram dose-response revisited using an alternative psychometric approach to evaluate clinical effects of four fixed citalopram doses compared to placebo in patients with major depression. *Psychopharmacology (Berl).* 2002; 163(1): 20-25.
6. Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials. *Br J Psychiatry.* 1999; 174: 297-303.
7. Ruhé HG, Booik J, v Weert HC, Reitsma JB, Franssen EJ, Michel MC, Schene AH. Evidence why paroxetine dose escalation is not effective in major depressive disorder: a randomized controlled trial with assessment of serotonin transporter occupancy. *Neuropsychopharmacology.* 2009; 34(4): 999-1010.
8. 8. Ruhé HG, Huyser J, Swinkels JA, Schene AH. Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: systematic review. *Br J Psychiatry.* 2006; 189: 309-316.
9. Fritsche KC, Herink M, Ketchum K. Drug Use Evaluation: Prevalence of High-dose Initiation of Selective Serotonin Reuptake Inhibitors in the Oregon Medicaid Pediatric, Adolescent, and Young Adult Population. http://www.orpdl.org/durm/meetings/meetingdocs/2014_11_20/finals/PedSSRIInitDoseDUE_final9_10_14.pdf. Accessed February 7, 201**.**
10. Moreland S, Bonin L. Effect of antidepressants on suicide risk in children and adolescents. *Up ToDate [on-line dataase].* Updated August 6th, 2014. http://www.-uptodate-com.liboff.ohsu.edu
11. Pediatric & Neonatal Lexi-Drugs Online™ , In *Lexi-Comp Online [on-line database].* 2014.
12. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC):II. Treatment and Ongoing Management. *Pediatrics.* 2007;120(5):e1313-e1326.
13. Paxil® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2011.

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Combating the Opioid Epidemic: Are Abuse-deterrent Formulations the Answer?

By Kayla Ruhl, Pharm.D. Candidate 2016, OSU College of Pharmacy, and Andrew Gibler, Pharm.D., OSU College of Pharmacy Drug Use Research and Management

Opioid misuse and abuse in the United States (U.S.) has dramatically increased over the past two decades with an estimated 4.5 million people using opioids for nonmedical reasons in 2013.[1] Increases in opioid misuse and abuse is directly correlated with increases in opioid prescribing, emergency department (ED) visits for opioid overdose, inpatient and substance treatment admissions, and opioid-related death.[2–4] Nationwide death rates from accidental opioid overdose now exceed death rates from suicide and motor vehicle accidents combined.[3] Of great public health concern are the number of women of reproductive age on opioids, most of which are enrolled in Medicaid programs, considering the well documented adverse neonatal outcomes associated with opioid use.[5]

Oregon currently leads the nation in nonmedical use of opioids for all age groups.[6] More than 900,000 Oregonians received an opioid prescription in 2012. Of the 1,500 hospitalizations related to drug abuse, nearly one-third were due to opioids. Opioid-related deaths in Oregon mirror national rates with a slight decline in 2012; however, death rates remain 2.5-times higher than rates in 2000.[7]

The risk of unintentional opioid overdose appears to be higher with long-acting (LA) opioids compared to short-acting (SA) opioids. In a population of U.S. Veterans, those prescribed a LA opioid were 2.5-times more likely to experience an unintentional overdose. The risk of unintentional overdose was greatest during the first two weeks following initiation when risk with LA opioids was 5-times higher than SA opioids.[8]

Actions to Address Opioid Misuse and Abuse

In response to the opioid epidemic, many interventions at the state and federal levels have been implemented. In 2012, the Food and Drug Administration (FDA) implemented a risk evaluation and mitigation strategy (REMS) for LA opioid products. In 2014, FDA Draft Guidance was released to assist industry in developing abuse-deterrent opioids and a Public Advisory Committee recommended changing hydrocodone products to Schedule II under the Controlled Substances Act.[9] Subsequently, the Drug Enforcement Agency accepted the recommendation with the rule taking effect last October.[10]

According to the FDA, an important step toward controlling opioid abuse is to formulate opioids in abuse-deterrent formulations (ADF) to overcome known or expected mechanisms of abuse.[11] Two properties of ADFs on the market include physical barriers to crushing, chewing and extraction, and opioids sequestered with opioid antagonists. Table 1 identifies the five opioids with ADFs currently approved to contain labeling describing the product's abuse-deterrent properties consistent with the 2014 FDA draft guidance.

Table 1. Current Long-acting Opioids with Abuse-Deterrent Formulations

Drug	Abuse-Deterrent Properties
OxyContin[12] (oxycodone)	Upon tampering, forms a viscous gel when crushed or dissolved that resists passage through a hypodermic needle
Targiniq ER[13] (oxycodone and naloxone)	Upon manipulation, naloxone will block the euphoric effects of oxycodone
Embeda[14] (morphine and naltrexone)	Upon manipulation, naltrexone will block the euphoric effects of morphine
Hysingla ER[15] (hydrocodone)	Upon tampering, forms a viscous gel when crushed or dissolved that resists passage through a hypodermic needle
Zohydro ER[16] (hydrocodone)	Upon tampering, forms a viscous gel when crushed or dissolved that resists passage through a hypodermic needle

At the state level, Prescription Drug Monitoring Programs (PDMPs) have been implemented to collect dispensing data on opioids and other controlled substances. Currently, 48 states have an actively operating PDMP.[17] The goals and requirements of individual PDMPs vary by state, but in general are designed to help identify sources of prescription diversion, inappropriate prescribing and dispensing, and provide practitioners, law enforcement and public health officials with applicable information.[17,18]

The Oregon PDMP requires pharmacies to submit data weekly for all schedule II-IV controlled substances and is accessible to prescribing health care professionals, pharmacists and their delegated office staff in Oregon and neighboring states.[19] To obtain further information regarding the Oregon PDMP or to apply for access, visit orpdmp.com/health-care-provider/.

Additional interventions have been implemented at the institutional level. In accordance with the guidelines developed by the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM)[20], many clinicians now include use of risk assessment tools, informed consent, opioid management plans and urine drug screening in their practice.[20]

It remains unclear which interventions, if any, are making an impact so far. A recent systematic review found inconsistent evidence regarding the use of risk assessment instruments for predicting opioid abuse or misuse and found no studies evaluating the effectiveness of risk mitigation strategies such as the use of PDMPs.[21]

Evidence for Decreased Abuse and Misuse of LA Opioids

The evidence for effectiveness of ADFs to limit abuse in real world populations is limited. Most information available comes from observations, surveys and expert opinion,[22–26] many of which are conducted by the pharmaceutical industry. Indeed, a review of data submitted to the FDA reveal evidence for "drug-liking" and "drug highs" in non-dependent recreational opioid users are limited to single-dose studies.

Purdue Pharma, the manufacturer of the reformulated OxyContin, utilized the National Poison Data System (NPDS) and found rates of intentional opioid abuse decreased by 36% (95% CI, -40 to -23%) the first two years after the product was introduced to market, but at the expense of a significant increase in cases of intentional heroin abuse.[27] A similar study utilizing data from Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) systems also found rates of heroin-related deaths increased from 2011 to 2013 and was inversely related to opioid availability.[28]

A subsequent study utilizing data from the RADARS system in conjunction with data from Poison Center and Drug Diversion programs, found similar results with regard to abuse exposures and therapeutic errors. The study found diversion reports declined 53% (95% CI, -63 to -41%). Additionally, the study determined the street price of OxyContin fell 22% (95% CI, -33 to -9%) after abuse-deterrent reformulation of OxyContin.[26]

Implications to Practice

Chronic non-cancer pain is common and increasingly treated with opioids.[21] However, there is low-quality evidence to support their use long-term.[20] A recent systematic review funded by the Agency for Health care Research and Quality (AHRQ) was unable to find a single study evaluating the outcomes of long-term opioid therapy on pain, function, or quality of life and concluded there is insufficient evidence to determine the effectiveness of long-term opioid therapy for chronic pain. The AHRQ review was able to find a plethora of low-quality studies evaluating the harms associated with opioids used for the treatment of chronic non-cancer pain. Use of opioids was

associated with significant increases in opioid overdose, opioid abuse and dependence, bone fractures, myocardial infarction, and increased use of medications to treat sexual dysfunction.[21]

Treatment of chronic pain should include a stepwise approach first utilizing non-pharmacologic therapies before progressing to non-opioid drugs and only progressing to opioid therapy if clinically appropriate and necessary.[29] The joint guideline developed by APS and AAPM aims to promote the safe and effective use of chronic opioid therapy for chronic non-cancer pain and includes multiple recommendations with regard to risk stratification, initiation, titration and monitoring and therapy discontinuation.[20]

Conclusion

The development of ADFs is a public health priority for the FDA though robust data evaluating strategies to deter opioid abuse are lacking. Clinicians should not be misguided to assume opioids are now safe. ADFs will only be effective in persons engaging in very high risk behaviors such as snorting, crushing or shooting up. Most overdoses are likely accidental when too high a dose is consumed without engaging in these high risk behaviors. There may be some progress, however, as rates of opioid overdoses and deaths have declined since 2011.[27,28] It is unlikely ADFs are solely responsible for this favorable trend as the institution of PDMPs, REMS, and increasing media coverage may also create awareness of this epidemic. Unfortunately, increased use of heroin may be the unintended consequence, a concerning trend that requires further investigation.

There is still a lack of quality evidence regarding the long-term effectiveness of LA opioids for the management of chronic non-cancer pain. LA opioids may be the best option for a subset of patients with chronic pain, but alternative effective treatments for many patients are available.[29] LA opioids use should be based on the benefits to patient functioning and quality of life compared to the risk of treatment. If opioids are necessary, using SA opioids at the lowest effective dose should be a consistent goal of therapy.[8]

Peer Reviewed By: Roger Chou, M.D., Director of the Pacific Northwest Evidence-based Practice Center and Professor of Medicine at the OHSU School of Medicine and Stacy Ramirez, Pharm D, Clinical Assistant Professor, OSU College of Pharmacy and Director of Pharmacy, Community Health Centers of Benton and Linn Counties.

References:

1. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf. Accessed 1 March 2015.
2. Yokell M, Delgado M, Zaller N, et al. Presentation of prescription and nonprescription opioid overdoses to US emergency departments. *JAMA Internal Medicine*. 2014; 174:2034-2037. http://archinte.jamanetwork.com.liboff.ohsu.edu/article.aspx?articleid=1918924. Accessed 1 March 2015.
3. Behavioral Health Coordinating Committee Prescription Drug Abuse Subcommittee. Addressing Prescription Drug Abuse in the United States: Current activities and future opportunities. http://www.cdc.gov/HomeandRecreationalSafety/pdf/HHS_Prescription_Drug_Abuse_Report_09.2013.pdfHHS_Prescription_Drug_Abuse_Report_09.2013.pdf. Accessed 4 March 2015.
4. CDC Vitalsigns: Prescription Painkiller Overdoses in the US. Centers for Disease Control and Prevention Website. http://www.cdc.gov/vitalsigns/pdf/2011-11-vitalsigns.pdf. Published November 2011. Accessed 7 March 2015.
5. Ailes E, Dawsom A, Lind J, et al. Opioid prescription claims among women of reproductive age -United States, 2008–2012.*Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report*. 2015;64:37-46.
6. Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality. The NSDUH Report: State Estimates of Nonmedical Use of Prescription Pain Relievers. January 8, 2013. http://archive.samhsa.gov/data/2k12/NSDUH115/sr115-nonmedical-use-pain-relievers.htm. Accessed 4 March 2015.
7. Oregon Health Authority Center for Prevention & Health Promotion, Injury & Violence Prevention Section. Drug Overdose Deaths, Hospitalizations, Abuse & Dependency among Oregonians. Published May 30, 2014; 1-89.
8. Miller M, Barber C, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Internal Medicine*. 2015; E1-8. http://archinte.jamanetwork.com. Accessed 1 March 2015.
9. Timeline of Selected FDA Activities & Significant Events Addressing Opioid Misuse & Abuse. Food and Drug Administration Website. http://www.fda.gov/downloads/Drugs/DrugSafety/InfromationbyDrugClass/UCM332288.pdf. Updated 2015. Accessed 2 March 2015.
10. Schedules of controlled substances: rescheduling of hydrocodone combination products from Schedule III to Schedule II. *Federal Register*. 2014;79(163):49661-682. https://www.federalregister.gov/articles/2014/08/22/2014-19922/schedules-of-controlled-substances-rescheduling-of-hydrocodone. Accessed 2 March 2015.
11. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry Abuse-Deterrent Opioids -- Evaluation and Labeling. Food and Drug Administration Website. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. Updated January 2013. Accessed 2 March 2015.
12. Oxycontin (oxycodone HCl controlled-release) [product information]. Stamford, CT: Purdue Pharma L.P, November 2007.
13. Targiniq (oxycodone HCl and Naloxone HCl extended-release) [product information]. Stamford, CT: Purdue Pharma L.P, July 2014.
14. FDA approves labeling with abuse-deterrent features for third extended-release opioid analgesic. Food and Drug Administration Website. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm. Updated October 2014. Accessed 2 March 2015.
15. Hysingla ER (hydrocodone bitartate) [product information]. Stamford, CT: Purdue Pharma L.P, 2014.
16. Zohydro (hydrocodone extended-release) [product information]. San Diego, CA: Zogenix, 2015.
17. Briefing on PDMP Effectiveness. PDMP Center of Excellence Website. http://www.pdmpexcellence.org/sites/all/pdfs/Briefing%20on%20PDMP%20Effectiveness%203rd%20revision.pdf. Updated September 2014. Accessed 2 March 2015.
18. Cobaugh D, Gainor C, Gaston C, et al. The opioid abuse and misuse epidemic: implications for pharmacists in hospitals and health systems. *American Journal of Health-System Pharmacists*. 2014;71:1539-1554.
19. Oregon Prescription Drug Monitoring Program Website. http://www.orpdmp.com/. Updated 2015. Accessed 2 March 2015.
20. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The Journal of Pain: official journal of the American Pain Society*. 2009;10(2):113-130.
21. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health pathways to prevention workshop. *Annals of Internal Medicine*. 2015;162(4):276-286.
22. Sellers EM, Perrino PJ, Colucci SV, et al. Attractiveness of reformulated OxyContin® tablets: assessing comparative preferences and tampering potential [abstract]. *Journal of Psychopharmacology*. 2013;27(9):808-816.
23. Cassidy TA, DasMahapatra P, Black RA, et al. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. *Pain Medicine*. 2014;15(3):440-451.
24. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. *The New England Journal of Medicine*. 2012;367(2):187-189.
25. Jamison RN. Is there support for abuse-deterrent and tamper-resistant opioid formulations? *The Journal of Pain*. 2013;14(4):359-360.
26. Severtson SG, Bartelson BB, Davis JM, et al. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *The Journal of Pain*. 2013;14(10):1122-1130.
27. Coplan PM, Kale H, Sandstrom L, et al. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiology & Drug Safety*. 2013;22(12):1274-1282.
28. Dart RC, Surratt HL, Cicero TJ, et al. Trends in Opioid Analgesic Abuse and Mortality in the United States. *New England Journal of Medicine*. 2015;372(3):241-248.
29. Reuben DB, Alvanzo AAH, Ashikaga T, et al. National Institutes of Health pathways to prevention workshop: the role of opioids in the treatment of chronic pain. *Annals of Internal Medicine*. 2015;162(4):295-300.

Hepatitis C Direct-Acting Antivirals

Goal(s):

- Approve cost effective treatments of chronic Hepatitis C, which are supported by the medical literature when there is available evidence.
- Treat the patient population in greatest need of treatment and who will benefit the most from therapy.
- Provide consistent patient evaluations across all hepatitis C treatments.

Length of Authorization:

- 8-12 weeks

Requires PA:

- All drug regimens in the Hepatitis C PDL Class

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for treatment of Chronic Hepatitis C Virus?	**Yes:** Go to #3	**No:** Pass to RPh; deny for appropriateness.
3. What regimen is requested?	**Document and Go to #4.**	
4. Does the regimen contain a drug not yet reviewed by P&T?	**Yes:** Go to #5	**No:** Go to #6
5. Will the prescriber change to a preferred product already reviewed for efficacy and safety by the P&T Committee?	**Yes:** Inform Provider of covered alternatives in class	**No:** Pass to RPh; deny for appropriateness. Forward to DMAP for further review to determine appropriateness and coverage in light of most recent community standards and comorbidity.

Approval Criteria		
6. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?	**Yes:** Go to #7.	**No:** Pass to RPh; deny for appropriateness. Forward to DMAP for further review to determine appropriateness of prescriber.
7. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score between 8 and 11), and expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #8.	**No:** Go to #9. **Note:** Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director. If patient has Metavir F0-F2, a treatment option remains pegylated interferon and ribavirin; refer to that specific PA Criteria
8. Does the patient have decompensated cirrhosis?	**Yes:** Pass to RPh; deny for appropriateness	No: Go to #11
9. Does the patient have one of the following extrahepatic manifestations of hepatitis C and who have formal documentation from a relevant specialist that their condition is HCV related, and expected survival from non-HCV associated morbidity should be greater than 5 years? a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis) b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis	**Yes:** Go to #11.	**No:** Go to 10.

Approval Criteria		
10. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios: a) Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b) Post-transplant patients with Stage 4 fibrosis c) Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection **And** expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #11.	**No:** Pass to RPh; deny for medical appropriateness. Note: Other scenarios not included can be brought to the Medical Director on a case by case basis.
11. Has the patient been abstinent from IV drug, illicit drugs and marijuana use, AND alcohol abuse for ≥ 6 months? AND If the patient has a history of alcohol abuse, has the patient been abstinent from alcohol use for ≥ 6 months?	**Yes:** Go to #12.	**No:** Pass to RPh; deny for appropriateness.
12. Does the patient have significant renal impairment (CrCl ≤30 mL/min) or end state renal disease (ESRD)?	**Yes:** Pass to RPh; deny for appropriateness.	**No:** Go to #13.
13. Does the patient have a baseline HCV RNA level?	**Yes:** Record value and go to #14	**No:** Pass to RPH. Request provider obtains baseline lab value.
14. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #15.	
15. Is the prescribed drug ledipasvir/sofosbuvir (Harvoni®) and is the regimen and duration appropriate for patient genotype based on the dosing and administration table below?	**Yes:** Approve for 8-12 weeks based on dosing and administration table.	**No:** Go to #16 If prescribed other DAA, encourage prescriber to use our preferred product
16. Is the prescribed drug sofosbuvir (Solvaldi®)?	**Yes:** Go to #17	**No:** Go to #18

Approval Criteria		
17. Does the patient have Genotype 2 hepatitis C infection?	**Yes:** Approve for 12 weeks based on dosing and administration table below	**No:** Go to #18 If prescribed other DAA, encourage prescriber to use our preferred product
18. Is the prescribed drug ombitasvir, paritaprevir, and ritonavir; dasabuvir (Viekira Pak®)?	**Yes:** Go to #19	**No:** Pass to RPh; deny for appropriateness. Encourage prescriber to use our preferred DAA.
19. Has the patient been off all ethinyl estradiol containing products for at least a week OR is willing to discontinue any products one week prior to starting therapy? If the patient is not on any ethinyl estradiol medications, go to #20.	**Yes:** Go to #20	**No:** Pass to RPh; deny for appropriateness.
20. If the patient was or is on any other medications that due to drug-drug interactions are contraindicated with the use of Viekira Pak (See Table 2 below), has the patient stopped this medication at least a week ago or is willing to discontinue this medication (and it is appropriate) at least one week prior to starting therapy? If the patient is not on any medications in Table 2 that are contraindicated, go to #21.	**Yes:** Go to #21	**No:** Pass to RPh; deny for appropriateness.
21. Does the patient have HIV coinfection?	**Yes:** Go to #22	**No:** Go to #23
22. Is the patient not receiving suppressive antiretroviral therapy (who may be at increased risk of HIV-1 protease inhibitor drug resistance) OR on therapy with significant antiretroviral drug-interactions (efavirenz, darunavir/ritonavir, lopinavir/ritonavir, rilpivirine).	**Yes:** Pass to RPh; deny for appropriateness.	**No:** Go to #23

Approval Criteria		
23. Is the patient treatment naïve with or without cirrhosis or treatment experienced without cirrhosis?	**Yes:** Approve for 12 weeks based on appropriate dosing and administration from table below	**No:** Go to #24
24. Has the patient failed previous therapy with a direct acting antiviral?	**Yes:** Pass to RPh; deny for appropriateness. Use of Viekira has not been studied in this population.	**No:** Go to #25
25. If the patient failed previous therapy with peginterferon/ribavirin dual therapy, did the patient relapse or have a partial response?	**Yes:** Approve for 12 weeks based on dosing and administration table below	**No:** Go to #26
26. Does the patient have cirrhosis and had a previous null response to dual therapy with peginterferon and ribavirin therapy or a post-liver transplant patient?	**Yes:** Approve for 24 weeks based on dosing and administration table below	**No:** Pass to RPh; deny for appropriateness. Encourage

Table 1: Dosage and Administration:

Genotype 1			
Naïve	Without Cirrhosis and HCV RNA < 6 million IU/mL	LDV/SOF 1 tablet QDay	8 weeks
	Without Cirrhosis and HCV RNA ≥ 6 million IU/mL	LDV/SOF 1 tablet QDay	12 weeks
	Without Cirrhosis; Genotype 1b	Paritaprevir/R+Ombitasvir+Dasabuvir	12 weeks
	Without Cirrhosis; Genotype 1a	Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks
	With Cirrhosis	LDV/SOF 1 tablet QDay Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks 12 weeks
Experienced	Without Cirrhosis	LDV/SOF 1 tablet QDay Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks 12 weeks
	With Cirrhosis	LDV/SOF 1 tablet QDay + RBV Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks 12 weeks-24 weeks*

Genotype 2			
Naïve and Experienced	With or Without Cirrhosis	SOF 400 mg QDay + RBV	12 weeks**
Genotype 3			
Naïve or Experienced	With or Without Cirrhosis	LDV/SOF 1 tablet QDay + RBV	12 weeks
Genotype 4 and 6			
Naïve or Experienced	With or Without Cirrhosis	LDV/SOF 1 tablet QDay	12 weeks

*24 weeks of therapy with Paritaprevir/R+Ombitasvir+Dasabuvir + RBV should be reserved for treatment experienced, genotype 1a, null responders or post-liver transplant patients
**Previous nonresponders to PEG/RBV with cirrhosis may benefit by extension of therapy to 16 weeks
Abbreviations: LDV/SOF: Ledipasvir and sofosbuvir (Harvoni®); RBV: ribavirin; SOF: sofosbuvir (Sovaldi®)

Table 2: Drugs Contraindicated with Viekira Pak	
Alfuzosin HCL	Methylergonovine
Carbamazepine	St. John's Wort
Phenytoin	Lovastatin
Phenobarbital	Pimozide
Gemfibrozil	Efavirenz
Rifampin	Sildenavil*
Ergotamine	Triazolam
Dihydroergotamine	Midazolam
Ergonovine	

*When dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)

P&T / DUR Action: 3/15(MH); 1/15(MH); 9/14(MH); 1/14(MH)
Revision(s): 3/15, 1/15; 9/14; 7/14; 3/14
Initiated:

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

Drug Use Evaluation: Prevalence of High-dose Initiation of Selective Serotonin Reuptake Inhibitors in the Oregon Medicaid Pediatric, Adolescent, and Young Adult Population

There is conflicting evidence in the literature regarding initiation of selective serotonin reuptake inhibitors (SSRIs) prescribed for major depressive disorder (MDD) and the increase of new-onset of deliberate self-harm thoughts and behaviors, or suicidality. The limitations of the existing evidence include short trial duration, the small number of suicide-related events observed, the different antidepressant types, doses administered and indications across trials and the confounding nature of the underlying mental illness.

As a result of case reports showing an increased risk of suicide-related events with fluoxetine and other SSRIs,[1] the FDA added a black box warning to the label of antidepressants for worsening of depression or suicidal thinking and behavior, suicidality, during initiation or dose titrations.[2] However, other studies disagree with this claim,[3] and the FDA warning led to fewer visits and prescriptions written for depression.[4,5,6,7] Clinicians have since argued the known risk of untreated depression is greater than the potential increased risk in suicidality.

To further evaluate the issue, the FDA conducted a meta-analysis to assess the risk of suicidality associated with antidepressant medication in pediatric and adolescent populations.[8] The rate of suicidality ranged from 0-8% across all trials with SSRIs, with only 1 trial demonstrating a statistically significant increase in suicidality between antidepressants and placebo.[9] SSRIs as a whole demonstrated a statistically significant increased risk for suicidality, (risk ratio [RR] 1.95 95% CI, 1.28-2.98), suicidal ideation, (RR 1.74 95% CI, 1.06-2.86) and suicidality in depression only, (RR 1.66 95% CI, 1.02-2.68).[8] From 17 trials that reported depression rating scales data at baseline and throughout study, there were no significant differences in worsening or emergence of suicidality.[8] Other meta-analyses have reported varying strengths of association[10,11] or no difference[12] between rate of suicide-related events with use of SSRIs compared to placebo. A more recent Cochrane review found an increased risk of suicide-related outcome for those on antidepressants compared to placebo (RR 1.58; 95% CI 1.02 to 2.45).[13]

One recent, large (n= 21,056), well-designed retrospective cohort study demonstrated a dose-related increase in deliberate self-harm among pediatrics, adolescents, and young adults (ages 10-24) initiated on high-dose SSRIs for MDD.[14] The rate of deliberate self-harm was found to be approximately double in the high dose group versus modal dose group (HR 2.2; 95% CI, 1.6-3.0). To date, no study has looked at the prevalence of high-dose initiation of SSRIs in Medicaid patients.

The primary objective of this drug use evaluation is to describe the frequency of high-dose (above modal dose for age group) SSRI initiation in the pediatric, adolescent and young adult Oregon Medicaid population by age group (<5, 5-9, 10-14, 15-19, and 20-24).

METHODS

A cross-sectional study of Oregon Medicaid patients was done. Patients were included if they had a paid claim for a SSRI (Appendix 1) with a service date of April 1, 2013 thru March 31, 2014. Patients were excluded if they were more than 24 years old on the date of the first SSRI claim, if they were covered by Medicare Part D (defined by benefit package BMM or BMD), if they were eligible for fewer than 75% of days in the 12 months prior to the first paid SSRI claim, or if they had a paid claim for any other antidepressant (Appendix 1) in the 12 months prior or concurrently. Patients <5 years old (n=19) or those on fluvoxamine (n=31) and paroxetine CR (n=10) were excluded from further analysis due to small numbers coupled with the lack of definitive dosing recommendations for these groups.

The daily SSRI initiation dose in milligrams was calculated for the first SSRI claim for each patient using the billed

quantity dispensed divided by the "days supply" entered by the pharmacy, resulting in units per day. The units per day were rounded to the nearest half-tablet as it is assumed a patient could only take units accurately in either whole or half-tablet quantity. Fluoxetine 90 mg was not subject to rounding as it is dosed weekly. The units per day were then multiplied by the unit strength to get the daily SSRI initiation dose.

The modal dose was then determined for the overall study population (i.e. pooled population modal dose) and then by age group, age-specific modal dose (Table 1). Patients were considered initiated at "high-dose" if their daily SSRI initiation dose was greater than the modal dose for their age group. The prevalence of high-dose initiation was then explored by age, sex, Caucasian race, SSRI, associated diagnoses, prescriber specialty (Appendix 2) and geographic location.

The recommended maximum daily dose for MDD or depression was determined from UpToDate, [15] Lexi-Comp Online, [16] and a pediatric guideline. [17] Patients were considered initiated at "above maximum recommended dose" if they were above the listed dose. In the case where there was a lack of recommendation for MDD, a recommended maximum daily dose for a different indication was used.

Patients found to be initiated above the recommended maximum dose were manually examined to verify the accuracy of SSRI initiation daily dose calculation by comparing the "days supply" entry to the number of days between fill dates. Those patients found to be entered incorrectly as high-dose or above maximum recommended dose were re-categorized appropriately.

RESULTS

There were 4,879 Oregon Medicaid patients newly initiated on a SSRI that met inclusion and exclusion criteria. Table 1 displays the recommended initial dose, recommended maximum dose, pooled population modal dose, and age-specific modal dose for each SSRI initiated. The pooled and age-specific modal doses did not exceed the recommended initial dose range. For those aged 20-24 years, the fluoxetine age-specific SSRI modal dose (20 mg) was greater than the pooled modal dose (10 mg).

Table 1 – Modal Dose by Medication [15,16,17]

SSRI	Recommended initial dose* (mg)	Recommended maximum dose* (mg)	Pooled population modal dose (mg)	Age – specific modal dose (mg)			
				Age range [years]			
				5 – 9	10 – 15	16 – 19	20 – 24
citalopram	10 – 20	40	20	10	10	20	20
escitalopram	5 – 10	20	10	5	10	10	10
fluoxetine	5 – 20	20 – 80	10	10	10	10	20
paroxetine (immediate release)	10 – 20	50	20	10	10	20	20
sertraline	12.5 – 50	200	50	25	25	50	50

*Doses for MDD or depression were used if listed and other indication doses were used if no MDD or depression dose was available.

Table 2 displays the demographic distribution. The mean age was 16.4 years and the majority was female (67.9%) and Caucasian (76.3%). The largest age group initiated on SSRI therapy was 10 to 15 years old (33.2%). Overall, 27.0% (n= 1301) of patients were initiated above the modal dose. Those ages 10 to 15 were initiated above the modal dose most often. After a manual review to verify the daily dose calculation, only three patients (0.06%) were identified as initiated above the recommended maximum dose. Two of these patients, one male and one female were between 20 and 24 years of age, and one was a female was between 16 and 19 years of age.

Table 2 – Initiation by Demographic Distribution

Demographic	SSRI initiated n (%)	SSRI initiated above the modal dose n (%)
Total population	4,819	1,301
Age (years)*		
Mean [min – max]	16.4 [5-24]	15.4 [5-24]**
5 - 9	410 (8.5)	63 (4.8)
10 - 15	1,601 (33.2)	700 (53.8)
16 - 19	1,542 (32.0)	389 (29.9)
20 - 24	1,266 (26.3)	149 (11.5)
Sex		
Male	1,547 (32.1)	462 (35.5)
Female	3,272 (67.9)	839 (64.5)
Ethnicity		
Caucasian	3,677 (76.3)	961 (73.9)**
Other	1,142 (23.7)	344 (26.4)**

*Age at time of index SSRI claim **Values unable to be adjusted after manual review and removal of 4 patients

Table 3 describes the distribution by medication. Fluoxetine, sertraline, and citalopram were the most frequent SSRI therapies initiated (86.9%). Fluoxetine was most frequently initiated above modal dose (47.2%). Of the three patients initiated above the recommended maximum daily dose, two patients received escitalopram and one citalopram.

Table 3 – Initiation by Medication

SSRI	SSRI initiated n (%)	SSRI initiated above the modal dose n (%)
	4,819	1,301
citalopram	961 (19.9)	167 (12.8)
escitalopram	440 (9.1)	69 (5.3)
fluoxetine	1,625 (33.7)	614 (47.2)
paroxetine (immediate release)	191 (4.0)	21 (1.6)
sertraline	1,602 (33.3)	430 (33.1)

Table 4 displays the number of patients with a claim for one or more of the selected diagnoses in the 12 months prior to the index claim. The three most common diagnoses for SSRI initiation were MDD or depression (30.7%), anxiety (29.6%), and adjustment reactions that includes post-traumatic stress disorder (PTSD) (21.4%). Those with a diagnosis of MDD or depression were most often initiated above modal dose (35.0%).

There were only three patients (0.06%) identified that were initiated on SSRI therapy above recommended maximum daily dose after manual review of the original eleven patients. One of these patients was a 22 year old male initiated on citalopram 60 mg daily. The maximum dose of citalopram was lowered to 40mg by the FDA in 2012 due to reports of heart arrhythmias associated with higher doses. The profile was sparse but included comorbid diagnoses of obesity, anxiety, and ADHD. A second patient was a 17 year old female initiated on escitalopram 40 mg daily with a diagnosis of PTSD. SSRIs are considered first-line therapy for PTSD and 30mg daily is a recommended therapeutic dose of escitalopram, however it is recommended to initiate at 10mg daily. The third patient was a 22 year old female initiated on escitalopram 30 mg daily. This patient did not have diagnoses codes reported, but was also taking atomoxetine, clonazepam, lamotrigine, and quetiapine under the care of a psychiatrist. This profile suggests a complex psychiatric situation with much missing information.

Table 4 – Initiation by Diagnosis

Diagnosis*	ICD-9 code	SSRI initiated n (%)	SSRI initiated above the modal dose n (%)
		4,819	1,301
With FDA indication for at least one SSRI			
MDD or Depression	296.2x – 296.3x 311.xx	1,480 (30.7)	455 (35.0)
Depressive episodes associated with bipolar disorders	296.0x – 296.1x; 296.4x – 296.9x	218 (4.5)	63 (4.8)
Anxiety disorders	300.xx	1,428 (29.6)	347 (26.7)
Personality disorders (includes OCD)	301.xx	20 (0.4)	6 (0.5)
Premenstrual tension syndromes	625.4x	13 (0.3)	5 (0.4)
Adjustment reactions (includes PTSD)	309.xx	1,029 (21.4)	286 (22.0)
Anorexia nervosa & eating disorders	307.1x; 307.5x	25 (0.5)	8 (0.6)
With off-label indications			
Alcoholism	303.xx	42 (0.9)	10 (0.8)
Pervasive development disorders (includes autism spectrum disorders)	299.xx	161 (3.3)	51 (3.9)
Disturbance of emotions specific to childhood and adolescents	313.xx	160 (3.3)	49 (3.8)
Migraine	346.xx	140 (2.9)	25 (1.9)
Fibromyalgia	729.1x; 729.2x	35 (0.7)	6 (0.5)
Hot flashes (male or female)	782.62	2 (<0.1)	1 (<0.1)
Insomnia	307.4x, 780.5x	132 (2.7)	35 (2.7)
Irritable bowel syndrome	564.1x	23 (0.5)	5 (0.4)
Nocturnal enuresis	788.36	12 (0.2)	2 (0.2)
Raynaud's syndrome	443.0x	2 (<0.1)	1 (<0.1)

* Patients could have more than one diagnosis and categories are not exclusive; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=post-traumatic stress disorder

Table 5 presents the distribution by provider specialty and geographic location by county of SSRI treatment initiation. Primary care providers initiated SSRI therapy most frequently at 31.2%. Pediatric providers initiated SSRI therapy at high-dose most frequently at 28.4%. No county had a significantly more prevalent high dose prescribing rate.

Table 5 – Initiation by Provider Specialty and Geographic Location

	SSRI initiated		SSRI initiated above modal dose	
Provider Specialty **	**n=4,819**	**%**	**n=1,301**	**%**
Pediatrics	960	19.9%	370	28.4%
Primary Care	1,505	31.2%	321	24.7%
Psychiatric	546	11.3%	185	14.2%
Other	1,192	24.7%	268	20.6%
Patient County ***				
Baker	27	0.6%	9	0.7%
Benton	73	1.5%	21	1.6%
Clackamas	367	7.6%	115	8.8%
Clatsop	52	1.1%	15	1.2%
Columbia	74	1.5%	20	1.5%
Coos	113	2.3%	33	2.5%
Crook	38	0.8%	9	0.7%
Curry	13	0.3%	8	0.6%
Deschutes	264	5.5%	78	6.0%
Douglas	172	3.6%	48	3.7%
Gilliam	0	0.0%	0	0.0%
Grant	12	0.2%	2	0.2%
Harney	19	0.4%	4	0.3%
Hood River	34	0.7%	9	0.7%
Jackson	295	6.1%	70	5.4%
Jefferson	34	0.7%	5	0.4%
Josephine	107	2.2%	27	2.1%
Klamath	102	2.1%	18	1.4%
Lake	7	0.1%	1	0.1%
Lane	559	11.6%	162	12.5%
Lincoln	91	1.9%	24	1.8%
Linn	220	4.6%	64	4.9%
Malheur	49	1.0%	11	0.8%
Marion	554	11.5%	149	11.5%
Morrow	10	0.2%	2	0.2%
Multnomah	690	14.3%	171	13.1%
Polk	100	2.1%	23	1.8%
Sherman	2	0.0%	0	0.0%
Tillamook	29	0.6%	7	0.5%
Umatilla	80	1.7%	25	1.9%
Union	56	1.2%	7	0.5%
Wallowa	12	0.2%	5	0.4%
Wasco	29	0.6%	5	0.4%
Washington	398	8.3%	130	10.0%
Wheeler	3	0.1%	1	0.1%
Yamhill	130	2.7%	24	1.8%

** Provider specialty definitions are located in Appendix 2; Counts reflect only those patients with an identifiable prescriber

***There were 4 patients whose county of residence was unable to be identified

DISCUSSION

These results demonstrate that a significant number (27%) of Oregon Medicaid patients aged 5 to 24 years were initiated on high-dose SSRI therapy during the study period thus, potentially putting these patients at risk for deliberate self-harm. Those aged 10 to 15 years were initiated at high-dose at a higher rate than any other age group. Patients in this age cohort comprised 53.8% of all patients initiated at high-dose. The mean age of all patients initiated at high-dose was slightly above 15 years of age.

Fluoxetine was most frequently prescribed (34%) and comprised 47.2% of all those above the modal dose. This could be due to a number of reasons. Compared with other SSRI therapies, fluoxetine is first line therapy, has a longer history of use, is FDA approved and has the most supporting evidence for treatment of MDD and additional indications. Therefore, practitioners may be more comfortable prescribing fluoxetine at higher doses because of past experience doing so. In addition, patients on fluoxetine may have diagnoses other than MDD that have recommended higher doses (e.g. OCD). Another potential explanation is the lower pooled modal dose (10 mg) obtained, which is in the lower range recommended by the manufacturer for heavier children 8 to 17 years old and half that typically recommended for adults (20mg). However, it is common practice to initiate adults on doses of 5 to 10 mg. The use of the lower pooled modal dose in the adolescent age groups could have led to an increased number of patients categorized as initiated above modal dose. Nonetheless, those prescribed fluoxetine were more likely to be initiated at high-dose and could increase the risk for suicidality.

Patients who had a diagnosis of MDD or depression were initiated at high-dose more often than other diagnoses. This is the population of most interest and similarity to the Miller paper linking risk of suicidality to initial dose of SSRI.

The Miller paper,[14] which the methods of this study were based upon, included only patients with a MDD diagnosis, only included citalopram, sertraline and fluoxetine and excluded patient under 10 years old. The rate of high-dose initiation (13.1%) in Miller[14] was significantly lower than in this study (27%). One possible explanation is the inclusion of patients with other diagnoses in this study. However, those with MDD were initiated at higher doses more prevalently than those with other diagnoses so it does not explain the higher prevalence of high dose initiation. The pooled modal doses in this study were similar to the pooled modes Miller[14] used for citalopram and sertraline but lower (10mg) for fluoxetine. Miller[14] used a pooled modal dose of 20mg to identify high dose initiation for all age groups. Additionally, given the long half-life of fluoxetine, prescribers may initiate at a higher dose to achieve steady state sooner. This study used an age-specific modal dose to determine high dose rather than the pooled population modal dose that Miller[14] used. The age-specific modes used in this study were lower than the pooled modes for patients less than 15 years old for citalopram, sertraline and paroxetine patients. Patients on fluoxetine and patients aged 10-15 were associated with the highest rates of high dose initiation and could account for the higher prevalence in this study compared to Miller.

One limitation is the method to calculate the daily SSRI initiation dose. The accuracy of calculating daily SSRI initiation doses correctly is dependent upon the correct entry of “days supply” by the pharmacy. This can ultimately lead to incorrect calculation of daily dose initiated, inappropriate categorization of the patient, and affect the validity of the results. However, with the exception of the few patients over the maximum dose, the pooled modal dose was similar to the Miller[14] paper and within recommended doses reported in the compendia, even when using an age specific modal dose. This suggests that overwhelmingly, pharmacies estimate and enter the days supply accurately. A second limitation is the extrapolation from the Miller[14] paper results to include a class effect for other SSRIs (i.e. paroxetine and escitalopram), to a younger population (i.e. 5-9 year olds), and to patients without a confirmed MDD diagnosis. The

vast majority (86.9%) of patients in this study were on the three drugs included in Miller[14] (i.e. fluoxetine, sertraline and citalopram) and were older than 9 (i.e. 91.5%). While only 30.7% carried a MDD diagnosis it has been documented previously that diagnoses are often absent from the administrative claims record and it was the most prevalent diagnoses reported.

This drug use evaluation identified 27% of Oregon Medicaid patients aged 5 to 24 years were initiated on high-dose SSRI therapy during the study period. The potential risk of self-harm due to SSRI use is still debated and relatively small (0-8%) in comparison to the burden of MDD. The Miller[14] paper suggests that limiting the dose at initiation is one way to limit the risk of self-harm while still treating the disease.

RECOMMENDATION

- Initiate a maximum dose prior authorization for patients less than 25 years starting SSRIs (i.e. those with no prior antidepressant claim in the previous 102 days). Set the dose at the age-specific modal doses used in this study (Table 1) except increase the fluoxetine dose to 20mg for 16-19 year olds.
- Exclude child psychiatrists from the prior authorization requirement.
- Consider age edit to restrict use of paroxetine and fluvoxamine to adults (>18) per expert opinion.
- Prior to implementation, educate prescribers via Oregon State Drug Review

REFERENCES

1. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry*. 1990;147(2):207-210. http://ajp.psychiatryonline.org.liboff.ohsu.edu/article.aspx?articleid=166551. Accessed July 13, 2014.

2. United States Food and Drug Administration. Labeling Change Request Letter for Antidepressant Medications. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm. Accessed July 13, 2014.

3. Beasley CM, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ*. 1991;303(6804):685-692. doi:dx.doi.org/10.1136/bmj.303.6804.685.

4. Valluri S, Zito JM, Safer DJ, Zuckerman IH, Mullins CD, Korelitz JJ. Impact of the 2004 Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression. *Med Care*. 2010;48(11):947-954. doi:10.1097/MLR.0b013e3181ef9d2b.

5. Chen S-Y, Toh S. National trends in prescribing antidepressants before and after an FDA advisory on suicidality risk in youths. *Psychiatr Serv Wash DC*. 2011;62(7):727-733. doi:10.1176/appi.ps.62.7.727.

6. Mittal M, Harrison DL, Miller MJ, Brahm NC. National antidepressant prescribing in children and adolescents with mental health disorders after an FDA boxed warning. *Res Soc Adm Pharm RSAP*. 2013. doi:10.1016/j.sapharm.2013.11.001.

7. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am J Psychiatry*. 2007;164(6):884-891. doi:10.1176/appi.ajp.164.6.884.

8. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006;63(3):332-339. doi:10.1001/archpsyc.63.3.332.

9. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA J Am Med Assoc*. 2004;292(7):807-820. doi:10.1001/jama.292.7.807.

10. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA J Am Med Assoc*. 2007;297(15):1683-1696. doi:10.1001/jama.297.15.1683.

11. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *The Lancet*. 2004;363(9418):1341-1345. doi:10.1016/S0140-6736(04)16043-1.

12. Williams SB, O'Connor E, Eder M, Whitlock E. *Screening for Child and Adolescent Depression In Primary Care Settings: A Systematic Evidence Review for the U.S. Preventive Services Task Force*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009. Available at: http://www.ncbi.nlm.nih.gov/books/NBK35127/. Accessed July 4, 2014.

13. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2012;11:CD004851. doi:10.1002/14651858.CD004851.pub3.

14. Miller M, Swanson SA, Azrael D, Pate V, Stürmer T. Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Intern Med*. 2014;174(6):899-909. doi:10.1001/jamainternmed.2014.1053.

15. Moreland S, Bonin L. Effect of antidepressants on suicide risk in children and adolescents. In: *UpToDate [on-line database].* Updated August 6, 2014. http://www-uptodate-com.liboff.ohsu.edu/contents/effect-of-antidepressants-on-suicide-risk-in-children-and-adolescents?source=search_result&search=Effect+of+antidepressants+on+suicide+risk+in+children+and+adolescents.&selectedTitle=1~150. Accessed Aug 2014.

16. Pediatric & Neonatal Lexi-Drugs Online™, In *Lexi-Comp Online [on-line database].* 2014. http://online.lexi.com.liboff.ohsu.edu/lco/action/home/switch. Accessed July 13, 2014.

17. Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein REK. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and Ongoing Management. *Pediatrics*. 2007;120(5):e1313-e1326. doi:10.1542/peds.2006-1395.

Appendix 1 – Drugs Included and Classification

Therapeutic Class Spec Code & Desc	Generic Drug Name
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	CITALOPRAM HYDROBROMIDE
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	ESCITALOPRAM OXALATE
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	FLUOXETINE HCL
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	FLUVOXAMINE MALEATE
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	PAROXETINE HCL
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	PAROXETINE MESYLATE
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	SERTRALINE HCL
H2S - SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	ST. JOHN'S WORT
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	AMITRIPTYLINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	AMOXAPINE
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	CLOMIPRAMINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	DESIPRAMINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	DOXEPIN HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	IMIPRAMINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	IMIPRAMINE PAMOATE
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	MAPROTILINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	NORTRIPTYLINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	PROTRIPTYLINE HCL
H2U - TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	TRIMIPRAMINE MALEATE
H7B - ALPHA-2 RECEPTOR ANTAGONIST ANTIDEPRESSANTS	MIRTAZAPINE
H7C - SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	DESVENLAFAXINE
H7C - SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	DESVENLAFAXINE FUMARATE
H7C - SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	DESVENLAFAXINE SUCCINATE
H7C - SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	DULOXETINE HCL
H7C - SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	LEVOMILNACIPRAN HYDROCHLORIDE
H7C - SEROTONIN-NOREPINEPHRINE REUPTAKE-INHIB (SNRIS)	VENLAFAXINE HCL
H7D - NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIB (NDRIS)	BUPROPION HBR
H7D - NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIB (NDRIS)	BUPROPION HCL
H7E - SEROTONIN-2 ANTAGONIST/REUPTAKE INHIBITORS (SARIS)	NEFAZODONE HCL
H7E - SEROTONIN-2 ANTAGONIST/REUPTAKE INHIBITORS (SARIS)	TRAZODONE HCL
H7J - MAOIS - NON-SELECTIVE & IRREVERSIBLE	ISOCARBOXAZID
H7J - MAOIS - NON-SELECTIVE & IRREVERSIBLE	PHENELZINE SULFATE
H7J - MAOIS - NON-SELECTIVE & IRREVERSIBLE	TRANYLCYPROMINE SULFATE
H8P - SSRI & 5HT1A PARTIAL AGONIST ANTIDEPRESSANT	VILAZODONE HYDROCHLORIDE
H8T - SSRI & SEROTONIN RECEPTOR MODULATOR ANTIDEPRESSANT	VORTIOXETINE HYDROBROMIDE
H2H - MONOAMINE OXIDASE(MAO) INHIBITORS	SELEGILINE

Appendix 2 – Provider Specialty Groupings

GROUP	PROVIDER SPECIALTY
OTHER	108 - Encounter Only
OTHER	115 - Oral Surgeon
OTHER	124 - Maternal Fetal Medicine
OTHER	216 - Sports Medicine
OTHER	218 - Radiation Oncology
PED	219 - Neonatal - Perinatal
OTHER	220 - Allergist
OTHER	221 - Abdominal Surgery
PED	222 - Adolescent Medicine
OTHER	223 - Allergy & Immunology
OTHER	224 - Aviation Medicine
OTHER	228 - Anesthesiologist
OTHER	229 - Otologist, Laryngologist
OTHER	230 - Blood Banking
OTHER	231 - Physician (Default Spec)
OTHER	232 - Cardiologist
OTHER	233 - Congregate Care Physician
OTHER	234 - Cardiovascular Diseases
OTHER	235 - Broncho-Esophagology
OTHER	236 - Child Neurology
OTHER	237 - Critical Care Medicine
OTHER	238 - Clinic
OTHER	239 - Clinical Pathology
OTHER	240 - Colon & Rectal Surgery
OTHER	241 - Cardiovascular Surgery
OTHER	242 - Dermatologist
OTHER	243 - Diabetes
PRIM	244 - Osteopathic Physician
OTHER	245 - Dermatopathology
OTHER	246 - Diagnostic Radiology
OTHER	247 - Emergency Med Practitioner
OTHER	248 - Forensic Pathology
PRIM	249 - Family Practitioner
OTHER	250 - Gastroenterologist
OTHER	251 - Geriatric Practitioner
PRIM	252 - General Practitioner
OTHER	253 - Gynecology
OTHER	254 - Hospital Administration
OTHER	255 - Hematology
OTHER	256 - Head & Neck Surgery
OTHER	257 - Hand Surgeon
OTHER	258 - Mobile Med. Care (HS CALL)
OTHER	260 - Infectious Diseases

OTHER	261 - Immunology
PRIM	262 - Internist
OTHER	263 - Industrial Medicine
OTHER	264 - Legal Medicine
OTHER	265 - Maxillofacial Surgery
OTHER	266 - Neuropathology
OTHER	267 - Neoplastic Diseases
OTHER	268 - Neurologist
OTHER	269 - Nephrologist
OTHER	270 - Nuclear Medicine
OTHER	271 - Nuclear Radiology
OTHER	272 - Neurological Surgeon
OTHER	273 - Nutritionist
OTHER	274 - Ophthalmology
OTHER	275 - Obstetrics
OTHER	276 - Obstetrics & Gynecology
OTHER	277 - Occupational Medicine
OTHER	278 - Oncologist
OTHER	279 - Orthopedic Surgeon
OTHER	280 - Otologist, Laryngologist, Rhinologist
OTHER	281 - Otologist, Laryngologist
OTHER	282 - Pathologist
PED	283 - Pediatrics
OTHER	284 - Pediatric Allergy
OTHER	285 - Pediatric Cardiology
OTHER	286 - Public Health
OTHER	287 - Pediatric Endocrinology
OTHER	288 - Pediatric Radiology
OTHER	289 - Pediatric Surgeon
OTHER	290 - Plastic Surgeon
OTHER	291 - Physical Medicine and Rehabilitation Practitioner
OTHER	292 - Pediatric Hematology-Oncology
OTHER	293 - Pediatric Nephrology
OTHER	294 - Pediatric Urology
OTHER	295 - Pulmonary Disease Specialist
OTHER	296 - Preventive Medicine
MH	297 - Psychosomatic Medicine
OTHER	298 - Pharmacology
OTHER	299 - Rheumatology
OTHER	300 - General Surgeon
OTHER	301 - Therapeutic Radiology
OTHER	302 - Traumatic Surgery
OTHER	303 - UOHSC Practitioners
OTHER	304 - Urologist
OTHER	305 - Rhinology

OTHER	306 - Thoracic Surgeon
OTHER	307 - Endocrinologist
OTHER	308 - Proctologist
MH	312 - Psychiatrist
OTHER	313 - Vascular Surgery
OTHER	314 - Student/Education
PRIM	328 - Primary Care - Federal Definition
OTHER	484 - Internal Medicine - Sleep Medicine
OTHER	108 - Encounter Only
PRIM	328 - Primary Care - Federal Definition
OTHER	360 - Advance Practice Nurse
OTHER	361 - Nurse Practitioner Clinic
PED	362 - Pediatric Nurse Practitioner
OTHER	363 - Obstetric Nurse Practitioner
PRIM	364 - Family Nurse Practitioner
OTHER	366 - Nurse Practitioner (default Spec)
OTHER	367 - Certified Nurse Midwife
OTHER	108 - Encounter Only
PRIM	328 - Primary Care - Federal Definition

Appendix 3

Initial Pediatric SSRI Antidepressant –Daily Dose Limit

Goal(s):

- Approve only for covered OHP diagnoses.
- Limit risk of new-onset of deliberate self-harm thoughts and behaviors, or suicidality associated with initiation of antidepressant therapy at above recommended doses

Length of Authorization:

- 12 months

Requires PA:

- Any SSRI above the doses in the table below for patients <25 years old on the date of the first antidepressant claim (i.e. no claim for any antidepressant in Specific Therapeutic Classes H2H, H2S, H2U, H7B, H7C, H7D, H7E, H7J, H8P or H8T in the 102 days prior)

GSN	SSRI	Age – specific modal dose (mg)			
		Age range [years]			
		5 – 9	10 – 15	16 – 19	20 – 24
70991, 46206, 46204, 46203, 46205	citalopram	10	10	20	20
50712, 51642, 51698, 50760	escitalopram	5	10	10	10
46219. 46216, 46217, 47571, 46215, 46214, 46213	fluoxetine	10	10	20	20
46222, 46224. 46225, 46223, 46226, 53387, 53390, 53389, 53388,	paroxetine (immediate release)	10	10	20	20
46229, 46228, 46227, 46230	sertraline	25	25	50	50

Covered Alternatives:

- Doses within recommended age-specific dose.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the client being treated for funded diagnoses on the OHP List of Prioritized Services?	Yes: Go to #3.	No: Pass to RPH; Deny, (Diagnosis not funded by OHP)

Approval Criteria		
3. Has the patient been treated previously with antidepressants and is the dose below the maximum recommended dose?	Yes: Approve x 12 months.	No: Go to #4
4. Is the requested dose above the recommended initial dose for the patient's age (i.e. was the days supply entered correctly, is the patient's age accurate)?	Yes: Pass to Pharmacist and Go to #5. .	No: Approve x 12 months
5. Are there clinical circumstances that justify an increased dose?	Yes: Pharmacist to evaluate on a case by case basis.	No: Deny, (Medical Appropriateness) Recommend lowering initial dose

P&T / DUR Action: *11/20/14*
Revision(s):
Initiated: *1/1/15??*

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

- Preferred PPIs beyond 60 days' duration
- Non-preferred PPIs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for a preferred PPI?	Yes: Go to 5	No: Go to 3
3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	Yes: Go to 4	No: Pass to RPh; deny, not funded by OHP.
4. Will the prescriber consider changing to a preferred PPI product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives.	No: Go to 5
5. Has the patient already received 68 days of PPI therapy for either of the following diagnoses: • GERD [esophageal reflux (53081), esophagitis (53010 – 53019)] or • *H. pylori* infection (04186)?	Yes: Go to 6	No: Go to 7
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalizations?	Yes: Approve for 1 year	No: Pass to RPh; not funded by OHP. RPh may approve a quantity limit of 30 doses (not to exceed the GERD dose in the **Table**) over 90 days if time is needed to taper off PPI. Note: No specific PPI taper regimen has proven to be superior. H2RAs may be helpful during the taper. Preferred H2RAs are available without PA.

7. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? • Age 65 years or older • Requires at least 3 months of continuous daily: i. Anticoagulant, ii. Aspirin or non-selective NSAID, or iii. Oral corticosteroid	Yes: Approve for 1 year	No: Go to 8
8. Are the indication, daily dose and duration of therapy consistent with criteria outlined in the **Table**? Message: OHP-funded conditions are listed in the **Table**.	Yes: Approve for recommended duration.	No: Pass to RPh. Deny; medical appropriateness or not funded by OHP Message: Patient may only receive 8 weeks of continuous PPI therapy.

Table. Dosing and Duration of PPI Therapy for OHP Funded Conditions.

Funded OHP Conditions*	**Maximum Duration**	**Maximum Daily Dose**
GERD: Esophageal reflux (53081) Esophagitis (5301x)	8 weeks* *Treatment beyond 8 weeks is not funded by OHP.	Dexlansoprazole 30 mg Esomeprazole 20 mg Lansoprazole 15 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg
H. pylori Infection (04186)	2 weeks	Dexlansoprazole 60 mg Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg
Achalasia and cardiospasm (5300x) Stricture & Stenosis of Esophagus (5303x) Perforation of Esophagus (5304x) Dyskinesia of esophagus (5305x) Gastroesophageal laceration-hemorrhage syndrome (5307x) Esophageal hemorrhage (53082) Gastric Ulcer (5310x – 53191) Duodenal Ulcer (5320x – 53291) Peptic ulcer site unspecified (5330x – 53391) Gastrojejunal ulcer (5340x – 53491) Gastritis and duodenitis (5350x – 53571) Zollinger-Ellison (2515x) Neoplasm of uncertain behavior of other and unspecified endocrine glands (2374x) Malignant mast cell tumors (2026x) Multiple endocrine neoplasia [MEN] type I (25801)	1 year	

*A current list of funded conditions is available at: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Policy Update: Ivacaftor (Kalydeco®) for Cystic Fibrosis

Month/Year of Review: May 2015 **Last Reviewed**: May 2014

Current PA Criteria:
See **Appendix 3**. Prior authorization (PA) criteria are in place to ensure appropriate drug use and limit to patient populations in which ivacaftor has demonstrated to be effective and safe.

Research Questions:
- Does new evidence for efficacy or harms change previous conclusions regarding the effectiveness and safety of ivacaftor?
- Are there unique patients or situations where ivacaftor may be more effective or safer than currently available agents?

Conclusions:
- There is insufficient to low quality evidence that ivacaftor does not significantly improve lung function in patients with Cystic Fibrosis (CF) with the *R117H* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, as measured by lack of improvement in percent-predicted FEV_1 compared to placebo (2.6% vs. 0.5%, respectively; p=0.19) based on one small, unpublished study. However, a post hoc subgroup analysis of adults 18 years of age or older showed a statistically significant improvement in FEV_1 compared to placebo (4.5% vs. -0.5%; p=0.01). However, a subgroup of patients aged 6 to 11 years demonstrated an unexplained negative effect, as absolute FEV_1 was significantly lower than placebo by 6.5% points (p=0.03). Based on this evidence alone, the FDA approved use of ivacaftor in adults with the *R117H* mutation based on this subgroup analysis. The FDA approved use of ivacaftor in pediatric patients 6 years of age and older based on an open-label extension study which subsequently showed a 6.4% improvement in mean change in FEV_1.
- There is insufficient to low quality evidence, based on one small pharmacokinetic study and one safety study in pediatric CF patients' aged 2 to 5 years (32 patients with the *G551D* mutation and 2 patients with the *S549N* mutation), that ivacaftor is relatively safe and improves sweat chloride concentrations. Based on this evidence alone, the FDA approved ivacaftor in patients aged 2 to 5 years with all of the following mutations: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R* or *R117H*.
- Evidence to support use of ivacaftor based on clinical outcomes remains very limited, with very small studies dealing with disease mutations that affect a small number of patients in the United States. It is difficult to determine the overall effectiveness and safety of ivacaftor for the treatment of CF and how it will affect disease progression. The strongest evidence remains in patients with the *G115D* mutation.

Author: M. Herink, Pharm.D. Date: May 2015

Ivacaftor should not be used in CF patients homozygous for the *F508del* mutation (the most common mutation) due to evidence for lack of benefit in this population.

Recommendations:

- Limited, inconsistent, and unpublished evidence at this time prohibits adequate and fair evaluation of the efficacy of ivacaftor for the new FDA-approved indications. It is prudent to further await published data supporting statistically significant improvements in FEV_1, or other clinically relevant outcomes, in patients with the R117H mutation in the CFTR gene and in pediatric patients aged 2 to 5 years before approving use in these populations.

Reason for Review:

Since the last P&T review of ivacaftor, the FDA approved ivacaftor for the treatment of CF in patients age 6 years and older who have an *R117H* mutation in the *CFTR* gene. In addition, the FDA approved ivacaftor for children aged 2 to 5 years who have one of the 10 FDA-approved mutations in the CFTR gene. Ivacaftor was already approved for people aged 6 years and older with these mutations. This review will evaluate the new indications and supporting evidence.

Previous Recommendations:

- There is low to moderate level of evidence to suggest that ivacaftor is superior to placebo in patients (≥12 years old) with the G551D mutation, as illustrated by an increase in forced expiratory flow rate at one second (FEV_1). There is also moderate evidence that ivacaftor is well tolerated with adverse effects resulting in discontinuations rates less than placebo. There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. There is insufficient evidence to grade ivacaftor treatment in children under 12. Limited unpublished data suggests similar efficacy and safety as in patients over 12 years of age.
- The efficacy and safety evaluation of ivacaftor is limited by small study populations; study durations of only one year and unpublished data. Ivacaftor has been shown to be effective only in the CF population with the G551D mutation, making ivacaftor a treatment option in only a small percentage of patients with CF. The effects of ivacaftor on long term disease progression and important clinical outcomes including pulmonary exacerbations and hospitalizations are unknown.
- It is recommended to use clinical prior authorization criteria (**Appendix 3**) to limit the use of ivacaftor to patients that are six years and older, diagnosed with CF, have the G551D mutation in the CFTR gene, is prescribed by or in consultation with a pulmonologist or a practitioner at an accredited Cystic Fibrosis Center, and has had an adequate trial of standard medication therapy. Renewal criteria will be implemented to monitor for a clinical response and adherence.
- There is insufficient to low quality evidence based on one unpublished, phase III trial, that in addition to CF patients with the G551D mutation, ivacaftor is more effective than placebo in improving lung function as measured by FEV_1 in patients with 8 additional mutations. These include: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. Evidence does not support use of the drug in patients with the G970R mutation.

Background:

Cystic Fibrosis (CF) is a genetic disease that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.[1] Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[2] Important outcomes for treatment include reducing mortality, pulmonary exacerbations, and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used outcome in clinical trials. The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focused on respiratory health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for this domain.[3] Weight is also a commonly measured secondary outcome in trials of CF patients, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, increased morbidity and mortality in children with CF. [3] Sweat chloride levels is the gold standard for a diagnosis of CF. Normal individuals typically have levels < 40 mmol/L and patients with CF have elevated levels > 60 mmol/L.[4] More recently, sweat chloride has been used as a biomarker for evaluating changes in the CFTR activity in clinical trials of ivacaftor.[5] However, there is no evidence that sweat chloride is correlated with meaningful clinical benefits and it has shown to correlate with improvement in FEV_1. [4]

Many different mutations have been identified in the gene that causes CF. Ivacaftor is a CF transmembrane conductance regulator (CFTR) potentiator approved by the FDA in 2012 for the treatment of CF in patients 6 years and older with the G551D mutation in the CFTR gene (approximately 4% of CF patients) by demonstrating statistically superior improvement in FEV_1 compared to placebo.[6–9] Ivacaftor is proposed to treat the underlying cause of CF, by influencing the basic gene defect, by normalizing airway surface liquid and helping to re-establish mucociliary clearance.[10,11] Ivacaftor is now indicated for the treatment of CF in patients in patients' aged 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.* Over 1900 mutations have been identified in the CFTR gene. Patients homozygous for the *F508*del CFTR mutation, the most common mutation in the CFTR gene accounting for approximately two thirds of mutations, do not receive benefit in lung function or patient-reported outcomes with ivacaftor and the drug should not be used in this population.[12]

There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 observed with ivacaftor are similar to other therapies used in the chronic management of CF.

Elevated transaminases should be assessed prior to initiating ivacaftor and every 3 months during the first year of treatment. Patients who develop increased transaminase levels should be closely monitored. Therapy should be stopped if increases in ALT or AST greater than 5-times the upper limit of normal are observed.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A Cochrane Collaboration Systematic Review was completed to evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with cystic fibrosis.[11] RCTs comparing CFTR potentiators to placebo were included in the review. At the time of this review, it had only been studied in those with the *G55aD* and *F508del* mutations, thus limiting the current relevance of the results. Primary outcomes were survival, quality of life, and change in FEV_1 from baseline. There were many secondary outcomes.

Four RCTs of parallel design (n=378) were included in the review, two of which have been published. Vertex Pharmaceuticals Incorporated sponsored all trials. Three trials included participants with the *G551D* mutation (one phase 2 and two phase 3) in adults and pediatrics, while one trial was in the *F508del* mutation. The primary endpoints in the trials were safety and/or FEV_1. There was a high risk of selective reporting bias and attrition bias in the included studies, with an overall moderate risk of bias across the included trials.[11]

No trial reported any deaths. Significantly higher quality of life scores in the respiratory domain were reported by the adult phase 3 G551D trial at 24 weeks, mean difference 8.10 (95% confidence interval (CI) 4.77 to 11.43) and 48 weeks, mean difference 8.60 (95%CI 5.27 to 11.93); but not by the pediatric phase 3 G551D trial. At 24 weeks in the 3 *G551D* trials, both children and adults in the ivacaftor group reported significant improvements in the change from baseline in FEV_1, with a mean difference of 16.8% (95% CI 13.5-20.1), or 0.37 liters at 48 weeks. At 16 weeks in the *F508* trial, there was no difference in FEV1 between ivacaftor and placebo (mean difference 2.4%; 95% CI -0.95 to 5.75). One study in adults with the *G551D* mutation reported significantly fewer episodes of pulmonary exacerbation requiring hospitalization in the ivacaftor group (OR 0.37; 95% CI 0.16 to 0.81).[11] Pooling data from the two of the G551D trials showed no statistical difference in number of pulmonary exacerbation (OR 0.64; 95% CI 0.36 to 1.12) or adverse effects requiring drug discontinuations (OR 0.25; 95% CI 0.04 to 1.56). [11]

The authors concluded that the *G551D* phase 3 trials demonstrated a clinically relevant impact at 24 and 48 weeks in adults and children but that there is no evidence to support ivacaftor in patients with the *F508del* mutation. [11]

New Guidelines:
No relevant guidelines were identified.

New FDA Approved Indications:
In December 2014, the FDA approved the use of ivacaftor for use in subjects with the *R117H* mutation in the CFTR gene. The *R117H* mutation is the third most common mutation, present in approximately 4% of people with CF, or approximately 700 people in the United States. This approval was based on the Phase 3, double-blind, randomized unpublished KONDUCT study in subjects aged 6 years and older.[9,13] The primary outcome was absolute change from baseline in percent (%)-predicted FEV_1 through week 24. Those with a %-predicted FEV_1 40-90% for subjects aged 12 years or older or 40-105% for subjects aged 6 to 11 years were included. A total of 70 subjects were randomized (34 in the ivacaftor group and 35 in the placebo group) and the majority of subjects were 18 years or older (72%). There was an absolute change from baseline in %-predicted FEV_1 of 2.6% in the ivacaftor group compared to 0.5% in the placebo with a least squares mean difference of 2.1% (95% CI -1.13 to 5.35%). This difference was not statistically significant (p=0.19) and therefore the study did not meet its primary endpoint. There was also no significant difference in time to first pulmonary exacerbation (p=0.8556) or change from baseline in body mass index (BMI) at week 24 (p=0.78). There was a statistically significant difference in change in FEV_1 relative to placebo in a subgroup of subjects aged 18 years and older (4.5% vs. -0.5%, respectively; p=0.01), which represented approximately 75% of subjects. In addition, there was a statistically significant difference in change in FEV_1 relative to placebo in subjects with the 5T poly-T status (6% vs. 0.7%; treatment difference 5.3; 95% CI 1.3 to 9.3), though subjects with 7T status only did not show a statistically significant difference in FEV_1 compared to placebo (-0.7% vs. -0.9%; treatment difference 0.2% [95% CI -8.1 to 8.5%]). However, the mean absolute change in FEV_1 in the subgroup of 17 subjects aged 6 to 11 years was significantly lower compared to placebo (-2.8% vs. 3.5%), demonstrating an unexplained negative effect in children. The company concluded that this was driven by the high baseline FEV_1 for these patients and the small sample size and that there was an overall neutral effect on lung function. There was a significantly greater decrease in sweat chloride in the ivacaftor group compared to placebo (-26.3 mmol/L vs. -2.3 mmol/L; $p<0.0001$)[13]; however there are no data available in patients aged 12 to 17 years. An unpublished, open-label extension period study (KONTINUE) showed an improvement in FEV_1 of 6.4% in the subgroup of 6 to 11 year olds. The initial decrease in the controlled trial should be taken into consideration and more evidence is needed to demonstrate an improvement. Results for KONTINUE were not available on clinicaltrials.gov.

Although the study did not meet the primary endpoint, adult approval was based on subgroup analysis from the trial and expected clinical benefit based on secondary outcomes in pediatric patients.

In March 2015, the FDA approved ivacaftor for use in children ages 2 to 5 years with CF who have one of the 10 mutations in the CFTR gene already approved in adults (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H*).[9] The expanded use in this population is based on results of an open-label, non-controlled, phase 3 study (KIWI) that evaluated the safety and pharmacokinetics of weight-based dosing of ivacaftor (50 mg or 75 mg twice daily) for 24 weeks. A total of 9 patients, all with the *G551D* mutation in the CFTR gene, were enrolled in the initial pharmacokinetic stage of the study. Pharmacokinetic properties for both doses were similar to that reported in adults in previous studies. The second part of the study, which included 32 patients with the *G551D* mutation and 2 patients with the *S549N* mutation, assessed safety outcomes over 24 weeks. Overall, 88.9% of patients experienced at least one adverse event; the most common being pyrexia, vomiting, ecchymosis, and

rhinorrhea. Five patients experienced elevations in liver transaminases and there were a total of 7 serious adverse events. There was a decrease in the sweat chloride concentration through week 24 (-46.86 mmol/L) but statistical analysis compared to placebo was not provided and other clinical efficacy outcomes, such as lung function, were not included.[14]

Randomized Controlled Trials:

The only relevant RCT identified was the KONNECTION trial.[15] This trial data were previously presented and reviewed by the P&T committee to support the expanded indication; however, it was unpublished at the time. A summary of the trial can be found below, with the abstract presented in **Appendix 1**.

Table 1. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
KONNECTION[15] Randomized, Crossover study	Ivacaftor 150 mg BID vs. placebo	Patients with CF ≥6 years old with non-*G551D* gating mutations (*G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* or *G1349D.* (N=39)	Absolute change in %-predicted FEV_1 through 8 weeks of treatment	Ivacaftor: 7.5% Placebo: -3.2% Mean difference: 10.7% (95% CI 7.3 to 14.1; P<0.0001) There was high variability among and within subgroups of genotypes; in many groups, FEV_1 did not significantly change from baseline and the number of patients in each subgroup was extremely small.	Poor

Abbreviations: BID = twice daily; CF = Cystic Fibrosis; FEV1 = Forced expiratory volume in 1 second;
*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

References:

1. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2014;18(18):1-106. doi:10.3310/hta18180.
2. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
3. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest*. 2009;135(6):1610-1618. doi:10.1378/chest.08-1190.
4. Durmowicz AG, Witzmann KA, Rosebraugh CJ, Chowdhury BA. Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience. *Chest*. 2013;143(1):14-18. doi:10.1378/chest.12-1430.
5. Accurso FJ, Van Goor F, Zha J, et al. Sweat chloride as a biomarker of CFTR activity: proof of concept and ivacaftor clinical trial data. *J Cyst Fibros*. 2014;13(2):139-147.
6. Aherns R, Rodriguez S, Yen K. VX-770 in subjects 6 to 11 years with cystic fibrosis and the G551D -CFTR mutation (abstract) Pediatr Pulmonol 2011;(suppl 34):283.
7. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672. doi:10.1056/NEJMoa1105185.
8. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219-1225. doi:10.1164/rccm.201301-0153OC.
9. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. March. 2015.
10. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *Ann Pharmacother*. 2012;46(7-8):1065-1075. doi:10.1345/aph.1R076.
11. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. 2015;3:CD009841. doi:10.1002/14651858.CD009841.pub2.
12. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. 2012;142(3):718-724. doi:10.1378/chest.11-2672.
13. ClinicalTrials.Gov. Study of Ivacaftor in Subjects with Cystic Fibrosis Who Have the R117H-CF Transmembrane Conductance Regulator Mutation (KONDUCT). https://clinicaltrials.gov/ct2/show/NCT01614457. Accessed April 15, 2015.
14. ClinicalTrials.Gov. Study of Ivacaftor in Cystic Fibrosis Subjects 2 Through 5 Years of Age with a CFTR Gating Mutation. ClinicalTrials.Gov Identifier: NCT01705145. https://clinicaltrials.gov/ct2/show/NCT01705145?term=KIWI+study&rank=2. Accessed April 27, 2015.
15. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014;13(6):674-680. doi:10.1016/j.jcf.2014.09.005.

Appendix 1: Abstracts of Clinical Trials

1. De Boeck K1, Munck A2, Walker S3, Faro A4, Hiatt P5, Gilmartin G6, Higgins M6. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014 Dec;13(6):674-80. doi: 10.1016/j.jcf.2014.09.005. Epub 2014 Sep 26.

BACKGROUND:
Ivacaftor is used to treat patients with CF and a G551D gating mutation; the KONNECTION study assessed the efficacy and safety of ivacaftor in patients with CF and a non-G551D gating mutation.

METHODS:
Patients with CF ≥6-years- old with non-G551D gating mutations received ivacaftor 150mg q12h or placebo for 8weeks in this 2-part, double-blind crossover study (Part 1) with a 16-week open-label extension (Part 2). The primary efficacy outcome was absolute change in FEV1 through 8 and 24weeks of ivacaftor treatment; secondary outcomes were changes in BMI, sweat chloride, and CFQ-R and safety through 8 and 24weeks of treatment.

RESULTS:
Eight weeks of ivacaftor resulted in significant improvements in percent predicted FEV1, BMI, sweat chloride, and CFQ-R scores that were maintained through 24weeks. Ivacaftor was generally well tolerated.

CONCLUSIONS:
Ivacaftor was efficacious in a group of patients with CF who had selected non-G551D gating mutations.

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions
1 ivacaftor.mp 65
2 Kalydeco.mp 11
3 cystic fibrosis.mp. or Cystic Fibrosis/ 23507
4 1 or 2 65
5 3 and 4 65
6 limit 5 to yr="2014-Current" 21
7 Limit 6 to (clinical trial or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews) 2

Both of the resulting two studies were published in March 2014 and were included in the previous update.

Ivacaftor (Kalydeco®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which ivacaftor has demonstrated to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of cystic fibrosis and is 6 years of age or older?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness)
3. Does the patient have a documented G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene?	Yes: Go to #4	No: Pass to RPH; Deny (medical appropriateness)
4. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	Yes: Go to #5	No: Pass to RPH; Deny (medical appropriateness)
5. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated: - Dornase alfa (Pulmozyme®) AND - Hypertonic saline (Hyper-Sal®) AND - Inhaled or oral antibiotics (if appropriate)	Yes: Go to #6	No: Pass to RPH; Deny (medical appropriateness)
6. Is ivacaftor dosed at no more than 150 mg twice daily (or appropriately dosed based on drug-drug interactions)?	Yes: Approve for 6 months	No: Pass to RPH; Deny (medical appropriateness)

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal?	Yes: Go to #2	No: Go to #3
2. Does the patient have documented	Yes: Go to #3	No: Pass to RPH; Deny (medical

response to therapy? Document response (e.g. improvement in FEV_1, weight gain, reduction in exacerbations or sweat test).		appropriateness)
3. Has the patient been compliant with therapy, as determined by refill claims history or as reported by requestor?	Yes: Go to #4	No: Pass to RPH; Deny
4. Is ivacaftor dosed no more than 150 mg twice daily (or appropriately dosed based on drug-drug interactions)?	Yes: Approve for 6 months	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Ivacaftor is not effective in patients with Cystic Fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene.
• Ivacaftor has not been adequately studied in populations with other mutations of the CFTR gene.

P&T Action: 5/15 (MH), 5/14, 6/12, 4/12
Revision(s): TBD
Initiated:

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Anticoagulants (oral and injectable)

Month/Year of Review: May 2015
Last Review: July 2014
New Drug Evaluation: Edoxaban (Savaysa®)

End date of literature search: March 2015

Dossier Received: Yes

Current Status of PDL Class:

- Preferred Agents: Lovenox® (branded product), dalteparin, unfractionated heparin (UFH), warfarin
- Non-Preferred Agents: enoxaparin, fondaparinux, rivaroxaban, dabigatran, apixaban

Current Prior Authorization (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.

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 prevention of stroke or systemic embolism in patients with atrial fibrillation (AF)?
- Is there and new evidence of differences in harms between the available anticoagulants products?
- Are there indications or subpopulations where one agent may be more effective or safer than other available agents?
- What is the evidence of efficacy and safety for edoxaban?

Conclusions:

- Canadian Cardiovascular Society Guidelines strongly recommend the DOAs in preference to warfarin, based on high-quality evidence from primary literature and meta-analyses, for patients with NVAF requiring anticoagulation. [1] This recommendation was based on evidence of non-inferiority to warfarin, with similar or less major bleeding and less risk of intracranial hemorrhage. American Academy of Neurology Prevention of Stroke in NVAF and the European Primary Care Cardiovascular Society (EPCCS) Consensus Guidance on Stroke Prevention in AF (SPAF) recommends all of the oral anticoagulant options, without preference, for patients with NVAF.[2,3] These recommendations were based on evidence from phase 3 trials. [4-7]
- There is moderate strength of evidence of no difference in efficacy between DOAs and standard therapy (enoxaparin and warfarin) in treating VTE, supported by indirect comparisons from four new systematic reviews.[8-11]

- There is moderate strength of evidence from a meta-analysis of 10 randomized controlled trials (RCT) that patients with mild (n=28,971) and moderate (n=11,722) renal insufficiency and AF, acute DVT or PE, or extended treatment of VTE that the DOAs are non-inferior to conventional anticoagulants with similar or less major bleeding or clinically relevant non-major bleeding (CRNM).[12]
- There is low strength of evidence that LMWH are superior to warfarin and placebo for the primary prophylaxis of VTE in patients with cancer.[13]
- Low strength of evidence demonstrated that DOA use in patients with VTE and cancer reduced the incidence of recurrent VTE and major bleeding when compared to conventional treatment of enoxaparin and warfarin.[14]
- There is moderate strength of evidence that edoxaban 60 mg daily and 30 mg daily are non-inferior to warfarin for the prevention of strokes and systemic embolism in patients with NVAF.[7] There is moderate strength of evidence, based on one good quality trial, that edoxaban 60 mg daily is non-inferior to warfarin for the treatment of VTE.[15]. Edoxaban is not recommended for patients with a CrCl >95 mL/min due to enhanced renal clearance, resulting in reduced efficacy in this population.[16]
- Common adverse reactions (≥1%) seen with edoxaban are: bleeding, anemia, rash and abnormal liver function tests.[16] There is moderate strength of evidence that both doses of edoxaban were associated with significantly less major bleeding and intracranial bleeds than warfarin in patients with NVAF and significantly more gastrointestinal (GI) bleeds in the high dose edoxaban group compared to warfarin.[7]

Recommendations:

- Atrial Fibrillation: Recommend removing the PA requirement for the DOAs, which are currently not preferred. Recommend all DOAs equally as an option for patients with NVAF and consider comparative pricing in executive session.
- VTE treatment: Recommend that all DOAs as options for the treatment of VTE and consider comparative pricing in executive session.
- Orthopedic Prophylaxis: Recommend all DOAs approved for orthopedic prophylaxis as options and consider comparative pricing in executive session.

Previous 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 NVAF based on high strength of evidence (SOE), however, clinical differences remain small. 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.[17,18]
- 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).[19] 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).[20,21] Low molecular weight heparins (LMWH) are preferred for long-term VTE prophylaxis in patients with cancer, based on high SOE.[22]
- 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.[23] There was no significant difference in efficacy outcomes between LMWH and dabigatran 220mg daily (strength not available).
- 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.[24]

Previous 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.
- Add "difficulty obtaining International Normalized Ratio (INR) monitoring" to questions #5 and #9 in Oral Direct Factor Xa Inhibitors PA criteria, and questions #3 and #8 in Oral Direct Thrombin Inhibitors PA.

Reasons for the Review:

A new factor Xa inhibitor, edoxaban, has received FDA approval for patients with NVAF and for the treatment of DVT and PE. The efficacy and safety evidence for edoxaban will be reviewed. Additionally, as the range of treatment options for patients requiring anticoagulation expands, new evidence becomes available. Data on DOAs 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 2014 will summarized.

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.[25] Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors.[26] Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) or factor Xa inhibition (rivaroxaban, apixaban and edoxaban).[27-30] Commonly used oral and injectable anticoagulants are presented in table 1.

Table 1. Anticoagulants – FDA Approved Indications[16,26-30]

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)	---	---
Edoxaban (Savaysa®)	---	+	+	---	---
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.[31] 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.[32] 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.[31]

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 GI bleeding.

VTE Prophylaxis

For patients undergoing total hip replacement (THR) or total knee replacement (TKR), prophylactic anticoagulants are considered standard practice. ACCP guidelines recommend the use of LMWHs over other available anticoagulants (moderate evidence).[32] A minimum treatment duration of 10-14 days is recommended (moderate evidence).[32] There is moderate evidence suggesting thromboprophylaxis be continued for up to 35 days from the day of the surgery.[32] 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.[26] 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. Guidelines favor LMWH over fondiparinux, apixaban, dabigatran, rivaroxaban or unfractionated heparin (UFH) based on moderate strength of evidence.[32]

4

For patients who are medically ill and at risk for VTE, prophylaxis is recommended with one of the following therapies; LMWH, UFH or fondaparinux.[32]

Acute VTE Treatment

ACCP guidelines recommend the use of LMWH, fondaparinux, intravenous (IV) UFH or subcutaneous (SC) UFH for the acute treatment of DVT and PE.[32] The treatment duration is indication dependent, however, long-term anticoagulation is recommended, ranging from 3 months to extended therapy.[32] 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.[32] American Society of Clinical Oncology recommends LMWH over VKAs for long-term anticoagulation, based on strong strength of evidence. Newer oral agents aren't recommended for patients with cancer due to insufficient evidence.[33]

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).[34] 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.[35] 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.[32,34]

Table2. $CHADS_2$ and CHA_2DS_2-VASc Classification Risk Stratification Scores for Subjects with Non-valvular AF[32,34]

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**

Treatments used for the prevention of embolic events in patients with AF are: warfarin, dabigatran, apixaban, rivaroxaban and edoxaban. 2014 AHA/ACC/HRS guidelines for the management of patients with AF recommend treatment with warfarin (level of evidence [LOE} A).[34] Dabigatran, apixaban and rivaroxaban are also recommended (LOE B) (edoxaban not approved at time guideline). AHA/ASA guidelines recommend warfarin and apixaban with a LOE A recommendation and dabigatran and rivaroxaban with a LOE B recommendation for patients with stroke or transient ischemic attack.[34]

5

Methods:

A Medline literature search beginning June 2014 (since last anticoagulant drug class update) and ending February 2015 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 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.

DERP – Literature Scan of Newer Anticoagulants

In March of this year the Drug Effectiveness Review Project (DERP) released a literature scan of their original drug class review of newer oral anticoagulants.[35] Literature focused on evidence for efficacy and harms of the DOAs in adults with AF, prevention or treatment of VTE in adults who are medically ill or VTE events in adults who have undergone orthopedic surgery. Dabigatran, apixaban, rivaroxaban and edoxaban were included treatments. Data from February 2014 to February 2015 was searched.

Edoxaban was approved in January of 2015 and evidence used for approval will be discussed in the new drug section of this document.

One new head-to-head trial comparing dabigatran (n=30) to rivaroxaban (n=30) in patients undergoing ablation of AF was published.[35] D-dimer levels were measured before the procedure, at the end of ablation and 24 and 48 hours after the procedure. D-dimer levels significantly increased following the procedure in patients taking rivaroxaban compared to patients on dabigatran. The clinical significance of this difference is unknown. A sub-analysis of patients with moderate renal impairment in the J-ROCKET AF trial, which compared rivaroxaban to VKA treatment in Japanese patients, was also reported.[35] Patients with a CrCl 30-49 mL/min were given a reduced dose of rivaroxaban, 10 mg once daily and patients with CrCl > 50 mL/min were given 15 mg once daily. The safety and efficacy of rivaroxaban compared to warfarin was similar in patients with moderate renal impairment and normal renal function. All other evidence presented in the DERP report was previously reviewed in the last DURM anticoagulant class update.

Systematic Reviews:

Sardar, et al. – Novel Oral Anticoagulants in Patients with Renal Insufficiency: A Meta-analysis of Randomized Trials

The focus of the review was to evaluate the efficacy and safety of the DOAs compared to conventional treatment in patients with renal insufficiency in studies with one or more comparators (warfarin or another VKA, LMWH, aspirin, or placebo). DOAS included were dabigatran, apixaban and rivaroxaban.[12] Ten trials satisfied the inclusion criteria, which included patients with AF, acute DVT or PE, or extended treatment of VTE. Patients with severe renal insufficiency were excluded; rivaroxaban and dabigatran studies excluded patients with CrCl <30 mL/min and apixaban trials excluded those patients with CrCl < 25 mL/min. Patients with mild (CrCl 50-79 mL/min) and moderate (CrCl 30-49 mL/min) renal impairment were analyzed.

6

Patients with mild renal insufficiency (n=28,971) were included in the analysis. Rates of major bleeding or CRNM bleeding was less in patients treated with DOAs compared to conventional treatment (OR 0.81; 95% CI, 0.72-0.90; NNT 143), which was similar for individual treatment comparisons.[12] DOAs were associated with significantly less stroke or systemic embolism than conventional treatments in patients with AF (OR, 0.70; 95% CI, 0.54 to 0.92; p = 0.010, NNT 105). For the prevention of VTE or VTE-related death, the DOAs were non-inferior to conventional treatment. Major and CRNM bleeding was lower with DOAs compared to conventional treatment in patients with AF (OR, 0.80; 95% CI, 0.71 to 0.90) but not in those with acute VTE (OR, 0.85; 95% CI, 0.64 to 1.11).[12] Patients treated with DOAs compared to warfarin were found to have less major and CRNM bleeding but similar rates when compared to LMWH or LMWH followed by VKA.

In over 11,000 patients with moderate renal impairment, (n=11,722), there was no difference in major bleeding or CRNM bleeding in patients taking DOAs compared to conventional treatment when using a random effects model (OR, 0.82; 95% CI, 0.59 to 1.14).[12] Significantly less major bleeding and CRNM bleeding in patients taking DOAs compared to conventional treatment when using a fixed effects model, though a random effects model is more appropriate when assessing rare binary outcomes such as bleeding.[12] DOAs were associated with significantly less risk of stroke or systemic embolism than conventional therapy (OR 0.72; 95% CI, 0.57 to 0.92; NNT 71).[12] VTE and VTE-related death rates were similar for DOAs and conventional therapy. In patients with AF or acute VTE, the risk of major or CRNM bleeding was similar in patients taking DOAs or other anticoagulants. The difference in major or CRNM bleeding was also not significantly different when warfarin, LMWH, LMWH followed by warfarin, aspirin or placebo was compared to DOAs.

Treatment of VTE

Four new systematic reviews indirectly comparing the DOAs in the treatment of VTE have been published since the last review.[8-11] Their findings demonstrate similar efficacy and safety of the DOAs to each other and to standard therapy (LMWH and VKAs). This evidence supports our previous conclusions.

Cochrane - Primary Prophylaxis for Venous Thromboembolism in Ambulatory Cancer Patients Receiving Chemotherapy

A Cochrane systematic review was done to determine the efficacy and safety of LMWHs for primary prophylaxis for VTE in patients undergoing chemotherapy.[13] Twelve randomized clinical trials were identified, involving 9861 patients. Most patients had advanced cancer. The primary outcomes for efficacy and safety were symptomatic VTE and major bleeding, respectively. In a comparison of LMWH to an inactive control and when compared to warfarin, LMWH was associated with a significant reduction in the risk of VTE. However, the differences in rates of VTE were not significant when LMWHs were compared to aspirin. Warfarin was associated with a non-significant decrease in the incidence of symptomatic VTE compared to LMWHs. No major bleeding was reported with LMWH or warfarin and low rates in patients taking aspirin (1%). The risk of major bleeding remains imprecise as data are associated with wide confidence intervals, thus limiting conclusions on safety.

Vedovati, et al. – Direct Oral Anticoagulants in Patients with VTE and Cancer

Ten studies were included in a systematic review of the efficacy of DOAs in patients with VTE and cancer.[14] Six of these studies were included in the meta-analysis for a total of 1132 patients. Drugs included were dabigatran, rivaroxaban, apixaban and edoxaban. All included studies used heparin and VKA combination as a comparator. The primary outcome was recurrent VTE but the rate of major bleeding and CRNM bleeding was also analyzed. The percentage of patients in each trial with cancer ranged from 2.5% to 9.4%. Recurrent VTE rates were lower in patients treated with DOAs compared to conventional treatment of enoxaparin and warfarin (OR 0.63; 95% CI, 0.37 to 1.10).[14] Major bleeding was also lower in patients treated with DOAs compared to conventional treatment, 3.2% and 4.2%, respectively. The DOAs may be a treatment option for patients with VTE and cancer but larger studies are needed.

New Guidelines:

2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

The Canadian Cardiovascular Society (CCS) updated their guidelines for AF in 2014.[1] No methodology for guideline development is outlined. The guideline implements a new simplified algorithm for determining appropriate candidates for anticoagulation therapy (Fig 1.). The first recommendation is that all patients with AF or atrial flutter (AFL) should be stratified based on risk of stroke (strong recommendation, high quality of evidence). Oral anticoagulant therapy is recommended for most patients aged ≥ 65 years or CHADS2 score ≥ 1 (strong recommendation, moderate-quality of evidence). Aspirin 81 mg daily is recommended for patients with no risk factors based on the algorithm (conditional recommendation, moderate-quality evidence). No anticoagulation therapy is recommended for patients with no risk factors (conditional recommendation, low-quality of evidence).

For patients with non-valvular AF, whom anticoagulation is indicated, dabigatran, rivaroxaban, apixaban or edoxaban are recommended in preference to warfarin (strong recommendation, high-quality evidence).[1] Dabigatran 150 mg twice daily compared to warfarin appears to be more favorable in patients < 75 years of age but less favorable in those aged ≥ 75 years. Dabigatran 110 mg twice daily is recommended for this older population, however, this dose is not currently available. Dabigatran has been associated with increased gastrointestinal bleeding compared to warfarin. In patients with estimated glomerular filtration rates (eGFR) of 30-50 mL/min/ 1.73 m^2, rivaroxaban or apixaban may be a better option than dabigatran due to less reliance on renal clearance. For patients with mechanical prosthetic valves, rheumatic mitral stenosis or eGFR of 15-30 mL/min/1.73m^2, warfarin is recommended (strong recommendation, moderate-quality of evidence). Patients at risk for stroke who refuse oral anticoagulants should be offered aspirin 81 mg per day with clopidogrel 75 mg daily (strong recommendation, high-quality of evidence). Patients that are candidates for cardioversion should receive at least 4 weeks of an oral anticoagulation

following procedure (conditional recommendation, moderate quality of evidence). Four weeks of anticoagulation is also recommended following immediate electrical cardioversion (strong recommendation, low-quality of evidence).

Fig. 1 Canadian Cardiovascular Society Algorithm[1]

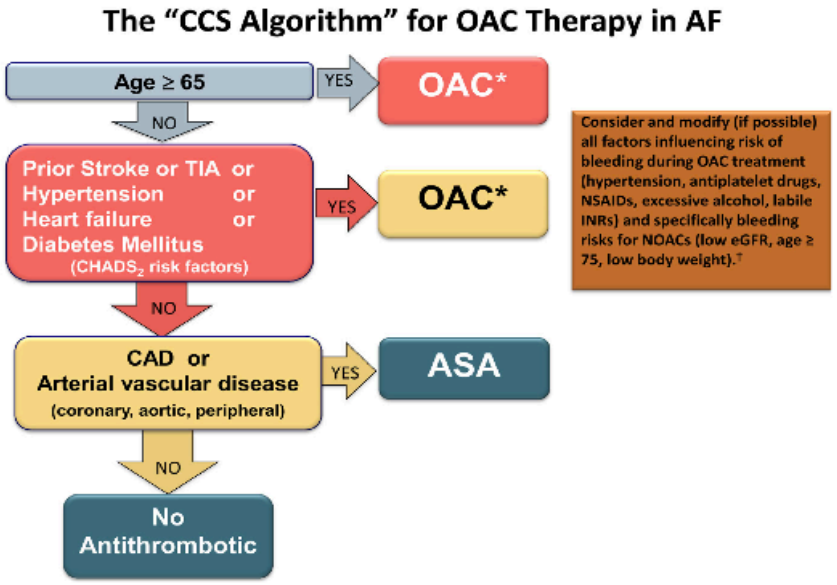

Figure 1. The simplified "CCS algorithm" for deciding which patients with atrial fibrillation (AF) or atrial flutter (AFL) should receive oral anticoagulation (OAC) therapy. * We suggest that a NOAC be used in preference to warfarin for non-valvular AF. † Might require lower dosing. ASA, acetylsalicylic acid; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NOAC, novel oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

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American Academy of Neurology – Summary of Evidence-based Guideline Update: Prevention of Stroke in Non-valvular Atrial Fibrillation

A systematic review of the literature was used to formulate recommendations regarding the prevention of stroke in patients with NVAF.[2] Edoxaban was not included in the recommendations. Recommendations were based on evidence and assigned levels of obligation (A,B,C,U) based on the modified Delphi process. The American Academy of Neurology recommends all patients be informed of increased risk of stroke with NVAF as well as the benefits and risks of treatment of anticoagulants (Level B). Patients with a history of TIA or stroke should be offered anticoagulation on a regular basis (Level B). Patients with low risk of stroke may be offered aspirin or no anticoagulation (Level C). Patients should be stratified by risk to determine the most appropriate patients for anticoagulation treatment (Level B). If anticoagulation is indicated, the following options should be considered based on current labeling: warfarin, dabigatran, rivaroxaban or apixaban (Level B). Patients already well controlled on warfarin should consider staying on warfarin treatment (Level C).[2] Patients with NVAF at higher risk of intracranial bleeding should be considered for dabigatran, rivaroxaban or apixaban therapy (Level B). Apixaban should be considered for patients requiring anticoagulation with a GI bleeding risk (Level C). Dabigatran, rivaroxaban or apixaban should be offered to patients unwilling or unable to submit to INR testing

(Level B). Apixaban should be offered to patients who are not candidates for warfarin treatment (Level B). If apixaban is unavailable, dabigatran or rivaroxaban should be considered (Level C). If anticoagulants are unavailable then aspirin and clopidogrel should be considered (Level C).

European Primary Care Cardiovascular Society (EPCCS) Consensus Guidance on Stroke Prevention in Atrial Fibrillation (SPAF) in Primary Care

The European Primary Care Cardiovascular Society recently updated their 2012 practice guidelines.[3] Recommendations are based on evidence from major clinical trials of DOAs and consensus expert recommendations. Recommendations are based on the NICE format, using wording such as a *strong* or *consider* which are applied to practice guidance. All of the recommendations presented below were strongly recommended.

The guidelines recommend the CHA_2DS_2-VASC scoring system, especially for patients with a $CHADS_2$ score of 1 or less, above the $CHADS_2$ system for determining stroke risk in patients with AF. Patients with a CHA_2DS_2-VASC score of 2 or above should be considered for anticoagulation.[3] Bleeding risks should be discussed with all patients (strong recommendation). Patients with mechanical heart valves or severe valve disease should be treated with a high intensity VKA. Warfarin (INR target of 2.5) or the DOAs should be considered for patients without mechanical valves or clinically significant valve disease. Patients unwilling or unable to take warfarin and patients that are unable to maintain a stable INR should be offered DOAs in preference to warfarin. Treatment adherence and the risks of benefits of treatment should be reviewed with all patients. In patients with a CrCl < 30 mL/min, dabigatran should not be used and factor Xa inhibitors should be used with caution.

NICE Guidance – Dabigatran Etexilate for the Treatment and Secondary Prevention of DVT and/or PE

The National Institute for Health and Care Excellence (NICE) has recommended that dabigatran be an option for treating DVT and PE and preventing recurrent DVT and PE in adults.[36] No specific preference for agents were recommended. This recommendation comes after a review of the primary literature, data submissions by the manufacturer and completion of a technology appraisal guidance.

NICE Guidance - Rivaroxaban for Preventing Adverse Outcomes After Acute Management of Acute Coronary Syndrome

Rivaroxaban with aspirin alone or with aspirin plus clopidogrel is recommended as an option for adults with acute coronary syndrome with elevated biomarkers for the prevention of atherothrombotic events.[37] This recommendation comes after a review of the primary literature and data submissions by the manufacturer and completion of a technology appraisal guidance.

Safety Alerts:

Black box warnings were updated for rivaroxaban on the timing of administration and neuraxial procedures and the risk of spinal/epidural anesthesia or puncture.[36] Apixaban prescribing information was updated with the warning of risk of thrombotic events upon premature discontinuation.[32] A drug safety communication was released for the risk of higher GI bleeding associated with dabigatran.[35]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Edoxaban was approved January 8, 2015 and is indicated for the reduction in the risk of stroke and systemic embolism in patients with NVAF and for the treatment of DVT and PE in patients already treated with 5-10 days of a parenteral anticoagulant.[16]

Non-valvular Atrial Fibrillation
The ENGAGE AF-TIMI 48 was a good quality, double-blind, double-dummy, phase 3 RCT in 21,105 patients with NVAF.[15] Patients were randomized to edoxaban 60 mg once daily (high-dose), edoxaban 30 mg once daily (low-dose) or warfarin (titrated to an INR of 2-3) and treated for a median of 2.5 years.[7] Patients were a median age of 72 years, 38% were female and a majority of patients had a CHADS2 score ≤3. Most common risk factors qualifying patients for treatment were advanced age, congestive heart failure and hypertension. Twenty-eight percent of patients in each group had a prior history of stroke or transient ischemic attack. Twenty-five percent of patients required a dosage reduction at time of randomization and 58% had previously used a VKA for at least 60 days. INRs were measured at least monthly with an encrypted point-of-care device, utilizing sham INR values in the edoxaban group to maintain blinding. The time in therapeutic range (TTR) was 65% for patients being treated with warfarin. The primary end point was a composite of stroke or systemic embolic event. Key secondary end points were all cause mortality and myocardial infarctions. Additional composite endpoints were included in the study, which may overestimate the treatment effect, and therefore are not presented.

High-dose edoxaban was noninferior to warfarin with 182 vs. 232 stroke or systemic embolic events, respectively (HR 0.79; 97.5% CI, 0.63 to 0.99; P<0.001 for noninferiority). Low-dose edoxaban was noninferior to warfarin with 253 events occurring in the edoxaban group compared to 232 in the warfarin group (HR 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiorty.[7] The noninferiority delta was set at 1.38 which preserved 50% of benefit of warfarin over placebo. The primary endpoint was driven by ischemic strokes. Hemorrhagic stroke rates were significantly lower in the high-dose and low-dose edoxaban groups compared to warfarin, with 49 events, 30 events and 90 events, respectively. Incidences of ischemic strokes were similar between high-dose edoxaban (n=236) and warfarin (n=235). Low-dose edoxaban was associated with a significantly higher rates of ischemic strokes compared to warfarin, HR 1.41 (95% CI, 1.19 to 1.67; P<0.001). All-cause mortality was significantly lower with low-dose edoxaban group compared to warfarin with an absolute risk reduction (ARR) of 1.0% and number need to treat (NNT) of 100.[15] Myocardial events were not statistically different between groups. Primary outcome event rates were low and similar among groups during the 30-day transition period from randomized anticoagulant to open-label treatment.

Subgroup analyses on efficacy and safety data were predominately similar across subgroups such as $CHADS_2$ score and geographical region.[7] However, patients treated with high-dose edoxaban with a CrCl >95 mL/min had an increased incidence of ischemic stroke compared to warfarin. Therefore, edoxaban is not recommended in these patients. Edoxaban blood levels have been strongly correlated with the effectiveness of edoxaban. Patients previously treated with vitamin K therapy had similar rates of stroke and systemic embolism in both high-dose edoxaban and warfarin groups compared to those patients naïve to vitamin K therapy, who experienced significantly fewer stroke and systemic embolisms with high-dose edoxaban compared to warfarin. Those patients on low-dose edoxaban and amiodarone or aspirin had an enhanced treatment effect compared to patients on low-dose therapy without those agents. Patients requiring a dose reduction of edoxaban demonstrated less bleeding in both edoxaban groups compared to warfarin.

VTE Treatment

Edoxaban 60 mg once daily was compared to warfarin (adjusted to INR 2-3) in a good quality phase 3, double-dummy design, RCT of 8240 patients receiving at least 5 days of enoxaparin for the treatment of VTE.[15] Patients with an estimated CrCl of 30-50 mL/min, body weight of ≤60 kg or use of a potent P-glycoprotein inhibitor received a reduced dose of edoxaban 30 mg once daily. Patients received treatment for 3-12 months, depending upon physician preference. Patient characteristics were the following: 57% males, average age of 56 years, 70% Caucasian and a majority had no VTE risk factors. Forty-one percent of patients presented with PE (with or without DVT) and 59% of patients with DVT only. Patients randomized to receive warfarin had therapeutic INRs 64% of the time. The median treatment duration with enoxaparin was 7 days. The primary endpoint was occurrence of adjudicated symptomatic recurrent VTE, which included DVT or nonfatal or fatal PE. A key secondary endpoint was mortality. Additional composite endpoints were included in the study, which may overestimate the treatment effect, and therefore are not presented.

This study found edoxaban 60 mg once daily was noninferior to warfarin for the treatment of VTE, HR 0.89 (95% CI 0.70 to 1.13; P<0.001 for noninferiority).[15] Candidates for the reduced edoxaban dose of 30 mg once daily experienced the primary endpoint more than those on warfarin (hazard ratio [HR] 0.73; 95% CI, 0.42 to 1.26). Rates of death were similar between groups (3.2% for edoxaban and 3.1% for warfarin). Acute coronary events and cerebrovascular events were not statistically different between the groups. Overall attrition rates in the study were low.

Off-Label Uses

Edoxaban was studied in two poor quality trials in Japanese patients undergoing total knee arthroplasty and hip fracture surgery.[38,39] The dose of enoxaparin and edoxaban were lower than comparative trials due to the lower average body weight of Japanese patients (mean weight 60 kg), making the data less applicable to our fee-for-service population. For these reasons these trials are excluded from the review.

Study Limitations

These studies have limitations, which should be considered. The ENGAGE AF-TIMI 48 trial had a high attrition rate, which was a significant limitation in that trial. Patients taking antiretroviral therapy or cyclosporine were excluded from the VTE trial and therefore the efficacy of edoxaban in this population is unknown. Careful attention needs to be given to the patient's renal function since edoxaban is highly cleared by the kidneys and has reduced efficacy in patients with CrCl >95 mL/min with a 40% reduction in blood levels.

Clinical Safety:

The most common adverse reactions occurring in ≥5% of NVAF patients were bleeding and anemia. In patients with VTE, the most common adverse events (≥1%) were the following: bleeding, rash, abnormal liver function tests and anemia. In the ENGAGE AF-TIMI 48 trial, severe adverse reactions were similar for low and high dose edoxaban and warfarin (37%, 36% and 39%, respectively).[7] Major bleeding was significantly less in patients with AF treated with low dose edoxaban compared to warfarin (HR 0.47; 95% CI, 0.41 to 0.55; P<0.001) and high dose edoxaban (HR 0.80; 95% CI, 0.71 to 0.91; P<0.001).[11] Intracranial bleeding was also significantly less for low and high dose edoxaban compared to warfarin (0.6%, 0.9% and 1.9%, respectively). Gastrointestinal bleeds were similar in low dose edoxaban patients and patients treated with warfarin. High dose edoxaban was associated with significantly more GI bleeds than warfarin (HR 1.23; 95% CI, 1.02 to 1.50; P=0.03; and NNT 167).[7] In patients being treated for VTE, edoxaban was associated with less first major or CRNM bleeding compared to warfarin (8.5% vs. 10.3%, respectively; P=0.004).[15] Major bleeding and serious adverse events were similar in edoxaban and warfarin treated patients with VTE.[15]

Pharmacology and Pharmacokinetic Properties:[16]

Parameter	
Mechanism of Action	Edoxaban is a selective inhibitor of factor Xa and prothrombinase activity and blocks thrombin-induced platelet aggregation
Oral Bioavailability	62%
Distribution and Protein Binding	Distribution is biphasic. In vitro protein binding is 55%
Elimination	Renal 50%
Half-Life	10-14 hours
Metabolism	Hydrolysis to predominately metabolite M-4

Comparative Clinical Efficacy

Clinically Relevant Endpoints:
1) Mortality
2) Thromboembolic events (DVT, PE and stroke)
3) Major Bleeding (intracranial hemorrhage, gastrointestinal, etc.)
4) Myocardial infarctions

Primary Study Endpoints:
1) Stroke or systemic embolism
2) Recurrent symptomatic VTE
3) Composite of symptomatic PE and symptomatic and asymptomatic DVT
4) Major bleeding

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Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes (% of patients /yr)	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Giugliano, et al[7] (ENGAGE AF-TIMI 48) RCT, DD, DB, Phase 3, noninferiority study	1. Edoxaban 30 mg daily (E30)* 2. Edoxaban 60 mg daily (E60)* 3. Warfarin** (W) * Dose was halved if estimated CrCl was 30-50 ml/min, body weight of ≤60 kg or use of verapamil, quinidine or dronedarone.	Demographics: Age: 72 years Female: 38% $CHADS_2$ score ≤3: 78% $CHADS_2$ score 4-6: 22% Key Inclusion Criteria: Age ≥21 y; non-valvular AF; $CHADS_2$ ≥2 Key Exclusion Criteria:	ITT: 1.7034 2.7035 3.7036 mITT: 1. 7002 2. 7012 3. 7012 PP: 1. 4616 2. 4529 3. 4506 Attrition: 1. 2309	Primary Endpoint: **Composite of stroke or systemic embolic event:** E30: 253 (3.6%) E60: 182 (2.6%) W: 232 (3.3%) E30 vs. W for noninferiority: HR 1.07 (97.5% CI 0.87 to 1.31) E60 vs. W for noninferiority: HR 0.79 (97.5% CI 0.63 to 0.99)	 NA NA	Major Bleeding: E30: 1.61% E60: 2.75% W: 3.43% E30 vs. W: HR 0.47 (95% CI 0.41 to 0.55) P<0.001) E60 vs. W: HR 0.80 (95% CI 0.71 to 0.91) P<0.001) Any Intracranial bleeding:	 1.82% / 55 0.68% / 147	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Patients were randomized via a central, 24-hour, interactive, computerized response system. Performance: All personal involved in the study were masked to treatment assignment. Double-dummy design and sham INRs were used to conceal study groups. Detection: Outcome assessment was done by committee that was unaware of study assignment. Attrition: Overall attrition was high with 34% off the study drug at the end of the trial and similar between groups but only 245 patients without follow-up data Cox proportional time

	** Titrated to an INR of 2-3 Treatment duration: 2.5 years	- CrCl <30 ml/min - cardiac co-morbidities - dual antiplatelet therapy	(33%) 2. 2415 (34%) 3. 2417 (35%)	**Stroke:** E30: 360 (5%) E60: 281 (4%) W: 317 (5%) **Hemorrhagic stroke:** E30: 30 (0.43%) E60: 49 (0.70%) W: 90 (1.3%) E30 vs. W: HR 0.33 (95% CI 0.22 to 0.50; P<0.001) E60 vs. W: HR 0.54 (95% CI 0.38 to 0.77; P<0.001) **Ischemic stroke:** E30: 333 (4.73%) E60: 236 (3.35%) W: 235 (3.33%) E30 vs. W: HR 1.41 (95% CI 1.19 to 1.67; P<0.001) **Systemic embolism:** E30: 29 (0.41%) E60: 15 (0.21%) W: 23 (0.33%) <u>Secondary Endpoints</u>: **Death any cause:** E30: 737 (11%) E60: 773 (11%) W: 839 (12%) E30 vs. W: HR 0.87 (95% CI 0.79 to 0.96; p=0.006) **Myocardial infarction:** E30: 169 (2.4%)	NS E30 vs. W: 0.9%/111 E60 vs. W: 0.6%/167 E30 vs.W: 1.4%/ NNH = 71 E60 vs.W: NS NS E30 vs. W: 1%/100	E30: 0.26% E60: 0.39% W: 0.85% E30 vs. W: HR 0.30 (95% CI 0.21 to 0.43) P<0.001) E60 vs. W: HR 0.47 (95% CI 0.34 to 0.63) P<0.001) <u>Gastrointestinal bleeding:</u> E30: 0.82%) E60: 1.51%) W: 1.23%) E30 vs. W: HR 0.67 (95% CI 0.53 to 0.83) P<0.001) E60 vs. W: HR 1.23 (95% CI 1.02 to 1.50) P=0.03) <u>Discontinuations due to adverse effects*</u>: E30: 1093 (15.6%) E60: 1204 (17.2%) W: 1168 (16.7%) p-value not reported <u>Serious adverse events*</u>: E30: 2618 (37.4%) E60: 2530 (36.1%) W: 2698 (38.5%) p-value not reported	0.59%/ 170 0.46%/ 217 0.41%/ 244 NA	to event hazards ratio used to deal with missing data. mITT was appropriately used for non-inferiority analysis and ITT was used for superiority analysis. Non-inferiority delta was set at 1.38 which preserved 50% of benefit of warfarin over placebo. **Applicability**: <u>Patients</u>: A majority of participants had comorbidities: hypertension 94%, CHF 57%, diabetes 36%, and prior stroke 28%. Twenty-five percent required dose reduction at randomization. Fifty-nine percent had received previous VKA therapy. <u>Intervention</u>: Edoxaban 60 mg daily and edoxaban 30 mg daily. Approximately 25% of edoxaban patients required dose reduction primarily due to reduced renal function. <u>Comparator</u>: Time in therapeutic range was a median of 68% and a mean of 65% for patients taking warfarin. <u>Outcomes</u>: stroke and systemic embolism is an appropriate outcome to establish efficacy in patients with AF. Composite outcomes may overestimate treatment effect. <u>Setting</u>: Forty six countries and 1393 outpatient centers. **Analysis**: In patients with a moderate risk of stroke due to AF, high-dose edoxaban was noninferior to warfarin with less major and intracranial bleeding. Low-dose edoxaban was found to be non-inferior to warfarin by a small margin, with less major and intracranial bleeding.

				E60: 133 (1.9%) W: 141 (2.0%)	NS	* Events not annualized		
2. Hokusai-VTE Investigators[15] RCT, DB, DD, noninferiority, Phase 3 3-12 months treatment 12 months follow-up	1. Edoxaban 60 mg daily (E60)* 3. Warfarin** (W) All patients received at least 5 days of enoxaparin or unfractionated heparin. Median duration of treatment with heparin was 7 days. * Dose was halved if estimated CrCl was 30-50 ml/min, body weight of ≤60 kg or use of potent P-glycoprotein inhibitors. ** Titrated to an INR of 2-3 Follow-up median 9 months	Demographics: Age: 56 years Men: 57% Unprovoked DVT or PE: 65% CrCl ≥30 to ≤50 ml/min: 7% Key Inclusion Criteria: Age ≥18 y; Objectively diagnosed acute, symptomatic DVT or PE Key Exclusion Criteria: - CrCl <30 ml/min; Therapeutic heparin >48 h; - Received >1 dose of VKA - Cancer with indication for long-term LMWH - Additional indication for warfarin therapy - ASA >100 mg/day - dual antiplatelet therapy - CrCl <30 ml/min	ITT: 1.4143 2.4149 mITT: 1. 4118 2. 4122 PP: 1. 3937 2. 3955 Attrition: 1. 181 (4.4%) 2. 167 (4.1%)	Primary Endpoint: Recurrent symptomatic VTE: E60: 130 (3.2%) W: 146 (3.5%) HR 0.89 (95% CI 0.70 to 1.13; P<0.001 for non-inferiority) Secondary Endpoints: All Cause Mortality: E60: 132 (3.2%) W: 126 (3.1%) CIs or p-value not reported	NA NA	First major or clinically relevant nonmajor bleeding: E60: 349 (8.5%) W: 423 (10.3%) HR 0.81 (95% CI 0.71 , 0.94) P=0.004 for superiority Major Bleeding: E60: 56 (1.4%) W: 66 (1.6%) HR 0.84 (95% CI, 0.59 to 1.21; P=0.35 for superiority) Serious Adverse Events: E60: 503 (12.2%) W: 544 (13.2%) p-value not reported Discontinuations due to adverse effects: E60: 121 (2.9%) W: 105 (2.5%) p-value not reported	1.8% / 56 NS	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Web-based system with stratification according to diagnosis, edoxaban dose and temporary risk factors. Performance: Double-dummy design and sham INRs were used to conceal study groups. Detection: Outcome assessment was done by a committee that was unaware of study assignment. Attrition: Attrition was low overall (4%). mITT analysis with LOCF and Cox proportional hazards model were used for primary outcome. Non-inferiority delta set at HR=1.5 which corresponds to 70% of treatment effect of warfarin. **Applicability**: Patients: Sixty-five percent of patients had an unprovoked VTE. A majority (70%) of patients were Caucasian. Patients were treated for a median of 9 months. Time in therapeutic range was 64% for patient taking warfarin. Intervention: Edoxaban 60 mg daily. Comparator: Warfarin titrated to INR of 2-3. Time in therapeutic range was 63.5%. Outcomes: Recurrent VTE is an appropriate outcome for this indication. Setting: Patients were enrolled from 439 centers and 37 countries. Eighty-seven percent of patients were enrolled in US sites. **Analysis**: In patients with symptomatic DVT or PE, initially treated with a heparin, edoxaban was noninferior to warfarin with less major or clinically relevant nonmajor bleeding.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind; DD = double-dummy; DVT = deep vein thrombosis; FAS = full analysis set; INR = international normalized ratio; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number

needed to treat; PE = pulmonary embolism, PP = per protocol; VKA = vitamin K antagonists

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References:

1. Verma A, Cairns J, Mitchell B, et al. 2014 Focused update of the Canadian cardiovascular society guidelines for the management of atrial fibrillation. Canadian J of Cardiology 2014; 30:1114-1130.
2. Hobbs FDR, FMedSci, Taylor CJ, et al. European primary care cardiovascular society (EPCCS) consensus guidance on stroke prevention in atrial fibrillation (SPAF) in primary care. Eur J Prev Cardiol. 2015 Feb 20. pii: 2047487315571890. [Epub ahead of print].
3. Culebras A, Messe S, Chaturvedi S, et al. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation. Neurology 2014;82:716-724.
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Eng J Med 2009;361:1139-51.
5. Granger C, Alexander J, McMurray J, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011;365:981-92.
6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883-91.
7. Giugliano R, Ruff C, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. NEJM 2013;269:2093-2104.
8. Castellucci L, Cameron C, Le Gal G, et al. Clinical and Safety Outcomes Associated with Treatment of Acute Venous Thromboembolism – A Systematic Review and Meta-analysis. JAMA 2014;312:1122-1135. Doi: 10.1001/jama.2014.10538.
9. Van Der Hulle T, Kooiman J, Exter P.L., et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb and Hemost 2014;12:320-8.
10. Kang N, Sobieraj D. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. Thromb Research 2014;133:1145-1151. Doi: 10.1016/j.thromres.2014.03.035.
11. Hirschl M, Kundi M. New oral anticoagulants in the treatment of acute venous thromboembolism – a systematic review with indirect comparisons. Vasa 2014; 43:353-64. Doi: 10.1024/0301-1526/a000373.
12. Sardar P, Chatterjee S, Herzog E, et al. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. Canadian J of Cardiol 2014;30:888-897.
13. Di Nisio M, Porreca E, Otten HM, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev 2014; Aug 29;8:CD008500. Doi: 10.1002/14651858.CD008500.pub3.
14. Vedovati M, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer. CHEST 2015;147:475-483.
15. The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. NEJM 2013;369:1406-15.
16. Savaysa Prescribing Information. *Daiichi Sankyo, Inc*. Parsippany, NJ; 2015.
17. Bruins Slot KMH, Berge E. Factor Xa Inhibitors Versus Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients with Atrial Fibrillation. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.:CD008980. DOI:10.1002/14651858. CD008980.pub2.
18. National Institute for Health and Care Excellence. Atrial Fibrillation: the Management of Atrial Fibrillation. Available at: http://www.nice.org.uk/nicemedia/live/14573/68037/68037.pdf. Accessed on June 20, 2014.
19. Agnelli G, Buller H, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. New Engl J of Med 2013;369:799-808.
20. Schulman S, Kearon C, Kakkar A, et al. Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism. N Engl J of Med 2013;368:709-718.

Author: Kathy Sentena

21. Schulman S, Kakkar A, Goldhaber S, et al. Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis. Circulation 2014;129:764-772.
22. Lynman G, Khorana A, Kuderer N, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2013;31:2189-2204.
23. Adams S, McDuffie J, Lachiewicz P, et al. Comparative Effectiveness of New Oral Anticoagulants and Standard Thromboprophylaxis in Patients Having Total Hip or Knee Replacement. Ann Intern Med 2013;159:275-284.
24. Cohen A, Spiro T, Bueller H, et al. Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients. N Engl J of Med 2013;368(6):513-23.
25. Carson S, Selph S, Thakurta S. New Oral Anticoagulant Drugs. Drug Effectiveness Review Project 2013.(Draft)
26. Sanofi-Aventis. Lovenox Label. US Food and Drug Administration. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020164s093lbl.pdf. Accessed September 9, 2012.
27. Janssen Pharmaceuticals, Inc. Xarelto Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022406s001s002s003lbl.pdf. Accessed November 15, 2012.
28. Bristol-Meyers Squibb. Eliquis Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf. Accessed March 19, 2013.
29. Bristol-Meyers Squibb. Coumadin Label. US Food and Drug Administration. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Accessed February 4, 2013.
30. Boehringer Ingelheim Pharmaceuticals, Inc. Pradaxa Label. US Food and Drug Administration. 2012. Available at : http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022512s017lbl.pdf. Accessed March 19, 2013.
31. Guyatt, G, Eikelboom J, Gould M, et al. Approach to Outcome Measurement in the Prevention of Thrombosis in Surgical and Medical Patients. CHEST 2012; 141(2)(suppl):e185S-e194S.
32. Guyatt G, Akl E, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: Executive Summary. CHEST 2012; 141(2)(Suppl):7S-47S.
33. Lynman G, Khorana A, Kuderer N, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2013;31:2189-2204.
34. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation, J of the Amer Coll of Cardiol (2014), doi: 10.1016/j.jacc.2014.03.022.
35. Drug Effectiveness Review Project. Drug class review newer oral anticoagulant drugs. Preliminary Scan Report #2. March 2015.
36. National Institute for Health and Care Excellence. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE Technology Appraisal [TA327]. December 2014. Accessed March 25, 2015. Available at: http://www.nice.org.uk/guidance/ta327/chapter/3-the-companys-submission.
37. National Institute for Health and Care Excellence. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. NICE Technology Appraisal [TA335]. March 2015. Accessed March 25, 2015. Available at: http://www.nice.org.uk/guidance/ta335.
38. Fuji T, Wang CJ, Fujita S, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thrombosis Research 2014;134:1198-1204.
39. Fuji T, Fujita S, Kawai Y, et al. Safety and efficacy of edoxaban in patients undergoing hip fracture surgery. Thrombosis Research 2014;133:1016-1022.

Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SAVAYSA™ safely and effectively. See full prescribing information for SAVAYSA.

SAVAYSA (edoxaban) tablets for oral use
Initial U.S. Approval: 2015

WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN
(B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS
(C) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.
(A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN: SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used (5.1).
(B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS: Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance (2.4, 5.2, 14).
(C) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures (5.4).

INDICATIONS AND USAGE

SAVAYSA is a factor Xa inhibitor indicated:
To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) (1.1)

- *Limitation of Use for NVAF*
  SAVAYSA should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg) (1.1)

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant (1.2)

DOSAGE AND ADMINISTRATION

- Treatment of NVAF:
  Assess CrCL before initiating therapy (2.1)
  The recommended dose is 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min. Do not use SAVAYSA in patients with CrCL > 95 mL/min (2.1)
  Reduce dose to 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min (2.1)

- Treatment of DVT and PE:
  The recommended dose is 60 mg once daily (2.2)
  The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 60 mg, 30 mg, and 15 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)

WARNINGS AND PRECAUTIONS

- Bleeding: Serious and potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss (5.2)
- Mechanical heart valves or moderate to severe mitral stenosis: Use is not recommended (5.5)

ADVERSE REACTIONS

Treatment of NVAF: The most common adverse reactions (≥ 5%) are bleeding and anemia (6.1)
Treatment of DVT and PE: The most common adverse reactions (≥ 1%) are bleeding, rash, abnormal liver function tests and anemia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Anticoagulants: Avoid concomitant use (7.1)
- Rifampin: Avoid concomitant use (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing (8.3)
- Impaired renal function (CrCL 15 to 50 mL/min): Reduce dose (2.1, 2.2, 8.6)
- Moderate or severe hepatic impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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Author: Kathy Sentena

Date: May 2015

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Policy Evaluation: Prior Authorization of non-preferred oral anticoagulants

Background:

The Oregon Health Plan fee-for-service program (FFS) implemented prior authorization (PA) criteria for the use of dabigatran (Pradaxa™), rivaroxaban (Xarelto™) and apixaban (Eliquis™). The goal of the FFS PA policy was to limit use of the newer agents to patients intolerant or who had a contraindication to preferred anticoagulants and limit use to indications where there was evidence to support efficacy and safety. The dabigatran PA was implemented on April 9, 2012; the apixaban PA was implemented on January 1, 2013; and the rivaroxaban PA was implemented on April 9, 2013.

Dabigatran is an oral direct thrombin inhibitor with Food and Drug Administration (FDA) approved indications to prevent stroke in non-valvular atrial fibrillation, and to treat acute and chronic deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] Rivaroxaban and apixaban are oral direct factor Xa inhibitors approved for similar FDA indications as dabigatran, with an additional indication for postoperative DVT prophylaxis following total knee or hip replacement.[2,3] Edoxaban was not included in the PA policy. It is the most recent oral anticoagulant which was approved in 2015 for patients with non-valvular atrial fibrillation and for the treatment of DVT and PE. [4]

The place in therapy for the direct-acting oral anticoagulants (DOACs) is evolving as demonstrated by the Anticoagulant Class Update and clinical guidelines.[5] The American College of Chest Physician's 9th Ed. 2012 Executive Summary recommends low molecular weight heparin (LMWH) as the preferred agent for DVT prophylaxis in orthopedic surgery but DOACs are included as alternative first line agents.[6] In patients with non-valvular atrial fibrillation at high risk for stroke, dabigatran is recommended over dose-adjusted warfarin. However, in patients with a diagnosis of acute coronary syndrome (ACS) and valvular atrial fibrillation, warfarin is still recommended first.[6]

The National Institute for Health and Care Excellence Collaborative Implementation recommends including all DOACs as first line agents for their approved indications and specifying: "The drugs must therefore be made available for prescribing within their licensed indications, and should be automatically included in local formularies. Local arrangements for use of antithrombotic therapies in atrial fibrillation should be reviewed and policies developed for integration of DOACs into the care pathway."[7]

Currently, the FFS program lists warfarin, a vitamin K antagonist, and branded Lovenox™ (enoxaparin), a LMWH, as preferred anticoagulants. The FFS PA policy approves DOACs use for patients to treat non-valvular atrial fibrillation or acute or chronic DVT/PE. It also approves up to 35 days of rivaroxaban and apixaban for patients requiring short-term (<45 days) anticoagulation for DVT prophylaxis after total knee replacement or hip replacement. Patients meeting the diagnostic criteria must also be unable to take warfarin therapy or Lovenox™ due to one of the following reasons:

- Allergy
- Contraindications to therapy
- Drug-drug interactions
- Intolerable side effects
- Unstable International Normalized Ratio (INR) (warfarin only)
- Difficulty obtaining routine INR monitoring (warfarin only)

If criteria are met, patients may be approved for up to one year of DOAC use. If the criteria are not met, PAs will be denied with DOAC allowance of 14 days (or until the patient is deemed adequately anticoagulated). Adequate anticoagulation is recommended when switching patients from DOACs. Drug labeling indicates that patients switching from rivaroxaban or apixaban to other anticoagulants are at increased risk of thrombotic events.[2,3]

State Medicaid programs have implemented similar PA criteria for DOACs with minor variations. These programs encourage warfarin or LMWH use when possible, and have developed specific inclusion criteria for prior authorization of DOACs.[8,9] Locally, CareOregon has implemented similar PA criteria for DOACs with minor variations, including more stringent criteria for use in patients with atrial fibrillation. Unlike the FFS PA criteria, CareOregon requires patients with atrial fibrillation to have additional thromboembolic risk factors in order to be approved for DOACs. Risk factors must include one or more of the following: history of stroke, TIA, or systemic embolism; age >75 years, hypertension, diabetes mellitus, moderately or severely impaired left ventricular systolic function or heart failure. CareOregon also limits dabigatran to patients with atrial fibrillation and will not approve its use in DVT.[10]

MODA Health and Providence are local commercial health plans that have taken a less restrictive approach toward DOACs. MODA Health PPO requires trial of or contraindication to rivaroxaban or apixaban before approving dabigatran.[11] However, there are no PA requirements in place for either rivaroxaban or apixaban.[12] Similarly, Providence Health Plan has neither PA nor step therapy criteria for rivaroxaban, apixaban, nor dabigatran.[13] These health plans are an example of the varying levels of restrictions placed on DOAC use. This variation reflects the current lack of literature evaluating outcomes or potential harms as a result of anticoagulation PA policies.

The aims of this policy evaluation are to: 1) describe anticoagulation utilization after the FFS PA policy was implemented to determine if DOACs are prescribed only for FDA indications, 2) quantify the number of patients switched from one anticoagulant to another, and 3) quantify number of patients encountering a PA for a DOACs that do not continue on any anticoagulant therapy.

Methods:

Patients were included if they had a paid FFS drug claim for any drug in Table 1 or a denied FFS drug claim for any drug in Table 1 with Explanation of Benefit (EOB) code 1056 (i.e. "PA Required") and simultaneously no EOB of 2017 (i.e. "Patient enrolled in MCO") from April 9, 2012 and through December 31, 2014. Patients were excluded if they had Medicare Part D coverage as indicated by benefit packages of BMM or BMD. Using only FFS claims, the *first anticoagulant paid or denied claim* per patient during the study period was designated the *index event*. Patients were excluded if they had less than 75% days of combined FFS or coordinated care organization eligibility from 4 months prior to the index month to 2 months after the index month (for a total of 7 months).

Table 1. Anticoagulant Drugs

HSN code	Route	Brand	Generic
007878	SUB-Q	ENOXAPARIN SODIUM	ENOXAPARIN SODIUM
007878	SUB-Q	LOVENOX	ENOXAPARIN SODIUM
002812	ORAL	COUMADIN	WARFARIN SODIUM
002812	ORAL	JANTOVEN	WARFARIN SODIUM
002812	ORAL	WARFARIN SODIUM	WARFARIN SODIUM
035604	ORAL	PRADAXA	DABIGATRAN ETEXILATE MESYLATE
035915	ORAL	XARELTO	RIVAROXABAN
037792	ORAL	ELIQUIS	APIXABAN

HSN = hierarchical ingredient code list (HICL) sequence number as reported by First DataBank™

Patients were categorized by whether the index event was a paid or denied claim. Patients were also categorized by the generic drug name of index event. Patients with a paid FFS or encounter claim at any time from January 1, 2012 through December 31, 2014 with an International Classification of Diseases (ICD-9) diagnosis code for each of the diagnostic groups (e.g. atrial dysfunction or thromboembolic events) from Table 2 or Table 3 were flagged.

Patients with paid index events were categorized in the following groups in order to describe drug switching.

1) New Anticoagulant start - no paid FFS or encounter anticoagulant claims within 102 days prior to *index event.*
2) Continuation Therapy - Patients where the *index event* is for the same generic drug as a paid FFS or encounter anticoagulant claim within 102 days prior.
3) Switch Preferred to DOAC - Patient where the *index event* is a DOAC and there is a previous warfarin or enoxaparin claim within 102 days prior.
5) Switch DOAC to Preferred – Patients where the *index event* is warfarin or enoxaparin and there is a previous paid FFS or encounter DOAC claim within 102 days.
6) Other - *Index event* does not fit in prior categories.

3

Patients with denied index events were categorized in the following groups to describe drug therapy disruption.

1) Anticoagulant > 90 days or no anticoagulant claims
2) Anticoagulant ≤ 14 days
3) Anticoagulant > 14 and < 90 days

The PA data was queried for all patients with denied index events. If a PA was requested for any anticoagulant within 5 days prior or ≤14 days after the index event they were counted as requesting a PA. The PA request could be for a different anticoagulant than the index event.

De-identified patient claim profiles were created for the following three patient groups: patients with paid DOAC claims; patients with denied DOAC claims who later received an anticoagulant within 14-90 days; patients with denied DOAC claims who received an anticoagulant >90 days or not at all. The de-identified patient profiles were reviewed for presence of diagnoses matching FDA labeled indications for anticoagulation and DOAC contraindications, precautions, or adverse events. Patients were labeled as having DOAC claim for FDA labeled indications if any diagnosis from Table 2 was found within the patient profile at any time, regardless of whether pre- or post-index date. Patients were labeled as having contraindications or precautions to DOAC use if any diagnosis from Table 3 was found within the patient profile at any time, regardless of whether pre- or post-index date. For patients denied a DOAC, adverse events were defined as any major clotting event (venous embolism, pulmonary embolism, or deep vein thrombosis) that occurred post-index date. For patients with paid DOAC claims, adverse events were defined as any major bleeding event (intracerebral hemorrhage or any major hemorrhage) that occurred post-index date.

Table 2. FDA Labeled Indications for warfarin, enoxaparin, dabigatran, rivaroxaban, or apixaban

	ICD-9 Code
Atrial Dysfunction	
Atrial fibrillation & atrial flutter	427.3x
Supraventricular premature beats	427.61
Thromboembolic Events	
Phlebitis & thrombophlebitis	451.xx
Other venous embolism & thrombosis	453.xx
Acute venous embolism & thrombosis of deep vessels of lower extremity	453.4x
Chronic venous embolism & thrombosis of deep vessels of lower extremity	453.5x
Personal history of venous thrombosis & embolism	V12.51
Pulmonary embolism & infarction	415.1x
Personal history of pulmonary embolism	V12.55
Orthopedic Procedures	
Total knee arthroplasty	81.54-81.55; V43.65
Total hip arthroplasty	81.51-81.53; V43.64, 820xx
Acute Coronary Syndrome	
Cardiac device in situ	V45.0x
Postsurgical aortocoronary bypass status	V45.81
Percutaneous transluminal coronary angioplasty status	V45.82
Angina pectoris	413.x
Acute myocardial infarction	410.xx

Table 3. Contraindications or precautions for DOACs

	ICD-9 Code
Valve Replacement	
Heart valve replaced by transplant	V42.2
Heart valve replaced by other means	V43.3
Valvular Disease/Dysfunction	
Other congenital anomalies of heart	746.xx
Anomalies of pulmonary valve congenital	746.0x
Diseases of mitral valve	394.x
Diseases of aortic valve	395.x
Disease of mitral & aortic valves	396.x
Disease of other endocardial structures	397.x
Diseases of tricuspid valve	397.0
Rheumatic diseases of pulmonary valve	397.1
Rheumatic diseases of endocardium valve unspecified	397.9
Cardiac	
Acute & subacute endocarditis	421.x
Aortic aneurysm & dissection	441.xx
Cranial Bleeding	
Subarachnoid hemorrhage	430
Intracerebral hemorrhage	431
Other & unspecified intracranial hemorrhage	432.x
Gastrointestinal	
Esophageal varices with bleeding	456.0
Esophageal varices in diseases classified elsewhere with bleeding	456.20
Hemorrhage unspecified	459.0
Ulcer of esophagus with bleeding	530.21
Gastric ulcer	531.xx
Duodenal ulcer	532.xx
Peptic ulcer	533.xx

Gastrojejunal ulcer	534.xx
Gastritis & duodenitis	535.xx
Gastrointestinal hemorrhage	578.x
Hematologic and Circulatory	
Hemorrhagic disorder due to intrinsic circulating anticoagulants	286.5x
Abnormality of red blood cells	790.0x
Abnormal coagulation profile	790.92
Coagulation defects	286.xx
Hepatic	
Chronic liver disease & cirrhosis	571.xx
Kidney Disease	
Acute kidney failure	584.x
Chronic kidney disease	585.x
Chronic kidney disease, stage IV	585.4
Chronic kidney disease, stage V	585.5
End stage renal disease	585.6
Other	
Purpura & other hemorrhagic conditions	287.xx
Other aneurysm	442.xx

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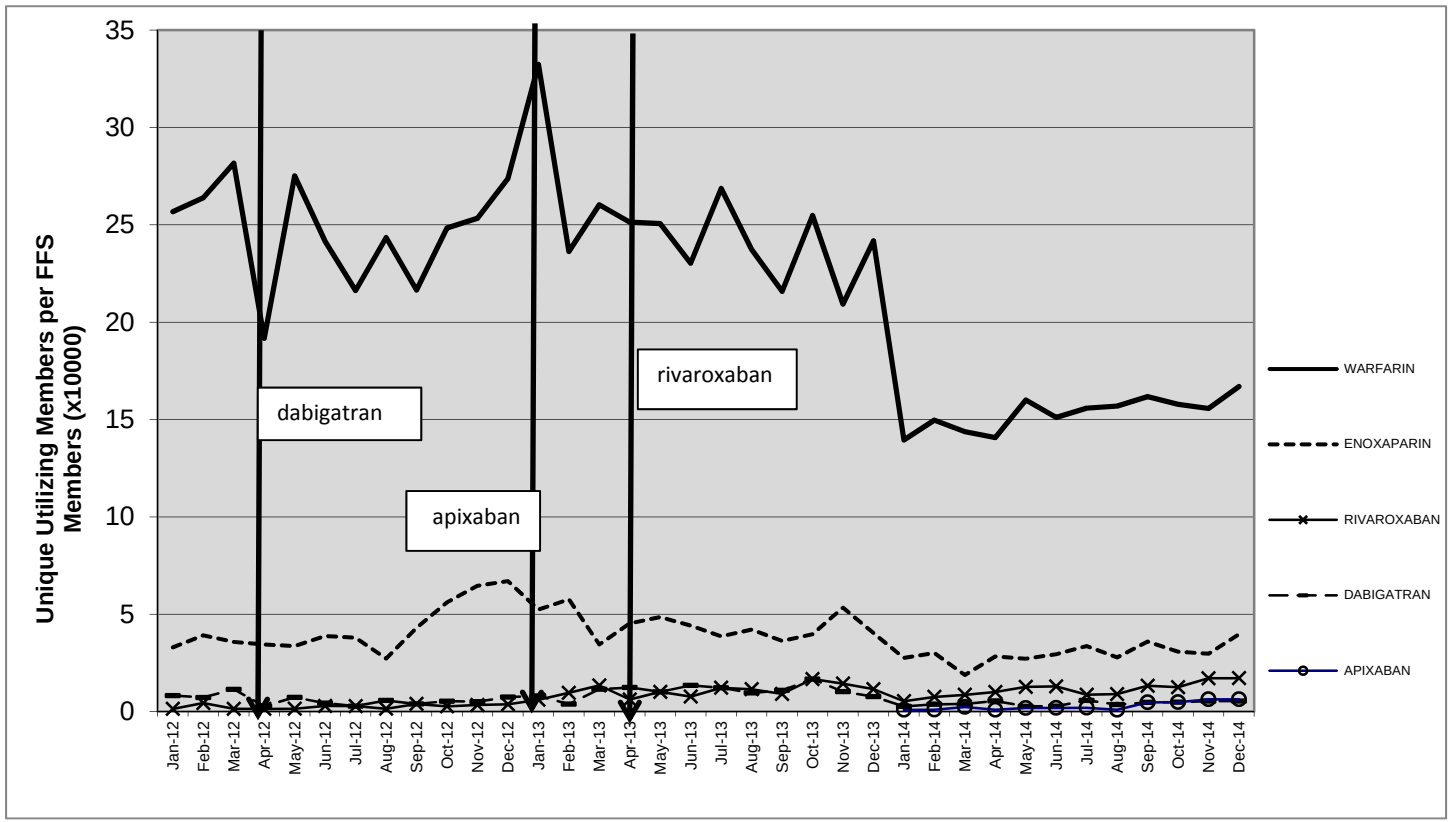
Results:

Figure 1 depicts the trend of anticoagulant usage per individual agent for the unique FFS patients with paid claims only. Warfarin was the most utilized anticoagulant; ranging from 14 patients per 10,000 FFS members to 34 patients per 10,000 FFS members per month). Enoxaparin was the second most utilized anticoagulant. There are no discernable trends at the implementation points for each PA but the warfarin use spiked down coincident of the dabigatran PA and spiked up coincident to the apixaban PA. Of the DOACs, rivaroxaban was prescribed most frequently; however, overall there was very low utilization of any DOAC. The seemingly decreased use seen in December 2013 corresponded with an increase in total number of patients enrolled due to the Affordable Care Act, rather than a true decrease in anticoagulant usage.

Figure 1. FFS Trend Line of Unique Patients per 10,000 members per Month for each Anticoagulant (January 1, 2012 – December 31, 2014)



There were 1,626 unique non-Medicare patients with FFS paid or denied anticoagulant claims identified between April 9, 2012 and December 31, 2014. After excluding patients with <75% of days of combined FFS and coordinated care organization eligibility from 4 months prior to the index month to 2 months after the index month (for a total of 7 months), 1,007 patients were included in the study. Of these patients, only 96 (9.5%) had a denied claim. Table 4 displays the patient demographics. The majority of patients (n= 961, 95.4%) fell in the age group of 19-64 years old. The mean age of patients included in the study was 47.3 years old, which was similar in patients with DOAC paid claims (47 years old) and denied claims (49.2 years old). There was a lower female rate for those with denied claims (39.6%), but the absolute numbers are very small. The study population was primarily self-identified as White (80.3%), with DOAC paid claims being slightly more diverse (70% White).

Table 4. Demographics of Study Population

	Total	Index = Denied
	1,007	**96**
Mean age (range)	47.3 (0-88)	49.2 (15-68)
<19 19-64 >64	28 (2.8%) 961 (95.4%) 18 (1.8%)	3 (3.1%) 91 (94.8%) 2 (2.1%)
Female	525 (52.1%)	38 (39.6%)
White	809 (80.3%)	74 (77.1%)

Tables 5 represents the distribution of paid (n=911, 90.5%) and denied (n=96, 9.5%) index claims by drug. The majority of paid index claims were for enoxaparin and warfarin, with only 20 (2.2%) for DOACs. There were 10 patients (10.4%) with denied claims for the non-preferred generic enoxaparin and the remaining balance of patients with denied index claims were for DOACs (n=86, 89.6%). It appears only 5 DOAC claims were subsequently paid for one of the preferred agents; 1 for enoxaparin and 4 for warfarin.

Table 5 also displays potential anticoagulation therapy disruptions after encountering a denied claim. Only 55 of the 96 (57.3%) denied patients received an anticoagulant within 14 days of the original denied claim. There were a total of 41 patients who did not receive an anticoagulant within 14 days. Twelve of these patients had a claim paid between 14 and 90 days after the denied index claim, while 29 patients received an anticoagulant after 90 days or not at all prior to December 31, 2014. Among the patients who received an anticoagulant between 14 and 90 days, the average number of days from the denied claim was 38.5 (15-89 days). No claims for enoxaparin were paid beyond 14 days, and all of the DOACs had similar percentages of subsequent paid claims within the 14-90 day period.

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Table 5. Drug Distribution

Total n=1007	**Index Drug Paid Claims**	**Total Index Drug Denied Claims**	*Index denied by **subsequent** paid anticoagulant claim*		
			≤ 14 days Mean = 4.7 (1-14)	*Between 14-90 days Mean= 38.5 (15 – 89.5)*	*>90 days or never*
Generic Name	**n=911**	**n=96**	*55*	*12*	*29*
ENOXAPARN	233 (25.6%)	10 (10.4%)	*11 (20.0%)*	*0 (0%)*	*NA*
WARFARIN	658 (72.2%)	0 (0%)	*4 (7.3%)*	*2 (16.7%)*	*NA*
DABIGATRAN	7 (0.8%)	24 (25.0%)	*12 (21.8%)*	*3 (25.0%)*	*NA*
RIVAROXABAN	12 (1.3%)	52 (54.2%)	*26 (47.3%)*	*3 (25.0%)*	*NA*
APIXABAN	1 (0.1%)	10 (10.4%)	*2 (3.6%)*	*4 (33.3%)*	*NA*

Table 6 shows the PA status for patients with a denied index claim by the drug requested, not by the originally denied index drug. A total of 56 PAs were requested for 54 patients, with 100% approval. Of the 56 total PA requests, 87.5% (n=49) were for one of the DOACs, and only 12.5% (n=7) for generic enoxaparin.

Table 6. Prior authorization status for patients with denied index claim, by *drug requested (not index drug)*

		PA Requested*	PA Approved	PA Denied
HSN	Generic	**54 (56.3%)**	**54 (100%)**	**0**
007878	ENOXAPARN	7	7	-
002812	WARFARIN	0	0	-
035604	DABIGATRAN	13	13	-
035915	RIVAROXABAN	33	33	-
037792	APIXABAN	3	3	-

**Requests made 5 days prior or ≤14 days after index claim*

Table 7 displays the diagnoses for the 20 patients with paid DOAC index claims. All 20 patients had claims with ICD-9 codes for FDA labeled indications. FDA indicated diagnoses found among the DOAC patients included atrial dysfunction, thromboembolic events, orthopedic procedures, and ACS. However, among the 20 patients with paid DOAC claims, a cumulative of 14 contraindications or precautions were found. These primarily included valvular dysfunction, hepatic impairment, and kidney disease. Table 7 also shows that there was 1 adverse event post-index date among the 20 paid DOAC claims.

Table 7. Associated diagnoses for patients with paid DOAC index claims (n=20)

	DABIGATRAN	RIVAROXABAN	APIXABAN
	7	12	1
FDA Indications			
Atrial Dysfunction	3 (42.9%)	2 (16.7%)	-
Thromboembolic Events	-	5 (41.7%)	1 (100%)
Orthopedic Procedures	-	5 (41.7%)	-
Acute Coronary Syndrome	4 (57.1%)	-	-
Contraindications or Precautions			
Valve Replacement	-	-	-
Valvular Disease/Dysfunction	-	1 (8.3%)	1 (100%)
Cardiac	-	-	-
Cranial Bleeding	-	-	-
Gastrointestinal	1 (14.3%)	1 (8.3%)	-
Hematologic and Circulatory	-	2 (16.7%)	-
Hepatic	1 (14.3%)	1 (8.3%)	-
Kidney Disease	2 (28.6%)	2 (16.7%)	1 (100%)
Other	1 (14.3%)	-	-
Adverse Events			
Unspecified Hemorrhage	-	1 (8.3%)	-

Table 8 displays additional details about the patients with denied DOAC index claims who did not have a subsequent paid anticoagulant within 14 days (n=41). The numbers listed in Table 8 are cumulative counts. Thirty-two patients (78.0%) had FDA labeled indications for anticoagulation. However, 18 of these 41 patients (43.9%) had contraindications or precautions to DOAC therapy and 6 of the 41 patients (17.1%) had an adverse event post-index date.

Table 8. Associated diagnoses for patients with denied DOAC index claims and no anticoagulant within 14 days (n=41)

	Denied DOAC with subsequent claim between 14-90 days after denial	Denied DOAC with subsequent paid anticoagulant claim >90 days or never
	12	**29**
FDA Indications		
Atrial Dysfunction	9 (75.0%)	7 (24.1%)
Thromboembolic Events	3 (25%)	10 (34.4%)
Orthopedic Procedures	-	4 (13.8%)
Acute Coronary Syndrome	2 (16.7%)	-
Contraindications or Precautions		
Valve Replacement	2 (16.7%)	1 (3.4%)
Valvular Disease/Dysfunction	2 (16.7%)	1 (3.4%)
Cardiac	1 (8.3%)	1 (3.4%)
Cranial Bleeding	1 (8.3%)	-
Gastrointestinal	-	1 (3.4%)
Hematologic and Circulatory	3 (25%)	2 (6.9%)
Hepatic	2 (16.7%)	7 (24.1%)
Kidney Disease	4 (33.3%)	4 (13.8%)
Other	-	-
Adverse Events		
Thrombophlebitis of deep veins of upper extremities	1 (8.3%)	-
Acute Myocardial Infarction	1 (8.3%)	-
Cerebral artery occlusion with cerebral infarction	-	4 (13.8%)

Table 9 quantifies the amount of anticoagulant switching among patients with paid claims (n=911). Most patients were new anticoagulant starts (n=574, 63%) or continuation of previous therapy (n=312, 34.2%). Anticoagulant switches were rare overall (n=35, 3.8%) and the majority of therapy switching occurred from one preferred agent to a different preferred agent (n=34, 97.1%). Only 1 patient was switched from a preferred agent to a DOAC. No patients were switched between DOACs or from one DOAC to a preferred agent.

Table 9. Anticoagulation Therapy Switching

Total Paid Claims (n = 911)	
New start	574 (63.0%)
Continuation of same therapy	312 (34.2%)
Continuation therapy switches	35 (3.8%)
Preferred to different preferred	34 (97.1%)
Preferred to DOAC	1 (2.9%)
DOAC to preferred	0 (0%)
DOAC to different DOAC	0 (0%)

Discussion:

The study demonstrated higher utilization of preferred agents, warfarin and enoxaparin. The vast majority of patient had index events that were initially paid. DOACs made up nearly 90% of the patients with denied index claims. In total, the number of patients with index events for DOACs accounted for only 9.5% of the total anticoagulant prescribing. Several reasons may be attributable to the overall low rate of DOAC prescribing, including lack of reversal agents, concerns with adherence, and cost issues.

Currently there are no direct reversal agents on the market for any of the DOACs. While one reversal agent was recently granted Fast Track designation by the FDA, with several more agents in phase II and III clinical trials, bleeding complications remain a large fear among providers.[14-17] Other concerns regarding DOAC use is the potential for poor adherence due to more frequent medication administration, fewer monitoring requirements, shorter half-lives and higher patient drug costs as compared with warfarin or enoxaparin.[16,17] As prescribers become more familiar with DOACs and guidelines evolve, there may be an increase in total number of DOAC prescriptions. Additionally, the increase in newly enrolled patients due to the Affordable Care Act may impact the number of DOAC prescriptions beyond what was shown in this study.

The PA policy was successful at limiting use of DOACs to FDA approved indications. However, DOAC claims were approved in patients with possible contraindications or precautions to use. The only absolute contraindications to DOACs are mechanical prosthetic heart valve, serious hypersensitivity reactions, and active pathological bleeding.[1-3] The findings are limited by the inability to determine whether the diagnoses from Table 3 ("Contraindications & Precautions for DOACs") found in the patient profiles occurred before or after the paid DOAC claim. Additionally, some conditions such as dosing for renal impairment , only require dose adjustments or temporarily holding a drug for an acute situation (i.e. acute kidney failure).[1] In some situations the severity of the condition from patient profiles were unclear (i.e. "chronic kidney disease, unspecified") and could affect the determination of appropriateness of using DOACs. Overall, the

identification of contraindications to DOACs among patients with paid claims indicates potential risk and a gap in the policy that should be considered to ensure that these agents are used appropriately.

The policy did not lead to frequent switching from one anticoagulant to another, which was a concern upon implementation. This data is particularly important since the switch from DOACs to other anticoagulants has been shown to increase risk of thrombosis.[1-3]

Overall, if requested, 100% of anticoagulation PAs were approved. However, only 54 (56.3%) patients who were originally denied an anticoagulant had a PA later requested. This number is alarmingly low, but is consistent with trends from previous PA policy evaluations.[18] Additionally, it was discovered that only 57.3% of the patients with originally denied claims received subsequent anticoagulation therapy within 14 days of the denied claim. Furthermore, 12.5% of the denied patients didn't receive an anticoagulant until 14-90 days later and nearly one-third of patients did not receive an anticoagulant within 90 days or at all after having a denied claim. This signifies that many patients with an indication for anticoagulation therapy were potentially at risk for thrombotic events. The high number of patients not receiving anticoagulation within an appropriate time period was not due to PA denial, but rather due to PAs not having been requested at all by providers. This may be a consequence of the burdens associated with submitting a PA request, including time and administrative costs.[19]

Thrombotic risk is increased in patients who are not properly anticoagulated within an appropriate amount of time.[6] Among the 41 patients not receiving anticoagulation within 14 days of the denied claim, profile reviews discovered a cumulative of 6 adverse clotting events that occurred post-index date. Adverse events included 1 patient with thrombophlebitis of deep veins of the upper extremities, 1 patient with an acute myocardial infarction, and 4 patients with cerebral artery occlusions with infarction. While the adverse event dates recorded did occur post-index claim and denial, it cannot be determined that lack of anticoagulation therapy directly contributed to these events since the event dates were compiled from claims data and not patient medical records. Some patients may have already had a high baseline risk for clotting events regardless of the presence or absence of anticoagulation therapy.

The FFS program originally implemented prior authorization criteria for DOACs to promote safe and effective anticoagulation therapy, while also directing prescribing toward lower cost agents. This study showed that the policy successfully approved claims for DOACs in patients with FDA labeled indications. However, findings from this study also suggest that the presence of a PA policy may be a concern in itself. The low rate of PA requests submitted by providers after having encountered a PA, along with the many patients who did not subsequently receive anticoagulation therapy within an appropriate time period are both factors potentially leading to increased risk of thrombotic events. The risk posed by the patients not receiving anticoagulation is high enough to consider making changes to the current PA policy.

Recommendation:

1. Given the high risk to patients from anticoagulation disruption, the high incidence of disruption among patients encountering the prior authorization requirement and the apparent low use of the DOACs it is recommended the clinical PA for DOACs be discontinued.
2. It is recommended that a Retrospective DUR program be developed to monitor appropriate dosing and use in the presence of contraindications, as these remain a concern.
3. It is recommended the class utilization be reviewed again in one year given the evolving evidence and new drugs in the class.

References:

1. Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2015. Available at: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath= /Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed April 19.
2. Xarelto [package Insert]. Titusville, NJ: Janssen Pharmaceuticals Inc; 2011. Available at: http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf. Accessed April 11, 2015.
3. Eliquis [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2012. Available at: http://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed April 11, 2015.
4. Savaysa [package insert]. Parsippany, NJ: Daiichi Sankyo Inc; 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed April 19.
5. Sentena K. Anticoagulants Class Update. Oregon State University Drug Use Research and Management - Oregon Pharmacy & Therapeutics Committee Meetings & Agenda. March 2015. Available at: http://pharmacy.oregonstate.edu/drug-policy/oregon-pharmacy-therapeutics-committee/meetings-agenda. Accessed April 16, 2015.
6. Guyatt GH, Akl EA, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST 2012;* 141(2)(Suppl):7S–47S. Available at: http://journal.publications.chestnet.org/pdfaccess.ashx?ResourceID=8182188&PDFSource=13. Accessed April 11, 2015.
7. Cowie MR, Antoniou S, Bacon S, et al. NICE Implementation Collaborative. Consensus: Supporting local implementation of NICE guidance on use of the non-Vitamin K antagonist oral anticoagulants (NOACs) in non-valvular atrial fibrillation. Published June 2014. Available at: https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-nic-consensus-statement-on-the-use-of-noacs2. Accessed April 11, 2015.
8. Ohio Department of Medicaid. Ohio Medicaid Fee-For-Service Pharmacy Benefit Manager Program: Preferred Drug List. http://medicaid.ohio.gov/Portals/0/Providers/ProviderTypes/MedicaidDrugProgram/PharmacyandTherapeuticsCommittee/2014-07-29-PDLrevised.pdf. Published July 29, 2014. Approved October 1, 2014. Accessed April 11, 2015.
9. Colorado Department of Health Care Policy and Financing. Colorado Department of Health Care Policy and Financing Preferred Drug List (PDL). https://www.colorado.gov/pacific/sites/default/files/PDL_04-1-2014.pdf. Published July 1, 2013. Approved: April 1, 2014. Accessed April 11, 2015.
10. CareOregon: Medicaid Prior Authorization Criteria. April 1, 2015. Available at: http://www.careoregon.org/HealthPlans/MedicaidServicesOHP.aspx. Accessed April 19, 2015.
11. Moda Health Plan, Inc. Prior Authorization Requirements. December 1, 2014. Available at: https://www.modahealth.com/pdfs/odsadv/2014/prior_auth_guidelines.pdf. Accessed April 19, 2015.
12. Moda Health PPORx: 2014 Comprehensive Formulary. December 1, 2014. Available at: https://www.modahealth.com/pdfs/odsadv/2014/formulary.pdf. Accessed April 19, 2015.
13. Providence Health Plan Commercial Formulary. April 2015. https://healthplans.providence.org/~/media/Files/Providence%20HP/pdfs/pharmacy/Documents/commercialformulary.PDF/. Accessed April 19, 2015.
14. Perosphere Receives FDA Fast Track Designation for Investigational Anticoagulant Reversal Agent PER977. April 2, 2015. Available at: http://perosphere.com/documents/PerosphereFDAFastTrack.pdf. Accessed April 19, 2015.

15. Costin J, et al. Reversal agents in development for the new oral anticoagulants. Postgrad Med. 2014 Nov;126(7):19-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25387210. Accessed April 19, 2015.
16. Yeh CH, Gross PL, Weitz JI. Evolving use of the new oral anticoagulants for treatment of venous thromboembolism. Blood Journal. 2014 Aug; 124(7). Available at: http://www.bloodjournal.org/ content/124/7/1020?sso-checked=true. Accessed April 19, 2015.
17. Ansell J. Controversies in cardiovascular medicine: New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation. 2012;125:165-170. Available at: http://circ.ahajounrals.org/content/125/1/165.full. Accessed April 19, 2015.
18. Ketchum K. Oregon State University Drug Use Research and Management Program. Policy Evaluation: Combination Inhaler Prior Authorization. Published September 2014. Available at: http://www.orpdl.org/durm/meetings/meetingdocs/2014_11_20/archives/2014_11_20_ICSLABAPolicyEvaluation.pdf. Accessed April 19, 2015.
19. Morley CP, et al. The impact of prior authorization requirements on primary care physicians' offices: report of two parallel network studies. J Am Board Fam Med. 2013;26(1):93-95. Available at: http://www.jabfm.org/content/26/1/93.full. Accessed April 19, 2015.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Policy Review: Leuprolide (Lupron®)

Reason for Review: Puberty suppression in adolescents with gender dysphoria is now a funded condition on the Oregon Health Plan (OHP) Prioritized List. The goal of this review is to summarize current evidence of leuprolide for puberty suppression in adolescents with Gender Dysphoria to inform policy options.

Key Questions:

1) What are the current recommendations for using puberty suppression agents to treat gender dysphoria?
2) What is the evidence of efficacy and safety of leuprolide when used to suppress puberty?

Conclusions:

- Gender dysphoria falls on line 412 on the OHP List Prioritized Services and treatment is currently funded.[1]
- GnRH analogues are recommended to suppress puberty in adolescents with gender dysphoria. Therapy should be initiated at the first signs of physical changes of puberty, confirmed by pubertal levels of hormone, but no earlier than Tanner stages 2-3.

Recommendations:

- GnRH analogues appear to be safe and effective in reversibly suppressing puberty.
- Modify PA criteria presented at the end of this review to allow approval of leuprolide in adolescents with documented gender dysphoria at the beginning of puberty, confirmed by pubertal levels of hormone but no earlier than Tanner stages 2-3.

1

Background:

Gender dysphoria or gender identity disorder (GID) is recognized in the Diagnostic and Statistical Manual of Mental Disorders. Individuals with GID have a persistent and profound discomfort with their biological sex and a strong identification with the gender of the opposite sex. The diagnosis is made when this is manifested by unrelenting cross-gender thought and behavior. Children as young as 3 years of age may experience GID and cross-gender behavior. However, only 16% of children will continue to have persistent gender dysphoria into adolescence and adulthood. [2] Childhood GID without treatment leads to a minority of these children identifying as transsexual or transgender in adulthood; the majority will become comfortable with their natural gender over time.[3] GID that persists into adolescence is more likely to persist into adulthood.[3]

Children do not have the legal ability to provide informed consent and must rely on parents or legal guardians to make treatment decisions on their behalf. There is a lack of randomized controlled studies regarding treatment of GID in children and adolescence, so treatment decisions must rely on expert opinion. It is not currently possible to differentiate between preadolescent children in whom GID will persist and those who it will not.[3] Indeed, no long-term data has demonstrated a statistically significant effect on gender identity in adulthood.[3]

Ongoing psychological support of children and adolescents with GID should be offered. In addition, peripubertal adolescents with persistent GID may be treated with a gonadotropin-releasing hormone (GnRH) analogue to suppress puberty once it has commenced, followed later by cross-hormone therapy to promote physical development in the affirmed gender. This is done to reduce the psychological distress associated with unwanted pubertal development which can result in hormonal self-medication, self-harm or suicide. Current evidence suggests that hormone treatment to suspend the development of puberty is associated with good outcomes and a low level of regret.[2] Giving adolescents the time for continued psychological support during the process of either resolving GID or coping with its persistence may help adjustment in adulthood.[4]

In January 2015, the Oregon Health Evidence Review Committee (HERC) published a new OHP Prioritized List, with gender dysphoria placed on Line 412 (above the Funding Line). Guideline Note 127 provides guidance on the treatment of Gender Dysphoria. Hormone treatment is included on this line for the express purpose of delaying the onset of puberty and/or continued pubertal development with GnRH analogues for gender questioning children and adults. The guideline note states that therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of hormone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression.

Tanner proposed a scale to describe the onset and progression of pubertal changes that is uniformly accepted. Children are rated on a scale of 1-5 with 1 being preadolescent and 5 being fully developed. Males are rated for genital development and pubic hair growth. Girls are rated for breast development and pubic hair growth. Stage 2 is where sparse, long, pigmented, downy hair which is straight or only slightly curled appears, mainly along labia and at the base of the penis. [5] Stage 3 is where considerably darker, coarser, and curlier sexual hair appears, usually spread over the junction of the pubes. [5] GnRH analogues have been used to suppress puberty for treating central precocious puberty since the 1980s; however, the use of these agents to treat GID is relatively new.

Several preparations of GnRH are available, including leuprolide, goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas). Leuprolide is available as a daily subcutaneous injection, and a monthly and every 3 months IM depot injection. Histrelin and goserelin are available as implants. Triptorelin is available as an IM depot injection. Histrelin, goserelin and triptorelin are covered under the OHP medical benefit. GnRH analogues have demonstrated to be safe and effective in treating precocious puberty.[6–14] Administration of these agents results in initial stimulation of pituitary gonadotropin secretion, followed by complete but reversible suppression of the pituitary-gonadal axis and suppression of puberty. GnRH therapy does not appear to induce polycystic ovarian syndrome or have negative long-term repercussions on either bone mineral density or body composition.[15] Evidence is insufficient to identify agent-specific differences in outcomes, reproductive function, and health of offspring.[15]

Systematic Reviews:
None identified.

Guidelines:
The American Psychiatric Association released guidelines in 2012 on GID.[3] They make specific recommendations surrounding psychotherapeutic treatment of GID in childhood and adolescence. In cases where children's cross-gender identification is affirmed by mental health professionals and family members, children are supported in transitioning to a cross-gendered role with the option of endocrine treatment to suspend puberty in order to suppress the development of unwanted secondary sex characteristics. The guideline recommends that adolescents with GID have the option to suspend puberty medically in order to prevent or minimize development of unwanted secondary sex characteristics. Sexual reassignment surgery is not performed prior to the age of 18 years in the United States. There is insufficient evidence to support the development of a practice guideline for treatment of GID in either childhood or adolescence.

The Endocrine Society guidelines on the endocrine treatment of transsexual persons (2009)[16] recommends that adolescents who fulfill eligibility and readiness criteria for gender reassignment undergo treatment to suppress puberty in those who first exhibit physical changes of puberty, confirmed by hormone levels, but no earlier than Tanner stages 2-3. They recommend GnRH analogs be used to suppress puberty and hormones of cross-sex gender be used starting at age 16 years for pubertal development of the desired opposite sex. They also recommend that hormone-treated adolescents be referred for gender reassignment surgery when the real-life experience has resulted in a satisfactory social role change, the individual is satisfied with the hormonal effects, and the individual desires definitive surgical changes. They suggest deferring surgery until the individual is 18 years old.

References:

1. PRIORITIZED LIST OF HEALTH SERVICES. Oregon Health Authority. 201AD. http://www.oregon.gov/oha/herc/PrioritizedList/1-1-2015%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed April 15, 2015.
2. Steensma, T. D., Biemond, R., de Boer, F. & Cohen-Kettenis, P. T. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry* **16,** 499–516 (2011).
3. Byne, W. *et al.* Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* **41,** 759–796 (2012).
4. Hewitt, J. K. *et al.* Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med. J. Aust.* **196,** (2012).
5. Feingold, David. 'Pediatric Endocrinology' In Atlas of Pediatric Physical Diagnosis, Second Edition, Philadelphia. W.B. Saunders, 1992, 9.16-19.
6. Tanaka, T. *et al.* Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J. Clin. Endocrinol. Metab.* **90,** 1371–1376 (2005).
7. Walvoord, E. C. & Pescovitz, O. H. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* **104,** 1010–1014 (1999).
8. Pasquino, A. M. *et al.* Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. *J. Clin. Endocrinol. Metab.* **84,** 449–452 (1999).
9. Rosenfield, R. L. Selection of children with precocious puberty for treatment with gonadotropin releasing hormone analogs. *J. Pediatr.* **124,** 989–991 (1994).
10. Comite, F. *et al.* Luteinizing hormone releasing hormone analogue therapy for central precocious puberty. Long-term effect on somatic growth, bone maturation, and predicted height. *JAMA* **255,** 2613–2616 (1986).
11. Crowley, W. F. *et al.* Therapeutic use of pituitary desensitization with a long-acting lhrh agonist: a potential new treatment for idiopathic precocious puberty. *J. Clin. Endocrinol. Metab.* **52,** 370–372 (1981).
12. Comite, F. *et al.* Short-term treatment of idiopathic precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. A preliminary report. *N. Engl. J. Med.* **305,** 1546–1550 (1981).
13. Klein, K. O., Barnes, K. M., Jones, J. V., Feuillan, P. P. & Cutler, G. B. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J. Clin. Endocrinol. Metab.* **86,** 4711–4716 (2001).
14. Lazar, L., Pertzelan, A., Weintrob, N., Phillip, M. & Kauli, R. Sexual precocity in boys: accelerated versus slowly progressive puberty gonadotropin-suppressive therapy and final height. *J. Clin. Endocrinol. Metab.* **86,** 4127–4132 (2001).
15. Thornton, P. *et al.* Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev* **11,** 306–317 (2014).
16. Hembree, W. C. *et al.* Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **94,** 3132–3154 (2009).

Leuprolide Hormone Therapy

Goal:

- Approve for OHP-funded conditions in children and adolescents up to 16 years of age.

Length of Authorization:

Precocious puberty: through age 12 years in females, age 13 years in males.
Gender dysphoria: through age 16 years.

Requires PA:

- Leuprolide in children and adolescents through 16 years of age.

Approval Criteria		
1. What diagnosis is being treated and what is the age and gender of the patient?	Record ICD9 code and age/gender.	
2. Is the patient female and aged <13 years or male and aged <14 years?	Yes: Go to #3	No: Go to #4
3. Is the diagnosis central precocious puberty (CPP)? [precocious sexual development and puberty, ICD-9 259.1] • Note CPP is often associated with hydrocephalus, cranial irradiation, Silver-Russell syndrome, hypothalamic tumor, or hamartoma. • All above diagnoses and conditions are rare in children and adolescents.	Yes: Approve through: • Age 12 years for females • Age 13 years for males	No: Go to #4
4. Is the diagnosis gender dysphoria (ICD-9 302.6, 302.85)?	Yes: Go to #5	No: Pass to RPH; deny for medical appropriateness

4

Approval Criteria		
5. Does the request meet all of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience treating gender dysphoria? • At least 6 months of counseling and psychometric testing for gender dysphoria? • Prescriber is trained in puberty suppression using a gonadotropin releasing hormone agonist • Confirmation of puberty (physical changes and hormone levels) no earlier than Tanner Stages 2-3 (bilateral breast budding or doubling to tripling testicular volume)	Yes: Approve through • Age 16 years	No: Pass to RPH; deny for medical appropriateness
RPH only: All other indications need to be evaluated as to whether it is an OHP-funded condition. Refer unique situations to Medical Director of DMAP.		

5

P&T / DUR Action: *5/15 (AM); 9/07*
Revision(s): *5/15 (AM)*
Initiated: *Via Retro DUR 11/07, 7/1/09 via PA*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update with New Drug Evaluation: Ototopical Antibiotics

Month/Year of Review: May 2015

Date of Last Review: January 2010
Source Document: Provider Synergies, L.L.C.
Brand Name (Manufacturer): Xtoro (Alcon Laboratories, Inc.)

New Drug: Finafloxacin

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
- Is there evidence of superior clinical efficacy/effectiveness of one ototopical antibiotic or antibiotic/corticosteroid combination over another for clinical resolution of acute otitis externa or for acute otitis media specifically in patients with tympanostomy tubes?
- Is there evidence of decreased harms of one ototopical antibiotic or antibiotic/corticosteroid combination over another when used to treat acute otitis externa or for acute otitis media specifically in patients with tympanostomy tubes?
- Are there subgroups of patients based on demographics, concomitant medications, or co-morbidities for which one ototopical antibiotic or antibiotic/corticosteroid combination is more effective or associated with less harms when used for these conditions?

1

Conclusions and Recommendations:
- There is insufficient evidence that one ototopical antibiotic or antibiotic/corticosteroid combination has superior clinical efficacy or comparative effectiveness over another product for clinical resolution of acute otitis externa.
- There is insufficient evidence that either ofloxacin or ciprofloxacin/dexamethasone, the only ototopical drugs with FDA indications for treating otitis media specifically in patients with tympanostomy tubes, is more efficacious or safer than the other for this indication. Since these patients have received multiple systemic antibiotics for acute otitis media prior to getting tympanostomy tube placement, higher rates of antibiotic resistance may be noted in these patients and the use of a broad spectrum quinolone antibiotic is appropriate. There is insufficient evidence for all other ototopical antibiotics or antibiotic/corticosteroid combinations for this indication.
- There is low quality evidence that ototopical quinolone antibiotics or quinolone/corticosteroid combinations may be safer than ototopical aminoglycoside antibiotics in patients with tympanostomy tubes due to potential risk for adverse effects from systemic absorption of the aminoglycoside in the inner ear.
- Keep either ofloxacin or ciprofloxacin/dexamethasone as a preferred product for treatment of acute otitis media in patients with tympanostomy tubes.
- Keep at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
- Maintain finafloxacin as non-preferred due to its limited indication for otitis externa only and lack of comparative evidence, unless it is cost-effective.
- Review comparative drug costs in the executive session.

Purpose for Class Update:
The otic antibiotic drug class has not been formally reviewed by the Pharmacy and Therapeutics Committee since 2010. In addition, finafloxacin was recently approved as a new otic antibiotic by the U.S. Food and Drug Administration (FDA) in December 2014.

Previous Conclusions:
- No evidence was found to support a difference in efficacy/effectiveness between drug products of this class.
- No evidence was found to support a difference in harms between drug products of this class.

Background:
Acute otitis externa (AOE), also known as "swimmer's ear", is one of the most common infections encountered by clinicians.[1] In 2007, there were 2.4 million visits to ambulatory care centers and emergency departments for AOE, with 600,000 hours spent by clinicians treating AOE and one-half billions dollars in direct costs.[1] Half of all cases occur in children 5 to 14 years of age.[1] AOE is characterized by rapid onset and diffuse inflammation of the external ear canal, which may also involve to pinna or tympanic membrane.[1] Symptoms of AOE commonly include severe otalgia, itching or fullness and hearing loss may occur.[1] AOE is a cellulitis of the ear canal skin and subdermis that occurs with acute inflammation and edema.[1] Nearly all cases of AOE in North America are polymicrobial, the most common pathogens involving *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[1] Ototopical antibiotics are beneficial for AOE but oral antibiotics have limited utility.[1] Nonetheless, 20-40% of patients with AOE receive oral antibiotics, which are usually inactive against *P. aeruginosa* and *S. aureus*, have undesirable side effects, and serve to select out resistant organisms.[1] Bacterial resistance is less concern with ototopical antibiotics because the high local concentration of drug in the ear canal will eradicate all susceptible organisms plus those that may otherwise be resistant to systemically administered antibiotics (which only achieve concentrations at the site of infection several magnitudes lower than when topically administered).[1]

Acute otitis media (AOM) typically has an acute onset of symptoms with presence of otalgia, middle ear effusion and signs of acute middle ear inflammation.[2] AOM remains the most common condition for which antibiotics are prescribed for children in the U.S.[2] Insertion of tympanostomy tubes is primarily performed in children with recurrent AOM and persistent middle ear effusion in order to reduce the incidence of future infections and, should AOM occur with tubes in place, the ability to manage infections with ototopical antibiotics.[3] Tympanostomy tubes can serve as a drug-delivery device, allowing concentrated antibiotic eardrops to reach to middle ear space directly through the tube lumen and reducing the use of systemic antibiotics. Otorrhea is common after placement of tympanostomy tubes, with a mean incidence of 26% (range, 4%-68%) in observational studies.[3] Most otorrhea is sporadic, brief, and relatively painless, with recurrent otorrhea affecting only about 7% of patients and chronic otorrhea occurring in about 4%.[3] Acute delayed otorrhea is usually a manifestation of AOM and is caused by the typical nasopharyngeal pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[3] Conversely, when acute otorrhea occurs after water exposure (e.g., bathing or swimming) or in older children, it is often caused by external auditory canal pathogens such as *P. aeruginosa* and *S. aureus*.[3]

All ototopical antibiotic and antibiotic/corticosteroid combination have an indication for otitis externa. However, ofloxacin and ciprofloxacin/dexamethasone have additional indications for otitis media in children with tympanostomy tubes. In general, broad-spectrum quinolone drugs will cover *P. aeruginosa*, *S. aureus, S. pneumoniae*, *H. influenza* and *M. catarrhalis*. The relevant outcome for these antibiotics in clinical studies is resolution of AOE and AOM in patients with tympanostomy tubes, which implies clinical resolution of all signs and symptoms (e.g., pain, fever, otorrhea).

Methods:
A Medline literature search from 2010 to present for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Due to the differences in international bacterial susceptibility, only studies performed in the United States were considered.

Systematic Reviews:
None identified.

New Guidelines:
The American Academy of Otolaryngology—Head and Neck Surgery Foundation published a guideline for the management of AOE. The guideline makes a strong recommendation that clinicians should not prescribe oral antibiotics as initial therapy for diffuse, uncomplicated AOE unless there is extension outside the ear canal or specific factors that would indicate a need for systemic therapy. Instead, the guideline recommends clinicians use topical antibiotic preparations for initial therapy in these cases. If the patient fails to respond to the initial therapy within 48 to 72 hours, the patient should be reassessed. The guideline recognizes there are no significant differences in clinical outcomes of AOE for ototopical antiseptic versus ototopical antibiotic, ototopical quinolone antibiotic versus ototopical non-quinolone antibiotic, or ototopical antibiotic/corticosteroid combination versus antibiotic alone. Regardless of ototopical agent used, about 65% to 90% of patients have clinical resolution within 7 to 10 days.[1]

Total aggregate quality of evidence was graded as a "B" [*Evidence is based on RCTs or overwhelmingly consistent evidence from observational studies*], with high level of confidence in the evidence based on RCTs with minor limitations but no direct comparisons of ototopical versus oral antibiotic therapy for AOE. The benefit of using ototopical antibiotics is the avoidance of side effects and reduction in risk for antibiotic resistance. The recommendation for initial ototopical therapy applies to the otherwise healthy patient with diffuse AOE that is not complicated by osteitis, abscess formation, middle ear disease, or recurrent episodes of infection. Topical therapy should be supplemented by oral antibiotics if the patient has a condition, especially diabetes, that is associated with markedly increased morbidity, or immune deficiency that could otherwise impair host defenses; or if the infection has spread beyond the confines of the ear canal into the pinna, skin of the neck or face, or into deeper tissues such as occurs with malignant external otitis.[1]

The American Academy of Otolaryngology—Head and Neck Surgery Foundation also published a guideline for management of tympanostomy tubes in children. The guideline makes strong recommendations to clinicians to prescribe an ototopical antibiotic only, without oral antibiotics, for children with tympanostomy tubes with acute uncomplicated otorrhea. In these cases, there is discharge from the middle ear through the tube, usually caused by AOM or external contamination of the middle ear from water entry (swimming, bathing, or hair washing). As mentioned already, ototopical antibiotic therapy avoids adverse events associated with systemic antibiotics and mitigates risk for antibiotic resistance. Only ototopical ofloxacin or ciprofloxacin-dexamethasone products are approved for use with tympanostomy tubes. Aminoglycoside-containing eardrops (e.g., containing neomycin), which are used to treat acute otitis externa,

should be avoided in these patients due to increased risk of ototoxicity. Prolonged or frequent use of ototopical quinolone antibiotics may induce fungal external otitis so therapy should be limited to a single course of no more than 10 days.[3]

Total aggregate quality of evidence was graded as a "B" [*Evidence is based on RCTs or overwhelmingly consistent evidence from observational studies*], with high level of confidence in the evidence based on RCTs demonstrating equal efficacy of ototopical versus oral antibiotic therapy for otorrhea as well as improved outcomes with ototopical antibiotic therapy when different topical preparations are compared. The benefits of using ototopical antibiotics include increased efficacy by covering common pathogens, including *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), and avoidance of unnecessary overuse and adverse effects associated with oral antibiotics. Exceptions when systemic antibiotics are indicated include children with complicated otorrhea, cellulitis of adjacent skin, concurrent bacterial infection requiring oral antibiotics (e.g., bacterial sinusitis, group A strep throat), or children who are immunocompromised.[3]

The American Academy of Pediatrics published a clinical practice guideline on the diagnosis and management of AOM. The guideline does not specifically state ototopical antibiotic preparations as a viable treatment option and these products are not recommended for AOM except in cases when a tympanostomy tube is present.[2]

New Safety Alerts:
None identified.

New Formulations or Indications:
Xtoro (finafloxacin 0.3% otic suspension) for ototopical administration was approved by the FDA in December 2014 for the treatment of AOE caused by susceptible strains of *P. aeruginosa* and *S. aureus*.[4]

Randomized Controlled Trials:
Fourteen clinical trials were evaluated from the literature search. After further review, no studies were eligible because they did not specifically evaluate formulations currently available in the U.S.

NEW DRUG EVALUATION:

Xtoro (finafloxacin 0.3% otic suspension)

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations, if applicable.

Clinical Efficacy:

Two unpublished, multi-centered, double-masked, vehicle-controlled, randomized parallel-group studies were conducted and reviewed by the FDA for approval to treat AOE. A total of 686 (age range 11 months to 84 years) and 548 patients (age range 2 to 82 years) were randomized and treated at multiple centers across U.S., Canada and Puerto Rico in studies C-10-018 and C-10-19, respectively. Four drops of finafloxacin or vehicle were applied twice daily in the affected ear(s) for 7 days. The primary efficacy endpoint in these studies was the proportion of patients who achieved clinical cure at Day 11. A clinical cure was attained if the sum of the numerical scores for the signs and symptoms of AOE (tenderness, erythema and edema) was 0 at Day 11 (method of scoring was not specifically defined). The primary efficacy analysis was the pathogen positive subset of the ITT population which included all patients who received study medication and had cultures positive for *P. aeruginosa* and/or *S. aureus* at baseline in the study ear. In C-10-018, 283 patients (41.2%) were included in the ITT pathogen positive subset and in C-10-109, 277 patients (50.5%) were included. Of these patients, 72.3% were positive with *P. aeruginosa* and 27.7% were positive for *S. aureus* isolates. Results in Table 1 show there was a statistically significant difference in clinical cure rates of finafloxacin in both trials compared to placebo vehicle in these patients. Median days till cessation of ear pain was also statistically shorter for finafloxacin compared to placebo vehicle (4.0 days vs. 7.0 days for C-10-18 and 3.0 days vs. 6.5 days for C-10-19, respectively; p <0.0001 for both). The FDA found these results to be clinically significant in this population.[5]

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Table 1. Clinical Cure Rates of Acute Otitis Externa at Day 11 in Patients Positive for Bacterial Pathogens in Studies C-10-18 and C-10-19.[5]

Study C-10-18	Finafloxacin	Placebo Vehicle	Difference	(95% CI) P-value
Clinical Cure	104/145 (72%)	46/138 (33%)	38.4%	(27.6 to 49.1%) P <0.0001
Study C-10-19	Finafloxacin	Placebo Vehicle	Difference	(95% CI) P-value
Clinical Cure	101/147 (69%)	52/130 (40%)	28.4%	(17.4 to 40.0%) P <0.0001

An evidence table was not created for these studies due to lack of information concerning study methodologies and data analyses.

Clinical Safety:
Finafloxacin was well tolerated on both studies. Attrition due to adverse events was lower for patients receiving finafloxacin compared to placebo in Study C-10-18 (1.7% vs. 4.3%, respectively) but not in Study C-10-18 (4.4% vs. 2.5%, respectively). Discontinuation due to treatment failure was more common in patients receiving placebo vehicle in both studies.

Table 2. Overall Frequency and Incidence of Adverse Events Occurring at Rates of At Least 1.0% in Studies C-10-18 and C-10-19.

Adverse Event	Finafloxacin (n=618)	Placebo Vehicle (n=616)
Ear Discomfort	2 (0.3%)	9 (1.5%)
Ear Pain	3 (0.5%)	9 (1.5%)
Ear Pruritus	8 (1.3%)	6 (1.0%)
Headache	11 (1.8%)	18 (2.9%)
Otitis Media	8 (1.3%)	14 (2.3%)
Otitis Externa	11 (1.8%)	9 (1.5%)
Nausea	7 (1.1%)	1 (0.2%)

Look-alike / Sound-alike Error Risk Potential: none

Pharmacology and Pharmacokinetic Properties:

6

Table 2. Pharmacological Properties of Finafloxacin.[4]

Parameter	
Mechanism of Action	Inhibits DNA gyrase and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.
Bioavailability	Ototopical doses yielded quantifiable concentrations in 2 of 36 patients with acute otitis externa.

References:

1. Rosenfeld R, Schwartz S, Cannon C. Clinical Practice Guideline: acute otitis externa. *Otolaryngology - Head and Neck Surgery*. 2014;150:S1-S24.

2. Lieberthal A, Carroll A, Chonmaitree T. The Diagnosis and Management of Acute Otitis Media. *Pediatrics*. 2013;131(3):e964-e999.

3. Rosenfeld R, Schwartz S, Pynnonen M. Clinical Practice Guideline: tympanostomy tube in children. *Otolaryngology - Head and Neck Surgery*. 2013;149:S1-S35.

4. Xtoro (finafloxacin otic suspension) 0.3% [prescribing information]. Fort Worth, TX: Alcon Laboratories, Inc., Nov 2014.

5. Food and Drug Administration Center for Drug Evaluation and Research. Xtoro Summary Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206307Orig1s000SumR.pdf. Accessed March 5, 2015.

Appendix 1: Current Status on Preferred Drug List

Preferred Otic Antibiotics	**Non-preferred Otic Antibiotics**
COLISTIN SULFATE/NEOMYCIN SULFATE/THONZONIUM BROMIDE/HYDROCORTISONE ACETATE SUSP	CIPROFLOXACIN SOL 0.2%
OFLOXACIN SOL 0.3%	CIPROFLOXACIN/DEXAMETHASONE SUSP 0.3%/0.1%
NEOMYCIN/POLYMYXIN B/HYDROCORTISONE SUSP 3.5 mg per mL / 10,000 units per mL / 1%	CIPROFLOXACIN/HYDROCORTISONE SUSP 0.2%/1%
	NEOMYCIN/POLYMYXIN B/HYDROCORTISONE SOL 3.5 mg per mL / 10,000 units per mL / 1%

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use XTORO safety and effectively. See full prescribing information for XTORO*

XTORO (finafloxacin otic suspension) 0.3%
For topical otic administration
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
XTORO* is a quinolone antimicrobial indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill four drops in the affected ear(s) twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops), followed by 4 drops instilled into the affected ear twice daily for seven days. (2)

----------DOSAGE FORMS AND STRENGTHS----------
5 mL of finafloxacin otic suspension, 0.3% in 8 mL bottle. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Prolonged use of this product may lead to overgrowth of nonsusceptible organisms. Discontinue use if this occurs. (5.1)
Allergic reactions may occur in patients with a history of hypersensitivity to finafloxacin, to other quinolones, or to any of the components in this medication. Discontinue use if this occurs. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions occurring in 1% of patients with XTORO were ear pruritus and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9785 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 11/2014

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 2 2015

1 exp Otitis Media/ 9195
2 exp Otitis Externa/ 873
3 otic.mp. 1676
4 exp Administration, Topical/ or ototopical.mp. 46643
5 drops.mp. 8833
6 suspension.mp. or exp Suspensions/ 31690
7 exp Solutions/ or solution.mp. 248099
8 neomycin.mp. 3932
9 exp Ciprofloxacin/ 7184
10 exp Ofloxacin/ 4129
11 finafloxacin.mp. 9
12 1 or 2 9937
13 3 or 4 or 5 or 6 or 7 325457
14 8 or 9 or 10 or 11 14476
15 12 and 13 and 14 132
16 limit 15 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 79
17 limit 16 to yr="2010 -Current" 14

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Review: Oxazolidinone Antibiotics

Month/Year of Review: May 2015

Research Questions:

- What is the evidence of efficacy or effectiveness for linezolid versus tedizolid for treatment of the following infections caused by susceptible gram-positive bacteria: nosocomial pneumonia, community acquired pneumonia, complicated or uncomplicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis) or vancomycin-resistant *Enterococcus faicium* (VRE) infections.
- What is the evidence of harms for linezolid versus tedizolid for treatment of the following infections caused by susceptible gram-positive bacteria: nosocomial pneumonia, community acquired pneumonia, complicated or uncomplicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis) or VRE infections.
- Is there evidence for specific patient populations or sub-groups where linezolid or tedizolid would be more effective or less harmful for treatment of the following infections caused by susceptible gram-positive bacteria: nosocomial pneumonia, community acquired pneumonia, complicated or uncomplicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis) or VRE infections.

Conclusions:

- No evidence was identified to support the use of tedizolid for treatment of nosocomial pneumonia or community acquired pneumonia caused by gram-positive bacteria. No evidence was identified to support the use of tedizolid for treatment VRE infections.
- There is moderate quality evidence from 2 good quality randomized active control trials (n=1333) that tedizolid is non-inferior to linezolid for treatment of complicated skin and skin structure infections (excluding diabetic foot infections).
- There is insufficient evidence from 2 good quality randomized active control trials to evaluate differences in harms between tedizolid and linezolid.
- Tedizolid has not been evaluated in an adequate numbers of children or elderly patients.

Recommendations:

- Create a new Preferred Drug List Oxazolidinone Antibiotics Class including linezolid and tedizolid.
- Prefer linezolid because of proven benefit for multiple indications caused by susceptible gram-positive bacteria: nosocomial pneumonia, community acquired pneumonia, complicated or uncomplicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis) or vancomycin-resistant *Enterococcus faicium* (VRE) infections.
- Recommend implementing prior authorization criteria to restrict use of tedizolid to complicated skin and skin structure infections or other infections caused by gram-positive bacteria and not susceptible to other first-line therapies (see Appendix 3).

Author: Ketchum Date: 3/16/15

Purpose for Class Review:
Linezolid was approved in April 2000 and tedizolid was approved June 2014 as a second drug in the oxazolidinone class. The goal of this review is to compare both drugs for effectiveness and harms and to consider their potential management via the Preferred Drug List.

Background:
Linezolid was approved in April 2000 under a Food and Drug Administration (FDA) priority review based upon 9 unpublished controlled clinical trials of more than 4000 patients.[1] It was the first drug in a new class and only the second drug approved to treat vancomycin-resistant *Enterococci* (VRE). It is indicated for both adults and children and for several infections caused by susceptible gram-positive bacteria (Table 1). Its role has been primarily for multiple drug resistant organisms (e.g. methicillin-resistant *Staphylococcus aureus* [MRSA] and VRE). Vancomycin is the "gold standard" treatment for MRSA but there is some emergence of less-susceptible strains, increased nephrotoxicity with the higher doses and it is not orally bioavailable. Tedizolid was approved June 2014 for use only for adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria.

Nosocomial pneumonia can be associated with various pathogens and varies across hospitals and time frames. MRSA is one of the most common causes.[2] The Infectious Diseases Society of America recommends vancomycin or linezolid as first-line treatment for nosocomial pneumonia caused by MRSA.[3] *Streptococcus pneumoniae* is the most common community acquired pneumonia pathogen[4] but MRSA has been associated with 2.4% cases in a recent prospective cohort study.[5] Linezolid or vancomycin is recommended for community acquired pneumonia cases caused by confirmed MRSA.[4] VRE is often resistant to multiple antibiotic classes and this is a concern because the incidence is increasing in the United States.[6] VRE can infect multiple sites. Linezolid and daptomycin are recommended for strains not susceptible to ampicillin.

The FDA has defined acute bacterial skin and skin structure infections (ABSSSI) as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration). ABSSSIs include major cutaneous abscess, cellulitis and wound infections. It is estimated that approximately 45 – 60% of skin abscesses, 50% of purulent cellulitis, and >50% of purulent wounds are due to MRSA.[7,8] Linezolid is recommended empirically as a first-line alternative to vancomycin only for severe abscesses or purulent skin infections due to susceptible MRSA.[9] Linezolid is an effective oral alternative to vancomycin. Myelosuppression (anemia, thrombocytopenia, leukopenia and pancytopenia) have been reported during clinical trials of linezolid.[10] Tedizolid is a second generation oxazolidinone active against all clinically relevant gram-positive pathogens, is also available orally and intravenously but has only been evaluated for ABSSSI.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing

Drug Name (Manufacturer)	Indication(s)	Strength	Dose, Route and Frequency
linezolid (Pfizer)[10]	Treatment of the following infections caused by susceptible Gram-positive bacteria: 1) Nosocomial pneumonia 2) Community acquired pneumonia 3) Complicated or uncomplicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis) 4) Vancomycin-resistant *Enterococcus faicium* infections	- 600 mg film-coated tablets - 100 mg/5mL powder for oral suspension - 2 mg/mL (200 and 600 mg) in sterile isotonic solution for intravenous infusion	Adults: - 600 mg PO or IV Q12H Pediatrics: - 10 mg/kg PO or IV Q8H Pediatric skin infections: < 5 yrs.: 10 mg/kg PO Q8H; 5-11 yrs.: 10 mg/kg PO Q12H; >11 years: 600 mg PO Q12H x 10 – 28 days (varies by site & organism)
tedizolid (Cubist Pharmaceuticals)[11]	Treatment of acute bacterial skin and skin structure infections caused by designated susceptible bacteria.	- 200 mg tablet - 200 mg powder for reconstitution for IV infusion	Adults: - 200 mg PO or IV Q24H x 6 days

Abbreviations: MDRSP = multidrug-resistant *Streptococcus pneumonia; MRSA* = methicillin-resistant *Staphylococcus aureus;* PO = oral; IV = intravenous; Q = every; H = hours

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. No randomized controlled trials were found that evaluated tedizolid for nosocomial pneumonia, community acquired pneumonia or VRE. As such, this review will focus only comparisons of linezolid to tedizolid for ABSSSI.

Table 2. Summary of Pivotal Studies Completed

Study	Comparison	Population	Primary Outcome	Results	Quality*
ESTABLISH-1[12] (Phase-3, RCT, DB, MC, non-inferiority)	tedizolid 200 mg po QDay x 6 days vs. linezolid 600 mg po Q12H x 10 days	Adults with complicated ABSSSI caused by MRSA or other gram positive organisms	Clinical response @ the 48-72 assessment	ITT T: 264/332 (79.5%) L: 266/335 (79.4%) ARR: 0.1% 95% CI: -6.1 to 6.2 (within Δ of -10%) PP at end of treatment T: 219 / 273 (80.2%) L: 232 / 286 (81.1%) ARR: -0.9% 95% CI: -7.7 to 5.4 (within Δ of -10%)	Good
ESTABLISH-2[13] (Phase-3, RCT, DB, MC, non-inferiority)	tedizolid 200 mg IV QDay x 6 days vs. linezolid 600 mg IV Q12H x 10 days step down to oral allowed after 2 days if met criteria	Patients aged ≥15 years with complicated ABSSSI caused by MRSA or other gram positive organisms	Clinical response @ the 48-72 assessment	ITT T: 283 / 332 (85.2%) L: 276 / 334 (82.6%) ARR: 2.6% 95% CI: -3.0 to 8.2 (within Δ of -10%) PP at end of treatment T: 268 / 290 (92.4%) L: 269 / 280 (96.1%) ARR: -3.7% 95% CI: -7.7 to 0.2 (within Δ of -10%)	Good

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; DB = double-blind; ITT = intention-to-treat; H = hours; MC = multi-center; MRSA = methicillin-resistant *Staphylococcus aureus;* PP= per protocol; Q = every; RCT = randomized controlled trial. *Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

Systematic Reviews:
None identified that included both linezolid and tedizolid.

Guidelines:
The Infectious Diseases Society of America published updated practice guidelines for the diagnosis and management of skin and soft tissue infections in June 2014.[9] The guidelines used a systematic GRADE approach to weigh the strength of recommendations and quality of the evidence. Linezolid is a recommended alternative to vancomycin for serious purulent skin and soft tissue infections caused by MRSA.[9] Tedizolid was not reviewed for the guidelines.

References:

1. Linezolid (Zyvox). *The Medical Letter on Drugs and Therapeutics*. 2000;42(W1079A):45-47.

2. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010;51 Suppl 1:S81-S87. doi:10.1086/653053.

3. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18-e55. doi:10.1093/cid/ciq146.

4. Said MA, Johnson HL, Nonyane BAS, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS ONE*. 2013;8(4):e60273. doi:10.1371/journal.pone.0060273.

5. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Prevalence of methicillin-resistant staphylococcus aureus as an etiology of community-acquired pneumonia. *Clin Infect Dis*. 2012;54(8):1126-1133. doi:10.1093/cid/cis022.

6. Vancomycin-resistant enterococci (VRE) infection. In: *DynaMed [online Database]*. 2014th ed. United States: EBSCO Information Services; 2014. http://web.b.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=14&sid=e137b987-275c-41aa-8f18-113fca76ebf1%40sessionmgr114&hid=116&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=193562. Accessed March 13, 2015.

7. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. *BMC Infect Dis*. 2013;13:252. doi:10.1186/1471-2334-13-252.

8. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant S. aureus infections among patients in the emergency department. *N Engl J Med*. 2006;355(7):666-674. doi:10.1056/NEJMoa055356.

9. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2):147-159. doi:10.1093/cid/ciu296.

10. Zyvox Label. Pfizer. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021130s032,021131s026,021132s031lbl.pdf. Accessed March 13, 2015.

11. Sivextro Label. Cubist Pharmaceuticals. 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/0205435s001,0205436s001lbl.pdf. Accessed March 13, 2015.

12. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: The establish-1 randomized trial. *JAMA*. 2013;309(6):559-569. doi:10.1001/jama.2013.241.

13. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. *The Lancet Infectious Diseases*. 2014;14(8):696-705. doi:10.1016/S1473-3099(14)70737-6.

Appendix 1: Specific Drug Information

Table 3. Clinical Pharmacology and Pharmacokinetics

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
linezolid[10]	-binds to bacterial 23S ribosomal RNA of the 50S subunit - prevents formation of a functional 70S initiation complex (an essential component of the bacterial translation process) - bacteriostatic against enterococci and staphylococci. - bactericidal for majority of streptococci isolates	~ 100% orally bioavailable - not affected by food	- primarily oxidated resulting in two inactive metabolites. - In vitro studies suggest minimal P450 metabolism but the metabolic pathway of linezolid is not fully understood - non-renal clearance accounts ~65% -~30% appears in the urine	• Half-life: 4.7 – 5.4 hours • Cmax: 11 – 21 mcg/mL • AUC: 73 – 138 mcg*h/mL • Vd: 40-50 liters
tedizolid[11]	- binds to 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis - bacteriostatic against enterococci, staphylococci, and streptococci	~ 91% orally bioavailable - not affected by food	- tedizolid phosphate (prodrug) is ~95% converted to tedizolid; not found to otherwise metabolized - 82% excreted in feces; 18% in urine	• Half-life: 1.2 – 3.5 hours • Cmax: 2 - 3 mcg/mL • AUC: 25 - 29 mcg*h/mL • Vd: 67-80 liters (70-90% protein bond)

6

Table 4. Use in Specific Populations:

	FDA Pregnancy Category	**Pediatrics**	**Geriatrics**
linezolid[10]	C	Safe and effective in children from birth – 12 years for nosocomial pneumonia, ABSSSI, community acquired pneumonia, VRE	No differences in safety or effectiveness observed in patients >65 which comprised 29% of 2046 patients in Phase 3 studies.
tedizolid	C	Safety and effectiveness not established for those < 18 years old	Insufficient number of subjects >65 in Phase 3 studies

Drug Safety:

Black Boxed Warnings: NA

Contraindications: Patients taking any monoamine oxidase inhibitor (MAOI) or within two weeks of taking an MAOI (linezolid only)

Table 5. Summary of Warnings and Precautions

Warning/Precaution	**linezolid**[10]	**tedizolid**[11]
Myelosuppression: Monitor complete blood counts weekly. Consider discontinuation in patients who develop or have worsening myelosuppression.	X	safety not established
Peripheral and optic neuropathy: Reported primarily in patients treated for longer than 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.	X	
Serotonin syndrome: Patients taking serotonergic antidepressants should receive ZYVOX only if no other therapies are available. Discontinue serotonergic antidepressants and monitor patients for signs and symptoms of both serotonin syndrome and antidepressant discontinuation.	X	
A mortality imbalance was seen in an investigational study in linezolid treated patients with catheter-related bloodstream infections.	X	
Clostridium difficile associated diarrhea: Evaluate if diarrhea occurs.	X	X
Potential interactions producing elevation of blood pressure: monitor blood pressure	X	
Hypoglycemia: Post-marketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents.	X	

7

Appendix 2: Medline Search Strategy

1) Search for published evidence for tedizolid used for pneumonia or VRE indications

```
Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to March Week 2 2015> Search Strategy:
--------------------------------------------------------------------------------
      1     tedizolid.mp. (38)
      2     Torezolid.mp. (50)
      3     TR-701.mp. (18)
      4     TR-700.mp. (32)
      5     1 or 2 or 3 or 4 (71)
      6     gram-positive bacterial infections/ or exp staphylococcal infections/ or exp streptococcal infections/ or
      exp pneumonia, staphylococcal/ (122578)
      7     exp Vancomycin-Resistant Enterococci/ (23)
      8     exp Methicillin-Resistant Staphylococcus aureus/ (7946)
      9     6 or 7 or 8 (124584)
      10     5 and 9 (28)
      11     limit 10 to (English language and humans and (clinical trial, all or meta-analysis or randomized
      controlled trial or systematic reviews)) (2)
```

Prokocimer P, Bien P, Deanda C, Pillar CM, Bartizal K. In vitro activity and microbiological efficacy of tedizolid (TR-700) against Gram-positive clinical isolates from a phase 2 study of oral tedizolid phosphate (TR-701) in patients with complicated skin and skin structure infections. *Antimicrobial Agents & Chemotherapy.* 2012; 56(9):4608-13. 8

EXCLUDED – IN VITRO

Prokocimer P, Bien P, Surber J, Mehra P, DeAnda C, Bulitta JB, Corey GR. Phase 2, randomized, double-blind, dose-ranging study evaluating the safety, tolerability, population pharmacokinetics, and efficacy of oral torezolid phosphate in patients with complicated skin and skin structure infections.
Antimicrobial Agents & Chemotherapy. 2011;55(2):583-92.

ABSTRACT
Torezolid (TR-700) is the active moiety of the prodrug torezolid phosphate ([TP] TR-701), a second-generation oxazolidinone with 4- to 16-fold greater potency than linezolid against Gram-positive species including methicillin-resistant Staphylococcus aureus (MRSA). A double-blind phase 2 study evaluated three levels (200, 300, or 400 mg) of oral, once-daily TP over 5 to 7 days for complicated skin and skin structure infections (cSSSI). Patients 18 to 75 years old with cSSSI caused by suspected or confirmed Gram-positive pathogens were randomized 1:1:1. Of 188 treated patients, 76.6% had abscesses, 17.6% had extensive cellulitis, and 5.9% had wound infections. S. aureus, the most common pathogen, was isolated in 90.3% of patients (139/154) with a baseline pathogen; 80.6% were MRSA. Cure rates in clinically evaluable patients were 98.2% at 200 mg, 94.4% at 300 mg, and 94.4% at 400 mg. Cure rates were consistent across diagnoses, regardless of lesion size or the presence of systemic signs of infection. Clinical cure rates in patients with S. aureus isolated at baseline were 96.6% overall and 96.8% for MRSA. TP was safe and well tolerated at all dose levels. No patients discontinued treatment due to an adverse event. Three-stage hierarchical population pharmacokinetic modeling yielded a geometric mean clearance of 8.28 liters/h (between-patient variability, 32.3%), a volume of the central compartment of 71.4 liters (24.0%), and a volume of the peripheral compartment of 27.9 liters (35.7%). Results of this study show a high degree of efficacy at all three dose levels without significant differences in the safety profile and support the continued evaluation of TP for the treatment of cSSSI in phase 3 trials.

EXCLUDED – NOT CONTROLLED

2) Search for published evidence for tedizolid versus linezolid

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Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to March Week 2 2015> Search Strategy:
--------------------------------------------------------------------------------
1     tedizolid.mp. (38)
2     Torezolid.mp. (50)
3     TR-701.mp. (18)
4     TR-700.mp. (32)
5     1 or 2 or 3 or 4 (71)
6     linezolid.mp. (3414)
7     5 and 6 (48)
8     limit 7 to (English language and humans and (clinical trial, all or meta-analysis or randomized controlled
trial or systematic reviews))(10)
```

3 duplicates eliminated - 7 remaining articles)

1-Ong V, Flanagan S, Fang E, Dreskin HJ, Locke JB, Bartizal K, Prokocimer P. Absorption, distribution, metabolism, and excretion of the novel antibacterial prodrug tedizolid phosphate. *Drug Metabolism & Disposition*. 2014; 42(8):1275-84.

2-Flanagan SD, Bien PA, Munoz KA, Minassian SL, Prokocimer PG. Pharmacokinetics of tedizolid following oral administration: single and multiple dose, effect of food, and comparison of two solid forms of the prodrug. *Pharmacotherapy*. 2014; 34(3):240-50, 2014

3-Bien P, De Anda C, Prokocimer P. Comparison of digital planimetry and ruler technique to measure ABSSSI lesion sizes in the ESTABLISH-1 study. *Surgical Infections.* 2014; 15(2):105-10, 2014 Apr.

EXCLUDED – OUTCOME NOT OF INTEREST

4-Flanagan S, Bartizal K, Minassian SL, Fang E, Prokocimer P. In vitro, in vivo, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions. Antimicrobial Agents & Chemotherapy. 2013; 57(7):3060-6.

5-Prokocimer P, Bien P, Deanda C, Pillar CM, Bartizal K. In vitro activity and microbiological efficacy of tedizolid (TR-700) against Gram-positive clinical isolates from a phase 2 study of oral tedizolid phosphate (TR-701) in patients with complicated skin and skin structure infections. *Antimicrobial Agents & Chemotherapy*. 2012; 56(9):4608-13.

EXCLUDED – IN VITRO

6-Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infectious Diseases.* 2014; 14(8):696-705.

7-Prokocimer P; De Anda C; Fang E; Mehra P; Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. *JAMA.* 2013; 309(6):559-69.

INCLUDED

Appendix 3: Suggested Prior Authorization Criteria

Non-preferred Oxazolidinone Antibiotics

Goal(s):

To optimize treatment of infections due to gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faicium* (VRE)

Length of Authorization:

6 days

Requires PA:

Non-preferred Oxazolidinone Antibiotics

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does the patient have an active infection with suspected or documented MRSA (e.g. 041.11-041.12, 482.42) or VRE (e.g. V09.8x) or other multi-drug resistant gram-positive cocci (e.g. V09.9x)?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Does the patient have a documented trial of linezolid, have a contraindication to linezolid, or is the treating organism not susceptible to linezolid?	Yes: Approve for up to 6 days	No: Pass to RPH; Deny (medical appropriateness)

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P&T / DUR Action: *5/15 (KK)*
Revision(s):
Initiated: *TBD*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Evaluation: rifaximin tablets, oral

Month/Year of Review: May 2015
End Date of Literature Search: February 2015
Generic Name: rifaximin
Brand Name (Manufacturer): Xifaxan® (Salix Pharmaceuticals)

Research Questions:

- Is rifaximin more effective than currently available alternative agents for the prevention or treatment of hepatic encephalopathy (HE)?
- Is rifaximin safer than currently available agents used to prevent or treat HE?
- Are there subgroups of patients in which rifaximin may be safer or more effective than other drugs to prevent or treat HE?

Conclusions and Recommendations:

- There is insufficient evidence that rifaximin is superior to lactulose for preventing episodes of overt HE. However, there is low quality evidence that adding rifaximin 550 mg twice daily to an adequate lactulose regimen for 6 months is statistically superior to lactulose alone at preventing episodes of HE by 24% (Hazard ratio [HR] 0.42 (95% CI, 0.28 to 0.64; p<0.001; number needed to treat [NNT] 4)[1] and improving quality-of-life, as shown by a difference of about 0.5 to 1 point on all 6 domains of the 7-point Chronic Liver Disease Questionnaire, in patients with a frequent history of hepatic encephalopathy.[2]
- There is low quality evidence that adding rifaximin at a daily dose of 1200 mg to an adequate lactulose regimen in hospitalized patients with overt HE is statistically superior to lactulose alone at treating overt HE within 10 days (76% vs. 44%, respectively; p=0.004), decreasing hospital stay (5.8±3.4 vs. 8.2±4.6 days, respectively; p=0.001), and improving 10-day mortality (24% vs. 49%, respectively; p<0.05).[3] Studies have not been conducted in the U.S. for this off-label use. Despite lack of evidence, both agents are increasingly used concomitantly to treat overt hepatic encephalopathy.
- There is low quality evidence that rifaximin is equivalent to lactulose for the treatment of overt encephalopathy.[4–6] Larger trials need to be conducted to adequately differentiate between these two treatments for this off-label use.
- There is insufficient evidence for the use of rifaximin without lactulose to prevent or treat hepatic encephalopathy.
- There is moderate quality evidence that rifaximin is associated with less diarrhea than lactulose.[4] Overall, rifaximin is well tolerated with no attributable serious adverse effects.[1,7] Cases of *Clostridium difficile* infection were observed in rifaximin-treated patients and it remains to be seen how long-term therapy may affect rates of infection in this already high-risk population.[7]
- There is insufficient evidence that any subgroups may benefit from rifaximin more than the general population for which it has been studied. Etiology of cirrhosis (alcohol, hepatitis C, fatty liver, etc.) does not appear to affect efficacy or safety. All patients studied were adults, most being white males under the age of 65 years.
- Establish Prior Authorization (PA) criteria so use of rifaximin is restricted to Oregon Health Plan (OHP)-funded conditions such as prevention or treatment of HE. Require concomitant use of adequately dosed lactulose when used to prevent or treat HE and discourage use of drugs known to precipitate hepatic encephalopathy (e.g., benzodiazepines). See Appendix 2 for the recommended PA criteria.

Background:

Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric complication of cirrhosis with wide variety of clinical manifestations.[8] The incidence and prevalence of HE are related to the severity of the underlying liver insufficiency. Patients with cirrhosis are most affected with an incidence of HE between 5-25% within 5 years of diagnosis, depending on other risk factors present.[9] Overt HE will occur in 30-40% of those with cirrhosis at some time during their clinical course, and will occur repeatedly in the survivors in most cases.[9] The prevalence of HE continues to rise primarily because patients with chronic hepatitis C, typically born between 1945 and 1965, are now developing cirrhosis and the obesity epidemic, which fuels nonalcoholic fatty liver disease and its complications, are developing at a more rapid pace.[10] More than 110,000 patients are admitted for overt HE every year to hospitals in the U.S.[9]

Hepatic encephalopathy can be classified in stages – often called West Haven criteria, or Conn scores[8]:

- Stage 0 = no detectable changes in personality or behavior, no asterixis;
- Stage 1 = trivial lack of awareness, shortened attention span, dyscalculia, euphoria, depression, anxiety, hypersomnia or insomnia, asterixis may be seen;
- Stage 2 = lethargy, apathy, disorientation, inappropriate behavior, slurred speech, subtle personality change, obvious asterixis;
- Stage 3 = gross disorientation, confusion, bizarre behavior, asterixis usually absent, somnolence or stupor;
- Stage 4 = coma

Asterixis or "flapping tremor" is often present in the early to middle stages of HE that precede stupor or coma. It is not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers.[9] Asterixis is graded as follows[1]:

- 0 = no tremors;
- 1 = few flapping motions;
- 2 = occasional flapping motions;
- 3 = frequent flapping motions;
- 4 = almost continuous flapping motions

The West Haven criteria are the gold standard for the diagnosis of overt HE. However, it is subjective with limited inter-observer reliability, especially for Stage 1 because signs are often overlooked in clinical examination.[9] In contrast, the detection of disorientation and asterixis has good inter-rater reliability and thus are chosen as marker symptoms of overt HE.[9]

The exact pathogenesis of HE is unknown but the common theory is nitrogenous compounds (i.e., ammonia) produced by colonic bacteria in the gastrointestinal tract build up in systemic circulation due to decreased hepatic function.[8] The nitrogenous substances cross the blood-brain barrier and enter brain tissue, causing extensive degeneration and increased rates of cellular apoptosis.[8] This neurotoxic effect on brain tissue results in cerebral edema, inflammation, and altered neurotransmission affecting consciousness and behavior.[8] However, although cirrhotic patients with HE often have elevated ammonia levels, there is no absolute correlation between ammonia and grade of HE.[10] Indeed, other proposed mechanisms of pathogenesis include inflammatory cytokines and benzodiazepine-like compounds, such as gamma-aminobutyric acid, which have been reported to play a role.[10] In addition, up to 80% of episodes of HE are precipitated by an event such as an infection, electrolyte abnormality or gastrointestinal bleeding.[11]

Treatment for HE aimed at managing the precipitating factors (i.e., electrolyte abnormality, constipation, infection, etc.) and reducing ammonia levels has resulted in clinical improvement.[10] At this time, only overt HE is routinely treated – during the acute episode and as secondary prophylaxis.[9] The non-absorbable disaccharide lactulose and the antibiotic rifaximin are the mainstay of pharmacological management. Lactulose reduces ammonia levels by its laxative effect combined with its acidification of the colon with resultant conversion of ammonia to ammonium, which shifts the colonic flora to non-urease-producing bacteria. Results from placebo-controlled studies of lactulose are limited by significant heterogeneity of types of HE (minimal vs. overt), differences in prognostic importance of precipitants and subjectivity of assessment tools.[11] Still, decades of clinical experience with lactulose speaks to its effectiveness for secondary prevention of HE and to its ability to effectively reverse episodic, overt HE.[11] Indeed, the current guideline by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommends lactulose as initial treatment for episodic, overt HE.[9] Rifaximin is a minimally absorbed oral antibiotic that is concentrated in the gastrointestinal tract and has broad-spectrum *in vitro* antimicrobial activity. Rifaximin has been primarily studied for secondary prevention of episodic, overt HE in patients in remission at time of enrollment.[1] Rifaximin is well-tolerated but no solid data support the use of rifaximin alone and it remains very costly.[9,11] As such, AASLD/EASL recommends rifaximin as an effective add-on therapy to lactulose for secondary prevention of overt HE.[9] The addition of rifaximin to lactulose for episodes of overt HE is an increasingly common practice.[11] Many other drugs (i.e., oral branched-chain amino acids, intravenous L-ornithine L-aspartate, neomycin, metronidazole, etc.) have been used for treatment of overt HE, but data to support their use are limited or lacking altogether.

Rifaximin received an FDA-approved indication in 2010 for reduction in risk of overt HE recurrence in adults. Rifaximin also has an FDA-approved indication for treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli*.[12] Both HE and infectious diarrhea are funded conditions under the OHP. See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Other uses of rifaximin with insufficient evidence includes relief of bloating and flatulence common in irritable bowel syndrome (IBS) and treatment for rosacea, purported to be induced by intestinal bacterial overgrowth.[13] Both IBS and rosacea are non-funded conditions under the OHP. Increasing use and substantial cost associated with this drug necessitates a formal review of its evidence for OHP-funded conditions.

Clinical Efficacy:

Data from one randomized controlled trial (RCT) by Bass, et al.[1] which compared rifaximin (n = 140) to placebo (n = 159) for the prevention of HE was evaluated by the FDA for approval.[1,14] In this study, more than 90% of patients in each group also received lactulose therapy. Mean age of the patients was 56 years, 86% of which were whites and 61% males. Most patients had a Conn score of 0 (67%) and 0 grade asterixis (68%) at baseline. Most patients (64%) had a Model for End-Stage Liver Disease (MELD) score of 11-18 (MELD range 6 to 40, with higher scores indicating more severe liver disease). Rifaximin or placebo was continued for 6 months or until an episode of HE occurred, whichever came earlier. The primary outcome studied was time to first episode of HE, defined as time to increase Conn score of 0 or 1 at baseline to 2 or greater; or time to increase Conn score of 0 at baseline to 1 plus an 1-grade increase in asterixis. The study did not report time to first episode of HE. Rather, it was reported that compared to placebo, patients in the rifaximin group had significantly greater reductions in first breakthrough HE episode (22.1% vs. 45.9%) during the study period. The associated HR was 0.42 (95% CI, 0.28 to 0.64; p<0.001; NNT 4). A secondary outcome was time to first hospitalization involving HE. Again, the study did not report time to first HE-related hospitalization. Rather, the proportion of patients with an HE-related hospitalization was reported, which favored rifaximin compared to placebo (13.6% vs 22.6%). The associated HR was 0.50 (95% CI, 0.29 to 0.87; p=0.01). Unfortunately, method of randomization, and thus concealment of allocation, are uncertain. A double-dummy design was not described so blinding may not have been maintained. Overall attrition rate was high with a substantial difference between the two groups. Another concern for bias is the use of Conn score because it is not known to be sensitive in differentiating milder severities of HE and is dependent on clinical judgement.[14] Adverse drug events and

mortality were similar in both groups. The authors concluded that rifaximin in combination with lactulose was effective in preventing breakthrough HE in patients with recurrent HE and cirrhosis. Detailed data and analysis of this study is provided in the **Comparative Evidence Table**.

In a concurrent study, the original investigators also evaluated the effect of rifaximin (n=101) versus placebo (n=118) on health-related quality of life (HRQL) in 219 patients.[2] Most patients in both groups (94%) concurrently took lactulose. The relationship between HRQL and breakthrough HE episode was also assessed. HRQL was measured by the Chronic Liver Disease Questionnaire (CLDQ), the first validated, disease-specific HRQL instrument developed to measure longitudinal change over time in patients with chronic liver disease. The CLDQ includes 29 items in the following 6 domains: abdominal symptoms (3 items), fatigue (5 items), systemic symptoms (5 items), activity (3 items), emotional function (8 items) and worry (5 items). Patient-rated responses for each question were ranked on a 7-point scale, with higher scores indicating better HRQL. Data are presented by domain and overall. Inclusion and exclusion criteria were identical to the Bass, et al. study[1] and baseline characteristics were similar as well. The mean duration of treatment was about 4 months in the rifaximin group and 3 months in the placebo group. Results showed that patients who received rifaximin had significant improvement in CLDQ scores compared to the placebo group. Differences in CLDQ scores were only presented visually but there appeared to be an improvement of 0.5 to 1 point for each domain. There also appeared to be a direct correlation between a poorer CLDQ score and experiencing an overt HE during the study period. The Spearman correlation coefficient for overall CLDQ and breakthrough HE was 0.5830 (95% CI, -0.67 to -0.49). The authors concluded that HRQL significantly improved in patients who received rifaximin in combination with lactulose and that worsening HRQL may predict HE events, irrespective of treatment.[2]

Rifaximin use for episodic overt HE in hospitalized patients, in addition to lactulose, have become a common 'off-label' practice despite little evidence.[11] Older trials that evaluated rifaximin for episodic HE used different comparators and generally enrolled small numbers of patients with acute, chronic, or unclear acuity of HE.[11] More recently however, a single-centered RCT was conducted in India to compare rifaximin with lactulose (n=63) to lactulose and placebo (n=57) in patients with overt HE.[3] Rifaximin was dosed at 1200 mg daily using 400 mg capsules which are not available in the U.S. Lactulose was appropriately dosed at 30-60 mL three times daily, titrated so that patients passed 2-3 semisoft stools per day. Treatment continued for a maximum of 10 days or until complete recovery of HE. Mean age was 39 years and 80% of patients had severe HE, grade III or IV, and 69% were Child Class C with primarily alcohol-related etiology. Patients in the lactulose and rifaximin group had a higher proportion of complete reversal of HE within 10 days (76% vs. 44%; p=0.004), shorter hospital stay (5.8±3.4 vs. 8.2±4.6 days; p=0.001), and a striking improvement in 10 day mortality (24% vs 49%; p<0.05).[3] Unfortunately, the very high mortality in the lactulose plus placebo arm raises some concerns about the validity of this study, which should be repeated in a larger number of patients at multiple sites. Overall quality of evidence from this study is methodologically poor due to poor blinding methods and small study size. Applicability of the study may be limited due to its single-centered design.

In addition to the clinical trials presented here, three systematic reviews[4–6] have been conducted looking at older studies evaluating rifaximin for the treatment of overt HE. The only exception is two trials identified in a recent systematic review[6] that also included evaluation of the FDA-approved indication for prevention of HE. Trials eligible for these reviews were primarily conducted in Italy, followed by South Korea or Spain using a 1200 mg per day dose which is slightly higher than the 1100 mg per day dose approved in the U.S. Trials evaluated in these reviews were small, with the Bass, et al.[1] study evaluating rifaximin for prevention of HE and used for FDA approval in the U.S. being the largest trial (n=299), as much as 7- to 8-fold larger than most of the other eligible studies included (n=30 to 50).

The most recent systematic review was performed to evaluate the effects of rifaximin for patients with HE.[6] Eligible studies included RCTs of rifaximin for the prevention of HE or in patients with minimal or overt HE. Over half of the included trials were conducted in Italy. Most trials were of patients with cirrhosis largely related to alcohol or viral hepatitis. Doses ranged from 1100 to 1200 mg per day and treatment lasted between 5 and 180 days. The study oddly included

control patients that received either a placebo, a non-absorbable oral disaccharide (i.e., lactulose) or another antibiotic. The primary outcomes were prevention, recovery and improved manifestation of HE. A statistically significant effect was found with rifaximin for the prevention of overt HE (Relative Risk [RR] 1.36; 95% CI, 1.06 to 1.65; n=2 RCTs) and for full resolution of overt HE (RR 1.34; 95% CI, 1.11 to 1.62; n=11 RCTs; I^2=54%; Number Needed to Treat [NNT] 6) without evidence of publication bias. There were no significant differences between rifaximin and controls for serious adverse events (n=13 RCTs).[6] Interpreting the results of this review is difficult considering the heterogeneity of the indications, populations and the combination of both placebo and active-control groups for treatment of overt HE.

The other two systematic reviews[4,5] analyzed trials comparing rifaximin against active controls for treatment of overt HE:

A very well conducted systematic review was performed to compare rifaximin with conventional oral therapy for overt HE.[5] Eligible studies included RCTs reporting on the effectiveness of rifaximin compared with non-absorbable oral disaccharides or other antibiotics in patients with overt HE. Primary outcomes included improvement in neurological function, the grade of HE according to Conn scores (see explanation in Evidence Table) and safety. All studies evaluated rifaximin 400 mg three times daily (1200 mg per day), which is slightly higher than the 1100 mg per day dose used in the U.S. Control arms primarily received lactulose 35-120 mL per day or neomycin 3000-4500 mg/day. Treatment duration ranged from 7 days to 6 months. Seven trials compared rifaximin with disaccharides (mostly lactulose) and reported that both groups experienced either full resolution of HE or a clinically significant improvement, but there was no statistically significant difference between the groups. A similar result was seen in the 5 trials comparing rifaximin with other antibiotics (mostly neomycin). The overall odds ratio (OR) for patients receiving disaccharides or antibiotics showed a trend that favored the use of rifaximin at improving neurological function in overt HE but the difference was not significantly different (OR 1.96; 95% CI, 0.94 to 4.08; I^2=27%). Patients with rifaximin had lower rates of diarrhea (OR 0.20; 95% CI, 0.04 to 0.92; 8 RCTs; I^2=66%) though rates of abdominal pain, nausea and weight loss were similar between the groups. The authors concluded rifaximin was similar to other oral therapies in its clinical efficacy for HE but has fewer adverse effects.[5]

5

When specifically comparing rifaximin to non-absorbable disaccharides, a separate systematic review evaluated RCTs treating overt HE.[4] Eight RCTs were eligible for inclusion, all conducted in South Korea, Italy or Spain for a total duration ranging from 7 days to 3 months using a dose of 1200 mg per day of rifaximin and 45-120 mL per day of lactulose (or 60 g per day of lactitol). The meta-analysis showed no significant difference between rifaximin and non-absorbable disaccharides in their efficacy for treating HE, serum ammonia levels, mental status and asterixis (flapping tremor). However, rifaximin was associated with lower rates of diarrhea (RR 0.11; 95% CI, 0.04 to 0.31; I^2=48%; 5 RCTs) and less abdominal pain (RR 0.34; 95% CI, 0.14 to 0.83; I^2=33%; 6 RCTs). Unfortunately, only five of the included trials described their randomization process, six trials described allocation concealment, and only three trials blinded the observers. In addition, the authors found presence of publication bias. The small sample sizes, some statistical heterogeneity and limitations in the quality of the included trials make the reliability of these findings uncertain.[4]

Clinical Safety:

The original investigators of the Bass, et al.[1] study further evaluated the effect of long-term (median exposure about 14 months) rifaximin on safety and durability of treatment in a phase 3, open-label, non-controlled maintenance study.[7] Inclusion and exclusion criteria were the similar to the original study. Most patients (mean age 57 years) concurrently took lactulose (90%) and had a MELD score of 11-18 (59%) with a Conn score of 0 (64%) and an asterixis grade of 0 (68%). Baseline characteristics were similar except that patients on rifaximin had a significantly longer duration of remission at time of enrollment compared to the historical control group from the original study. The results showed that rifaximin remained well-tolerated. Adverse event rates did not increase compared to the historical rates seen in the original 6-month study. Most adverse events observed were related to the underlying liver disease. A total of 76 patients (19%) died during the study of which most could be attributed to complications of cirrhosis, followed by cardiac causes and infection. Six cases of *Clostridium difficile*

infection were identified in patients treated with rifaximin versus none in the historical control group. None of the deaths were attributed to rifaximin treatment. Overall, morality and rate of hospitalizations for overt HE were similar to the historical control group in the original 6-month study.[7]

The adverse events associated with 6-month use of rifaximin compared to placebo are summarized in Table 1. There were no statistically significant differences between the two groups for these events and most observed events were related to the underlying chronic liver disease.[1] Note that 91% of patients in both groups concurrently received lactulose therapy.

Table 1. Adverse Events Associated with Rifaximin and Placebo.[1]

Event	Rifaximin (n=140)	Placebo (n=159)	Event	Rifaximin (n=140)	Placebo (n=159)
Any Event	80.0%	79.9%	Vomiting	7.1%	8.8%
Nausea	14.3%	13.2%	Insomnia	7.1%	6.9%
Diarrhea	10.7%	13.2%	Depression	7.1%	5.0%
Fatigue	12.1%	11.3%	Cough	7.1%	6.9%
Peripheral Edema	15.0%	8.2%	Constipation	6.4%	6.3%
Ascites	11.4%	9.4%	Upper Abdominal Pain	6.4%	5.0%
Dizziness	12.9%	8.2%	Pyrexia	6.4%	3.1%
Headache	10.0%	10.7%	Back Pain	6.4%	6.3%
Muscle Spasms	9.3%	6.9%	Arthralgia	6.4%	2.5%
Pruritus	9.3%	6.9%	Dyspnea	6.4%	4.4%
Abdominal Pain	8.6%	8.2%	Urinary Tract Infection	5.7%	8.8%
Abdominal Distension	7.9%	7.5%	Rash	5.0%	3.8%
Anemia	7.9%	3.8%	Asthenia	2.9%	7.5%

6

Look-alike / Sound-alike Error Risk Potential: none

Pharmacology and Pharmacokinetic Properties[12]:

Parameter	
Mechanism of Action	Binds the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of RNA synthesis
Oral Bioavailability	Minimal systemic absorption
Distribution and Protein Binding	Moderately bound to human plasma protein (62% in patients with hepatic impairment)
Elimination	97% excreted unchanged in feces
Half-Life	Not applicable
Metabolism	Not applicable

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Rate of Hospitalization due to Overt HE
3) Episodes of Overt HE
4) Health-related Quality of Life

Primary Study Endpoint:
1) Time to First Episode of Overt HE

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Bass, et al.[1,14] 2010 MC, DB, RCT U.S., Canada, Russia	1. Rifaximin 550 mg PO BID (R) 2. Placebo PO BID (P) Duration 6 months or until first episode of HE	Demographics: Mean Age: 56 y Males: 61% White: 86% Conn score* of 0: 67% Asterixis grade of 0: 68% MELD scale 11-18: 64% Lactulose: 91% Inclusion Criteria: •Age ≥18 y; •≥2 episodes of OHE (Conn score ≥2) caused by cirrhosis in last 6 months; •Remission at enrollment; •MELD score ≤25 Exclusion Criteria: •Expectation of liver transplant <1 month; •Presence of known precipitants of HE: GI bleed; portosystemic shunt; transjugular	ITT: NA mITT: R: 140 P: 159 Attrition: R: 52 P: 93	**Primary Endpoint:** Time to First Episode of HE: *Time to increase Conn score of 0 or 1 at baseline to ≥2*; or *Time to increase Conn score of 0 at baseline to 1 plus 1-grade increase in asterixis*. Note: Study reported proportion of patients with a HE episode: R: 31/140 (22%) P: 73/159 (46%) HR 0.42 (95% CI, 0.28 to 0.64; p<0.001) **Secondary Endpoint:** Time to First Hospitalization Involving HE: Note: Study reported proportion of patients hospitalized with HE as cause of admission or if HE occurred during hospitalization: R: 19/140 (13.6%) P: 36/159 (22.6%)	24%/4 9%/9	Attrition due to AE: R: 8 (5.7%) P: 7 (4.4%) p-value NR Death: R: 9 (6.4%) P: 11 (6.9%) p-value NR Peripheral Edema: R: 21 (15.0%) P: 13 (8.2%) p-value NS Diarrhea: R: 15 (10.7%) P: 21 (13.2%) p-value NS Ascites: R: 16 (11.4%) P: 15 (9.4%) p-value NS Dizziness: R: 18 (12.9%) P: 13 (8.2%) p-value NS	NA	**Quality Rating**: Poor **Internal Validity (Risk of Bias)**: Selection: Method of randomization not provided; concealment of allocation questionable. Performance: Method of blinding not provided; no apparent double-dummy design; adverse effects fairly equal between groups which may limit some performance bias. Detection: modified ITT analysis performed; no details whether data analysts were blinded to treatment allocation. Censoring rules transparent. Attrition: high attrition differential primarily due to breakthrough HE. **Applicability**: Patient: Racial and ethnic minority groups not represented. Etiologies of cirrhosis not defined. Patients with severe hepatic impairment not represented (Child-Pugh C). Extensive exclusion criteria may not adequately reflect population. Intervention: Phase 3 trial evaluating new dose of 1100 mg/day. Older studies have evaluated 1200 mg/day, using formulations other than the 550 mg tablet approved for prevention of HE. Comparator: 91% of all patients concurrently took lactulose so rifaximin was largely studied as an adjunctive therapy.

		intrahepatic portosystemic shunt in last 3 months; •Renal insufficiency (SCr >2.0 mg/dL) •Respiratory insufficiency •Anemia (Hgb <8.0 g/dL) • Electrolyte abnormalities (Na+ <125 mEq/L or K+ <2.5 mEq/L or Ca+2 >10 mg/dL) •Active infection •Active SBP •BZDs or BZD-like drugs •Narcotics •Psychotropic drugs		HR 0.50 (95% CI, 0.29 to 0.87; p=0.01)				Outcomes: Conn Score is known not to be sensitive in differentiating milder severities of HE. It is somewhat imprecise (it can fluctuate throughout the day) and depends on clinical judgment. Setting: Not detailed but probably outpatient clinics. Not studied in hospitalized patients with OHE. **Analysis**: •Study designed and sponsored by Salix Pharmaceuticals; data collected under the supervision of Salix Pharmaceuticals; final manuscript edited by Salix Pharmaceuticals. •Study stopped after first episode of HE. Mean duration (±SD) of treatment of rifaximin was 130.3±56.5 days and placebo was 105.7±62.7 days.

Abbreviations [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; BID = twice daily; BZD = benzodiazepines; Ca+2 = serum calcium; CI = confidence interval; DB = double-blind; dL = deciliter; g = grams; HE = hepatic encephalopathy; Hgb = hemoglobin; ITT = intention to treat; K+ = serum potassium; L = liter; MC = multicenter; MELD = Model for End-Stage Liver Disease scale (score range 6 to 40, with higher scores indicated more severe disease); mEq = milliequivalents; mg = milligrams; mITT = modified intention-to-treat; N = number of subjects; Na+ = serum sodium; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; OHE = overt hepatic encephalopathy; PO = by mouth; RCT = randomized controlled trial; SBP = spontaneous bacterial peritonitis; SCr = serum creatinine; SD = standard deviation; y = years.

*Conn Scores:

0 = no personality or behavioral abnormality detected;
1 = trivial lack of awareness, euphoria or anxiety, shortened attention span, or impairment of ability to add or subtract;
2 = lethargy, disorientation with respect to time, obvious personality change, inappropriate behavior;
3 = somnolence or semi-stupor, responsiveness to stimuli, confusion, gross disorientation, or bizarre behavior; and
4 = coma

**Asterixis Grades:

0 = no tremors;
1 = few flapping motions;
2 = occasional flapping motions;
3 = frequent flapping motions; and
4 = almost continuous flapping motions

References:

1. Bass N, Mullen K, Sanyal A. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071-1081.

2. Sanyal A, Younossi Z, Bass N. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy: a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2011;34:853-861.

3. Sharma B, Sharma P, Lunia M. A randomized, double-blind, controlled-trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol*. 2013;108:1458-1463.

4. Wu D, Wu S, Lu J. Rifaximin versus nonabsorbable disaccharides for the treatment of hepatic encephalopathy: a meta-analysis. *Gastroenterology Research and Practice*. 2013;2013:236963.

5. Eltawil K, Laryea M, Peltekian K. Rifaximin vs conventional oral therapy for hepatic encephalopathy: a meta-analysis. *World J Gastroenterol*. 2012;18:767-777.

6. Kimer N, Krag A, Moller S. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. *Aliment Pharmacol Ther*. 2014;40:123-132.

7. Mullen K, Sanyal A, Bass N. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. *Clinical Gastroenterology & Hepatology*. 2014;12:1390-1397.

8. DynaMed [internet database]. Ipswich, MA: EBSCO Publishing, Inc. Updated 9 Jan 2015. Accessed 2 Mar 2015.

9. Vilstrup H, Amodio P, Bajaj J. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of Liver. *Hepatology*. 2014;60:715-735.

10. Rahimi R, Rockey D. Hepatic encephalopathy: how to test and treat. *Curr Opin Gastroenterol*. 2014;30:265-271.

11. Leise M, Poterucha J, Kamath P. Management of hepatic encephalopathy in the hospital. *Mayo Clin Proc*. 2014;89:241-253.

12. Xifaxan (rifaximin) [prescribing information]. Morrisville, NC: Salix Pharmaceuticals, Inc., March 2014.

13. Rifaximin. Wikipedia Webpage. http://en.wikipedia.org/wiki/Rifaximin. Accessed March 4, 2015.

14. Rifaximin Summary Review. U.S. Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022554Orig1s000SumR.pdf. Accessed March 2, 2015.

Appendix 1: Highlights of Prescribing Information [12]

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIFAXAN safely and effectively. See full prescribing information for XIFAXAN.

XIFAXAN® (rifaximin) Tablets
Initial U.S. Approval: 2004

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

----------RECENT MAJOR CHANGES----------

Indications and Usage, Hepatic Encephalopathy (1.2)	03/2010
Dosage and Administration, Hepatic Encephalopathy (2.2)	03/2010

----------INDICATIONS AND USAGE----------

XIFAXAN is a rifamycin antibacterial indicated for:

- The treatment of patients (≥ 12 years of age) with travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* (1.1)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age (1.2)

Limitations of Use

- TD: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli* (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Travelers' diarrhea: One 200 mg tablet taken orally three times a day for 3 days, with or without food (2.1)
- Hepatic encephalopathy: One 550 mg tablet taken orally two times a day, with or without food (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg and 550 mg tablets (3)

----------CONTRAINDICATIONS----------

History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of XIFAXAN (4.1)

----------WARNINGS AND PRECAUTIONS----------

- Travelers' Diarrhea Not Caused by *E. coli*: XIFAXAN was not effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *E. coli*. If diarrhea symptoms get worse or persist for more than 24-48 hours, discontinue XIFAXAN and consider alternative antibiotics (5.1)
- *Clostridium difficile*-Associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)
- Hepatic Impairment: Use with caution in patients with severe (Child-Pugh C) hepatic impairment (5.4, 8.7)
- Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor is needed (5.5,7.2).

----------ADVERSE REACTIONS----------

- Most common adverse reactions in travelers' diarrhea (≥ 5%): Flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency and nausea (6.1)
- Most common adverse reactions in HE (≥ 10%): Peripheral edema, nausea, dizziness, fatigue, and ascites (6.1)

To report suspected adverse reactions, contact Salix Pharmaceuticals at 1-800-508-0024 and www.Salix.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2014

Rifaximin (Xifaxan®)

Goal:

- To optimize appropriate pharmacological management of prevention and treatment of hepatic encephalopathy.

Length of Authorization:

6 months to Lifetime

Requires PA:

- Rifaximin

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the treating diagnosis prevention or treatment of hepatic encephalopathy (572.2)?	**Yes:** Go to 4	**No:** Go to 3
3. Is the treating diagnosis treatment of traveler's diarrhea (009.2)?	**Yes:** Approve 3-day supply Note: FDA-labelled dosing is 200 mg three times daily for 3 days	**No:** Pass to RPH. Deny if treating condition is not funded by OHP. Approve for 6 months if condition is funded by OHP with adequate supporting literature.
4. Is the patient currently managed with an adequate daily dose of lactulose?	**Yes:** Go to 5	**No:** Go to 7
5. Is the patient currently prescribed a benzodiazepine drug?	**Yes:** Go to 6	**No:** Approve for lifetime
6. Will the prescriber consider safely tapering the patient off the benzodiazepine (tapering process may be several months)?	**Yes:** Approve for 1 year	**No:** Inform prescriber that studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy. If justification is given for not tapering off the benzodiazepine, approve for 6 months.

11

Approval Criteria		
7. Does the patient have a contraindication to lactulose?	**Yes:** Approve for lifetime	**No:** Inform prescriber studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose. If justification is given for not treating with lactulose, approve for 6 months.

P&T / DUR Action: 5/15 (AG)
Revision(s):
Initiated: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Antibiotics for *Clostridium difficile* Infection

Month/Year of Review: May 2015 **Date of Last Review:** April 2012

Current Status of PDL Class:
See **Appendix 1**.

Current Prior Authorization Criteria:
Fidaxomicin. See **Appendix 4**.

Conclusions and Recommendations:

- There is moderate strength of evidence oral vancomycin is superior to oral metronidazole for clinical cure of first episode of mild to moderate *Clostridium difficile* infection (CDI).
- There is moderate strength of evidence of no difference between oral vancomycin and oral fidaxomicin in clinical cure rate of first episode of CDI. There is insufficient evidence to compare efficacy between metronidazole and fidaxomicin.
- There is high strength evidence that oral vancomycin is superior to oral metronidazole in severe or complicated CDI but there is insufficient evidence to support the use of fidaxomicin alone for complicated or fulminant CDI.
- There is moderate strength of evidence to repeat the initial antibiotic course for first recurrence of CDI, though moderate quality evidence suggests a course of fidaxomicin is superior to a course of oral vancomycin at preventing further recurrences of CDI. However, following a full-dose course of vancomycin with a slow taper or pulsed dosing over several weeks may also decrease recurrent cases of CDI.
- There is high quality evidence for 10 days of CDI treatment with insufficient evidence to support longer duration of therapy; the exception being pulsed or tapered vancomycin in cases of multiple recurrent CDI that may be given for several weeks after a full dose 10-day course is completed.
- There is insufficient evidence to support the combination of two orally administered antibiotics. Anecdotal evidence, however, suggests intravenous metronidazole or rectal enema administration of vancomycin may be helpful as adjunctive therapy in complicated or fulminant CDI, but never as monotherapy.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:

- There is moderate strength evidence that there is no difference in clinical cure rate between fidaxomicin, vancomycin, and metronidazole.
- There is moderate strength evidence that recurrence of CDI occurs less frequently with fidaxomicin versus vancomycin.
- There is insufficient evidence to compare efficacy or effectiveness of fidaxomicin to metronidazole.

- Make fidaxomicin a non-preferred antimicrobial for CDI and require a documented trial of appropriate therapy of vancomycin (125 mg oral four times daily) or metronidazole (500 mg orally three times daily) for first recurrence or contraindication to therapy and excluding use of fidaxomicin in patients with severe CDAD (life-threatening or fulminant infection or toxic megacolon).
- Recommend adding oral metronidazole and oral vancomycin as preferred agents on the PDL for the treatment of CDI.
- Consider requiring metronidazole as first line therapy for mild CDAD in non-hospitalized patients.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Treatment of CDI

The AHRQ published on April 20, 2015, draft for public comment on an updated report of early detection, prevention and treatment of CDI. The AHRQ increased strength of evidence from moderate to high for oral vancomycin as a more effective drug than metronidazole for CDI, with moderate strength evidence of the effect regardless of disease severity. The report recognizes that the increased strength of evidence found for vancomycin should prompt changes in the next updated treatment guideline from the Infectious Diseases Society of America (IDSA), which currently supports vancomycin as the drug of choice for severe CDI and metronidazole as the drug of choice for mild to moderate CDI. In addition, there is continuing moderate strength evidence that fidaxomicin is similar to vancomycin for the initial cure of CDI, and increased strength of evidence that fidaxomicin is superior to vancomycin for the prevention of recurrent CDI. The desired outcome with CDI treatment is cure of the initial illness without subsequent recurrence, and it is well documented each episode of CDI recurrence increases the likelihood of further episodes. For these clinical reasons, evidence for fidaxomicin for initial treatment of CDI is growing, though per-course price of the drug makes treatment cost prohibitive in most cases. Lastly, there is low quality evidence that largely confirms current clinical practice that intravenous metronidazole performs significantly worse than oral metronidazole or vancomycin for treatment of CDI.[1]

Studies of diagnostic testing and treatment of CDI published in English between January 1978 and October 31, 2014 were identified in a 2015 systematic review. Appropriate diagnostic testing and markers of disease severity were reviewed but will not be detailed here. The odds ratio of antibiotic use and CDI risk is reported to be 3.2 for third-generation cephalosporins and 2.86 for clindamycin. Other beta-lactam antibiotics (penicillins and cephalosporins) are also particularly associated with risk of CDI. Fluoroquinolones are associated with increased risk of the BI/NAP1/027 strain. Historically, antibiotic withdrawal was a stand-alone treatment option as about 15% of patients recover after the offending antibiotic is stopped. However, the effectiveness of antibiotic withdrawal for mild CDI is remains unclear, but it is clear that failure to stop the offending antibiotics is associated with CDI recurrence.[2]

Metronidazole vs. Vancomycin

Metronidazole and vancomycin have been primary therapies for CDI since the 1980s. Early studies suggested that oral metronidazole and oral vancomycin had equivalent efficacy and relapse rates, but newer data suggest higher treatment failure rates when metronidazole is used in *severe* or *complicated* CDI. However, there are conflicting data whether oral metronidazole treatment failures have increased after the emergence of BI/NAP1/027. For mild CDI, cure rates for oral metronidazole and oral vancomycin were not statistically different (73-90% vs. 81-98%, respectively). However, among patients with severe CDI, differences in cure rates were more pronounced and fair better for vancomycin (79-97%) compared to metronidazole (66-76%). Overall, treatment failures with oral metronidazole have been higher than with oral vancomycin from 2001-2010 (22.4% vs. 14.2%; p=0.002) but recurrence rates remained similar (27.1% vs. 24.0%; p=0.26). Patients receiving metronidazole also have a longer time to symptomatic improvement than patients receiving vancomycin. Factors associated with metronidazole failure include age older than 60 years, presence of fever or leukocytosis, hypoalbuminemia, ICU admission and abnormal abdominal CT imaging findings. Oral vancomycin is typically well tolerated as both oral and rectal administration is rarely systemically absorbed. Metronidazole is associated with gastrointestinal adverse effects, a disulfiram-like reaction when ingested with alcohol, and peripheral neuropathy with prolonged therapy.[2]

Mild to Moderate CDI

For mild to moderate CDI, oral metronidazole 500 mg 3-times daily for 10 days remains the preferred therapy, in part because of its low cost. For patients unable to take oral medications, metronidazole may be administered intravenously as adjunctive therapy, but not as monotherapy since CDI recurrence is common when the intravenous dose is given as monotherapy. Newer evidence is shifting away from metronidazole to oral vancomycin and it is reasonable to consider oral vancomycin 125 mg orally 4-times daily for 10 days for mild to moderate CDI. Randomized studies demonstrate similar cure rates between fidaxomicin 200 mg orally twice daily for 10 days (87.7-88.2%) and oral vancomycin (85.8-86.8%) but fidaxomicin may be associated with fewer recurrences (15.4% vs. 25.3%; p=0.005). When antibiotics cannot be discontinued because of ongoing infection, clinical cure rates for concomitant CDI are higher with fidaxomicin than with vancomycin. However, fidaxomicin is not considered first-line therapy for mild or uncomplicated CDI because of its higher cost.[2]

Severe or Complicated CDI

Vancomycin is the preferred therapy for severe or complicated CDI. The recommended dose is 125 mg orally 4-times daily for 10 days but expert opinion often favors higher doses in severe or complicated cases. Vancomycin may be administered rectally in the setting of ileus, as an adjunctive therapy, though evidence is limited to case reports. Rectally administered vancomycin is not typically used alone because the drug may not reach the entire affected area. In severe or complicated CDI, or in cases when rectal vancomycin must be given, it may be appropriate to give intravenous metronidazole as adjunctive therapy since this route can achieve detectable levels of drug throughout the colon. However, evidence for this practice is remains very limited. No data support the use of fidaxomicin in complicated or fulminant CDI.[2]

Recurrent CDI

Recurrent CDI is more common in older patients and in those with concomitant antibiotic use, presence of comorbidities, concomitant use of proton pump inhibitors, and if the initial CDI is severe. Repeating the initial therapy of oral metronidazole or vancomycin is reasonable for the first recurrence of mild to moderate CDI. However, growing evidence suggests vancomycin 125 mg orally 4-times daily for several weeks using pulsed or tapering doses, or fidaxomicin 200 mg orally twice daily for 10 days, are preferred for any subsequent recurrences. In patients with a recurrence rate of 45%, one study found a slow tapering or pulsed courses of vancomycin lower the recurrence rate by 31% (p=0.01) and 14.3% (p=0.02), respectively. Fidaxomicin may be a reasonable option for recurrent CDI or when administered immediately after a course of vancomycin in patients with multiple CDI recurrences. Use of rifaximin as an adjunctive therapy for recurrent CDI after standard therapy is limited to anecdotal evidence only and monotherapy should be avoided given its propensity for resistance. Evidence is also limited for use of nitazoxanide as an adjunctive therapy for recurrent CDI. Fecal microbiota transplantation restores gut microbiota diversity via the instillation of donor stool into the gastrointestinal tract and has good clinical response without reports of adverse events for refractory or recurrent CDI.[2]

Treatment of Recurrent CDI

A 2014 systematic review of studies of the treatment of recurrent CDI (RCDI) without language or date publication restrictions was performed. Ultimately, 105 studies were analyzed for the review.[3]

Vancomycin

Evidence supporting the use of vancomycin is moderate. There is considerable variability in dosing and duration for RCDI, but it is currently the standard of care in treating RCDI. Examining high-quality trials using vancomycin, three studied a metronidazole comparator and two fidaxomicin. The metronidazole comparator studies included 179 patients given metronidazole compared to 310 receiving vancomycin. Using sustained response (e.g., no recurrence), vancomycin was as efficacious as metronidazole [relative risk (RR) 1.08; 95% confidence interval (CI), 0.85 to 1.35; I^2=0%, p=0.53). Studies comparing fidaxomicin to vancomycin, discussed further below, included a total of 79 patients in each arm, and appeared slightly more efficacious than vancomycin (RR 1.86; 95% CI, 1.04–3.31; I^2=0%, p=0.04). Pulsing or tapering doses of vancomycin has demonstrated efficacy in small studies and subgroups, and has been adopted as part of the current guidelines but has not yet been evaluated in large RCTs. Tapering vancomycin involves a prolonged regimen where the dose is slowly reduced over several weeks. Pulsing involves a dose of vancomycin every 3 days for several weeks following completion of a full 10-day course.[3]

Metronidazole

All of the identified studies of metronidazole were of high quality, and found a fairly consistent efficacy, similar to vancomycin. Current Infectious Disease Society of America (IDSA) guidelines endorse one repeat course of metronidazole as the standard of care for the first recurrence. A temporal correlation of treatment failure has been noted since the emergence of the BI/NAP1/027 strain. It is not recommended beyond a first recurrence because of the risk of accumulation of neurotoxic metabolites. A total of 283 patients were treated with metronidazole-containing regimens, with a second recurrence in 86 patients (29%). Rates of initial response were between 77 and 100%. One study concluded that metronidazole was non-inferior to vancomycin in a first relapse, while two favored vancomycin regimens.[3]

Fidaxomicin

Evidence for fidaxomicin is moderate in light of two positive, high-quality studies. Fidaxomicin is the only drug other than vancomycin approved by the U.S. Food and Drug Administration (FDA) for CDI. Both of the existing studies on fidaxomicin compared the drug to vancomycin and found non-inferiority, with pooled results showing the slight superiority of vancomycin. Both studies were presented to the OHA Pharmacy & Therapeutics committee in 2012. It is worth noting that this medication is considerably more expensive than oral vancomycin, and may have decreased activity against the BI/NAP1/027 strain.[3]

The current evidence for nitazoxanide and rifaximin for RCDI remain weak.[3]

Treatment Failure and Recurrence of CDI Following Treatment with Vancomycin or Metronidazole

The objective of this 2012 review was to evaluate the frequency of treatment failure and recurrence of CDI following treatment with vancomycin or metronidazole in studies performed in the last 10 years. In total, 39 articles (7005 patients) were selected for inclusion in the systematic review. However, the follow-up period was short for most studies: up to 1 month in 6 studies, 1 to 2 months in 12 studies, 2 to 3 months in 12 studies, 6 months in 2 studies and an unknown length of follow-up for the remainder of studies. In addition, the definitions of treatment failure and recurrence were not identical in 53.8% and 15.4% of the studies, respectively. All studies required the presence of symptoms (diarrhea, abdominal pain, fever) and a positive stool test for *C. difficile* toxin A or B for the diagnosis of CDI. Sixteen studies reported treatment failure with metronidazole (22.4%) and 8 studies reported treatment failure with vancomycin

(14.2%). Recurrence of CDI after initial treatment with metronidazole was demonstrated in 18 studies (27.1%) and in 8 studies with vancomycin (24.0%), a significant difference (p=0.26). Fourteen studies did not provide outcomes for metronidazole and vancomycin separately, but reported the outcomes of the entire population. In all studies combined, mean treatment failure and incidence of recurrence were similar for metronidazole (22.3%) and vancomycin (22.1%). However, there were studies that reported very high (66.7%) or very low (2.9%) failure or recurrence depending on the study design. Mean treatment failures and recurrences in RCTs were 16.0% and 19.4%, respectively. In prospective observational cohort studies, the mean treatment failure was 26.8% (p<0.001, higher compared with RCTs) and the mean recurrence was 19.0% (p=0.86, similar to that of RCTs). In retrospective studies, the mean treatment failure was 22.7% (p=0.002, higher compared with RCTs) and the mean recurrence was 23.3% (p=0.03, higher compared with RCTs). There was no significant difference in the mean treatment failure between observational prospective and retrospective studies (p=0.06), but significantly more recurrences were reported in retrospective than observational prospective studies (p=0.005).[4]

New Guidelines:

The European Society of Clinical Microbiology and Infectious Disease (ESCMID)

Recommendations in the recently updated ESCMID guideline were based on a systematic assessment of the quality of evidence. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was used to grade the strength of our recommendations and the quality of the evidence. Strength of recommendations (SoR) followed the standard grades (A=strong; B=moderate; C=marginal; D=against). The guideline followed the Appraisal of Guidelines Research and Evaluation Collaboration (AGREE) self-assessment tool. The objectives of the guideline were to: 1) provide an overview of currently available CDI treatment options and 2) develop an evidence-based update of treatment recommendations. The following definitions were used in reviewing the evidence and developing their recommendations[5]:

> Treatment response is present when either stool frequency decreases or stool consistency improves and parameters of disease severity (clinical, laboratory, radiological) improve and no signs of severe disease develop. All other cases are considered treatment failure.[5]
>
> Recurrent CDI is present when CDI re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment.[5]

In cases of non-severe CDI (no signs of severe colitis) in non-epidemic situations and with the CDI clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 hours, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. Metronidazole 500 mg orally 3-times daily for 10 days is recommended as the first antibiotic-of-choice for treatment of initial CDI in mild/moderate disease (Grade 1; SoR A). Alternative therapy options include vancomycin 125 mg orally 4-times daily or fidaxomicin 200 mg orally 2-times daily for 10 days (Grade 1, SoR B). There may be marginal benefit in using a higher dose of vancomycin 500 mg orally 4-times daily but data are limited (Grade 1, SoR C). There is no evidence to support the practice of extending anti-CDI therapy for the duration of therapy if the patient is also on a non-CDI antibiotic.[5]

Vancomycin 125 mg orally 4-times daily for 10 days (Grade 1, SoR A) is considered superior to metronidazole 500 mg orally 3-times daily (Grade 1, SoR D) in severe CDI based on clinical evidence, largely due to its pharmacokinetic properties. The use of high doses of vancomycin 500 mg orally 4-times daily (Grade 3, SoR B) was included in the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America treatment guidelines for management

of severe complicated CDI as defined by the treating physician. However, there is insufficient evidence to support the use of doses higher than 125 mg 4-times daily in the absence of ileus. Fidaxomicin is non-inferior to vancomycin for initial cure of CDI, but there are no data available on the efficacy of this drug in severe, life-threatening disease (Grade 1, SoR B).[5]

Vancomycin 125 mg orally 4-times daily or fidaxomicin 200 mg orally 2-times daily for 10 days (Grade 1, SoR B) is recommended for both treatment of mild or moderate CDI with risk for recurrent CDI, or for treatment of first recurrence of CDI. The incidence of a second recurrent of CDI after treatment of a first recurrence with oral metronidazole or vancomycin is similar. Fewer secondary recurrences are reported with oral fidaxomicin compared to vancomycin after treatment of a first recurrence. However, the evidence on fidaxomicin for this specific subgroup of CDI patients is limited to two phase 3 studies and based on a retrospective subset analysis of data and a limited number of patients. There are no prospective RCTs performed with metronidazole, vancomycin or fidaxomicin for this specific subgroup. In addition, fidaxomicin was not associated with fewer recurrences of CDI due to the BI/NAP1/027 strain. Therefore, based on the evidence currently available, the SoR for treating a first recurrence of CDI with oral vancomycin or oral fidaxomicin is considered equal, unless the disease has progressed from non-severe to severe. There may be some marginal benefit to adding metronidazole or higher doses of vancomycin (Grade 3, SoR C for both).[5]

In non-severe second (or later) recurrences of CDI, oral vancomycin or fidaxomicin is recommended. Vancomycin and fidaxomicin are equally effective in resolving CDI symptoms (Grade 2, SoR B for both), though fidaxomicin may lower likelihood of CDI recurrence after a first recurrence. However, there are no prospective RCTs investigating the efficacy of fidaxomicin in patients with *multiple* recurrence of CDI. In these cases, vancomycin is preferably administered using a pulsed regimen (125 mg 4-times daily for 10 days, followed by 125-500 mg per day every 2-3 days for at least 3 weeks) or tapered regimen (125 mg 4-times daily for 10 days, then gradually decreasing the dose to 125 per day) (Grade 2, SoR B for both).[5]

When oral administration is not possible, intravenous metronidazole 500 mg 3-times daily for 10 days (Grade 2, SoR A) may be added to vancomycin 500 mg/100 mL 4-times daily via oral/nasogastric tube for 10 days (Grade 3, SoR B). Alternatively, vancomycin 500 mg/100 mL can be given 4-times daily as a retention enema for 10 days (Grade 3, SoR B).[5]

<u>The American College of Gastroenterology</u>

The American College of Gastroenterology published evidence-based guidelines for the diagnosis, treatment and prevention of CDI. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was used to grade the strength of our recommendations and the quality of the evidence.[6] The guideline is designed to complement the ESCMID guidelines reported previously and the IDSA guidelines which are currently being updated.

In the management of mild, moderate and severe uncomplicated CDI, any inciting antibiotic agents should be discontinued (strong recommendation, high-quality evidence). However, there is no evidence to support the practice of extending anti-CDI treatment beyond the standard duration of therapy if non-CDI antibiotics cannot be discontinued. Patients with mild or moderate CDI should begin on metronidazole 500 mg orally 3-times daily for 10 days (strong recommendation, high-quality evidence). Failure to respond to metronidazole after 5-7 days should prompt a change to vancomycin 125 mg 4-times daily for 10 days (strong recommendation, moderate-quality evidence). Patients with severe CDI should be initially treated with vancomycin 125 mg 4-times daily for 10 days (conditional recommendation, moderate-quality evidence). Vancomycin may be delivered via enema in patients unable to take oral routes of administration (conditional recommendation, low-quality evidence).[6]

Vancomycin 125 mg orally 4-times daily plus intravenous metronidazole 500 mg 3-times daily is the treatment of choice in patients with severe and complicated CDI who have no significant abdominal distention (strong recommendation, low-quality evidence). In patients with complicated CDI with ileus or toxic colon

and/or abdominal distension, vancomycin 500 mg orally 4-times daily or 500 mg/500 mL per rectum 4-times daily plus intravenous metronidazole 500 mg 3-times daily are recommended (strong recommendation, low-quality evidence).[6]

The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. However, if the recurrence is severe, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen (conditional recommendation, low-quality evidence). However, fecal microbiota transplant should be considered if there is a third recurrence after using a pulsed vancomycin regimen (conditional recommendation, moderate-quality evidence).[6]

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:

1. Early Diagnosis, Prevention, and Treatment of C. difficile: Update - Research Review - Draft | AHRQ Effective Health Care Program. http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=2062. Accessed April 27, 2015.

2. Bagdasarian N, Rao K, Malani P. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. *JAMA*. 2015;313:398-408. doi:10.1001/jama.2014.17103.

3. O'Horo J, Jindai K, Kunzer B, Safdar N. Treatment of recurrent Clostridium difficile infection: a systematic review. *Infection*. 2014;42:43-59. doi:10.1007/s15010-013-0496-x.

4. Vardakas K, Polyzos K, Patouni K, Rafailidis P, Samonis G, Falagas M. Treatment failure and recurrence of Clostridium difficile infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *International Journal of Antimicrobial Agents*. 2012;40:1-8. doi:10.1016/j.ijantimicag.2012.01.004.

5. Debast S, Bauer M, Kuijper E. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect*. 2014;20(Suppl. 2):1-26. doi:10.1111/1469-0691.12418.

6. Surawicz C, Brandt L, Binion D, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013;108:478-498. doi:10.1038/ajg.2013.4.

Appendix 1: Current Status on Preferred Drug List

Form	Brand	Generic	PDL
TABLET	FLAGYL	METRONIDAZOLE	Y
TABLET	METRONIDAZOLE	METRONIDAZOLE	Y
TABLET	METRYL	METRONIDAZOLE	Y
CAPSULE	FLAGYL	METRONIDAZOLE	Y
CAPSULE	METRONIDAZOLE	METRONIDAZOLE	Y
TABLET ER	FLAGYL ER	METRONIDAZOLE	Y
CAPSULE	VANCOCIN	VANCOMYCIN	Y
CAPSULE	VANCOMYCIN HCL	VANCOMYCIN HCL	Y
CAPSULE	VANCOCIN HCL	VANCOMYCIN HCL	Y
VIAL	VANCOLED	VANCOMYCIN HCL	Y
VIAL	VANCOMYCIN HCL	VANCOMYCIN HCL	Y
VIAL	VANCOCIN HCL	VANCOMYCIN HCL	Y
TABLET	DIFICID	FIDAXOMICIN	N

Appendix 2: New Clinical Trials

Fifty-one potentially relevant articles were evaluated from the literature search. After further review, all articles were either post-hoc analyses of older trials, meta-analyses of select studies, or studies without evaluation of clinical outcomes, and were therefore excluded.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 5 2015

1 exp Clostridium difficile/ 5041
2 vancomycin.mp. or exp Vancomycin/ 15403
3 metronidazole.mp. or exp Metronidazole/ 8154
4 fidaxomicin.mp. 133
5 2 or 3 or 4 22851
6 1 and 5 937
7 limit 6 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 156
8 limit 7 to (english language and yr="2012 -Current") 51

Fidaxomicin (Dificid®)

Goal(s):

- To optimize appropriate treatment of *Clostridium difficile*-associated diarrhea.

Length of Authorization:

10 days

Requires PA:

- Fidaxomicin (Dificid®)

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does the patient have a diagnosis of *Clostridium difficile*-associated Diarrhea (CDAD)? (ICD-9 008.45)?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a preferred antibiotic? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	Yes: Inform Provider of covered alternatives in class.	No: Go to #4
4. Does the patient have a documented trial of appropriate therapy with vancomycin or metronidazole for a first recurrence or contraindication to therapy?	Yes: Go to #5.	No: Pass to RPH; Deny (medical appropriateness)
5. Does the patient have severe, complicated CDAD (life-threatening or fulminant infection or toxic megacolon)?	Yes: Pass to RPH; Deny (medical appropriateness)	No: Approve for up to 10 days

P&T / DUR Action: *5/15; 4/12*
Revision(s):
Initiated: *7/12*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Fluoroquinolone Antibiotics

Month/Year of Review: May 2015 **Date of Last Review:** January 2013

Current Status of PDL Class:
See **Appendix 1**.

Conclusions and Recommendations:

- Moderate quality evidence continues to support previous conclusions that there is no difference in effectiveness of fluoroquinolones (FQs) to susceptible bacteria.
- Low quality evidence suggests there may be some differences in harms between FQs. In particular, ofloxacin may be associated with highest risk of tendon injury while levofloxacin may be associated with least risk. Levofloxacin may be associated with higher risk of hyperglycemia or hypoglycemia and moxifloxacin may be associated with no risk for dysglycemia. Ciprofloxacin and levofloxacin appear to have little risk for QT-interval prolongation relative to other FQs. Levofloxacin may be associated with the least risk for neurotoxicity-related adverse events. All FQs are associated with *Clostridium difficile* infection and there does not appear to be any differences in risk among this class.
- Continue to maintain at least one FQ with broad coverage of gram-negative bacteria (ciprofloxacin, levofloxacin) and at least one "respiratory" third-generation FQ (gemifloxacin, levofloxacin, moxifloxacin).
- No further review or research needed at this time. Review comparative drug costs in the executive session.

1

Previous Conclusions and Recommendations:

- 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 medication with pseudomonas coverage and at least one "respiratory" quinolone (gemifloxacin, levofloxacin, moxifloxacin).

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Effectiveness Outcomes of Fluoroquinolones:

Acute pyelonephritis is a common condition that results in thousands of hospitalizations annually in the U.S. Current recommendations for duration of therapy for acute pyelonephritis is 7 days for FQs, 10-14 days for beta-lactams and 14 days for trimethoprim/sulfamethoxazole (TMP/SMX) in non-hospitalized, otherwise healthy and non-pregnant female patients. No recommendations are available for male patients, hospitalized patients, and patients with significant comorbidities. Studies demonstrate a wide variation in prescribing practice regarding antibiotic selection and duration of therapy. Eliakim-Raz, et al. performed a systematic review of all RCTs of adult females and males hospitalized or treated in the community for acute pyelonephritis and urinary tract infection (UTI) with sepsis and compared duration of antibiotic therapy of 7 days or less to longer than 7 days.[1] Eight RCTs were eligible for the review, four of which compared FQs, one compared a FQ with TMP/SMX, and three compared beta-lactams. The trials included 2515 patients (n=1239 treated for ≤7 days vs. n=1276 treated for >7 days). The primary outcome assessed was clinical failure, defined as a lack of resolution of fever or signs and symptoms of UTI, or modification of antibiotics at the end of the long-treatment arm (EOT, at 10-14 days). Outcomes were assessed for the per-protocol population and for the intent-to-treat (ITT) population (all randomized patients, regardless of treatment administration) because in non-inferiority and equivalence studies, ITT analysis tends toward equivalence. Clinical failure at EOT for the per-protocol population did not significantly differ between the two treatment arms (RR 0.63, 95% CI, 0.33 to1.18; I^2=41%, n=1076). The observed heterogeneity was due to one trial that compared FQs in the short-treatment arm with TMP/SMX in the long-treatment arm and showed a significant advantage for the short-treatment arm. Other studies compared FQs in both treatment arms, and in these studies clinical failure did not significantly differ between the short- and long-treatment arms (RR 0.76, 95% CI, 0.49 to 1.17; I^2=0%; n=852). When outcomes were analyzed at end of follow-up, which ranged from 22-63 days post-therapy, and in one study up to 6 months post-therapy, there was also no significant difference between treatment arms (RR 0.79; 95% CI, 0.56 to 1.12; I^2=1%; n=1398 patients). The authors concluded that 7 days of treatment is equivalent to longer treatment durations in patients with acute pyelonephritis and UTIs with sepsis. However, a pre-specified sub-group analysis found that patients with urogenital abnormalities had lower microbiological failure with longer therapy, though evidence is weak.

2

Chronic bacterial prostatitis (CBP) involves infection and inflammation of the prostate gland in men. It can cause problems urinating, including discomfort and pain, increased frequency and urge, or problems emptying the bladder. Bacteria infecting the prostate are the cause of CBP, which may be sexually transmitted. To cure CBP, antibiotics must be administered for extended periods of time (four weeks or longer), but a permanent cure is not always guaranteed. A Cochrane Review assessed the safety and efficacy of antibiotic therapy for CBP.[2] Few antibiotics are able to distribute to the prostatic tissue and achieve sufficient concentrations at the site of infection. These drugs include FQs, macrolides, tetracyclines and trimethoprim. After the introduction of FQs into clinical practice, a number of studies have been performed to optimize the antimicrobial treatment of CBP, and to improve eradication rates and symptom relief. All 18 included randomized controlled comparisons (n=2196 patients) were of one antibiotic versus placebo or one or more comparator antibiotics, with or without non-antimicrobial drugs. The oral FQs included were ciprofloxacin, levofloxacin and ofloxacin. Three studies were double-blinded, one study was single-blinded and the remaining 14 studies were open-label. Overall quality of evidence ranged from very low to moderate. There were no significant differences in clinical or microbiological efficacy or in the rate of adverse effects between these FQs. The only notable difference was in chlamydial prostatitis, where azithromycin demonstrated improved eradication rates and clinical cure rates compared to ciprofloxacin, but with no significant differences in adverse effects.

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with gradually worsening shortness of breath and cough with sputum because of permanent pulmonary and bronchial damage. A Cochrane Review recently evaluated prophylactic antibiotic therapy for COPD to determine if these antibiotics reduce COPD exacerbations or affect quality of life.[3] All 7 eligible studies were RCTs that compared prophylactic antibiotics to placebo in patients with at least moderate severity of COPD (n=3170). Five studies were of continuous antibiotic prophylaxis and two studies were of intermittent (pulsed) antibiotic prophylaxis. The only FQ reviewed was moxifloxacin in addition to the macrolide antibiotics azithromycin, erythromycin and clarithromycin. Study durations ranged form 3 to 36 months and most evidence was of moderate quality. Continuous use of these antibiotics reduced COPD exacerbations (odds ratio [OR] 0.55; 95% CI, 0.39 to 0.77; 3 studies; n=1262; high quality evidence), with 54% of patients in the treatment group experiencing an exacerbation compared to 69% in the control group (number needed to treat to prevent one exacerbation [NNT] of 8 patients (95% CI, 5 to 18). Antibiotic pulse therapy, however, did not significantly reduce the number of patients with exacerbations (OR 0.87; 95% CI, 0.69 to 1.09; 1 study; n=1149; moderate quality evidence), which was significantly difference from the effect on exacerbations found with continuous use of prophylactic antibiotics. Interestingly, there was statistically significant improvement in quality of life with both continuous and pulse antibiotic treatment but this result was smaller than the 4-unit improvement regarded as being clinically significant (MD -1.78; 95% CI, -2.95 to -0.61; 2 studies; n=1962; moderate quality evidence). Neither continuous use or pulse use of antibiotic prophylaxis reduced frequency of hospital admissions or all-cause mortality (moderate quality evidence). Adverse events that led to drug discontinuation, such as development of prolonged QT-interval or tinnitus, did not occur significantly more frequently in the treatment group than the placebo group. Other notable adverse events included a high rate of gastrointestinal events with moxifloxacin and an association between azithromycin and significant hearing loss. Consideration for lifetime prophylaxis to reduce COPD exacerbations, but not hospitalizations or mortality, with antibiotics should be balanced with the increased risk for these aforementioned harms and antibiotic resistance.

Safety of Fluoroquinolones:

The evidence for associations between antibiotic classes and hospital-acquired *Clostridium difficile* infection (HA-CDI) was recently systematically studied.[4] The strongest associations for risk of HA-CDI were for the third-generation cephalosporins (OR 3.20; 95% CI, 1.80 to 5.71; n=6 studies; I^2=79.2%), followed by clindamycin (OR 2.86; 95% CI, 2.04 to 4.02; n=6 studies; I^2=28.5%), fourth-generation cephalosporins (OR 2.14; 95% CI, 1.30 to 3.52; n=2 studies; I^2=0.0%), carbapenems (OR 1.84; 95% CI, 1.26 to 2.68; n=6; I^2=0.0%), TMP/SMX (OR 1.78; 95% CI, 1.04 to 3.05; n=5 studies; I^2=70%); FQs (OR 1.66; 95% CI, 1.17 to 2.35; n=10; I^2=64%; and penicillin/beta-lactamase inhibitor combinations (OR 1.45; 95% CI, 1.05 to 2.02; n=6 studies; I^2=54%). The risk associated with FQs fell from 66% to 39% after excluding one study that measured antibiotic exposure during hospital admission only. Fluoroquinolone antibiotics are more specifically related to *C. difficile* infections with the NAP1/RT027 FQ-resistant epidemic strain.[4]

A second systematic review studied the association between antibiotic classes and risk of *C. difficile* infection (CDI) in the community setting.[5] No differentiation was made between different antibiotics within a class. Clindamycin was associated with the highest risk for CDI in this population (OR 16.80; 95% CI, 7.48 to 37.76), followed by the beta-lactams cephalosporins, monobactams or carbapenems (OR 5.68; 95% CI, 2.12 to 15.23), and FQs (OR 5.50; 95% CI, 4.26 to 7.11). Macrolides (OR 2.65; 95% CI, 1.75 to 4.21), TMP/SMX (OR 1.81; 95% CI, 1.34 to 2.43) and penicillins (OR 2.71; 95% CI, 1.75 to 4.21) had lower but still significant associations with CDI. Tetracycline antibiotics were not associated with increased risk of CDI.

A systematic evaluation of safety and tolerability data of the third- and fourth-generation FQs was performed to evaluate their risks, especially in susceptible populations where the risk-to-benefit may be unfavorable.[6] The only third-generation FQ approved in the U.S. is levofloxacin; fourth-generation FQs approved include moxifloxacin and gemifloxacin. Ciprofloxacin, ofloxacin and norfloxacin antibiotics are second-generation FQs and were not included in this review unless compared to third- or fourth-generation FQs. The primary adverse effects reported for third- and fourth-generation FQs are summarized in Table 1. For each type of adverse effect, differences between individual FQs and their comparisons with other antibiotics are described if data are available.

Table 1. Adverse Effects Associated with Fluoroquinolones and Comparative Risk.[6]

Adverse Effect (AE)	Notes
Gastrointestinal (GI) Effects	Clinical Manifestations: nausea, diarrhea, vomiting, abdominal pain, dyspepsia, anorexia, *C. difficile*-associated diarrhea (CDAD). Comparative FQ Risk: No differences between FQs for most GI AEs noted. There appears to be no differences between ciprofloxacin, levofloxacin or moxifloxacin and risk for CDAD.
Neurotoxicity	Clinical Manifestations: dizziness, headache, drowsiness, agitation, restlessness, nervousness, insomnia, nightmares, tremors, confusion, hallucinations, paranoia, depression, suicidal ideation, delirium, psychosis, catatonia, seizures, abnormal vision. Comparative FQ Risk: Gemifloxacin has been associated with more neurotoxicity than either levofloxacin or moxifloxacin. Levofloxacin is considered safe, with an overall rate of neurotoxicity AEs between 0.2 to 1.1%.
Phototoxicity	Clinical Manifestations: sun-exposed skin reactions (erythema, bullous eruptions, carcinoma, melanoma), mutagenicity, carcinogenicity. Comparative FQ Risk: Unable to assess clinical differences between FQs based on studies. Phototoxicity is a class-effect with FQs due to their chemical structures, which indicate higher potential with gemifloxacin, followed by levofloxacin. Moxifloxacin has the least potential of third- and fourth generation FQs.
Skin Reactions	Clinical Manifestations: rash, pruritus, urticaria, erythema, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis. Comparative FQ Risk: Gemifloxacin may have an increased rate of rash, which appears to be associated with prolonged use (more than 5 days), particularly in women aged less than 40 years. Serious skin reactions with FQs are very rare.
Cardiotoxicity	Clinical Manifestations: ventricular arrhythmia (e.g., torsades de pointes). Comparative FQ Risk: Moxifloxacin may pose a higher risk while ciprofloxacin and levofloxacin are least likely to be associated with FQ-induced QT interval prolongation or serious arrhythmias.
Hepatotoxicity	Clinical Manifestations: elevated liver enzymes, hepatitis, pancreatitis, jaundice, liver injury, hepatic failure. Comparative FQ Risk: Transient, elevated levels of liver enzymes greater than 2-3 times the upper limit of normal occur in 2-3% of patients treated with FQs. Risk among FQs are similar though reports of moxifloxacin-induced liver injury and death have been reported.
Dysglycemia	Clinical Manifestations: hyperglycemia and hypoglycemia. Comparative FQ Risk: Levofloxacin is associated with higher risk for hyperglycemia or hypoglycemia relative to ciprofloxacin. Moxifloxacin appears to have no known risk for dysglycemia.
Anthropathy and Tendinopathy	Clinical Manifestations: arthralgias, arthritis, tendinitis and tendon rupture. Comparative FQ Risk: Evidence is limited but multiple case reports show levofloxacin may be associated with a lower risk than ciprofloxacin.
Ocular Effects	Clinical Manifestations: corneal perforation, diplopia, optic neuropathy, retinal hemorrhages and detachment. Ocular irritation/discomfort, tearing, ocular burning/stinging/pruritus, chemosis, keratitis, conjunctival hyperemia, decreased visual acuity, dry eye and ocular pain. Comparative FQ Risk: No differences noted, but ocular effects are more common with ophthalmic preparations. However, there are cases of oral FQs associated with retinal detachment.

Tendon injury has been associated with the use of FQs but the risk associated with newer FQs has not been established. A systematic review specifically evaluating the risk of tendon injury with FQ use using available studies was recently conducted.[7] Only observational studies reported on tendon injury, of which 16 were eligible to be included in the review. Population-based observational studies reflect real-life clinical practice but can underestimate the prevalence of adverse events. Because observational studies rely heavily on self-reporting, the true effect of FQs on tendon injury may be much higher than that reported here. Five studies specifically evaluated Achilles tendon rupture; four found a significant increase risk, whereas one reported an increased, but not significant risk. Three studies that evaluated Achilles tendinitis as an outcome found statistically significant increased risk with FQs; one prospective cohort which examined 1841 patients exposed to FQs and 9406 controls found a non-significant increase (relative risk [RR] 3.7; 95% CI, 0.93 to 15.14). However, a sub-group analysis of patients aged 60 years or older found a statistically significant increased risk for Achilles tendinitis (OR 3.1; 95% CI, 2.0 to 4.8). In another large cohort, three FQs were examined: ofloxacin, ciprofloxacin and norfloxacin. Ofloxacin appeared to have the highest rare of developing tendinitis (RR 4.9; 95% CI, 1.57 to 15.06) and Achilles tendinitis (RR 10.1; 95% CI, 2.20 to 46.04), whereas ciprofloxacin and norfloxacin was not statistically significant compared with controls. The time between FQ exposure and outcome varied between 15 days and 18 months but risk seemed to be highest in the first month after exposure. Another study found a differential risk of tendon disorders among FQs (ofloxacin, moxifloxacin and levofloxacin) compared with the reference population of subjects who received cephalosporins. Ofloxacin again was associated with the highest risk (RR 80.2; 95% CI, 9.5 to 680.5), followed by moxifloxacin (RR 15.7; 95% CI, 3.1 to 81.0) and levofloxacin (RR 5.2; 95% CI, 1.7 to 15.5). Overall, however, tendon complications in patients who received FQs were still rare.

New Guidelines:
The American Society of Clinical Oncology (ASCO) published a clinical practice guideline on antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy.[8] The purpose of the guideline was to provide guidance on antimicrobial prophylaxis for adult neutropenic oncology outpatients and on selection and treatment as outpatients of those with fever and neutropenia. Key recommendations include use of antibacterial or antifungal prophylaxis only if neutrophils are expected to remain less than 100 µL for more than 7 days, unless other factors increase risk for complications or mortality. An oral FQ (ciprofloxacin or levofloxacin) is preferred for antibacterial prophylaxis. This recommendation was primarily based from meta-analyses from Cochrane reviews which showed that systemically absorbed oral FQs are the most tolerable choice for prophylaxis in neutropenic oncology patients and are equally protective whether used alone or combined with other antibiotics active against gram-positive bacteria. An oral FQ plus amoxicillin/clavulanate (or plus clindamycin for those with penicillin allergy) is recommended for initial empiric therapy of cancer patients with febrile neutropenia who are at low risk of medical complications, unless FQ prophylaxis was used before fever developed or the prevalence of FQ resistance is greater than 20%. This recommendation was not based on RCTs directly comparing different oral regimens; rather, the panel of guideline writers relied on indirect comparison of results of separate RCTs studying outpatient management of febrile neutropenia, nearly all of which used FQ antibiotics.[8]

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
Oral ciprofloxacin received an expanded indication in November 2014 for Plague in adult and pediatric patients.[9]

New FDA Safety Alerts:
All FQ antibiotics received updated labeling of Warning and Precautions regarding peripheral neuropathy in August 2013. The antibiotic should be discontinued immediately if symptoms occur in order to prevent irreversibility.[9]

References:

1. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection— 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2013;68:2183-2191. doi:doi:10.1093/jac/dkt177.

2. Perletti G, Marras E, Wagenlehner F, Magri V. Antimicrobial therapy for chronic bacterial prostatitis. *Cochrane Database of Systematic Reviews*. 2013;(Issue 8. Art. No.: CD009071). doi:10.1002/14651858.CD009071.pub2.

3. Herath S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews*. 2013:Issue 11. Art. No.: CD009764. doi:0.1002/14651858.CD009764.pub2.

4. Slimings C, Riley T. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69:881-891. doi:10.1093/jac/dkt477.

5. Brown K, Khanafer N, Daneman N, Fisman D. Meta-Analysis of Antibiotics and the Risk of Community-Associated Clostridium difficile Infection. *Antimicrobial Agents and Chemotherapy*. 2013;57:2326-2332. doi:doi:10.1128/AAC.02176-12.

6. Sousa J, Alves G, Fortuna A, Falcao A. Third and Fourth Generation Fluoroquinolone Antibacterials: A Systematic Review of Safety and Toxicity Profiles. *Current Drug Safety*. 2014;9:89-105.

7. Stephenson A, Wu W, Cortes D, Rochon P. Tendon Injury and Fluoroquinolone Use: A Systematic Review. *Drug Saf*. 2013;36:709-721. doi:10.1007/s40264-013-0089-8.

8. Flowers C, Seidenfeld J, Bow E, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology Clinical Practice Guideline. *J Oncol Pract*. 2013;31:794-810. doi:doi:10.1200/JOP.2012.000815.

9. Drugs@FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 13, 2015.

Appendix 1: Current Status on Preferred Drug List

Brand	Generic	PDL
CIPRO	CIPROFLOXACIN HCL	Y
CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	Y
CIPRO	CIPROFLOXACIN HCL	Y
LEVAQUIN	LEVOFLOXACIN	Y
LEVOFLOXACIN	LEVOFLOXACIN	Y
FLOXIN	OFLOXACIN	N
OFLOXACIN	OFLOXACIN	N
AVELOX	MOXIFLOXACIN HCL	N
AVELOX ABC PACK	MOXIFLOXACIN HCL	N
MOXIFLOXACIN HCL	MOXIFLOXACIN HCL	N
FACTIVE	GEMIFLOXACIN MESYLATE	N
CIPRO XR	CIPROFLOXACIN ER	N
CIPROFLOXACIN ER	CIPROFLOXACIN ER	N
NOROXIN	NORFLOXACIN	N

Appendix 2: New Clinical Trials

Ninety-seven citations were evaluated from the literature search. After further review, three prospective clinical trials compared FQ antibiotics and were therefore included. These trials are briefly described in the table below. Full abstracts and references are included in Appendix 3.

Table 2. Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Asicioglu O, et al. P, R, PG, OL Turkey	Ofloxacin 400 mg PO BID + Metronidazole 500 mg PO BID x14d (n=543) Vs. Moxifloxacin 400 mg PO Qday x14d (n=560)	Women 14-45 years old w/ uncomplicated pelvic inflammatory disease (uPID)	Clinical cure (≥60% reduction in total pain score at day 21 compared w/ baseline and absence of pelvic discomfort and tenderness, temperature <37 °C, and WBC <10,000/mm^3)	Ofloxacin+Metronidazole: 82.7% Moxifloxacin: 79.5% Difference: p=0.172 (NS)
Kern WV, et al. P, DB, MC, DD, R	Moxifloxacin 400 mg PO Qday x 5d or until resolution of infection (n=169) Vs. Ciprofloxacin 750 mg PO + amoxicillin/clavulanate 1000 mg PO BID x 5d or until resolution of infection (n=164)	Adults w/ cancer w/ fever and neutropenia and an MASCC score >20	Response (defervescence and improvement in clinical status during treatment, remaining free of relapsing infection, and no documented infection caused by bacteria in vitro resistant to study drugs)	Moxifloxacin: 80.5% Ciprofloxacin + Amoxicillin/Clavulanate: 81.7% Difference 1.2% (p=NS)
Schaper NC, et al. P, R, DD, DB, MN, MC, NI Sub-group analysis	Moxifloxacin 400 mg IV Qday, followed by PO x7-21d (n=110) Vs. Piperacillin/tazobactam 4/0.5 g IV TID, followed by amoxicillin/clavulanate 875/125 mg BID x7-21d (n=96)	Adults w/ diabetic foot infection	Clinical cure (as assessed by independent data review committee)	Moxifloxacin: 76.4% PIP/TAZO-AMC: 78.1% Difference: 1.7% (95% CI, -14.5% to 9.0%)

Abbreviations: BID = twice daily; d = days; DB = double blind; DD = double dummy; MASCC = Multinational Association for Supportive Care in Cancer algorithm predicting complications in adults patients with febrile neutropenia; MC = multi-centered; MN = multinational; NI = non-inferiority; NS = not significant; OL = open label; P = prospective; PG = parallel group; PO = orally; Qday = once daily; R = randomized; TID = three times daily.

Appendix 3: Abstracts of Clinical Trials

Asicioglu O, Gungorduk K, Ozdemir A, et al. Single daily dose of moxifloxacin versus ofloxacin plus metronidazole as a new treatment approach to uncomplicated pelvic inflammatory disease: a multicentre prospective randomized trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2013;171:116-121. DOI 10.1016/j.ejogrb.2013.08.012.

Objectives: To evaluate the efficacy and safety of moxifloxacin versus ofloxacin plus metronidazole in patients with uncomplicated pelvic inflammatory disease (uPID; defined as PID symptoms and signs, but no complications such as septicemia, perihepatitis, and tubo-ovarian abscess) in Turkey.
Study design: This was a multicenter, prospective, randomized, parallel-group study conducted between June 2010 and March 2013 in four hospitals in Turkey. Women received a 14-day course of either oral moxifloxacin at 400 mg once daily (n = 560) or oral ofloxacin at 400 mg twice daily plus oral metronidazole at 500 mg twice daily (n = 543).
Results: A total of 1156 women were randomized to the study. Total compliance was achieved in 1103 patients. For the primary measure of efficacy (clinical cure), moxifloxacin showed no difference compared with ofloxacin plus metronidazole (445/560 [79.5%] vs. 449/543 [82.7%]; p = 0.172). Bacteriological cure rates were high and comparable between treatment arms (99/119 [83.2%] vs. 93/110 [84.5%]; p = 0.781). Drug-related adverse events occurred less frequently with moxifloxacin than with ofloxacin plus metronidazole (210/560 [37.5%] vs. 252/543 [46.4%]; p = 0.003). Furthermore, moxifloxacin treatment was lower in cost and achieved higher patient compliance compared with ofloxacin plus metronidazole (31.4 Euros vs. 23.4 Euros and 7/578 (1.2%) vs. 22/578 (3.8%), respectively; p = 0.005).
Conclusions: In patients with uPID, once-daily moxifloxacin monotherapy was clinically and microbiologically as efficacious as twice-daily ofloxacin plus metronidazole therapy and was associated with fewer drug-related adverse events, lower patient non-compliance, and a lower treatment cost.

Kern WV, Marchetti O, Drgona L, et al. Oral antibiotics for fever in low-risk neutropenic patients with Cancer: a double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy – EORTC Infectious Diseases Group Trial XV. *J Clin Oncol*. 2013;31:1149-56.

Purpose: This double-blind, multicenter trial compared the efficacy and safety of a single daily oral dose of moxifloxacin with oral combination therapy in low-risk febrile neutropenic patients with cancer.
Patients and Methods: Inclusion criteria were cancer, febrile neutropenia, low risk of complications as predicted by a Multinational Association for Supportive Care in Cancer (MASCC) score 20, ability to swallow, and one single intravenous dose of empiric antibiotic therapy before study drug treatment initiation. Early discharge was encouraged when a set of predefined criteria was met. Patients received either moxifloxacin (400 mg once daily) monotherapy or oral ciprofloxacin (750 mg twice daily) plus amoxicillin/clavulanic acid (1,000 mg twice daily). The trial was designed to show equivalence of the two drug regimens in terms of therapy success, defined as defervescence and improvement in clinical status during study drug treatment (< 10% difference).
Results: Among the 333 patients evaluated in an intention-to-treat analysis, therapy success was observed in 80% of the patients administered moxifloxacin and in 82% of the patients administered combination therapy (95% CI for the difference, -10% to 8%, consistent with equivalence). Minor differences in tolerability, safety, and reasons for failure were observed. More than 50% of the patients in the two arms were discharged on protocol therapy, with 5% readmissions among those in either arm. Survival was similar (99%) in both arms.

Conclusion: Monotherapy with once daily oral moxifloxacin is efficacious and safe in low-risk febrile neutropenic patients identified with the help of the MASCC scoring system, discharged early, and observed as outpatients.

Schaper NC, Dryden M, Kujath P, et al. Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study. *Infection*. 2013; 41:175-86.

Objective: The aim was to compare the efficacy and safety of two antibiotic regimens in patients with diabetic foot infections (DFIs).
Methods: Data of a subset of patients enrolled in the RELIEF trial with DFIs requiring surgery and antibiotics were evaluated retrospectively. DFI was diagnosed on the basis of the modified Wagner, University of Texas, and PEDIS classification systems. Patients were randomized to receive either intravenous/oral moxifloxacin (MXF, n=110) 400 mg daily or intravenous piperacillin/tazobactam 4.0/0.5 g TID followed by oral amoxicillin/clavulanate 875/125 mg BID (PIP/TAZ–AMC, N = 96), for 7–21 days until the end of treatment (EOT). The primary endpoint was clinical cure rates in the per-protocol (PP) population at the test-of-cure visit (TOC, 14–28 days after EOT).
Results: There were no significant differences between the demographic characteristics of PP patients in either treatment group. At TOC, MXF and PIP/TAZ–AMC had similar efficacy in both the PP and intent-to-treat (ITT) populations: MXF: 76.4 % versus PIP/TAZ–AMC: 78.1 %; 95 % confidence interval (CI) -14.5 %, 9.0 % in the PP population; MXF: 69.9 % versus PIP/TAZ–AMC: 69.1 %; 95 % CI -12.4 %, 12.1 % in the ITT population. The overall bacteriological success rates were similar in both treatment groups (MXF: 71.7 % versus PIP/TAZ–AMC: 71.8 %; 95 % CI -16.9 %, 10.7 %). A similar proportion of patients (ITT population) experienced any adverse events in both treatment groups (MXF: 30.9 % versus PIP/TAZ– AMC: 31.8 %, respectively). Death occurred in three MXF-treated patients and one PIP/TAZ–AMC-treated patient; these were unrelated to the study drugs.
Conclusion: Moxifloxacin has shown favorable safety and efficacy profiles in DFI patients and could be an alternative antibiotic therapy in the management of DFI.

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Appendix 4: Medline Search Strategy
Ovid MEDLINE(R) without Revisions 1996 to April Week 1 2015
1 exp Fluoroquinolones/ 18874
2 exp Ciprofloxacin/ 7194
3 exp Levofloxacin/ 2228
4 exp Ofloxacin/ 4141
5 moxifloxacin.mp. 2941
6 gemifloxacin.mp. 400
7 exp Norfloxacin/ 887
8 1 or 2 or 3 or 4 or 5 or 6 or 7 19602
9 limit 8 to (yr="2013 -Current" and (case reports or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 565
10 limit 9 to (english language and humans) 468
11 oral.mp. or exp Administration, Oral/ 295047
12 oral*.mp. 320127
13 11 or 12 321846
14 10 and 13 97

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Ophthalmic Anti-inflammatory Drugs

Month/Year of Review: May 2015

Date of Last Review: December 2009
Source Document: Provider Synergies

Current Status of PDL Class:
See **Appendix 1**.

Conclusions and Recommendations:
- There is high quality evidence that there is no difference in efficacy/effectiveness or in safety between ophthalmic corticosteroid agents.
- There is high quality evidence that there is no difference in efficacy/effectiveness or in safety between ophthalmic nonsteroidal anti-inflammatory drugs.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:
- There is high quality evidence that there is no difference in efficacy/effectiveness or in safety between agents.
- Consider at least one medication from each class (corticosteroids and NSAIDs).

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Methods:
A Medline literature search for new randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A Cochrane Review performed by Sivaprasad, et al.[1] investigated the effectiveness of non-steroidal anti-inflammatory inhibitors (NSAIDs) in cystoids macular edema following cataract surgery. Cystoid macular edema (CMO) is the accumulation of fluid in the central retina (the macula) due to leakage from dilated

capillaries. It is the most common cause of poor visual outcome following cataract surgery. Acute CMO, defined as edema of less than four months duration, often resolve spontaneously. CMO that persists for four months or more is termed chronic CMO. The primary outcome measures were: 1) an improvement of 2 or more lines in Snellen visual acuity or equivalent at end of treatment; and 2) persistence of improvement of vision one month after discontinuation of treatment. This review included seven randomized controlled trials with a total of 266 participants. Three trials studied the effects of topical NSAIDs in chronic CMO while the other three examined the effect of topical NSAIDs in acute CMO.[1] Two trials showed that topical 0.5% ketorolac tromethamine ophthalmic solution significantly improves 2 or more lines in Snellen visual acuity versus placebo on chronic CMO and a third trial assessing topical 1% fenoprofen was also supportive of this finding but did not find a statistically significantly difference versus placebo. Further work is needed for a more conclusive decision regarding use of ophthalmic NSAIDS in chronic CMO. A meta-analysis was performed for these drugs but 95% confidence intervals showed very imprecise estimates of their effect.[1] Similar results were also seen in Snellen visual acuity when either topical ketorolac or prednisolone was used in acute CMO, though both drugs used together were more effective than either agent alone. Persistent improvement of vision one month after discontinuing treatment was also noted for all 3 arms. In another study, 0.1% diclofenac sodium and 0.5% ketorolac tromethamine yielded similar results in Snellen visual acuity. A third cross-over study yielded less compelling results with ketorolac. All 3 studies were underpowered to show anything but major effects. Spontaneous resolution and drug effect in acute CMO are hard to distinguish in these very small studies. Because of the significant heterogeneity and small sample sizes of these studies, a meta-analysis was not performed and the effects of NSAIDs in acute CMO remain promising but unclear.[1]

A systematic review performed by Kessel, et al.[2] compared the efficacy of topical corticosteroids with topical NSAIDs in controlling inflammation and preventing pseudophakic cystoid macular edema (PCME, also termed “Irvine-Gass syndrome) after uncomplicated cataract surgery. The swelling of the fovea that results in occurs due to fluid accumulation occurring a few weeks to months after cataract surgery and is the most common cause of visual decline after cataract surgery. The primary outcome assessed was postoperative inflammation and PCME. Fifteen RCTs were identified.[2] The anti-inflammatory effect of these drugs was evaluated by examining signs of intraocular inflammation: cells and flare. Only studies used laser cell-flare photometry to identify inflammation were included in the meta-analysis because other methods did not use comparable grading systems. Inflammation measured as number of cells detected did not find a statistically significant difference between corticosteroids and NSAIDs; however, inflammation measured as amount of flare by laser flare photometry week 1 after surgery demonstrated superiority with NSAIDs relative to low potency corticosteroids but NSAIDs were equally effective to medium to high potency corticosteroids. The prevalence of PCME was significantly higher in the corticosteroid group (25.3%) than in the NSAID group (3.8%), a risk ratio of 5.35 (95% CI, 2.94 to 9.76). There was no significant difference in visual acuity after cataract surgery or adverse events between the two groups. Significant heterogeneity between the studies, as well as extensive exclusion criteria (i.e., history of uveitis, diabetes, diabetic retinopathy) limits the applicability of these results. The authors concluded there is low to moderate quality of evidence that topical NSAIDs are more effective in controlling postoperative inflammation after cataract surgery and high quality evidence that topical NSAIDs are more effective than topical corticosteroids in preventing PCME.[2]

A Cochrane Review performed by Herretes, et al.[3] assessed the effectiveness and safety of corticosteroids as adjunctive therapy for bacterial keratitis. Four eligible RCTs (n=612 eyes) that had evaluated adjunctive therapy with topical corticosteroids in people with bacterial keratitis who were being treated with antibiotics were included in the review. One of the three smaller trials was a pilot study of the largest study: the Steroids for Corneal Ulcers Trial.[4] All trials reported data on visual acuity ranging from three weeks to one year, and none of them found any important difference between the corticosteroid group and the control group. The pilot study of the SCUT reported that time to re-epithelialization in the steroid group was 53% slower than the placebo group after adjusting for baseline epithelial defect size (hazard ratio (HR) 0.47; 95% confidence interval (CI) 0.23 to 0.94). However, the SCUT did not find any important difference in time to re-epithelialization (HR 0.92; 95% CI 0.76 to 1.11). For adverse events, none of the three small trials found any important difference between the two treatment groups. The investigators of the largest trial reported that more patients in the control group developed intraocular pressure (IOP)

elevation (risk ratio (RR) 0.20; 95% CI 0.04 to 0.90). One trial reported quality of life and concluded that there was no difference between the two groups (data not available). Although the four trials were generally of good methodological design, all trials had considerable losses to follow-up (10% or more) in the final analyses. Three of the four trials were underpowered to detect treatment effect differences between groups. Heterogeneity between the outcomes studied prohibited a meta-analysis of the data. The authors concluded there is inadequate evidence as to the effectiveness and safety of adjunctive topical corticosteroids compared with no topical corticosteroids in improving visual acuity or adverse events.[3]

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations or Indications:
LOTEMAX® (loteprednol etabonate) 0.5% ophthalmic ointment is a corticosteroid approved by the FDA in April 2011 for the treatment of postoperative inflammation and pain following ocular surgery. Loteprednol was initially approved in the U.S. in 1998 as 0.2% and 0.5% ophthalmic suspensions.[5] Data submitted to the FDA provided evidence of effectiveness in adequate and well controlled studies that demonstrated the superiority of loteprednol etabonate 0.5% ophthalmic ointment to placebo vehicle in both the complete resolution of postoperative anterior chamber cell and flare and in complete resolution of postoperative pain following ocular surgery for up to 18 days.[5]

ILEVRO™ (nepafenac) 0.3% ophthalmic suspension is an NSAID approved by the FDA in 2012 for the treatment of pain and inflammation associated with cataract surgery. It was initially approved in the U.S. in 2005 as a 0.1% formulation given three times daily. The re-formulated suspension is 3-fold more potent but given only once daily. The suspension was shown to be effective and safe for the treatment of pain and inflammation associated with cataract surgery based on superiority to a placebo vehicle and non-inferiority to the previously approved formulation. No new adverse effects were identified in the two Phase 3 trials testing this formulation.[6]

LOTEMAX® (loteprednol etabonate) 0.5% ophthalmic gel is a corticosteroid approved by the FDA in September 2012 for the treatment of postoperative inflammation and pain following ocular surgery. Loteprednol was initially approved in the U.S. in 1998 as 0.2% and 0.5% ophthalmic suspensions.[7] The ointment, as noted previously, was approved in 2011. Data submitted to the FDA was contained in the results of two randomized, multicenter, double-blind, vehicle placebo-controlled Phase 3 trials in 813 patients randomized to one of the two arms: loteprednol etabonate four times daily for 14 days after cataract surgery (n=409) or vehicle control (n=404). Significantly more patients receiving loteprednol had complete resolution of anterior chamber cell inflammation versus placebo (30.5%-31.1% vs. 16.3%-13.9%, respectively; $p<0.001$). In addition, significantly more patients receiving loteprednol had complete resolution of pain versus placebo (72.9%-75.7% vs. 41.9%-45.8%, respectively; $p<0.001$).[7]

PROLENSA™ (bromfenac) 0.07% ophthalmic solution is an NSAID approved by the FDA in 2013 for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. Bromfenac was initially approved in the U.S. as a 0.09% solution in 2005. The newer, less concentrated, suspension was shown to be effective and safe in two Phase 3 trials for the treatment of pain and inflammation associated with cataract surgery

based on superiority to a placebo vehicle. The primary efficacy endpoint was the proportion of patients with cleared inflammation by day 15, which was defined as the summed ocular inflammation score of Grade 0 (0 cells and absence of flare) at any post-surgery visit prior to and included day 15.[8]

New FDA Safety Alerts:
None identified.

References:

1. Sivaprasad S, Bunce C, Crosby-Nwaobi R. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD004239. DOI: 10.1002/14651858.CD004239.pub3.

2. Kessel L, Tendal B, Jorgensen K. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology*. 2014;121:1915-1924.

3. Herretes S, Wang X, Reyes JMG. Topical corticosteroids as adjunctive therapy for bacterial keratitis. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD005430. DOI: 10.1002/14651858.CD005430.pub3.

4. Srinivasan M, Mascarenhas J, Rajaraman R. Corticosteroids for bacterial keratitis: the Steroids for Corneal Ulcers Trial (SCUT). *Arch Ophthalmol*. 2012;130(2). doi:doi:10.1001/archophthalmol.2011.315.

5. Loteprednol Ophthalmic Ointment Summary Review. Drugs@FDA: FDA Approved Drug Products. *US Food and Drug Administration CDER Website*. 2011. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed February 18, 2015.

6. Nepafenac Ophthalmic Suspension Summary Review. Drugs@FDA: FDA Approved Drug Products. *US Food and Drug Administration CDER Website*. 2012. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed February 18, 2015.

7. Loteprednol Ophthalmic Gel Summary Review. Drugs@FDA: FDA Approved Drug Products. *US Food and Drug Administration CDER Website*. 2012. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed February 18, 2015.

8. Bromfenac Ophthalmic Solution Summary Review. *CDER Homepage Food and Drug Administration Drugs@FDA: FDA Approved Drug Products*. 2013. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed February 18, 2015.

9. Maca S, Amon M, Findl O. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eyedrops after cataract surgery. *Am J Ophthalmol*. 2010;149:777-784.

10. Foster C, DaVanzo R, Flynn TE. Durezol (difluprednate ophthalmic emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. *Journal of Ocular Pharmacology and Therapeutics*. 2010;26:475-483.

11. Donnenfeld E, Holland E, Solomon KD. A multicenter randomized controlled fellow eye trial of pulse-dosed difluprednate 0.05% versus prednisolone acetate 1% in cataract surgery. *Am J Ophthalmol*. 2011;152:609-617.

12. Miyake K, Ota I, Miyake G. Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. *J Cataract Refract Surg*. 2011;37:1581-1588.

13. Almeida D, Khan Z, Xing L. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. *J Cataract Refract Surg*. 2012;38:1537-1543.

14. Wang Q, Yao K, Xu W. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. *Ophthalmologica*. 2013;229:187-194.

15. Lane S, Holland E. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. *J Cataract Refract Surg*. 2013;39:168-173.

16. Ray K, Srinivasan M, Mascarenhas J. Early addition of topical corticosteroids in the treatment of bacterial keratitis. *JAMA Ophthalmol*. 2014;132:737-741.

17. Srinivasan M, Mascarenhas J, Rajaraman R. The Steroids for Corneal Ulcers Trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial. *Am J Ophthalmol*. 2014;157:327-333.

18. Celik T, Turkoglu E. Comparative evaluation of olopatadine 0.01% combined with fluorometholone 0.1% treatment versus olopatadine 0.01% combined with ketorolac 0.4% treatment in patients with acute seasonal allergic conjunctivitis. *Current Eye Research*. 2014;39:42-46.

19. Price M, Price F, Kruse F. Randomized comparison of topical prednisolone acetate 1% versus fluorometholone 0.1% in the first year after Descemet membrane endothelial keratoplasty. *Cornea*. 2014;33:880-886.

20. Sheppard J, Toyos M, Kempen J. Difluprednate 0.05% versus prednisolone acetate 1% for endogenous anterior uveitis: a phase III, multicenter, randomized study. *Invest Ophthalmol Vis Sci*. 2014;55:2993-3002.

Appendix 1: Current Status on Preferred Drug List

Current Preferred Agents	Current Non-Preferred Agents
Ophthalmic Corticosteroids	
Dexamethasone (MAXIDEX) suspension Dexamethasone sodium phosphate suspension Fluorometholone (FML; FML S.O.P.; FLUOR-OP) suspension Loteprednol etabonate (LOTEMAX) suspension Prednisolone (OMNIPRED; PRED FORTE) suspension	Dexamethasone sodium phosphate (DECADRON) ointment Difluprednate (DUREZOL) emulsion Fluorometholone (FML FORTE) suspension Fluorometholone acetate (FLAREX) suspension Loteprednol etabonate (ALREX) suspension Loteprednol etabonate (LOTEMAX) gel and ointment Prednisolone acetate (PRED MILD) suspension Prednisolone sodium phosphate (INFLAMASE MILD; INFLAMASE FORTE) suspension Rimexolone (VEXOL) suspension
Ophthalmic Non-steroidal Anti-inflammatory Drugs (NSAIDs)	
Diclofenac sodium (VOLTAREN) solution Flurbiprofen (OCUFEN) solution Ketorolac tromethamine (ACULAR; ACULAR LS) solution	Bromfenac (PROLENSA) solution Ketorolac (ACUVAIL) solution Nepafenac (ILEVRO; NEVANAC) suspension

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Appendix 2: New Clinical Trials

One hundred eight-six citations were scanned from the literature search. After further review, 103 articles were excluded because the study design did not meet our criteria. The remaining 13 RCTs are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
Maca SM, et al.[9] 2010 RCT, PG, SB	Preservative-free diclofenac 0.1% (n=31), preserved diclofenac 0.1% (n=29) or preserved ketorolac tromethamine 0.5% (n=33) eyedrops	Patients who underwent small-incision phacoemulsification cataract surgery.	Not explicitly mentioned. Pre-specified outcomes were: anterior chamber flare and mean retinal (foveal) thickness and tolerability assessed by observer-based grading of conjunctival hyperemia and ocular discomfort as well as subjective ratings of ocular tolerability on a visual analog scale at 1-month follow-up	All 3 formulations had equal anti-inflammatory efficacy as measured by reduction of anterior chamber flare after surgery, mean foveal thickness and prevention of postoperative macular edema between week 1 and 1 month. Patients treated with preservative-free diclofenac eyedrops reported significantly better subjective tolerability values (p=0.001) and less ocular discomfort (p<0.001).	Poor
Foster CS, et al.[10] 2010 MC, RCT, DB	Difluprednate emulsion 0.05% (n=48) vs. Prednisolone acetate 1% (n=39).	Patients ≥2 years of age with endogenous anterior uveitis in at least one eye.	A noninferiority trial, assessing the change from baseline in mean AC cell grade on day 14, compared between difluprednate and prednisolone.	Difluprednate dosed 4-times daily was noninferior to prednisolone acetate dosed 8-times daily, with a mean AC cell grade improvement of 2.1, compared with 1.9 in the prednisolone group.	Good
Donnenfeld ED, et al.[11] 2011 MC, RCT, DB	Pulse-dosed difluprednate 0.05% (n=104 eyes) versus prednisolone acetate 1% (n=alternative 104 eyes)	Patients who underwent bilateral phacoemulsification cataract surgery.	Change from baseline in corneal thickness between the difluprednate- and prednisolone acetate-treated groups at day 1.	At day 1, the mean central corneal thickness of difluprednate-treated eyes increased by 28 microm (from 562 to 590 microm), roughly half the increase seen in the prednisolone-treated eyes, in which the increase was by 57 microm (from 562 to 619 microm), a difference of 33 microm which was statistically significant (p=0.026).	Fair

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Miyake K, et al.[12] 2011 RCT, DM	Nepafenac 0.1% and flurometholone 0.1% (n=30) vs. flurometholone 0.1% alone (n=29)	Patients who underwent small-incision phacoemulsification cataract surgery.	Not explicitly mentioned. Outcomes included incidence of cystoid macular edema (CME) and blood-aqueous barrier (BAB) disruption after surgery.	Five weeks postoperatively, the incidence of fluorescein angiographic CME was significantly lower in the nepafenac group (14.3%) than in the fluorometholone group (81.5%) (P<.0001). CME classified as "severe" was 5 eyes in the fluorometholone group vs. no eyes in the nepafenac group; the difference in severity of CME was significant (p<0.0001).	Poor
Almeida D, et al.[13] 2012 SC, DB, PC, PG, RCT	Prophylactic ketorolac 0.5% (n=54) vs. nepafenac 0.1% (n=54) vs. placebo (n=54) in addition to routine topical antibiotic and prednisolone 1.0%	Patients with a cataract expected to have phacoemulsification with implantation of a posterior chamber intraocular lens.	Change in domain optical coherence tomography (OCT) macular cube central subfield thickness (CST), macular cube volume (VOL), and average macular tube thickness (AVG) at 1 month.	At 1 month, the VOL increased by 0.76 mm^3 in the placebo group (P<0.0001), by 0.43 mm^3 in the ketorolac group (P=0.0085), and by 0.48 mm^3 in the nepafenac group (P<0.0001). Similarly, the AVG increased by 21.2 microm (P<0.0001), 10.3 microm (P=0.0398), and 12.9 microm (P<0.0001) in the placebo, ketorolac, and nepafenac groups, respectively. For the CST at 1 month, there was an increase of 17.1 microm (P<0.0001) in the placebo group. In contrast, there was no significant increase in the CST in the ketorolac group (14.5 microm; P=0.0578) or the nepafenac group (10.2 microm; P=0.0578).	Good
Srinivasan M, et al.[4] 2012 MC, DB, PC, RCT	Prednisonlone sodium phosphate 1.0% (n=250) vs. placebo (n=250) as adjunctive therapy to topical moxifloxacin.	Culture-positive bacterial corneal ulcer (keratitis) receiving topical moxifloxacin for at least 48 hrs.	Best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment.	No significant difference was observed in the 3-month BSCVA between groups (95% CI, -0.085 to 0.068; p = 0.82)	Good
Wang, et al.[14] 2013 OL, RCT	Bromfenac 0.1% x1 month vs. bromfenac 0.1% x2 months vs. fluorometholone 0.1% x1 month vs. dexamethasone 0.1% x1 month.	Age-related cataract patients undergoing phacoemulsification with posterior chamber intra-ocular lens implantation	Not explicitly mentioned. Outcomes included Best corrected visual acuity, IOP, endothelial cell density, photon count value and retinal foveal thickness.	There were no significant differences in IOP among the groups at any time point duringthe follow-up period. There were also no significant differences in endothelial cell density among the groups at any time point. Flare, retinal foveal thickness and incidences of cystoid macular edema were significantly lower in the bromfenac groups than the other fluorometholone and dexamethasone groups.	Poor

Lane SS, et al.[15] 2013 MC, SB, RCT	Loteprednol etabonate (Lotemax) 0.5% (n=48) vs. prednisolone acetate (Pred Forte) 1.0% (n=45).	Routine post-operative cataract surgery patients	Not explicitly mentioned. Likely level of anterior chamber cell and flare intensity in patients treated with loteprednol etabonate or prednisolone acetate.	No significant difference in mean IOP or control of inflammation (based on cell and flare grading) at 1, 3, 7 and 21 days postoperatively.	Poor
Ray KJ, et al.[16] 2014 Subgroup Analysis of Srinivasan[4]	Prednisonlone sodium phosphate 1.0% to placebo as adjunctive therapy to topical moxifloxacin.	Culture-positive bacterial corneal ulcer (keratitis) receiving topical moxifloxacin for at least 48 hrs.	Timing of administration of prednisolone (after 2-3 days vs. 4 or more days after starting topical moxifloxacin) on best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment.	Adjunctive prednisolone given within 2-3 days after starting topical moxifloxacin yielded 1-line better visual acuity at 3 months than did those given placebo. No significant difference was seen when prednisolone was administered 4 days or more after starting the antibiotic.	N/A – subgroup analysis
Srinivasan M, et al.[17] 2014 Extension of Srinivasan[4]	Prednisonlone sodium phosphate 1.0% to placebo as adjunctive therapy to topical moxifloxacin.	Culture-positive bacterial corneal ulcer (keratitis) receiving topical moxifloxacin for at least 48 hrs.	BSCVA and scar size at 12 months.	No significant difference seen in visual acuity (BSCVA -0.04 logMAR; 95% CI, -0.12 to 0.05; p=0.39) or scar size (0.03 mm; 95% CI, -0.12 to 0.18 mm; p=0.69). A significant advantage with prednisolone was only observed for these two outcomes when infections caused by *Nocardia sp*. were omitted.	N/A – extension study
Celik T, et al.[18] 2014 MC, PC, RCT	Fluoromethalone 0.1% and olopatadine 0.01% (n=52) vs. ketorolac 0.4% and olopatadine 0.01% in one eye (n=52) and placebo in contralateral eye.	Patients with acute seasonal allergic conjunctivitis	Not explicitly stated. Clinical signs (chemosis, mucus secretion, eyelid edema) and symptoms (itching, redness, burning and tearing) were evaluated using a 3-point scale (0 pt=absent; 1 pt=mild; 2 pts=moderate; 3 pts=severe)	All parameters improved; albeit very little by day 1; however, a significant reduction in the clinical signs and symptoms were seen by day 10 compared with those receiving placebo. There was a statistically significant greater response in redness, mucus secretion, chemosis, and eyelid edema with the olopatadine-fluoromethalone group vs. the olopatadine-ketorolac group.	Poor
Price MO, et al.[19] 2014 OL, RCT	Prednisolone 1% (n=164 eyes) vs. fluorometholone 0.1% (n=161 eyes)	Descemet membrane endothelial keratoplasty (DMEK) corneal transplant recipients	The proportion of eyes that exceeded a defined IOP elevation threshold and the proportion of eyes that experienced an immunologic graft rejection episode	The proportion of eyes that exceeded the defined IOP elevation threshold (≥24 mm Hg or ≥10 mm Hg increase over preoperative reading) was 21.9% in the prednisolone arm versus 6.1% in the fluorometholone arm (RR 3.5; 95% CI, 1.7 to 7.1; p=0.00012). Among the eyes that completed the study on the assigned intervention, none (0%) assigned to prednisolone and 2 (1.4%) assigned to fluorometholone experienced a possible or probable graft rejection episode.	Fair

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Sheppard J, et al.[20] 2014 MC, DB, PG, RCT	Difluprednate 0.05% (n=46) vs. prednisolone acetate 1% (n=47).	Patients ≥2 years of age with endogenous anterior uveitis in at least 1 eye.	A noninferiority study, assessing change from baseline to day 14 in anterior chamber cell grade.	The mean (SD) changes in anterior chamber cell grade from baseline to day 14 were -2.2 (1.0) (a mean decrease of 2.2 grades) for the difluprednate group and -2.0 (1.0) (mean decrease, 2.0 grades) for the prednisolone acetate group (p=0.16; mean difference, -0.22). Given that the upper boundary of the 95% confidence interval (-0.53 to 0.09) was less than 0.5, the primary end point of difluprednate 0.05% being noninferior to prednisolone acetate 1% was met.	Fair

Abbreviations: DB = double blind; IOP = intra-ocular pressure; MC = multi-center; PC = placebo controlled; PG = parallel group; RCT = Randomized controlled trial; RR = relative risk; SB = single blind; SC = single-center.

*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

Appendix 3: Abstracts of Clinical Trials

Maca SM, Amon M, Findl O, et al. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eyedrops after cataract surgery. *Am J Ophthalmol*, 2010.

Purpose: To compare the anti-inflammatory efficacy and subjective tolerability of preservative-free and preserved diclofenac 0.1% and preserved ketorolac 0.5% eye drops for prophylaxis and management of inflammation after cataract surgery.
Design: Prospective, randomized, investigator-masked, parallel-group, comparative clinical trial.
Methods: One hundred two patients who underwent small-incision phacoemulsification cataract surgery in an institutional setting were assigned randomly to receive preservative-free diclofenac sodium 0.1% (Voltaren ophtha SDU; Novartis Pharma), preserved diclofenac sodium 0.1% (Voltaren ophtha; Novartis Pharma), or preserved ketorolac tromethamine 0.5% (Acular; Pharm Allergan) eye drops 4 times daily for 4 weeks after surgery. During the 1-month follow-up, anterior chamber flare and mean foveal thickness were evaluated for objective comparison of the anti-inflammatory effect. Ocular tolerability was assessed by observer-based grading of conjunctival hyperemia and ocular discomfort, as well as obtaining subjective ratings of ocular tolerability on a visual analog scale. Distance and near visual acuity and intraocular pressure served as safety measures.
Results: All 3 formulations demonstrated equal anti-inflammatory efficacy as measured by reduction of anterior chamber flare after surgery and prevention of postoperative macular edema. Patients treated with preservative-free diclofenac eye drops reported significantly better subjective tolerability values (P = .001), were classified as having less ocular discomfort (P < .001), and experienced earlier reduction of postoperative conjunctival hyperemia (P = .029).
Conclusions: Anti-inflammatory efficacy was comparable for all 3 agents. However, preservative-free diclofenac 0.1% eyedrops exhibited a significantly better postoperative subjective and objective tolerability when compared with preserved eye drops containing ketorolac or diclofenac.

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Foster CS, DaVanzo R, Flynn T, et al. Durezol (Difluprednate Ophthalmic Emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. *Journal of Ocular Pharmacology and Therapeutics*, 2010.

Purpose: The aim of this study was to evaluate the efficacy and safety of difluprednate ophthalmic solution 0.05% (Durezol; Alcon Laboratories, Fort Worth, TX) compared with prednisolone acetate ophthalmic suspension 1% (Pred Forte; Allergan, Inc., Irvine, CA) for endogenous anterior uveitis.
Methods: In this phase 3, multicenter, randomized, noninferiority trial, 90 patients with endogenous anterior uveitis [>10 anterior chamber (AC) cells and an AC flare score of ≥2 in at least 1 eye] received either difluprednate 4x/day (QID) (n=50) or prednisolone 8x/day (n=40) for 14 days, followed by a 2-week tapering regimen. The main outcome measure was change from baseline in AC cell grade on day 14.
Results: At day 14, mean AC cell grade improvement for difluprednate-treated patients was similar to prednisolone-treated patients (2.1 vs. 1.9, respectively), proving noninferiority. At day 14, 68.8% of difluprednate patients had AC cell clearing (grade 0: ≤1 cell) compared with 61.5% of prednisolone patients. In the prednisolone-treated group, 12.5% of patients were withdrawn because of investigator-determined lack of efficacy; no difluprednate-treated patients were withdrawn for this reason (P¼0.01). Clinically significant intraocular pressure elevation occurred in 3 difluprednate-treated patients (6.0%) and 2 prednisolone-treated patients (5.0%).
Conclusions: Difluprednate administered QID is at least as effective as prednisolone administered 8x/day in resolving the inflammation and pain associated with endogenous anterior uveitis. Difluprednate provides effective treatment for anterior uveitis and requires less frequent dosing than prednisolone acetate.

Donnenfeld ED, Holland EJ, Solomon KD, et al. A multicenter randomized controlled fellow eye trial of pulse-dosed difluprednate 0.05% versus prednisolone acetate 1% in cataract surgery. *Am J Ophthalmol*, 2011.

Purpose: To compare the effects of 2 corticosteroids on corneal thickness and visual acuity after cataract surgery.
Design: Multicenter, randomized, contralateral-eye, double-masked trial.
Methods: Fifty-two patients (104 eyes) underwent bilateral phacoemulsification. The first eye randomly received difluprednate 0.05% or prednisolone acetate 1%; the fellow eye received the alternative. Before surgery, 7 doses were administered over 2 hours; 3 additional doses were given after surgery, before discharge. For the remainder of the day, corticosteroids were administered every 2 hours, then 4 times daily during week 1 and twice daily during week 2. Corneal pachymetry, visual acuity, and corneal edema were evaluated before surgery and at days 1, 15, and 30 after surgery. Endothelial cell counts were evaluated before surgery and at 30 days after surgery. Retinal thickness was evaluated before surgery and at 15 and 30 days after surgery.
Results: Corneal thickness at day 1 was 33 µm less in difluprednate-treated eyes (P = .026). More eyes were without corneal edema in the difluprednate group than in the prednisolone group at day 1 (62% vs 38%, respectively; P = 0.019). Uncorrected and best-corrected visual acuity at day 1 were significantly better with difluprednate than prednisolone by 0.093 logMAR lines (P = .041) and 0.134 logMAR lines (P < .001), respectively. Endothelial cell density was 195.52 cells/mm(2) higher in difluprednate-treated eyes at day 30 (P < .001). Retinal thickness at day 15 was 7.74 µm less in difluprednate-treated eyes (P =0.011).
Conclusions: In this high-dose pulsed-therapy regimen, difluprednate reduced inflammation more effectively than prednisolone acetate, resulting in more rapid return of vision. Difluprednate was superior at protecting the cornea and reducing macular thickening after cataract surgery.

Miyake K, Ota I, Miyake G, et al. Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. *J Cataract Refract Surg*, 2011.

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Purpose: To compare a topical nonsteroidal antiinflammatory drug (nepafenac 0.1%) and a topical steroidal antiinflammatory drug (fluorometholone 0.1%) in preventing cystoid macular edema (CME) and blood-aqueous barrier (BAB) disruption after small-incision cataract extraction with foldable intraocular lens (IOL) implantation.
Setting: Shohzankai Medical Foundation, Miyake Eye Hospital, Nagoya, Japan.
Design: Randomized double-masked single-center clinical trial.
Methods: Patients were randomized to receive nepafenac 0.1% eyedrops or fluorometholone 0.1% eyedrops for 5 weeks after phacoemulsification with foldable IOL implantation. The incidence and severity of CME were evaluated by fluorescein angiography, retinal foveal thickness on optical coherence tomography, and BAB disruption on laser flare-cell photometry.
Results: Thirty patients received nepafenac and 29 patients, fluorometholone. Five weeks postoperatively, the incidence of fluorescein angiographic CME was significantly lower in the nepafenac group (14.3%) than in the fluorometholone group (81.5%) (P<.0001). The fovea was thinner in the nepafenac group than in the fluorometholone group at 2 weeks (P=.0266) and 5 weeks (P=.0055). At 1, 2, and 5 weeks, anterior chamber flare was significantly less in the nepafenac group than in the fluorometholone group (P<.0001, P<.0001, and P=.0304, respectively). The visual acuity recovery from baseline was significantly greater in the nepafenac group (80.0%) than in the fluorometholone group (55.2%) (P=.0395). There were no serious side effects in either group.
Conclusion: Nepafenac was more effective than fluorometholone in preventing angiographic CME and BAB disruption, and results indicate nepafenac leads to more rapid visual recovery.

Almeida D, Khan Z, Xing L, et al. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. *J Cataract Refract Surg*, 2012.

Purpose: To evaluate the efficacy of prophylactic ketorolac 0.5% versus nepafenac 0.1% versus placebo on macular volume 1 month after uneventful phacoemulsification and evaluate the healthrelated quality-of-life (HRQOL) of topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the context of cataract surgery.
Setting: Hotel Dieu Hospital, Kingston, Ontario, Canada.
Design: Prospective placebo-controlled parallel-assignment double-masked randomized clinical trial.
Methods: In this study, patients 18 years or older scheduled for routine phacoemulsification were randomized to a placebo, ketorolac 0.5%, or nepafenac 0.1% and dosed 4 times a day starting 1 day before surgery and continuing for 4 weeks. Spectral-domain macular cube ocular coherence tomography scans measuring central subfield thickness, macular cube volume, and average macular cube thickness were performed at baseline and 1 month postoperatively. The HRQOL metrics were determined with the Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire.
Results: Each study group comprised 54 patients. One month postoperatively, although a trend toward significance occurred for nepafenac and ketorolac, analysis of the means of differences showed no statistically significant differences between the 3 study groups (PZ.2901). The COMTOL analysis found no difference in tolerability, compliance, side-effect frequency and bother, and effects on HRQOL between ketorolac and nepafenac compared with the placebo.
Conclusions: One month after uneventful phacoemulsification, there was no difference in macular volume between the placebo, ketorolac, and nepafenac. Ketorolac and nepafenac were well tolerated with minimal side-effect profiles. Thus, for patients without risk factors having routine surgery, prophylactic topical NSAIDs are not recommended.

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Srinivasan M, Mascarenhas J, Rajaraman R, et al. Corticosteroids for bacterial keratitis: the steroids for corneal ulcers trial (SCUT). *Arch Ophthalmol*, 2012.

Objective: To determine whether there is a benefit in clinical outcomes with the use of topical corticosteroids as adjunctive therapy in the treatment of bacterial corneal ulcers.
Methods: Randomized, placebo-controlled, double-masked, multicenter clinical trial comparing prednisolone sodium phosphate, 1.0%, to placebo as adjunctive therapy for the treatment of bacterial corneal ulcers. Eligible patients had a culture-positive bacterial corneal ulcer and received topical moxifloxacin for at least 48 hours before randomization.
Main outcome measures: The primary outcome was best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment. Secondary outcomes included infiltrate/scar size, reepithelialization, and corneal perforation.
Results: Between September 1, 2006, and February 22, 2010, 1769 patients were screened for the trial and 500 patients were enrolled. No significant difference was observed in the 3-month BSCVA (-0.009 logarithm of the minimum angle of resolution [logMAR]; 95% CI, -0.085 to 0.068; P = .82), infiltrate/scar size (P = .40), time to reepithelialization (P = .44), or corneal perforation (P > .99). A significant effect of corticosteroids was observed in subgroups of baseline BSCVA (P = .03) and ulcer location (P = .04). At 3 months, patients with vision of counting fingers or worse at baseline had 0.17 logMAR better visual acuity with corticosteroids (95% CI, -0.31 to -0.02; P = .03) compared with placebo, and patients with ulcers that were completely central at baseline had 0.20 logMAR better visual acuity with corticosteroids (-0.37 to -0.04; P = .02).
Conclusions: We found no overall difference in 3-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers.

Wang Q, Yao K, Xu W, et al. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. *Ophthalmologica*. 2013;229:187-194.

Purpose: To compare bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for the control of postoperative inflammation and prevention of cystoid macular edema (CME) after phacoemulsification.
Methods: Patients were randomized to receive bromfenac sodium 0.1% for 1 month (OBS1) or 2 months (OBS2), or fluorometholone 0.1% for 1 month (OFM) or dexamethasone 0.1% for 1 month (ODM). Best-corrected visual acuity, intraocular pressure, endothelial cell density, photon count value and retinal foveal thickness were measured.
Results: Mean photon count values were lower in the OBS1 and OBS2 groups compared with the ODM group during the first week. Bromfenac sodium cleared the ocular inflammation more rapidly than fluorometholone and dexamethasone. The foveal thickness was thinner in the second month and the incidence of CME was lower in the OBS1 and OBS2 groups compared with the OFM and ODM groups.
Conclusion: Bromfenac sodium was more effective and safer than fluorometholone and dexamethasone as an anti-inflammatory, decreasing macular thickness and preventing CME in age-related cataract patients after cataract surgery.

Lane SS, Holland EJ. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. *J Cataract Refract Surg*, 2013.

Purpose: To evaluate the efficacy of loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the control of postoperative inflammation in patients having routine cataract surgery.
Methods: Patients were at least 18 years of age and scheduled for routine cataract surgery. Patients were excluded from the study if they had preexisting medical conditions (ie, elevated intraocular pressure [IOP], retinopathy, maculopathy, uveitis) or required medications the investigator believed would put the patient at risk or confound the study. Patients were randomized to receive loteprednol etabonate or prednisolone acetate 4 times daily in addition to bromfenac 0.09% and besifloxacin 0.6% after surgery. Visual acuity, IOP, and anterior chamber cell and flare intensity were assessed over 3 weeks after cataract surgery. The primary endpoint was the level of anterior chamber cell and flare intensity in patients treated with loteprednol etabonate or prednisolone acetate.
Results: The study enrolled 88 patients (46 loteprednol etabonate, 42 prednisolone acetate). Equivalency was achieved between the 2 treatment groups with no significant differences throughout the 3-week follow-up. There was less fluctuation in IOP assessments in patients treated with loteprednol etabonate than in patients treated with prednisolone acetate, in particular 1 day and 3 days postoperatively.
Conclusions: The results indicate that equivalent control of inflammation can be obtained through treatment with loteprednol etabonate or prednisolone acetate after cataract surgery. In addition, treatment with loteprednol etabonate may result in less IOP fluctuation.

Ray KJ, Srinivasan M, Mascarenhas J, et al. Early addition of topical corticosteroids in the treatment of bacterial keratitis. *JAMA Ophthalmol*, 2014.

Purpose: To determine whether topical corticosteroids are beneficial as an adjunctive therapy for bacterial keratitis if given early in the course of infection.
Design, Setting, and Participants: The Steroids for Corneal Ulcers Trial (SCUT) was a randomized, double-masked, placebo-controlled trial that overall found no effect of adding topical corticosteroids to topical moxifloxacin hydrochloride in bacterial keratitis. Here, we assess the timing of administration of corticosteroids in a subgroup analysis of the SCUT. We define earlier administration of corticosteroids (vs placebo) as addition after 2 to 3 days of topical antibiotics and later as addition after 4 or more days of topical antibiotics.

Main Outcomes and Measures: We assess the effect of topical corticosteroids (vs placebo) on 3-month best spectacle-corrected visual acuity in patients who received corticosteroids or placebo earlier vs later. Further analyses were performed for subgroups of patients with non-*Nocardia* keratitis and those with no topical antibiotic use before enrollment.
Results: Patients treated with topical corticosteroids as adjunctive therapy within 2 to 3 days of antibiotic therapy had approximately 1-line better visual acuity at 3 months than did those given placebo (–0.11 logMAR; 95%CI, –0.20 to –0.02 logMAR; P = .01). In patients who had 4 or more days of antibiotic therapy before corticosteroid treatment, the effect was not significant; patients given corticosteroids had 1-line worse visual acuity at 3 months compared with those in the placebo group (0.10 logMAR; 95%CI, –0.02 to 0.23 logMAR; p=0.14). Patients with non-*Nocardia* keratitis and those having no topical antibiotic use before the SCUT enrollment showed significant improvement in best spectacle-corrected visual acuity at 3 months if corticosteroids were administered earlier rather than later.
Conclusions and Relevance: There may be a benefit with adjunctive topical corticosteroids if application occurs earlier in the course of bacterial corneal ulcers.

Srinivasan M, Mascarenhas J, Rajaraman R, et al. The Steroids for Corneal Ulcers Trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial. *Am J Ophthalmol*, 2014.

Purpose: To determine whether topical corticosteroids as adjunctive therapy for bacterial keratitis improves long-term clinical outcomes.
Methods: This multicenter trial compared 1.0% prednisolone sodium phosphate to placebo in the treatment of bacterial keratitis among 500 patients with culture positive ulcers receiving 48 hours of moxifloxacin before randomization. The primary endpoint was 3 months from enrollment, and 399 patients were evaluated at 12 months. The outcomes examined were best spectacle corrected visual acuity (BSCVA) and scar size at 12 months. Based on previous results, regression models with adjustments for baseline status and/or causative organism were used for analysis.
Results: No significant differences in clinical outcomes by treatment group were seen with the prespecified regression models (BSCVA: -0.04 logMAR, 95% CI, -0.12 to 0.05, P=0.39; scar size: 0.03 mm, 95% CI, -0.12 to 0.18, P=0.69). A regression model including a *Nocardia*-treatment arm interaction found corticosteroid use associated with a mean 1-line improvement in BSCVA at 12 months among patients with non-*Nocardia* ulcers (-0.10 logMAR, 95% CI, -0.19 to -0.02, P=0.02). No significant difference was observed in 12-month BSCVA for *Nocardia* ulcers (0.18 logMAR, 95% CI, -0.04 to 0.41, P=0.16). Corticosteroids were associated with larger mean scar size at 12 months among *Nocardia* ulcers (0.47 mm, 95% CI, 0.06-0.88, P=0.02) and no significant difference was identified by treatment for scar size for non-*Nocardia* ulcers (-0.06 mm, 95% CI, -0.21 to 0.10, P=0.46).
Conclusions: Adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by *Nocardia* species.

Celik T, Turkoglu EB. Comparative evaluation of olopatadine 0.01% combined with fluorometholone 0.1% treatment versus olopatadine 0.01% combined with ketorolac 0.4% treatment in patients with acute seasonal allergic conjunctivitis. *Current Eye Research*, 2014.

Purpose: To evaluate the therapeutic effects of low-effective steroid fluorometholone 0.1% and non-steroidal anti-inflammatory ketorolac 0.4% when concomitantly used with olopatadine 0.01% in relieving clinical signs and symptoms of acute seasonal allergic conjunctivitis (SAC).
Methods: In this randomized, placebo-controlled, multi-center study, 104 eyes of 52 patients with the diagnosis of SAC were conducted. The patients were assigned into two groups to receive either olopatadine and fluorometholone one eye and placebo in the contralateral eye or olopatadine and ketorolac one eye and placebo in the contralateral. The clinical signs (chemosis, mucus secretion, eyelid edema) and symptoms (itching, redness, tearing, burning) of the patients

were evaluated by summing up the scores using a 3-point scale. Results were analyzed by Mann-Whitney U test, p values less than 0.05 were defined as significant.
Results: All parameters were improved less amount on the first day of the treatment in both groups, however, significant reduction in clinical signs and symptoms were seen on the 10th day compared with those receiving placebo. Fluorometholone was found superior to ketorolac in reducing redness, mucus secretion, chemosis and eyelid edema ($p = 0.032$ for redness, $p = 0.028$ for mucus secretion, $p = 0.030$ for chemosis, $p = 0.042$ for eyelid edema) and both drugs were similar in alleviating the symptoms itching, burning and tearing ($p = 0.074$ for itching, $p = 0.064$ for burning, $p = 0.072$ for tearing).
Conclusions: Fluorometholone was better than ketorolac in relieving redness, chemosis, mucus secretion and eyelid edema when concomitantly used with olopatadine, however, these two drugs were found equal in attenuating the symptoms itching, burning and tearing.

Price M, Price F, Kruse F, et al. Randomized comparison of topical prednisolone acetate 1% versus fluorometholone 0.1% in the first year after Descemet membrane endothelial keratoplasty. *Cornea*, 2014.

Purpose: The aim of this study was to compare the efficacy and side effects of prednisolone acetate 1% versus fluorometholone 0.1% after Descemet membrane endothelial keratoplasty (DMEK).
Methods: DMEK recipients used prednisolone acetate 1% for 1 month, and they were randomized to either prednisolone or fluorometholone for months 2 through 12. Dosing was 4 times daily in months 1 to 3, thrice daily in month 4, twice daily in month 5, and once daily in months 6 to 12. The main outcomes were immunologic rejection episodes and intraocular pressure (IOP) elevation (defined as ≥24 mm Hg or ≥10 mm Hg increase over the preoperative baseline level), assessed by the Kaplan–Meier survival analysis.
Results: The study included 325 eyes (99% were white, 96% had Fuchs dystrophy, and 9% had a previous glaucoma diagnosis). No eyes (0%) assigned to prednisolone versus 2 eyes (1.4%) assigned to fluorometholone experienced a possible (n = 1) or probable (n = 1) rejection episode (P = 0.17). Both rejection episodes resolved successfully with increased topical steroids. In the prednisolone arm, a significantly higher proportion exceeded the defined IOP elevation threshold (22% vs. 6%, P = 0.0005), and glaucoma medications were initiated or increased more often (17% vs. 5%, P = 0.0003). The most frequent reasons for discontinuing the assigned intervention were IOP management (n = 13 eyes assigned to prednisolone) or inflammation management (n = 3 eyes assigned to fluorometholone). One-year endothelial cell loss was comparable in both arms (30% vs. 31%, P = 0.50).
Conclusions: DMEK has a remarkably low rejection episode rate (<1% through 1 year), as confirmed in this prospective randomized study. This provides a unique opportunity to reduce postoperative topical corticosteroid strength and thereby reduce the risk of steroid-associated complications.

Sheppard JD, Toyos MM, Kempen JH, et al. Defluprednate 0.05% versus prednisolone acetate 1% for endogenous anterior uveitis: a phase III, multicenter, randomized study. *Investigative Ophthalmology & Visual Science*, 2014.

Purpose: Endogenous anterior uveitis (AU), when untreated, may lead to vision loss. This study compared the safety and efficacy of difluprednate versus prednisolone acetate for the treatment of this condition.
Methods: This phase III, double-masked, noninferiority study randomized patients with mild to moderate endogenous AU to receive difluprednate 0.05% (n=56) four times daily, alternating with vehicle four times daily, or prednisolone acetate 1% (n=54) eight times daily. The 14-day treatment period was followed by a 14-day dose-tapering period and a 14-day observation period. The primary efficacy end point was change in anterior chamber cell grade (range, 0 for 1 cell to 4 for >50 cells) from baseline to day 14.

Results: At day 14, the mean change in anterior chamber cell grade with difluprednate was noninferior to that with prednisolone acetate -2.2 vs. -2.0, p=0.16). The proportions of difluprednate-treated patients versus prednisolone acetate–treated patients demonstrating complete clearing of anterior chamber cells at day 3 were 13.0% vs. 2.1% (p=0.046) and at day 21 were 73.9% vs. 63.8% (p=0.013). A significant between-group difference in the mean IOP increase was seen at day 3 (2.5 mm Hg for difluprednate-treated patients and 0.1 mm Hg for prednisolone acetate–treated patients, p=0.0013) but not at other time points. The mean IOP values in both groups remained less than 21 mm Hg throughout the study.
Conclusions: Difluprednate 0.05% four times daily is well tolerated and is noninferior to prednisolone acetate 1% eight times daily for the treatment of endogenous AU.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 2 2015

1 exp Dexamethasone/ 21442
2 exp Fluorometholone/ 152
3 loteprednol.mp. 93
4 exp Prednisolone/ 21144
5 difluprednate.mp. 26
6 exp Fluocinolone Acetonide/ 378
7 rimexolone.mp. 35
8 exp Anti-Inflammatory Agents/ or exp Glucocorticoids/ 218574
9 1 or 2 or 3 or 4 or 5 or 6 or 7 42422
10 exp Diclofenac/ 4525
11 exp Flurbiprofen/ 831
12 exp Ketorolac Tromethamine/ or exp Ketorolac/ 1222
13 bromfenac.mp. 112
14 nepafenac.mp. 70
15 exp Triamcinolone/ 3763
16 exp Anti-Inflammatory Agents, Non-Steroidal/ 87571
17 10 or 11 or 12 or 14 or 15 10240
18 9 or 17 52120
19 exp Ophthalmic Solutions/ or exp Administration, Ophthalmic/ or ophthalmic.mp. 19650
20 exp Uveitis, Anterior/ or exp Uveitis, Suppurative/ or exp Uveitis/ or exp Uveitis, Posterior/ or exp Uveitis, Intermediate/ 12485
21 exp Conjunctivitis/ or exp Conjunctivitis, Allergic/ 6337
22 exp Cataract Extraction/ or exp Cataract/ 21829
23 19 or 20 or 21 or 22 56520
24 18 and 23 2237
25 limit 24 to (yr="2010 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)) 186

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Inhaled medications for Cystic Fibrosis

Month/Year of Review: May 2015 **Date of Last Review:** May 2014

Current PDL Class:
See **Appendix 1**.

Conclusions:

- There is limited new evidence on the efficacy or safety of inhaled agents for the treatment of Cystic Fibrosis (CF) that would change current PDL class management.
- There remains insufficient comparative evidence to directly compare inhaled tobramycin (TIS) to inhaled aztreonam (AZLI) for the treatment of *P. aerugonisa* in patients with CF and there is no evidence that continuous use is superior to the recommended 28-day cycle (on 28 days, off 28 days).
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- For the early eradication of *P. aeruginosa,* there is evidence that treatment with inhaled antibiotics is better than no treatment in eradication; but there is no strong evidence of a superior regimen over another. There is also moderate quality evidence that there is no significant difference between 28 days of TIS and 56 days of therapy.
- There is low quality evidence that TIS administered by the PARI LC PLUS Nebulizer is effective in improving lung function in patients with CF.

Recommendations:

- Evaluate comparative costs in executive session; maintain at least one formulation of either inhaled tobramycin or aztreonam as preferred on the PDL for the treatment of chronic infection with *P. aerugonisa.*

Current Quantity Limit:

- A quantity limit of 56 vials/56 days and 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy) is in place for inhaled tobramycin solution (TIS) and aztreonam lysine for inhalation (AZLI), respectively.

Previous Recommendations:

- There is moderate quality evidence that both inhaled tobramycin and inhaled aztreonam improve lung function and quality of life in moderate to severe disease for individuals with CF and *Pseudomonas (P.) aeruginosa* persistently present in cultures of the airways. However, there is evidence that inhaled tobramycin reduces exacerbations in patients with CF, while the trials of inhaled aztreonam are short term with limited follow up.
- There is insufficient comparative evidence for the efficacy and safety of TIS and AZLI.
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- There is insufficient evidence to recommend oral anti-psuedomonal antibiotics for pulmonary exacerbations or long-term treatment of chronic infection.
- There is low quality evidence that Tobi Podhaler is noninferior to tobramycin inhalation nebulizer solution in improving lung function.
- There is low quality evidence that Tobi Podhaler results in a higher incidence of discontinuations due to adverse events (14% vs. 8%) and total discontinuations (26.9% vs. 18.2%) than tobramycin nebulizer, respectively.
- There is moderate quality evidence that treatment with hypertonic saline for patients six years of age and older improves short term lung function, decreased pulmonary exacerbations, and has a small effect on improvement in quality of life. There is insufficient evidence to determine the long term effects of hypertonic saline on mortality in patients with CF.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

After limiting the Medline search to RCTs and systematic reviews, a total of 7 studies resulted, including 3 systematic reviews.[11,12,1] The remaining 4 trials were excluded due to irrelevant intervention, incorrect population, and no outcome of interest. One of the systematic reviews evaluated ivacaftor for the treatment of patients with the G551D mutation[1]; however, this was previously reviewed as part of the May 2014 P&T CF Class Update.

New Systematic Reviews:

1. An updated Cochrane Collaboration review was completed to evaluate which antibiotic treatment eradicates *P. aeruginosa,* delays the onset of chronic infection, and results in clinical improvement from the treatment of early infection (at the time of first isolation).[11] It is well known that once chronic infection occurs, it is very difficult to eradicate it and it is associated with negative outcomes. Therefore, research has been done to determine if early infection might be easier to eradiate. Only RCTs were included in the comparisons. A total of seven RCTs were selected for inclusion, with a duration of 28 days to 27 months. Most of these were small trials with a short follow-up period. The most common primary outcome measure was eradication of *P. aeruginosa* from respiratory secretions, though definitions of eradication varied considerably between trials. The trials could not be combined for the purpose of a meta-analysis due to the different interventions and outcomes evaluated in the trials.

   Two small trials showed that TIS was better than no treatment in eliminating early infection from *P. aeruginosa (*OR 0.15; 95% CI 0.03-0.65) and that this effect may last for up to 12 months. Another trial (n=88) showed no difference between 28 days and 56 days of nebulized tobramycin, as measured by time to next isolation of *P. aeruginosa* (26.12 months vs. 25.82 months). Four direct comparisons were identified and found no difference between any antibiotic combinations (oral or inhaled).

   One of the RCTs compared culture-based inhaled tobramycin therapy to cycled-based therapy, as well as oral ciprofloxacin versus placebo for two weeks with each 28 day course of TIS. There was a non statistically significant difference in the number of children having one ore more isolates on oral ciprofloxacin compared to placebo (34% vs. 37%, respectively). There was also no significant difference in time to severe exacerbation between those on oral ciprofloxacin and placebo.

   The authors of this review concluded that the data did not establish significant improvements in clinical outcomes following the early treatment of *P. aeruginosa* but nebulized antibiotics were better than no treatment for eradication of early infection. However, due to the small numbers and short durations, there may be insufficient power to detect differences in long-term clinical outcomes. While there is evidence that treatment to eradicate infection is better than no treatment, there is not strong evidence to support using one regimen over another.

2. Another Cochrane Systematic review assessed prophylactic oral antibiotic therapy for infections caused by *S. aureus* in young children with CF.[12] Overall, continuous oral anti-staphylococcal antibiotic prophylaxis may not be more effective than on-demand ("as needed") treatment for improving lung function, reducing hospital admissions, or other outcomes in infants and children with CF. Only four trials were included in the systematic review, which included 402 infants and children aged 0 to 7 years with CF. The studies had some methodological flaws, particularly two older studies which were not blinded. Continuous prophylaxis was associated with a reduced isolation of *S. aureus* from sputum at 1 year in an analysis of 2 trials (OR 0.27; 95% CI 0.15 to 0.48) with no significant difference in lung function (FEV1), bacterial growth, hospital admission or need for additional antibiotics. The authors concluded that although prophylaxis led to fewer children with *S. aureus* isolates, the clinical significance of this is unknown and further research is warranted.

New Guidelines:

1. **European Cystic Fibrosis Society:**
   A best practice statement was released in 2014 for the treatment of CF. [13] The following best practice recommendations were provided regarding the treatment of CF:
   - Treatment for the eradication of *P. aeruginosa* should be started promptly after a positive culture result. Options include 28 days of TIS and up to 3 months of a combination of nebulized colistin and oral ciprofloxacin.
   - If eradication fails, long term inhaled antibiotic therapy should be started with TIS on alternate months, with AZLI as an alternative option.
   - There is insufficient evidence to support prophylactic antibiotic therapy for other bacteria.

   These recommendations are clearly best practice statements and are not systematically developed from a thorough evidence review and evaluation.

New FDA Approved Indications:
None identified (ivacaftor reviewed separately).

Randomized Controlled Trials:
No relevant comparative RCTs identified.

New Formulations/Delivery Device:
In December 2014, the FDA approved a new formulation of generic TIS with a PARI LC PLUS Nebulizer (Kitabis pak®).[13] This is the first nebulized drug and device combination to be approved for patients with CF and is dosed as one single-use ampule (300 mg) administered via nebulizer twice daily (28 day on/off cycle). The product is co-packaged with tobramycin and the PARI LC PLUS nebulizer device. This is the only nebulizer studied for the delivery of TIS. It is indicated for the management of CF in adults and children 6 years of age and older with *P. aeruginosa.*

Two unpublished, identically designed, double-blind, randomized, placebo-controlled 24-week studies compared 28 days of TIS using the PARI Nebulizer (n=258) as an outpatient treatment to placebo (n=262), followed by 28 days off of therapy for 3 cycles. Lung function was significantly improved in the TIS group compared to those on placebo as measured by change in FEV1% predicted from baseline (11% vs. 0%).[13] There was a decrease in the number of days hospitalized for those on tobramycin; however the data and statistics were not available for full analysis. These studies are not published and there was not enough available information to adequately assess for the risk of bias and quality appraisal.

The most common adverse effects in the TIS group were cough, pharyngitis, and increased sputum. More patients treated with TIS experienced voice alteration compared to placebo patients (13% vs. 7%).[13]

References:

1. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2014;18(18):1-106. doi:10.3310/hta18180.
2. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
3. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155(6 Suppl):S73-S93. doi:10.1016/j.jpeds.2009.09.001.
4. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *American Journal of Respiratory and Critical Care Medicine*. 2013;187(7):680-689. doi:10.1164/rccm.201207-1160OE.
5. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. March. 2015.
6. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *Ann Pharmacother*. 2012;46(7-8):1065-1075. doi:10.1345/aph.1R076.
7. Aherns R, Rodriguez S, Yen K. VX-770 in subjects 6 to 11 years with cystic fibrosis and the G551D -CFTR mutation (abstract) Pediatr Pulmonol 2011;(suppl 34):283.
8. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672. doi:10.1056/NEJMoa1105185.
9. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219-1225. doi:10.1164/rccm.201301-0153OC.
10. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. 2012;142(3):718-724. doi:10.1378/chest.11-2672.
11. Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004197.pub4/abstract. Accessed March 9, 2015.
12. Smyth AR, Walters S. Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev*. 2014;11:CD001912. doi:10.1002/14651858.CD001912.pub3.
13. Smyth AR, Bell SC, Bojcin S, et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *J Cyst Fibros*. 2014;13 Suppl 1:S23-S42. doi:10.1016/j.jcf.2014.03.010.

Appendix 1: Current Status on Preferred Drug List

- Preferred: SODIUM CHLORIDE FOR INHALATION, TOBRAMYCIN 300 MG/5 ML (TOBI®), TOBRAMYCIN 300 MG/4 ML (BETHKIS®), DORNASE ALFA (PULMOZYME®)
- Non-Preferred: TOBRAMYCIN CAP (TOBI PODHALER®), AZTREONAM (CAYSTON®)

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Literature Scan: Analgesics for Gout

Month/Year of Review: April 2015 **Date of Last Review:** January 2014

Current Status of PDL Class:
See Appendix 1

Conclusions and Recommendations:

- There is low quality evidence a greater proportion of patients respond to treatment, defined as a 50% or greater decrease in pain score, with high-dose (4.8 mg over six hours) colchicine compared to placebo (absolute risk difference 28%; RR 2.16; 95% CI 1.28 to 3.65; NNT 4) and low quality evidence significantly decreases inflammation scores more than placebo (absolute risk difference 45%; RR 10.50; 95% CI 1.48 to 74.38).
- There is low quality evidence of no significant difference between high- (4.8 mg over six hours) and low-dose (1.8 mg over one hour) colchicine in treatment response (RR 0.86; 95% CI 0.53 to 1.41) with fewer gastrointestinal events with low-dose colchicine.
- There remains insufficient evidence of any significant difference between allopurinol and febuxostat for treatment of acute gout flares.
- There is low-quality evidence of uncertainty around the difference in prevention of acute gout attacks between probenecid and allopurinol after 18 months of treatment (53% vs. 55%; RR 0.96; 95% CI 0.53 to 1.75) with no significant difference found.
- Continue to include one xanthine oxidase inhibitor as preferred on the PDL for the treatment of chronic gout and hypeuricemia.
- No further review or research needed; evaluate comparative costs in executive session.

Previous Conclusions and Recommendation:

- Therapy with xanthine oxidase inhibitors remains first-line therapy for chronic gout and hyperuricemia.
- There is insufficient evidence of any significant difference between allopurinol and feboxostat on clinical outcomes such as gout flares. The American College of Rheumatology guidelines give no preference to either agent and both are recommended as first line treatment.
- There is insufficient evidence for the treatment of intra-articular corticosteroids for the treatment of gout.
- There is moderate quality evidence of no difference in efficacy/effectiveness or safety between agents.
- Colchicine is the only agent for gout and Familial Mediterranean Fever.
- Febuxostat reduces serum urate below 6 mg/dL in a significantly greater proportion of patients with gout and hyperuricemic compared to patients receiving allopurinol but there was no difference in gout flares.
- Block pharmacy claims for pegloticase.

Author: M. Herink, Pharm.D. Date: May 2015

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

1. A systematic review was completed to evaluate current evidence for the treatment of acute gout.[1] A high quality literature search was done and the methodological quality of the trials was assessed using the Jadad scale. Thirty RCTs were included in the analysis, of which 21 were double blinded. The majority of the trials assessed evaluated NSAIDs, including indomethacin, and cox-2 inhibitors for the treatment of acute gout and will not be discussed here. Two trials were identified evaluating the use of colchicine for acute gout. Compared to placebo, colchicine had greater efficacy in reducing pain when administered within 12 hours of an acute attack. Compared to high dose colchicine (4.8 mg over six hours), low dose colchicine (1.8 mg over one hour) had a significantly greater tolerability profile and were similar in efficacy.

2. The Cochrane Collaboration recently evaluated colchicine for the treatment of acute gout with a literature search up to April 2014.[2] Only two trials were identified (n=618) which resulted in low quality evidence of a greater proportion of patients responding to treatment, defined as a 50% or greater decrease in pain score, with high-dose colchicine (total 4.8 mg over six hours) compared to placebo (absolute risk difference 28%; RR 2.16; 95% CI 1.28 to 3.65; NNT 4) and low quality evidence for a greater decrease in inflammation score compared to placebo (absolute risk difference 45%; RR 10.50; 95% CI 1.48 to 74.38). There was no evidence to evaluate quality of life, functioning, or withdrawals due to adverse events. The smaller study evaluated a high-dose regimen that is no longer recommended in clinical practice (1 mg colchicine, then 0.5 mg every two hours until relief or side effects) and the mean dose given was not included. The second trial compared colchicine 1.8 mg over one hour, 4.8 mg over 6 hours, and placebo. Those on the lower dose of colchicine also had a significantly greater response compared to placebo (RR 2.74; 95% CI 1.05 to 7.13) and there was low quality evidence of no significant difference between the higher and lower doses of colchicine in response to treatment (RR 0.86; 95% CI 0.53 to 1.41). There was a significantly higher rate of total adverse events and gastrointestinal side effects with the high-dose colchicine compared to low-dose.

   The authors concluded that, based on only two trials, there is low-quality evidence that low-dose colchicine is likely to be an effective treatment for acute gout with some uncertainty around the estimated effect. There are no studies comparing colchicine in populations with comorbidities or in comparison with other commonly used medications, such as NSAIDs and glucocorticoids.

3. Another systematic review and meta-analysis from the Cochrane Collaboration evaluated the use of allopurinol for the treatment of chronic gout.[3] All RCTs comparing allopurinol to placebo or active treatment in adults with chronic gout were included. The primary outcomes were frequency of acute gout attacks, achievement of normal serum urate levels, pain, function, tophus regression, withdrawals due to adverse events, and serious adverse events.

Eleven trials were identified from the literature search and included in the review. The most relevant active comparison was allopurinol compared to febuxostat (four trials). Only one trial was found to have a low risk of bias in all domains.

There was moderate quality evidence from 1 study (n=51) that compared to placebo, allopurinol did not significantly reduce acute gout attacks (7.7% in allopurinol group vs. 12% in placebo; RR 0.64; 95% CI 0.12 to 3.52) but did significantly increase the proportion of subjects achieving target serum urate levels (RR 49.11; 95% CI 3.15 to 765.58) with no significant difference in withdrawals due to adverse events (RR 1.36; 95% CI 0.61 to 3.08) or serious adverse events (RR 1.93; 95% CI 0.48 to 7.80).

Data from four trials with unclear to high risk of bias were pooled and showed low quality evidence of no difference in the frequency of acute gout attacks with allopurinol compared to febuxostat 80 mg (RR 0.89; 95% CI 0.71 to 1.10). Subjects taking allopurinol had significantly fewer acute gout attacks compared with those on higher doses of febuxostat 120 mg (RR 0.62; 95% CI 0.51 to 0.76). Compared to febuxostat 80 mg, those on allopurinol were less likely to achieve target serum urate levels (RR 0.55; 95% CI 0.48 to 0.63). There was moderate quality evidence of no difference in withdrawals due to adverse events between allopurinol and feboxostat 80 mg (RR 0.89; 95% CI 0.62 to 1.26). Trials did not report pain reduction or functioning.

All other comparisons were based only on small studies. The authors concluded there was low- to moderate- quality evidence demonstrating similar effects on withdrawals due to adverse events and incidence of acute gout attacks when allopurinol was compared to placebo or febuxostat 80 mg daily. Allopurinol seemed more effective than placebo and less effective than febuxostat in achieving a target serum urate level of 6 mg/dL or less based on low- to moderate-quality evidence.

4. Lastly, a Cochrane Collaboration systematic review evaluated the evidence for uricosuric medications for the treatment of chronic gout.[4] Controlled clinical trials comparing uricosuric agents (probenecid, sulphinpyrazone or benzbromarone) to other treatments or placebo were included. Probencid is the only agent available in the US and only data for probencid will be summarized here. Five trials were identified; however, only one of these included probenecid. A single center, controlled clinical trial compared probecid to allopurinol in 40 subjects with chronic gout. Study outcomes were acute gout attacks, serum urate, and tophus regression. This small study with high risk of bias provided low-quality evidence of uncertainty around the difference in acute gout attacks between probenecid and allopurinol after 18 months of treatment (53% vs. 55%; RR 0.96; 95% CI 0.53 to 1.75). The study did not report proportion of patients achieving target serum urate levels, pain reduction, functioning, withdrawals due to adverse events or total adverse events. In addition, 29% (5/17) of subjects treated with probenicid changed therapy to sulphinpyrazone due to minor adverse events.

Guidelines:
None identified.

New drugs:
None identified.

New Formulations/Indications:
None identified.

New FDA safety alerts:
None identified.

References:
1. Khanna PP, Gladue HS, Singh MK, et al. Treatment of acute gout: a systematic review. *Semin Arthritis Rheum*. 2014;44(1):31-38. doi:10.1016/j.semarthrit.2014.02.003.

2. Van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014;8:CD006190. doi:10.1002/14651858.CD006190.pub2.

3. Seth R, Kydd ASR, Buchbinder R, Bombardier C, Edwards CJ. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;10:CD006077. doi:10.1002/14651858.CD006077.pub3.

4. Kydd ASR, Seth R, Buchbinder R, Edwards CJ, Bombardier C. Uricosuric medications for chronic gout. *Cochrane Database Syst Rev*. 2014;11:CD010457. doi:10.1002/14651858.CD010457.pub2.

Appendix 1: Current Status on Preferred Drug List

- Preferred Agents: ALLOPURINOL, COLCHICINE/PROBENECID
- Non-Preferred Agents: COLCHICINE (COLCRYRS®), FEBUXOSTAT (ULORIC®), PROBENECID, PEGLOTICASE (KRYSTEXXA)

Appendix 2: New Clinical Trials

Seventeen potentially relevant articles were evaluated from the literature search. After further review, all articles were either post-hoc analyses of older trials, non relevant comparisons, meta-analyses of select studies, or studies without evaluation of clinical outcomes, and were therefore excluded.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April 20 2015
1 Allopurinol.mp. 4133
2 colchicine.mp 5988
3 probenecid.mp. 1287
4 febuxostat.mp. 261
5 pegloticase.mp. 72
6 Gout 2816
7 Hyperuricemia 1769
8 1or 2o r 3 or 4 or 5 11279
9 6 or 7 4071
10 8 and 9 1017
11 limit 10 to (english language and humans and yr="2014 -Current" and (clinical trial, phase iii or clinical trial or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews)) 17

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Short-acting Opioids

Month/Year of Review: May 2015 **Date of Last Review: July 2013**

Current Status of PDL Class:
See **Appendix 1**.

Current Prior Authorization Criteria:
Fentanyl Buccal, Intranasal and Sublingual Products and **Opioid/non-narcotic Combinations and Excessive Dose Limits** (see **Appendix 4**).

Conclusions and Recommendations:
- Update current PA criteria for excessive dose limits on opioid/non-narcotic combination products. Propoxyphene products and combination products containing 500 mg of acetaminophen were removed, and the maximum recommended daily aspirin dose was decreased from 8 g/day to 4 g/day.
- No further review or research needed at this time. Compare drug costs in the executive session.

Previous Conclusions and Recommendations:
- Fentanyl products should only be used in opioid-tolerant patients
- Should have long acting analgesic therapy instituted
- Consider quantity limits

Methods:
A Medline OVID search was conducted with the following search terms: codeine, hydrocodone, oxycodone, hydromorphone, morphine, oxymorphone, fentanyl, buprenorphine, tramadol, tapentadol, acetaminophen, opioids, opioid analgesics, short-acting opioids, pain, pain relief, and treatment. The search was limited to English language articles of randomized control trials in humans published from 2013 to February 2015. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

A summary of potentially relevant trials are available in **Appendix 2**. Abstracts of these trials are available in **Appendix 3**.

New Systematic Reviews:
Chaparro, et al.[1] conducted a systematic review of the use of opioids and other treatments for lower back pain. The review included 15 trials lasting longer than 4 weeks comparing at least one opioid to placebo, except two trials which used celecoxib in the control arm. Tramadol was compared to placebo in five trials. There is low quality evidence that tramadol is better than placebo in improving pain [standardized mean difference (SMD) -0.55, 95% CI -0.66 to -0.44]. Two included studies compared transdermal buprenorphine to placebo, with very low quality evidence that buprenorphine is better than placebo in improving pain (SMD -2.47, 95% DI -2.69 to -2.25). There was moderate quality evidence from six trials that opioids are better than placebo in reducing pain (SMD -0.43, 95% CI -0.52 to -0.33). Patients treated with opioids had a statistically significantly higher incidence of nausea (10%, 95% CI 7% to 14%), dizziness (8%,

95% CI 5% to 11%), constipation (7%, 95% CI 4% to 11%), vomiting (7%, 95% CI 4% to 9%), somnolence (6%, 95% CI 3% to 9%) and dry mouth (6%, 95% CI 2% to 10%) than people treated with placebo. There were no head-to-head comparisons conducted in this systematic review.

An update of a systematic review and meta-analysis evaluating opioids for neuropathic pain was published.[2] 17 short-term (single dose or intravenous infusion) and 14 intermediate-term (more than a single dose but not long enough to make conclusion about chronic administration) studies were included. The short-term trials were too small to draw conclusions regarding reduction in pain. When the number of participants achieving at least 50% pain relief was analyzed in the intermediate-term trials, the overall point estimate of risk difference for opioids versus placebo was 0.17 (95% CI. 0.02 to 0.33; p=0.03). The intermediate-term studies were also of small size, short duration, and at risk of bias due to inadequate handling of dropouts. Well-conducted RCTs are needed to establish long-term efficacy, safety and quality of life estimates.

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:

1. Chaparro, L. E. *et al.* Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev* **8,** CD004959 (2013).
2. McNicol, E. D., Midbari, A. & Eisenberg, E. Opioids for neuropathic pain. *Cochrane Database Syst Rev* **8,** CD006146 (2013).
3. Chang, A. K., Bijur, P. E., Munjal, K. G. & John Gallagher, E. Randomized clinical trial of hydrocodone/acetaminophen versus codeine/acetaminophen in the treatment of acute extremity pain after emergency department discharge. *Acad Emerg Med* **21,** 227–235 (2014).
4. Kuivalainen, A.-M., Ebeling, F. & Rosenberg, P. H. Pre-medication with sublingual fentanyl did not relieve pain associated with bone marrow aspiration and biopsy: a randomized feasibility trial. *Eur J Pain* **17,** 1357–1364 (2013).
5. Kwong, W. J. *et al.* Bowel function after tapentadol and oxycodone immediate release (IR) treatment in patients with low back or osteoarthritis pain. *Clin J Pain* **29,** 664–672 (2013).

Appendix 1: Current Status on Preferred Drug List

Route	Form	Brand	Generic	PDL
NASAL	SPRAY	BUTORPHANOL TARTRATE	BUTORPHANOL TARTRATE	Y
ORAL	TABLET	CODEINE SULFATE	CODEINE SULFATE	Y
ORAL	TABLET	HYDROCODONE W/ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	LORTAB	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	VICODIN	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	ANEXSIA	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	NORCO	HYDROCODONE/ACETAMINOPHEN	Y
ORAL	TABLET	HYDROMORPHONE HCL	HYDROMORPHONE HCL	Y
ORAL	TABLET	DILAUDID	HYDROMORPHONE HCL	Y
ORAL	SOLUTION	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	TABLET	MORPHINE SULFATE	MORPHINE SULFATE	Y
ORAL	SOLUTION	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	OXYCODONE HCL	OXYCODONE HCL	Y
ORAL	TABLET	ROXICODONE	OXYCODONE HCL	Y
ORAL	CAPSULE	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	PERCOCET	OXYCODONE HCL/ACETAMINOPHEN	Y
ORAL	TABLET	TRAMADOL HCL	TRAMADOL HCL	Y
ORAL	TABLET	ULTRAM	TRAMADOL HCL	Y
ORAL	SUSPENSION	CAPITAL W-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	TABLET	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	TABLET	TYLENOL-CODEINE NO.3	ACETAMINOPHEN WITH CODEINE	N
ORAL	TABLET	TYLENOL-CODEINE NO.4	ACETAMINOPHEN WITH CODEINE	N
ORAL	ELIXIR	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	SOLUTION	ACETAMINOPHEN-CODEINE	ACETAMINOPHEN WITH CODEINE	N
ORAL	CAPSULE	BUTALB-CAFF-ACETAMINOPH-CODEIN	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	FIORICET WITH CODEINE	BUTALBIT/ACETAMIN/CAFF/CODEINE	N
ORAL	CAPSULE	ASA-BUTALB-CAFFEINE-CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEINE	N
ORAL	CAPSULE	FIORINAL W/CODEINE	CODEINE/BUTALBITAL/ASA/CAFFEINE	N
ORAL	SOLUTION	CODEINE SULFATE	CODEINE SULFATE	N
ORAL	CAPSULE	SYNALGOS-DC	DIHYDROCODEINE/ASPIRIN/CAFFEINE	N
ORAL	CAPSULE	TREZIX	DIHYDROCODEINE/APAP/CAFFEINE	N
ORAL	CAPSULE	ASPIRIN-CAFFEINE-DIHYDROCODEIN	DIHYDROCODEINE/ASPIRIN/CAFFEINE	N
ORAL	CAPSULE	SYNALGOS-DC	DIHYDROCODEINE/ASPIRIN/CAFFEINE	N
BUCCAL	LOZENGE HD	ACTIQ	FENTANYL CITRATE	N
BUCCAL	LOZENGE HD	FENTANYL CITRATE	FENTANYL CITRATE	N
NASAL	SPRAY/PUMP	LAZANDA	FENTANYL CITRATE	N
SUBLINGUAL	SPRAY	SUBSYS	FENTANYL	N
BUCCAL	TABLET EFF	FENTORA	FENTANYL CITRATE	N
SUBLINGUAL	TAB SUBL	ABSTRAL	FENTANYL CITRATE	N
ORAL	ELIXIR	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	SOLUTION	HYDROCODONE-ACETAMINOPHEN	HYDROCODONE/ACETAMINOPHEN	N
ORAL	TABLET	HYDROCODONE-IBUPROFEN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	VICOPROFEN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	REPREXAIN	HYDROCODONE/IBUPROFEN	N
ORAL	TABLET	XYLON 10	HYDROCODONE/IBUPROFEN	N
ORAL	LIQUID	DILAUDID	HYDROMORPHONE HCL	N

ORAL	LIQUID	HYDROMORPHONE HCL	HYDROMORPHONE HCL	N
ORAL	SOLUTION	MEPERIDINE HCL	MEPERIDINE HCL	N
ORAL	TABLET	DEMEROL	MEPERIDINE HCL	N
ORAL	TABLET	MEPERIDINE HCL	MEPERIDINE HCL	N
RECTAL	SUPP.RECT	MORPHINE SULFATE	MORPHINE SULFATE	N
ORAL	SYRINGE	MORPHINE SULFATE	MORPHINE SULFATE	N
RECTAL	SUPP.RECT	BELLADONNA-OPIUM	OPIUM/BELLADONNA ALKALOIDS	N
ORAL	CAPSULE	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	CONC SOL	OXYCODONE HCL	OXYCODONE HCL	N
ORAL	TABLET	OXYCODONE-ACETAMINOPHEN	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	SOLUTION	ROXICET	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	ROXICET	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	OXYCODONE HCL-ASPIRIN	OXYCODONE HCL/ASPIRIN	N
ORAL	TABLET	PERCODAN	OXYCODONE HCL/ASPIRIN	N
ORAL	TABLET	OXYCODONE HCL-IBUPROFEN	OXYCODONE/IBUPROFEN HCL	N
ORAL	TABLET	OPANA	OXYMORPHONE HCL	N
ORAL	TABLET	OXYMORPHONE HCL	OXYMORPHONE HCL	N
ORAL	TABLET	PENTAZOCINE-NALOXONE HCL	PENTAZOCINE HCL/NALOXONE HCL	N
ORAL	SOLUTION	NUCYNTA	TAPENTADOL HCL	N
ORAL	TABLET	NUCYNTA	TAPENTADOL HCL	N
ORAL	TABLET	TRAMADOL HCL-ACETAMINOPHEN	TRAMADOL HCL/ACETAMINOPHEN	N
ORAL	TABLET	ULTRACET	TRAMADOL HCL/ACETAMINOPHEN	N

Appendix 2: New Clinical Trials

84 potentially relevant clinical trials were evaluated from the literature search. After further review, 79 trials were excluded due to wrong study design (observational), comparator (placebo), drug (long-acting opioid) or outcome (nonclinical) and were therefore excluded. The remaining 5 trials are briefly described in the table below. Full abstracts are included in Appendix 3.

Table 1. Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Chang, et al.[3]	Hydrocodone/ APAP 5/500 mg vs. Codeine/APAP 30/300 mg	Adults with acute extremity pain discharged home from the Emergency Department (n=240)	Change from baseline pain as measured by the Numeric Rating Scale	Mean decrease in pain scores were 3.9 units (hydrocodone/APAP) vs 3.5 units (codeine/APAP) (difference 0.4 units; 95% CI: -0.3 to 1.2 units). No differences found in side effects or patient satisfaction
Kuivalainen, et al.[4]	Sublingual fentanyl 200 mcg or 100 mcg or placebo	Adult patients undergoing bone marrow aspiration and/or biopsy (n=160)	Pain scores at 6 time points before, during and after the procedure	There were no differences in pain scores between either active comparison and placebo at any time point.
Kwong, et al.[5]	Tapentadol IR vs. Oxycodone IR	Adult patients with OA of the knee or hip joint	Bowel function assessed using the Bowel Movement Questionnaire (BMQ), the Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM), and laxative use	The proportions of treatment days with no or incomplete bowel movements were similar with placebo and tapentadol, but higher in the oxycodone group ($p<0.05$) after 10 days of treatment as assessed with the BMQ. When assessing bowel function with the PAC-SYM, tapentadol had significantly lower overall PAC-SYM scores and abdominal symptoms. Other differences were not statistically different.

Appendix 3: Abstracts of Clinical Trials

Chang, et al. Randomized clinical trial of hydrocodone/acetaminophen versus codeine/acetaminophen in the treatment of acute extremity pain after emergency department discharge.

OBJECTIVES: The objective was to test the hypothesis that hydrocodone/acetaminophen (Vicodin [5/500]) provides more efficacious analgesia than codeine/acetaminophen (Tylenol #3 [30/300]) in patients discharged from the emergency department (ED). Both are currently Drug Enforcement Administration (DEA) Schedule III narcotics.
METHODS: This was a prospective, randomized, double-blind, clinical trial of patients with acute extremity pain who were discharged home from the ED, comparing a 3-day supply of oral hydrocodone/acetaminophen (5 mg/500 mg) to oral codeine/acetaminophen (30 mg/300 mg). Pain was measured on a valid and reproducible verbal numeric rating scale (NRS) ranging from 0 to 10, and patients were contacted by telephone approximately 24 hours after being discharged. The primary outcome was the between-group difference in improvement in pain at 2 hours following the most recent ingestion of the study drug, relative to the time of phone contact after ED discharge. Secondary outcomes compared side-effect profiles and patient satisfaction.
RESULTS: The median time from ED discharge to follow-up was 26 hours (interquartile range [IQR] = 24 to 39 hours). The mean NRS pain score before the most recent dose of pain medication after ED discharge was 7.6 NRS units for both groups. The mean decrease in pain scores 2 hours after pain medications were taken were 3.9 NRS units in the hydrocodone/acetaminophen group versus 3.5 NRS units in the codeine/acetaminophen group, for a difference of 0.4 NRS units (95% confidence interval [CI] = -0.3 to 1.2 NRS units). No differences were found in side effects or patient satisfaction.
CONCLUSIONS: Both medications decreased NRS pain scores by approximately 50%. However, the oral hydrocodone/acetaminophen failed to provide clinically or statistically superior pain relief compared to oral codeine/acetaminophen when prescribed to patients discharged from the ED with acute extremity pain. Similarly, there were no clinically or statistically important differences in side-effect profiles or patient satisfaction. If the DEA reclassifies hydrocodone as a Schedule II narcotic, as recently recommended by its advisory board, our data suggest that the codeine/acetaminophen may be a clinically reasonable Schedule III substitute for hydrocodone/acetaminophen at ED discharge. These findings should be regarded as tentative and require independent validation in similar and other acute pain models.

Kuivalainen, et al. Pre-medication with sublingual fentanyl did not relieve pain associated with bone marrow aspiration and biopsy: a randomized feasibility trial.

BACKGROUND: Bone marrow aspiration and/or biopsy (BMAB) is often an unpleasant and painful procedure in spite of local anaesthetic infiltration. This randomized placebo-controlled trial compared the pain relieving effect of sublingual fentanyl and placebo during BMAB.
METHODS: One hundred sixty patients were randomized to receive either sublingual fentanyl 200 μg, 100 μg (patients ≥ 70 years old, weight ≤ 50 kg or in poor health) or placebo before BMAB. The grade of anxiety before the procedure and the grade of pain during local anaesthetic infiltration, aspiration, biopsy and immediately after the BMAB were assessed using the Numeral Rating Scale (0-10). Possible side effects of the study drugs were recorded.
RESULTS: Sublingual fentanyl proved inadequate in relieving pain during BMAB as no significant differences in the pain scores of the fentanyl and placebo patients were observed. However, fentanyl caused significantly more dizziness than placebo.
CONCLUSIONS: The results suggest that sublingual fentanyl in a dose of 200 μg (100 μg in infirm patients) is not a feasible preventive analgesic during BMAB. Pain scores were similar and side effects more frequent in the fentanyl group than in the placebo group.

Kwong, et al. Bowel function after tapentadol and oxycodone immediate release (IR) treatment in patients with low back or osteoarthritis pain.

OBJECTIVES: Constipation is a common side effect of opioid therapy. Tapentadol immediate release (IR) was better tolerated than oxycodone IR in 2 clinical trials involving patients with low back or osteoarthritis pain. The objective of this study was to examine patient-reported bowel function during those trials.
METHODS: Bowel function was assessed during secondary post hoc analyses using: the bowel movement questionnaire (BMQ; 10-d trial); the Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM; 90-day trial); and laxative use (both trials). Random effects maximum likelihood regressions were run to examine PAC-SYM data. BMQ data were analyzed using 1-way analyses of variance and a multinomial logistic regression. Rates of laxative use were compared using $\chi(2)$ statistics.
RESULTS: The 10- and 90-day trials consistently showed that tapentadol IR caused less impairment of bowel function than oxycodone IR. BMQ data were comparable between patients receiving tapentadol IR and placebo, and better versus oxycodone IR including: lower proportion of days where bowel movement was absent ($P<0.05$); lower risks of reporting hard stools ($P<0.001$); and moderate or severe straining ($P<0.001$). All PAC-SYM summary scores (abdominal, rectal, stool, overall) indicated fewer symptoms among patients receiving tapentadol IR versus oxycodone IR ($P<0.001$). In both trials, rates of laxative use was lower for tapentadol IR treatment groups versus oxycodone IR ($P<0.001$).
DISCUSSION: Patient-reported bowel function associated with tapentadol IR treatment was similar to that associated with placebo (10-d trial) and significantly better than that associated with oxycodone IR treatment (10- and 90-d trials).

Fentanyl Buccal, Intranasal and Sublingual Products

Goal(s):

The purpose of this prior authorization policy is to ensure that fentanyl for breakthrough pain is appropriately prescribed in accordance to FDA black box warnings:

- Short-acting fentanyl is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
- Patients considered opioid-tolerant are those who are taking at least 60 mg/day morphine, 50 mcg/hour transdermal fentanyl, or an equianalgesic dose of another opioid for a week or longer.
- Because life-threatening respiratory depression can occur at any dose in patients not taking chronic opiates, transmucosal and buccal fentanyl is contraindicated in the management of acute or postoperative pain.
- This product must not be used in opioid-naïve patients. Short acting (SA) fentanyl is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable and skilled in the use of Schedule II opioids to treat cancer pain.
- When prescribing, do not convert patients from other fentanyl products on a mcg per mcg basis. Pharmacokinetic differences between products could cause fatal over-dose.
- Caution should be used when combining these agents with CYP3A4 inhibitors. Increases in fentanyl concentrations can cause fatal respiratory depression.
- Patients and their caregivers must be instructed that fentanyl products contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

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Length of Authorization:

Up to 6 months (with quantity limit)

Requires PA:

- Non-preferred short-acting fentanyl buccal, intranasal and sublingual products

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria	
1. What is the diagnosis for which fentanyl is being requested?	Record ICD9 code.

Approval Criteria		
2. Is the pain diagnosis above the line or below the line? (for DMAP, short acting fentanyl is not limited to cancer pain but must be severe chronic pain)	**Above the line:** go to #3.	**Below the line:** No, Pass to RPH; Deny, (Not Covered by the OHP).
3. Is the prescriber an oncologist or pain specialist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny, (Medical Appropriateness), with message: "The described use is not consistent with the FDA labeling which SA fentanyl be used only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."
4. Is client tolerant to opioids (**Check profile)**, defined as chronic long-acting opioid dose of: • Morphine greater than 60 mg per day? OR • Transdermal fentanyl 50 mcg per hour? OR • Equianalgesic dose of another opioid for at least one week?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request was reviewed and denied because it is not consistent with the FDA labeling. A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."*
5. Has the client tried and failed immediate release morphine or oxycodone? OR is the client allergic, unable to swallow or intolerant to morphine and oxycodone?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request was reviewed and denied based on the following: A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."*

Approval Criteria		
6. Is the quantity >4 doses per day?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request for a quantity greater than 4 has been denied because it exceeds limits."*	**No:** Approve for up to 6 months with quantity limit of 4 lollipops/tablets per day (i.e. 120/30 days).

P&T / DUR Action: *5/15; 6/13; 3/10; 12/09, 9/05, 5/05*
Revision(s): *1/14 (MH), 4/10; 4/08, 6/08, 1/10*
Initiated: *9/06*

Opioid/non-narcotic Combinations and Excessive Dose Limits

Goal(s):

- Decrease risk for adverse events attributed to high doses of acetaminophen (APAP) or aspirin (ASA) when combined with an opioid product.
- Pay only for conditions funded on the OHP list of prioritized services.

Length of Authorization:

None

Requires PA:

- Non-preferred drugs.
- Prescriptions exceeding FDA recommendations of 4000 mg/day of APAP or ASA.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Pharmacy may need to adjust day's supply entry.
- Prescriber may choose a product with a higher ratio of narcotic to keep APAP or ASA within maximum limits or use a single-ingredient opioid.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does daily dose of APAP or ASA exceed the maximum daily dose?	Yes: Go to #3.	No: Instruct pharmacy to correct day's supply entry
3. Is the diagnosis funded on the OHP list of prioritized services?	Yes: Pass to RPH, DENY, (Medical Appropriateness) Review FDA maximum dose and provide alternatives.	No: Pass to RPH, DENY, (Not Covered by the OHP) Review FDA maximum dose and provide alternatives

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Examples of products containing ASA:

Aspirin Combinations			
Drug	**Maximum quantity per day**	**Drug**	**Maximum quantity per day**
Codeine/ASA/Caffeine/ Butalbital 30/325/40/50 mg	12 tablets	Oxycodone/ASA 4.8355/325 mg	12 tablets
Codeine/ASA/Carisoprodol 16/325/200 mg	12 tablets	Dihydrocodeine/ASA/Caffeine 16/356.4/30 mg	11 capsules

Examples of products containing APAP:

Hydrocodone/APAP combinations			
Drug	**Maximum quantity per day**	**Drug**	**Maximum quantity per day**
Hydrocodone/APAP 5/300 mg	13 tablets	Hydrocodone/APAP 2.5/108 mg per 5 mL	185 mL
Hydrocodone/APAP 7.5/300 mg	13 tablets	Hydrocodone/APAP 5/217 mg per 10 mL	184 mL
Hydrocodone/APAP 10/300 mg	13 tablets	Hydrocodone/APAP 7.5/325 mg per 15 mL	184.5 mL
Hydrocodone/APAP 2.5/325 mg	12 tablets	Hydrocodone/APAP 10/325 mg per 15 mL	184.5 mL
Hydrocodone/APAP 5/325 mg	12 tablets		
Hydrocodone/APAP 7.5/325 mg	12 tablets		
Hydrocodone/APAP 10/325 mg	12 tablets		

Oxycodone/APAP combinations	
Oxycodone/APAP 5/300 mg	13 tablets
Oxycodone/APAP 7.5/300 mg	13 tablets
Oxycodone/APAP 10/300 mg	13 tablets
Oxycodone/APAP 2.5/325 mg	12 tablets
Oxycodone/APAP 5/325 mg	12 tablets
Oxycodone/APAP 7.5/325 mg	12 tablets
Oxycodone/APAP 10/325 mg	12 tablets
Oxycodone/APAP 5/325 per 5 mL	61.5 mL

Codeine/APAP combinations	
Codeine/APAP 12/120 mg per 5 mL	166.5 mL
Codeine /APAP 15/300 mg	13 tablets
Codeine /APAP 30/300 mg	13 tablets
Codeine /APAP 60/300 mg	13 tablets

Other Combinations	
Tramadol/APAP 37.5/325 mg	12 tablets
Dihydrocodeine/APAP/caffeine 16/320.5/30 mg	12 tablets

P&T / DUR Action: *5/15; 2/06; 11/99; 2/99*
Revision(s) *9/05; 5/05; 12/03; 5/03*
Initiated:

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Oral Tetracyclines

Month/Year of Review: May 2015

Date of Last Review: 2010
Source Document: Provider Synergies

Current Status of PDL Class:

Preferred Agents

DOXYCYCLINE HYCLATE, CAPSULE	DOXY-LEMMON™, ED DOXY-CAPS™, MORGIDOX™, VIBRAMYCIN™
DOXYCYCLINE HYCLATE, TABLET	ACTICLATE™, DOXY-LEMMON™
DOXYCYCLINE MONOHYDRATE, CAPSULE	ADOXA™, MONODOX™
DOXYCYCLINE MONOHYDRATE, SUSPENSION	VIBRAMYCIN™
TETRACYCLINE HCL, CAPSULE	ACHROMYCIN V™, ALA-TET™, SUMYCIN™

Non-Preferred Agents

DEMECLOCYCLINE HCL, TABLET	
DOXYCYCLINE CALCIUM, SYRUP	VIBRAMYCIN™
DOXYCYCLINE HYCLATE, TABLET DR	DORYX™
DOXYCYCLINE MONOHYDRATE, CAPSULE IR DR	ORACEA™
DOXYCYCLINE MONOHYDRATE, TABLET	ADOXA PAK™, ADOXA™ AVIDOXY™
MINOCYCLINE HCL, CAPSULE	DYNACIN™, MINOCIN™
MINOCYCLINE HCL, TABLET ER 24HR	SOLODYN™
MINOCYCLINE HCL, TABLET	

Conclusions and Recommendations:

- Doxycycline is the most commonly recommended tetracycline and is recommended for multiple indications as first line, second line, or as part of combination therapy base on limited, low quality evidence.
- Tetracycline is recommended for select indications based on expert opinion and low quality evidence.
- Minocycline is a potential agent for methicillin-susceptible S. aureus (MSSA) and MRSA in non-pregnant adults and children over 7 years base on limited, low quality evidence.
- Compare relative cost in executive session.

Previous Conclusions and Recommendations:

- Recommend inclusion of one or more agents from this class including doxycycline.
- Recommend limiting use in the last half of pregnancy.
- Recommend limiting use in pediatrics under age 8 years.
- Recommend considering limiting use of demeclocycline to treatment of SIADH.

Indications for tetracyclines:

- Sexually transmitted diseases (e.g. infections due to Neisseria gonorrhoeae, Chlamydia trachomatis, etc.)
- Respiratory tract infections (e.g. Community Acquired Pneumonia)
- Urinary tract infections (e.g. due to Klebsiella species)
- Acne vulgaris
- Rosacea
- Other less common infections/illnesses cause by
    - Rickettsiae species
    - Borrelia recurrentis
    - *Haemophilus ducreyi*
    - *Yersinia pestis (plague)*
    - *Francisella tularensis*
    - *Brucella* species
    - *Bartonella bacilliformis*
    - *Calymmatobacterium granulomatis*
    - Bacillus anthracis (Anthrax)
    - Treponema pertenue (Yaws)
    - Actinomyces israelii

Methods:

A Medline OVID search was conducted with the following search terms: demeclocycline, doxycycline, minocycline, and tetracycline. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to March 2015. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. 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). Treatments for Acne vulgaris and rosacea are excluded from coverage in the Oregon Health Plan. Therefore guidelines and reviews for these indications were excluded from this evaluation.

A summary of potentially relevant trials are available in **Appendix 1**. Abstracts of these trials are available in **Appendix 2**.

New Systematic Reviews:

1. A 2012 Cochrane Collaborative report evaluated treatments for brucellosis.[1] Eight studies evaluated doxycycline plus rifampicin vs. doxycycline plus streptomycin. Doxycycline plus rifampicin was found to be less effective than doxycycline plus streptomycin (RR 1.91, 95% CI 1.07-3.42). There was no significant difference in adverse reactions. Five studies evaluating doxycylcine plus rifampicin vs. fluroquinolones vs. rifampicin found no significant difference in efficacy or adverse reactions.

New Guidelines:

1. The Infectious Disease Society of America (IDSA) published guidelines for the management of community-acquired pneumonia in children in 2011.[2] Doxycycline is included as alternative therapy for the outpatient treatment of mycoplasma pneumonia and Chlamydia infections in children over 7 years old. Doxycycline is also included as alternative empiric therapy for presumed atypical pneumonia in immunize and non-immunized children over 7 years in inpatient and outpatient settings. These recommendations are extrapolated from studies in adults.
2. The Department of Health and Human Services Center for Disease Control (CDC) published guidelines for the treatment of sexually transmitted diseases in 2010.[3] These recommendations stated that tetracyclines are no longer suitable for the treatment of *N. gonorrhoeae* in the U.S. due to the development of antibiotic resistance. Based on two studies, the CDC recommends doxycycline or tetracycline for the treatment of primary, secondary, late latent and latent syphillis in non-pregnant, penicillin-allergic patients. Doxycycline is also recommended for the treatment of granuloma inguinale, lymphogranuloma venereum, chlamydial urethritis, cervicitis, uncomplicated gonococcal infections of the cervix, urethra, and rectum, chlamydial infections in non-pregnant adults and children over 7 years old. Doxycycline is recommended for use in pelvic inflammatory disease (PID) as both step down therapy post gentamicin therapy or for mild to moderate PID with or without metronidazole. Based on one trial, doxycycline is recommended in combination with ampicillin/sulbactam for the treatment of *C. trachomatis*, *N. gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess. In men, doxycycline is recommended for the treatment of epididymitis and proctitis in adult men.
3. In 2012, the CDC issued an update to the 2010 recommendations.[5] Doxycycline, in combination with ceftriaxone, was recommended for uncomplicated gonorrhea. There were no other tetracycline-related changes to treatment recommendations.
4. In 2014, the IDSA updated guidelines for the treatment of skin and soft tissue infections.[6] Recommendations for tetracycline antibiotics in this guideline are based on a limited, low quality studies. Either tetracycline or doxycycline were recommended over penicillin for treatment of mild cases of tularemia based on low quality evidence from two studies. Despite a lack of controlled trials, tetracyclines were recommended for the treatment of cutaneous anthrax. Tetracycline was identified as a potential treatment for bubonic plague, despite the lack of comparative clinical trials. Doxycycline is strongly recommended as one of several alternatives for the treatment of Impetigo and Ecthyma when methicillin-resistant S. aureus (MRSA) is suspected in penicillin allergic patients, though no references are cited. Likewise, doxycycline and minocycline are listed as potential agents for methicillin-susceptible *S. aureus* (MSSA) and MRSA in non-pregnant adults and children over 7 years. Doxycycline is recommended for the treatment of bacillary angiomatosis, glanders and mild tularemia.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:

1. Yousefi-Nooraie, Reza, Mortaz-Hejri S, Mehrani M, Sadeghipour P. Antibiotics for treating human brucellosis. *The Cochrane Database of Systematic Reviews*. 2012;(10). doi:10.1002/14651858.CD007179.pub2.

2. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e25-e76. doi:10.1093/cid/cir531.

3. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1-110.

4. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infectious Diseases*. 2011;52(5):e103-e120. doi:10.1093/cid/ciq257.

5. Centers for Disease Control and Prevention (CDC). Update to CDC's Sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61(31):590-594.

6. Stevens DL, Bisno AL, Chambers HF, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2014;59(2):e10-e52. doi:10.1093/cid/ciu296.

7. Kayabas U, Karahocagil MK, Ozkurt Z, et al. Naturally Occurring Cutaneous Anthrax: Antibiotic Treatment and Outcome. *Chemotherapy*. 2012;58(1):34-43.

8. Mile B, Valerija K, Krsto G, Ivan V, Ilir D, Nikola L. Doxycycline-rifampin versus doxycycline-rifampin-gentamicin in treatment of human brucellosis. *Tropical Doctor*. 2012;42(1):13-17. doi:10.1258/td.2011.110284.

9. Baltacioglu E, Aslan M, Saraç Ö, Saybak A, Yuva P. Generalized Aggressive Periodontitis: A Pilot Study. *J Can Dent Assoc*. 2011;77:b97.

10. Cerar D, Cerar T, Ružić-Sabljić E, Wormser GP, Strle F. Subjective Symptoms after Treatment of Early Lyme Disease. *The American Journal of Medicine*. 2010;123(1):79-86. doi:10.1016/j.amjmed.2009.05.011.

Appendix 1: New Clinical Trials

Ten (10) potentially relevant clinical trials were evaluated from the literature search. Three trials studied surrogate measures, kinetics or in vitro and were therefore excluded. Two trials evaluated tetracycline as part of H. pylori eradication treatment, which is outside the scope of this review, and were therefore excluded. One trial was for parenteral therapy, which is outside the scope of this review, was also excluded. One non-controlled trials was excluded. The remaining trials are briefly described in the table below.
Full abstracts are included in Appendix 2.

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Analysis of clinical results of systemic antimicrobials combined with nonsurgical periodontal treatment for generalized aggressive periodontitis: a pilot study.[9]	Full-mouth scaling and root planing (FRP) alone vs. A. FRP + metronidazole 250 mg and amoxicillin 250 mg three times daily for 10 days B. FRP + doxycycline 200 mg day one and 100 mg days 2-14	18-40 years old, 20 or more teeth, clinical attachment loss and probing pocket depth of 6mm or greater at 2 or more sites in 12 or more teeth.	Changes in periodontal index values at 2 months.	PPD and CAL in the FRP + metronidazole/amoxicillin was significantly less than the other two group. PPD and CAL in the FRP + doxycycline group was significantly less than FRP alone.
Subjective Symptoms after treatment of early Lyme disease.[10]	Doxycycline 100 mg twice daily for 15 days vs. cefuroxime axetil 500 mg twice daily	Patients 15 years or older with either typical solitary erythema migrans or skin lesions less than 5cm in diameter with a recent tick bite. Exclusion: previous lyme disease, pregnant, lactating, immunocompromised, meningitis, recent antibiotic, multiple erythema migrans lesions, or allergic to either medication	Complete response at 2,6, and 12 months	No significant difference in response rates at any time interval.

Appendix 2: Abstracts of Clinical Trials

Title:
Analysis of clinical results of systemic antimicrobials combined with nonsurgical periodontal treatment for generalized aggressive periodontitis: a pilot study
OBJECTIVE:
To assess the clinical benefit of either metronidazole and amoxicillin or doxycycline administered immediately after completion of full-mouth scaling and root planing (FRP) for treatment of generalized aggressive periodontitis.
METHODS:
Patients, 18 to 40 years of age, referred to the Karadeniz Technical University department of periodontology between January 2009 and September 2009 were randomly chosen for inclusion in the study if radiographic examination showed they had > 20 teeth, clinical attachment loss and a probing pocket depth (PPD) > 6 mm at 2 sites in > 12 teeth, > 3 of which were not first molars or incisors. Patients were divided into 3 groups and received FRP alone, FRP combined with metronidazole and amoxicillin, or FRP combined with doxycycline. PPD, clinical attachment level, gingival index, gingival bleeding index and plaque index values were measured at baseline and 2 months after treatment.
RESULTS:
Thirty-eight patients with untreated generalized aggressive periodontitis participated in the study. In all 3 groups, the periodontal index values 2 months after treatment were significantly lower than baseline values ($p < 0.05$). Values for PPD and clinical attachment level were more improved in the antibiotic groups than in the FRP group, and more improved in the metronidazole and amoxicillin group than in the doxycycline group ($p < 0.05$). However, no statistically significant intergroup difference was observed in the other clinical parameters ($p > 0.05$). Systemic use of metronidazole and amoxicillin or doxycycline was clinically superior to FRP for reducing PPDs > 7 mm ($p < 0.05$).
CONCLUSION:
Treatment of generalized aggressive periodontitis with FRP alone or FRP combined with systemic antibiotics provided significant clinical benefits that reduced the need for periodontal surgery. Both antibiotic treatments had additional clinical benefits over those of FRP alone

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Title:
Subjective Symptoms after treatment of early Lyme disease
BACKGROUND:
Controversy exists over the significance and even the existence of post-Lyme disease symptoms because of the high rate of similar background symptoms in the general population.
METHODS:
A European, prospective clinical trial in which doxycycline and cefuroxime axetil were compared in the treatment of adult patients with erythema migrans included a control group to address this question. Evaluations of patients were conducted at baseline, 14 days, and 2, 6, and 12 months after enrollment. Control subjects were evaluated at baseline and at 6 and 12 months. Subjective symptoms that newly developed or intensified since the onset of erythema migrans or the date of enrollment for controls were referred to as "new or increased symptoms."
RESULTS:
Doxycycline and cefuroxime axetil had comparable efficacy. At both 6 and 12 months, the frequency of new or increased symptoms in patients with erythema migrans did not exceed the frequency of such symptoms in a control group of individuals of similar gender and age without a clinical history of Lyme disease. At 12 months after enrollment, only 5 (2.2%) of 230 evaluable patients reported new or increased symptoms, and in none of the patients were these symptoms of sufficient severity to be functionally disabling.

CONCLUSION:
No significant differences were identified between doxycycline and cefuroxime axetil in the treatment of European patients with erythema migrans. The frequency of nonspecific symptoms in patients did not exceed that of a control group at > or =6 months after enrollment. We advocate inclusion of appropriate non-Lyme disease control groups in future studies in which nonspecific subjective symptoms are assessed after antibiotic therapy

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 3 2015
1. Demeclocycline/
2. Doxycycline/
3. Minocycline/
4. Tetracycline/
5. 1 or 2 or 3 or 4
6. limit 5 to (humans and yr="2010 -Current" and controlled clinical trial)

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project – Literature Scan Summary

Month/Year of Review: January 2015
PDL Class: Second-generation Antihistamines

Date of Last Review: January 2013
Source Document: DERP Scan Reports

Current Status of PDL Class:
See **Appendix 1**.

Conclusions and Recommendations:

- Comparative systematic reviews and trials have found insufficient evidence to support superior efficacy/effectiveness or harms of any single second-generation antihistamine.
- No further review or research needed at this time. Only minor administrative edits to the current PA criteria are needed (see **Appendix 2**). Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:

- There is insufficient evidence for differences in efficacy/effectiveness or harms between newer antihistamines. Prior Authorization (PA) criteria are currently in place to assure use of these drugs are for conditions funded by the OHP, or in situations where conditions funded by the OHP are complicated by allergic rhinitis or urticaria (see **Appendix 2**).

Research Questions:

- For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?
- For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in harms?
- Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), co-morbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer harms?

Methods:
The Drug Effectiveness Review Program (DERP) has published two literature scans since the P&T committee last reviewed this drug class in January 2013.[1,2] The 2015 scan is available for P&T review and contains all pertinent evidence identified in the 2014 scan. These scans were used to identify any new comparative research of oral second-generation antihistamines. Randomized controlled trials (RCTs), controlled clinical trials and systematic reviews were used to assess efficacy and effectiveness outcomes. Controlled clinical trials, RCTs, pre- and post-studies, and observational studies were used to assess harms outcomes.

Summary:
No systematic reviews evaluating antihistamines for either allergic rhinitis or urticarial were identified. However, an evidence-based practice center systematic review protocol on the treatments for seasonal allergic rhinitis sponsored by the Agency for Healthcare Research and Quality (AHRQ) was identified. No differences in the efficacy or safety with the second-generation oral antihistamines were noted. The choice of which second-generation antihistamine to use should therefore be influenced by cost, insurance coverage, and drug interactions. The optimal treatment of seasonal allergic rhinitis during pregnancy is unknown. The risk of congenital malformation is greatest during organogenesis in the first trimester. If medication cannot be avoided during this time, intranasal treatments with minimal systemic effects, such as intranasal cromolyn (pregnancy category B) and nasal saline, are preferred. Pregnancy category B oral second-generation antihistamines that may be considered for use after the first trimester include loratadine, cetirizine, and

levocetirizine. Children with occasional symptoms may be treated with antihistamines on days when symptoms are present or expected. The second-generation antihistamines loratadine, desloratadine, and cetirizine are approved by the FDA for use in children older than 2 years of age.

From the DERP scans, four head-to-head studies directly comparing two oral second-generation antihistamines were identified (levocetirizine vs. cetirizine and desloratidine for allergic rhinitis and two studies of levocetirizine vs. desloratidine for utricaria).

No new oral antihistamines were identified.

No new serious harms with oral antihistamines were identified.

References:

1. Holzhammer B and Selph S. Drug Class Review on Newer Antihistamines, Preliminary Scan Report #3, February 2015. Drug Effectiveness Review Project. Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University.
2. Thakurta S. Drug Class Review on Newer Antihistamines, Preliminary Scan Report #2, January 2014. Drug Effectiveness Review Project. Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University.

Appendix 1. Current Status of PDL Class.

Route	FormDesc	Brand	Generic	PDL
ORAL	TABLET	ALL DAY ALLERGY	CETIRIZINE HCL	Y
ORAL	TABLET	ALL DAY ALLERGY RELIEF	CETIRIZINE HCL	Y
ORAL	TABLET	ALLERGY	CETIRIZINE HCL	Y
ORAL	TABLET	ALLERGY RELIEF	CETIRIZINE HCL	Y
ORAL	TABLET	ALLER-TEC	CETIRIZINE HCL	Y
ORAL	TABLET	CETIRIZINE HCL	CETIRIZINE HCL	Y
ORAL	TABLET	WAL-ZYR	CETIRIZINE HCL	Y
ORAL	TABLET	ZYRTEC	CETIRIZINE HCL	Y
ORAL	SOLUTION	ALL DAY ALLERGY	CETIRIZINE HCL	Y
ORAL	SOLUTION	CETIRIZINE HCL	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S ALL DAY ALLERGY	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S ALLERGY	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S ALLERGY COMPLETE	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S ALLERGY RELIEF	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S ALLER-TEC	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S CETIRIZINE HCL	CETIRIZINE HCL	Y
ORAL	SOLUTION	CHILDREN'S WAL-ZYR	CETIRIZINE HCL	Y
ORAL	SOLUTION	WAL-ZYR	CETIRIZINE HCL	Y
ORAL	SOLUTION	ALLERGY RELIEF	LORATADINE	Y
ORAL	SOLUTION	CHILDREN'S ALLERGY RELIEF	LORATADINE	Y
ORAL	SOLUTION	CHILDREN'S CLARITIN	LORATADINE	Y
ORAL	SOLUTION	CHILDREN'S LORATADINE	LORATADINE	Y
ORAL	SOLUTION	CLARITIN	LORATADINE	Y
ORAL	SOLUTION	LORATADINE	LORATADINE	Y
ORAL	SOLUTION	LORATADINE ALLERGY	LORATADINE	Y
ORAL	SOLUTION	LORATADINE HIVES RELIEF	LORATADINE	Y
ORAL	SOLUTION	WAL-ITIN	LORATADINE	Y
ORAL	TABLET	ALLERCLEAR	LORATADINE	Y
ORAL	TABLET	ALLERGY	LORATADINE	Y
ORAL	TABLET	ALLERGY RELIEF	LORATADINE	Y
ORAL	TABLET	CLARITIN	LORATADINE	Y
ORAL	TABLET	LORADAMED	LORATADINE	Y
ORAL	TABLET	LORATADINE	LORATADINE	Y
ORAL	TABLET	NON-DROWSY ALLERGY	LORATADINE	Y
ORAL	TABLET	VICKS QLEARQUIL ALLERGY	LORATADINE	Y
ORAL	TABLET	WAL-ITIN	LORATADINE	Y
ORAL	TAB RAPDIS	ALAVERT	LORATADINE	Y
ORAL	TAB RAPDIS	ALLERGY RELIEF	LORATADINE	Y
ORAL	TAB RAPDIS	CLARITIN	LORATADINE	Y
ORAL	TAB RAPDIS	LORATADINE	LORATADINE	Y
ORAL	TAB RAPDIS	WAL-ITIN	LORATADINE	Y
ORAL	TAB CHEW	CHILDREN'S CLARITIN	LORATADINE	N
ORAL	TAB RAPDIS	CLARITIN	LORATADINE	N
ORAL	CAPSULE	CLARITIN	LORATADINE	N
ORAL	TABLET	ALLEGRA ALLERGY	FEXOFENADINE HCL	N
ORAL	TABLET	ALLER-EASE	FEXOFENADINE HCL	N
ORAL	TABLET	ALLERGY RELIEF	FEXOFENADINE HCL	N
ORAL	TABLET	FEXOFENADINE HCL	FEXOFENADINE HCL	N
ORAL	TABLET	WAL-FEX ALLERGY	FEXOFENADINE HCL	N
ORAL	TABLET	ALLEGRA ALLERGY	FEXOFENADINE HCL	N
ORAL	TABLET	ALLER-EASE	FEXOFENADINE HCL	N

ORAL	TABLET	ALLER-FEX	FEXOFENADINE HCL	N
ORAL	TABLET	ALLERGY RELIEF	FEXOFENADINE HCL	N
ORAL	TABLET	FEXOFENADINE HCL	FEXOFENADINE HCL	N
ORAL	TABLET	MUCINEX ALLERGY	FEXOFENADINE HCL	N
ORAL	TABLET	WAL-FEX ALLERGY	FEXOFENADINE HCL	N
ORAL	TABLET	CHILDREN'S ALLEGRA ALLERGY	FEXOFENADINE HCL	N
ORAL	ORAL SUSP	CHILDREN'S ALLEGRA ALLERGY	FEXOFENADINE HCL	N
ORAL	ORAL SUSP	CHILDREN'S ALLERGY RELIEF	FEXOFENADINE HCL	N
ORAL	ORAL SUSP	FEXOFENADINE HCL	FEXOFENADINE HCL	N
ORAL	TAB RAPDIS	CHILDREN'S ALLEGRA ALLERGY	FEXOFENADINE HCL	N
ORAL	TABLET	CLARINEX	DESLORATADINE	N
ORAL	TABLET	DESLORATADINE	DESLORATADINE	N
ORAL	TAB RAPDIS	DESLORATADINE	DESLORATADINE	N
ORAL	SYRUP	CLARINEX	DESLORATADINE	N
ORAL	TABLET	LEVOCETIRIZINE DIHYDROCHLORIDE	LEVOCETIRIZINE DIHYDROCHLORIDE	N
ORAL	TABLET	XYZAL	LEVOCETIRIZINE DIHYDROCHLORIDE	N
ORAL	SOLUTION	LEVOCETIRIZINE DIHYDROCHLORIDE	LEVOCETIRIZINE DIHYDROCHLORIDE	N
ORAL	SOLUTION	XYZAL	LEVOCETIRIZINE DIHYDROCHLORIDE	N

Appendix 2. Current Prior Authorization Criteria.

Antihistamines

Goal(s):

- Approve antihistamines only for conditions funded by the OHP.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. asthma, sleep apnea).
- Promote use that is consistent with Oregon Asthma Guidelines and medical evidence. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx

Length of Authorization:

6 months

Requires PA:

- Non-preferred oral antihistamines and combinations

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Will the prescriber 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 Health Resource Commission (HRC).	Yes: Inform provider of covered alternatives in class.	No: Go to #3.
3. Does client have diagnosis of allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharyngitis? (372.14, 472.x, 477.x)	Yes: Go to #4.	No: Go to #8.
4. Does the client have asthma or reactive airway disease exacerbated by chronic/allergic rhinitis or allergies (493.xx)?	Yes: Go to #5.	No: Go to #6.

Approval Criteria		
5. Does the drug profile show an asthma controller medication (e.g. ORAL inhaled corticosteroid, leukotriene antagonist, etc.) and/or inhaled rescue beta-agonist (e.g. albuterol) within the last 6 months? *Keep in mind: albuterol may not need to be used as often if asthma is controlled on other medications.*	Yes: Approve for 6 months.	No: Pass to RPH; Deny, (Medical Appropriateness) *Oregon Asthma guidelines recommend all asthma clients have access to rescue inhalers and those with persistent disease should use anti-inflammatory medicines daily (preferably orally inhaled corticosteroids).*
6. Does client have other co-morbid conditions or complications that are above the line? • Acute or chronic inflammation of the orbit (376.00-376.10) • Chronic Sinusitis (473.xx) • Acute Sinusitis (461.xx) • Sleep apnea (327.20,327.21,327.23, 327.27, 327.29, 780.51, 780.53, 780.57) • Wegener's Granulomatosis (446.4)	Yes: Document ICD-9 codes and Go to #7.	No: Pass to RPH; Deny, (Not Covered by the OHP).
7. Does client have contraindications (e.g. Pregnant), or had insufficient response to available alternatives? Document.	Yes, Approve 6 months.	No: Pass to RPH; Deny, (Cost-Effectiveness).
8. Is the diagnosis COPD (496) or Obstructive Chronic Bronchitis (491.20-491.22)?	Yes: Pass to RPH; Deny, (Medical Appropriateness). Antihistamine not indicated.	No: Go to #9.
9. Is the diagnosis Chronic Bronchitis (491.0, 491.1, 491.8, 491.9)?	Yes: Pass to RPH; Deny, (Not Covered by the OHP).	No: Pass to RPH; Go to #10.
10. RPH only: Is the diagnosis above the line or below the line? • Above: Deny, Medical Appropriateness • Below: Deny, Not Covered by the OHP (e.g., acute upper respiratory infections (465.9) or urticaria (708.0, 708.1. 708.5, 708.8, and 708.9 should be denied).		

P&T / DUR Action: *5/15 (AG), 9/10, 9/08, 2/06, 9/04, 5/04, 2/02*
Last Revision(s): *1/11, 7/09, 7/06, 3/06, 10/04, 8/02, 9/06*
Initiation:

Author: A Gibler, Pharm.D. Date: May 2015

Drug Class Review

Newer Antihistamines

Preliminary Scan Report #3

February 2015

Last Report: Update #2, May 2010

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:
Brittany Holzhammer, MPH
Shelley Selph, MD, MPH

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 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 #2, May 2010 (searches through December 2009)

Dates of Previous Scan Reports

Scan #1: November 2012
Scan #2: January 2014

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. The Participating Organizations of Drug Effectiveness Review Project 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. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?

2. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in harms?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), co-morbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer harms?

Inclusion Criteria

Populations

- Adult or pediatric outpatients with the following conditions:
  - Seasonal allergic rhinitis
  - Perennial allergic rhinitis
  - Urticaria (acute and chronic)
- Subgroups of interest included, but were not limited to, different races, ages (older adult compared with younger adult), concomitant use of other medications (in consideration of drug-drug interactions), persons with various comorbidities (pregnancy and consideration of drug-disease interactions), and sex.

Interventions

Table 1. Included drugs and their labeled indications

Drug	Trade name(s)	Labeled indications	Dosage form/Route
Cetirizine hydrochloride	Zyrtec®	SAR; PAR; Chronic Urticaria	Syrup/Oral
Loratadine	Claritin®	SAR; PAR; Chronic Urticaria	Tablet; ODT; Syrup; Capsule/Oral
Fexofenadine hydrochloride	Allegra®	SAR; PAR; Chronic Urticaria	Tablet; ODT; Suspension; Capsule/Oral
Desloratadine	Clarinex®	SAR; PAR; Chronic Urticaria	Tablet; ODT; Syrup/Oral
Levocetirizine	Xyzal®	SAR; PAR; Chronic Urticaria	Tablet; Solution/Oral
Azelastine	Astelin®	SAR	Spray; Metered/Nasal
	Astepro®	SAR; PAR	Spray; Metered/Nasal
Olopatadine	Patanase®	SAR	Spray; Metered/Nasal

Abbreviations: ODT, orally disintegrating tablet; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.

Study designs (from previous update report)

1. Efficacy and effectiveness
   a. Randomized controlled trials, controlled clinical trials, and systematic reviews of fair or better quality.
   b. Direct comparisons (head-to-head studies) were preferred over indirect comparisons using active or placebo-controlled trials. Inclusion of indirect evidence will be considered where there is insufficient direct evidence.
   c. Studies ≥1 week in duration were included.
   d. Studies conducted in artificial study settings (for example, antigen exposure chambers) were not be included. Abstracts and conference proceedings are also excluded.

2. Harms
   a. Randomized controlled trials, controlled clinical trials, pre-compared with post-design studies, and observational studies with comparative groups.

b. To be included, reports about overall harms or adverse events had to report total withdrawals, withdrawals due to specific adverse events (for example, central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention, etc.), or the frequency and severity of these specific adverse events.

Outcomes

- Efficacy and effectiveness
  - Symptoms (nasal congestion, rhinorrhea, sneezing, itching and pain from skin irritations)
  - Functional capacity (physical, social and occupational functioning, quality of life)
  - Time to relief of symptoms (time to onset, duration of relief)
  - Duration of effectiveness (switch rate)
- Harms
  - Total withdrawals
  - Withdrawals due to adverse events
  - Serious adverse events or withdrawals due to specific adverse events (central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention)

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from January 2014 through January 2015 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for identification of new drugs, new populations, and new serious harms. To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. 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 - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials, controlled clinical trials, and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
Dymista™ (azelastine hydrochloride and fluticasone propionate) was approved in May 2012 for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

New Serious Harms

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
None.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan
The Agency for Healthcare Research and Quality comparative effectiveness review identified in the previous scan was published on July 16, 2013. The review, entitled "Treatments for Seasonal Allergic Rhinitis" is potentially relevant, but would not stand in place of a DERP review because it does not include perennial allergic rhinitis or urticaria. The executive summary for this review can be found at the following link:
http://www.effectivehealthcare.ahrq.gov/ehc/products/376/1587/allergy-seasonal-executive-130711.pdf

No other new comparative effectiveness reviews were identified that would stand in place of a DERP review.

Identified in previous Preliminary Update Scan(s)
We identified a protocol of a potentially relevant comparative effectiveness review produced by the Agency for Healthcare Research and Quality Effective Health Care Program. See Appendix A for the key questions that describe the scope of the project.

Treatments for Seasonal Allergic Rhinitis, published online March 8, 2012
http://effectivehealthcare.ahrq.gov/ehc/products/376/1000/SAR_Protocol_20120308.pdf

Randomized Controlled Trials

Trials identified since the most recent Full Report
Medline searches for this scan resulted in 21 citations. Of these, 1 is a potentially relevant new head-to-head trial. This trial compared the effectiveness and safety of olopatadine, a newer

antihistamine, in treating chronic urticaria in comparison to the established second generation antihistamine levocetirizine.

Together with trials found in previous scans, we have identified a total of 26 potentially relevant new trials since the last update report (8 head-to-head and 18 placebo-controlled trials). Table 1 summarizes the populations and comparisons included in these studies. The majority of the head-to-head evidence pertains to levocetirizine in populations with allergic rhinitis or urticaria. The majority of the placebo-controlled trial evidence pertains to azelastine in populations with seasonal allergic rhinitis. Abstracts for head-to-head trials are provided in Appendix B. Abstracts for placebo-controlled trials are available upon request.

Table 2. Characteristics of potentially relevant head-to-head trials* (N=8)

Author, Year	N, Duration	Population	Comparison	Focus
Allergic Rhinitis				
Tzanetos, 2011	30, 1 week	Patients with perennial allergic rhinitis	Cetirizine vs. Levocetirizine	Sedation
Ciebiada, 2011	40, 32 weeks	Adults with allergic rhinitis	Desloratadine vs. Levocetirizine	Symptom relief and score
LaForce, 2010	NR, 14 days	Patients ≥12 years of age with seasonal allergic rhinitis	Olopatadine vs. Azelastine	Symptom relief and scores, harms
Urticaria				
Hong, 2010 (no abstract)	NR	Chronic idiopathic urticaria	Desloratadine vs. Levocetirizine	NR
Staevska, 2010	80, NR	Adults with urticaria	Desloratadine vs. Levocetirizine	Symptom relief and scores, harms
Okubo, 2013	51, 13 days	Patients with urticaria	Olopatadine vs. Cetirizine	Wheal, itching, quality of life
Sil, 2013	120, 9 weeks	Adults with chronic urticaria	Olopatadine 5 mg vs. Levocetirizine 5 mg	Urticaria activity and severity scores and adverse events
Other				
Wang, 2013	174, 2 weeks	Chinese patients with cutaneous pruritus	Cetirizine vs. Olopatadine	Symptom score, harms

*Shading indicates studies found in the current scan.

Placebo-controlled trials (N=18)

Azelastine

- Hampel, 2010 (seasonal allergic rhinitis)
- Howland, 2011 (seasonal allergic rhinitis)
- Meltzer, 2012 (seasonal allergic rhinitis)
- Meltzer, 2013 (***post-hoc***; seasonal allergic rhinitis)
- Shah, 2009 (seasonal allergic rhinitis)
- Van Bavel, 2009 (seasonal allergic rhinitis)

Desloratadine

- Bousquet, 2009 (intermittent allergic rhinitis)

- Bousquet, 2010 (persistent allergic rhinitis)
- Bousquet, 2013 (persistent allergic rhinitis)
- Weller, 2013 (chronic urticaria)

Fexofenadine

- Mosges, 2009 (seasonal allergic rhinitis)

Levocetirizine

- Hampel, 2009 (***2 studies***; chronic urticaria)
- Mansfield, 2010 (seasonal allergic rhinitis)
- Segall, 2010 (seasonal allergic rhinitis)

Olopatadine

- Berger, 2009 (children with allergic rhinitis)
- Okubo, 2010 (children with perennial allergic rhinitis)
- Yamamoto, 2010 (seasonal allergic rhinitis)

SUMMARY

No new drugs were identified in the present scan. One new drug, the azelastine hydrochloride and fluticasone propionate combination product Dymista™, has been identified since the most recent update report. No new serious harms have been identified since the last update report. One new comparative effectiveness review for which the protocol was identified in the previous scan has since been published. However, it would not stand in place of a DERP review on newer antihistamines because it pertains only to seasonal allergic rhinitis (not perennial allergic rhinitis or urticaria). No other potentially relevant new comparative effectiveness reviews have been identified since the last update report.

We have identified 26 new trials of newer antihistamines since the last update report (8 head-to-head trials and 18 placebo-controlled trials). One new head-to-head trial studying the effects of olopatadine versus levocetirizine on activity and severity scores and adverse events in adults with chronic urticaria was identified in the present scan.

APPENDIX A. SYSTEMATIC REVIEW PRODUCED BY THE EFFECTIVE HEALTH CARE PROGRAM

Treatments for Seasonal Allergic Rhinitis

The Key Questions

Question 1

What is the comparative effectiveness of pharmacologic treatments, alone or in combination with each other, for adults and adolescents (≥12 years of age) with mild or with moderate/severe seasonal allergic rhinitis (SAR)?

1. How does effectiveness vary with long-term (months) or short-term (weeks) use?
2. How does effectiveness vary with intermittent or continuous use?
3. For those with symptoms of allergic conjunctivitis, does pharmacologic treatment of SAR provide relief of eye symptoms (itching, tearing)?
4. For those codiagnosed with asthma, does pharmacologic treatment of SAR provide asthma symptom relief?

Question 2

What are the comparative adverse effects of pharmacologic treatments for SAR for adults and adolescents (≥12 years of age)?

1. How do adverse effects vary with long-term (months) and short-term (weeks) use?
2. How do adverse effects vary with intermittent or continuous use?

Question 3

For the subpopulation of pregnant women, what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

1. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
2. How do effectiveness and adverse effects vary with intermittent or continuous use?

Question 4

For the subpopulation of children (<12 years of age), what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

1. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
2. How do effectiveness and adverse effects vary with intermittent or continuous use?

APPENDIX B. ABSTRACTS OF POTENTIALLY RELEVANT NEW HEAD-TO-HEAD TRIALS OF NEWER ANTIHISTAMINES (N=8)

*Shading indicates trials identified in the current scan

Ciebiada, M., M. Gorska-Ciebiada, et al. (2011). "Use of montelukast alone or in combination with desloratadine or levocetirizine in patients with persistent allergic rhinitis." American Journal of Rhinology & Allergy **25**(1): e1-6.

BACKGROUND: We assessed the course of treatment in patients with persistent allergic rhinitis (AR) treated with montelukast, levocetirizine, or desloratadine alone or combinations of antihistamine and montelukast.

METHODS: A 32-week randomized, double-blind, placebo-controlled, crossover, double-armed study in 40 adult patients with history of persistent AR, clinical allergy to house-dust mites, and a total nasal symptom score of at least 5 (congestion of at least 2) has been performed. Patients with asthma, chronic obstructive pulmonary disease, nonallergic rhinitis with clinical allergy associated with seasonal allergens, and other serious diseases were excluded. There were four 6-week treatment periods separated by 2-week washout periods. Twenty patients received either montelukast or antihistamine, a combination of montelukast and antihistamine, or placebo. The sequence of treatment was randomly assigned. Nasal symptoms were assessed using a 4-point scale at baseline, daily during the 1st week and on days 14, 21, 28, 35, and 42 of treatment.

RESULTS: Montelukast alone, levocetirizine alone, desloratadine alone, and the montelukast/antihistamine combinations significantly improved nasal symptoms during the first 24 hours. Improvement gradually increased during the 6 weeks of treatment, especially in patients receiving montelukast alone or in combination therapy with the antihistamine in both arms. Improvement at 42 days of treatment was significantly greater than that achieved on the 1st day of therapy in patients treated with the combination of montelukast and levocetirizine.

CONCLUSION: Montelukast alone or in combination with antihistamines gave a gradual increase in nasal symptom improvement within 6 weeks of treatment in patients with persistent AR.

Hong, J.-B., H.-C. Lee, et al. (2010). "A randomized, double-blind, active-controlled, parallel-group pilot study to compare the efficacy and sedative effects of desloratadine 5 mg with levocetirizine 5 mg in the treatment of chronic idiopathic urticaria." Journal of the American Academy of Dermatology **63**(5): e100-102.

LaForce, C. F., W. Carr, et al. (2010). "Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis." Allergy & Asthma Proceedings **31**(2): 132-140.

The combination of intranasal antihistamines and intranasal corticosteroids results in superior relief of seasonal allergic rhinitis (SAR) symptoms compared with monotherapy. This study was designed to evaluate the safety and efficacy of olopatadine hydrochloride nasal spray, 0.6% (OLO), administered in combination with fluticasone nasal spray, 50 micrograms (FNS), relative to azelastine nasal spray, 0.1% (AZE), administered in combination with FNS in the treatment of SAR. This was a multicenter, double-blind,

randomized, parallel-group comparison of OLO + FNS versus AZE + FNS administered for 14 days to patients > or =12 years of age with histories of SAR. Efficacy assessments recorded by patients in a daily diary included nasal symptom scores. Safety was evaluated based on adverse events (AEs). Pretreatment values for reflective total nasal symptoms scores (rTNSS) were similar for both treatment groups. The mean (SD) 2-week average rTNSS was 4.28 (2.63) for OLO + FNS and 4.15 (2.63) for AZE + FNS; these scores were not statistically different between treatment groups. No significant differences ($p > 0.05$) between OLO + FNS and AZE + FNS were observed for the average 2-week percent changes from baseline in rTNSS or in the individual nasal symptoms (nasal congestion, rhinorrhea, itchy nose, and sneezing). Compared with baseline, both groups had statistically significant improvement in rTNSS ($p < 0.05$). No serious AEs were reported in either group during the study period. Overall, 19 AEs were reported in the OLO + FNS group and 29 AEs were reported in the AZE + FNS group. OLO, when administered adjunctively with FNS, is effective, safe, and well-tolerated in patients with SAR.

Okubo, Y., Y. Shigoka, et al. (2013). "Double dose of cetirizine hydrochloride is effective for patients with urticaria resistant: a prospective, randomized, non-blinded, comparative clinical study and assessment of quality of life." Journal of Dermatological Treatment **24**(2): 153-160.

OBJECTIVE: An increased dose of the prescribed drug or a change of the drug is recommended in the treatment for the patients with urticaria refractory to the standard dose of antihistamines. Efficacy and safety of doubling the dose of cetirizine were compared with olopatadine in the patients with symptoms like wheal or itching, despite the treatment with the standard dose of cetirizine.

METHODS: Cetirizine was administered at 10 mg once daily to 51 patients with urticaria for a mean of 10.1 + 7.3 days (period A). Patients with inadequate responses were randomized to either cetirizine 20 mg once daily (dose-increase group) or olopatadine 5 mg twice daily (drug-change group) for a mean of 13.3 + 8.3 days (Period B). The severity of wheal and itching, and the quality of life (QOL) measured by Skindex-16 were evaluated.

RESULTS: In period A, an adequate response was obtained in 64.7% (33/51). Nine patients each with inadequate response were randomized to either the drug-change or dose-increase groups. A significant improvement was observed in the severity of wheal and itching in the dose-increase group in period B. The QOL was significantly improved in all sub-scales of Skindex-16.

CONCLUSION: Doubling the dose of cetirizine may be efficacious to the patients with urticaria refractory to the regular dose of cetirizine.

Sil, A., et al. (2013). "Olopatadine versus levocetirizine in chronic urticaria: an observer-blind, randomized, controlled trial of effectiveness and safety." Journal of Dermatological Treatment **24**(6): 466-472.

OBJECTIVES: Chronic urticaria (CU) is characterized by frequent appearance of wheals for > 6 weeks. This study was undertaken to compare effectiveness and safety of olopatadine, a newer antihistamine with additional anti-inflammatory properties, in treating CU in comparison to the established second-generation antihistamine levocetirizine.

METHODS: A single center, assessor-blind, randomized (1:1), active-controlled, parallel group, Phase IV trial (CTRI/2011/08/001965) was conducted with 120 adult CU patients of

either sex. Subjects received either olopatadine (5 mg b.i.d.) or levocetirizine (5 mg/day) for 9 weeks, continuously for first 4 weeks and then on demand basis for last 5 weeks. Primary outcome measures were urticaria activity score (UAS) and urticaria total severity score (TSS). Routine hematological and biochemical tests and treatment-emergent adverse events were monitored for safety.

RESULTS: Data from 54 subjects on olopatadine and 51 on levocetirizine were analyzed for effectiveness. UAS and TSS values declined significantly with both drugs over the treatment period but the reduction was greater with olopatadine. Adverse event profiles were comparable with sedation being the commonest complaint.

CONCLUSIONS: Olopatadine is a safe and more effective alternative to levocetirizine in the treatment of CU.

Staevska, M., T. A. Popov, et al. (2010). "The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria." Journal of Allergy & Clinical Immunology **125**(3): 676-682.

BACKGROUND: H(1)-antihistamines are first line treatment of chronic urticaria, but many patients do not get satisfactory relief with recommended doses. European guidelines recommend increased antihistamine doses of up to 4-fold.

OBJECTIVE: To provide supportive evidence for the European guidelines.

METHODS: Eighty tertiary referral patients with chronic urticaria (age range, 19-67 years) were randomized for double-blind treatment with levocetirizine or desloratadine (40/40). Treatment started at the conventional daily dose of 5 mg and then increased weekly to 10 mg, 20 mg, or 20 mg of the opposite drug if relief of symptoms was incomplete. Wheal and pruritus scores, quality of life, patient discomfort, somnolence, and safety were assessed.

RESULTS: Thirteen patients became symptom-free at 5 mg (9 levocetirizine vs 4 desloratadine), compared with 28 subjects on the higher doses of 10 mg (8/7) and 20 mg (5/1). Of the 28 patients nonresponsive to 20 mg desloratadine, 7 became symptom-free with 20 mg levocetirizine. None of the 18 levocetirizine nonresponders benefited with 20 mg desloratadine. Increasing antihistamine doses improved quality of life but did not increase somnolence. Analysis of the effect of treatment on discomfort caused by urticaria showed great individual heterogeneity of antihistamine responsiveness: approximately 15% of patients were good responders, approximately 10% were nonresponders, and approximately 75% were responders to higher than conventional antihistamine doses. No serious or severe adverse effects warranting discontinuation of treatment occurred with either drug.

CONCLUSION: Increasing the dosage of levocetirizine and desloratadine up to 4-fold improves chronic urticaria symptoms without compromising safety in approximately three quarters of patients with difficult-to-treat chronic urticaria.

Tzanetos, D. B., J. M. Fahrenholz, et al. (2011). "Comparison of the sedating effects of levocetirizine and cetirizine: a randomized, double-blind, placebo-controlled trial." Annals of Allergy, Asthma, & Immunology **107**(6): 517-522.

BACKGROUND: Compared with placebo, levocetirizine has been found to be less sedating than cetirizine in separate trials. However, whether levocetirizine is less sedating than its parent drug cetirizine has not yet been studied in a randomized trial.

OBJECTIVE: To determine whether levocetirizine is less sedating than cetirizine.
METHODS: We conducted a randomized, double-blind, crossover, placebo-controlled trial examining sedation and allergy symptoms in patients with perennial allergic rhinitis who had previously reported significant sedation with cetirizine. Enrollment ran from January 28, 2009, to February 25, 2009. All patients completed the study by April 17, 2009. Thirty patients enrolled, and 29 patients completed the study (1 patient did not return her questionnaire). In a double-blind fashion, the 29 study participants received levocetirizine, 5 mg daily for 1 week, cetirizine, 10 mg daily for 1 week, and an equivalent placebo pill for 1 week in randomized order with washout periods before each treatment arm. At the end of each washout period and each treatment period, participants completed a 1-page questionnaire. This questionnaire included questions about sedation or sleepiness in the form of a modified Epworth Sleepiness Scale, a Likert scale measuring general or global sedation, and allergy symptoms as measured by the total rhinitis symptom score.
RESULTS: Sedation as measured by both the modified Epworth Sleepiness Scale and the Likert scale was not significantly different between the levocetirizine and cetirizine treatments.
CONCLUSIONS: In patients with a perceived history of sedation with cetirizine, most were able to tolerate levocetirizine. However, this controlled trial also suggests that many of these patients would tolerate cetirizine if given in a masked manner. Therefore, patients with a history of mild to moderate sedation with cetirizine are unlikely to experience a different sedation profile with levocetirizine.

Wang, T., Y. Liu, et al. (2013). "A multicenter, double-blind, randomized, noninferiority comparison of 14 days' treatment with oral olopatadine 10 mg or cetirizine 10 mg in Chinese adults with cutaneous pruritus." Pharmacology **91**(1-2): 117-122.
OBJECTIVES: To assess whether olopatadine hydrochloride (OH) was noninferior to cetirizine in the treatment of cutaneous pruritus (CP).
PATIENTS AND METHODS: Patients with CP presenting at seven centers in China were randomly allocated to double-blind treatment with 5 mg of OH orally twice a day or cetirizine 10 mg orally once a day for 2 weeks. Patients were followed up on days 7 and 14. Noninferiority was predefined as a 20% maximum difference in the reduction of symptom score reducing indices (SSRI). Both intention-to-treat (ITT) and per-protocol populations were analyzed.
RESULTS: 174 patients (86 receiving OH and 88 cetirizine) were included in the ITT population. In the ITT population, the mean reduction in SSRI was 0.640 + 0.274 in the OH group and 0.603 + 0.289 in the cetirizine group. The one-sided 97.5% CI (-0.047) met the criteria for noninferiority. Noninferiority was also demonstrated for SSRI in the per-protocol population, with reductions of 0.640 + 0.271 with OH and 0.596 + 0.287 with cetirizine (97.5% CI -0.043).The total effectiveness rate (TER) was similar in the OH (90.0%) and cetirizine (80.0%) groups. The corresponding one-sided 97.5% CI (-1.0%) also demonstrated noninferiority. The incidence of adverse events was 47.1% in the OH group and 41.4% in the cetirizine group (p = 0.453).
CONCLUSION: The efficacy of OH was noninferior to that of cetirizine in controlling itching indicating that it can be considered as a clinically relevant alternative therapy to cetirizine

for the management of CP in adult Chinese patients. Copyright 2013 S. Karger AG, Basel.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project – Literature Scan Summary

Date of Current Review: May 2015 **Date of Last Review:** January 2014
PDL Class: Beta-blockers

Current Status of PDL Class:
See **Appendix 1**.

Conclusions and Recommendations:

- There is no significant new comparative evidence supporting a difference in efficacy or harms between agents.
- Based on previous recommendations, at least one of the following drugs with evidence of effectiveness in moderate to severe chronic heart failure should be preferred on the PDL: carvedilol or metoprolol succinate.
- Based on previous recommendations, at least one of the following drugs with evidence of effectiveness in recent myocardial infarction should be preferred on the PDL: acebutolol, carvedilol, metoprolol tartrate, propranolol or timolol.
- Based on previous recommendations, at least one of the following drugs with evidence of effectiveness for reducing esophageal variceal bleeds should be preferred on the PDL: atenolol, nadolol, propranolol or propranolol extended-release.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:

- There is no significant new comparative evidence supporting a difference in efficacy or harms between agents.

Research Questions:

1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta-blocker drugs differ in effectiveness?
2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta-blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

Methods:
The DERP scan was used to identify any new comparative research that has emerged since the last P&T review.

Summary:
No new beta-blocker drugs, new indications, new formulations or new serious harms were identified in the literature scan. No new comparative high-quality systematic reviews have been performed. Since the original DERP report, published head-to-head studies identified in literature scans have typically involved carvedilol. Specifically, the three new head-to-head trials identified in this scan involved carvedilol in populations with heart failure. However, no new trials demonstrate evidence of differences between beta-blockers for the conditions studied.

References:

1. Holzhammer B, Peterson K. Drug Class Review on Beta Adrenergic Blockers, Preliminary Scan Report #3, February 2015. Drug Effectiveness Review Project. Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University.

Appendix 1: Current Status on Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	CAPSULE	ACEBUTOLOL HCL	ACEBUTOLOL HCL	Y
ORAL	CAPSULE	SECTRAL	ACEBUTOLOL HCL	Y
ORAL	TABLET	ATENOLOL	ATENOLOL	Y
ORAL	TABLET	TENORMIN	ATENOLOL	Y
ORAL	TABLET	CARVEDILOL	CARVEDILOL	Y
ORAL	TABLET	COREG	CARVEDILOL	Y
ORAL	TABLET	LABETALOL HCL	LABETALOL HCL	Y
ORAL	TABLET	TRANDATE	LABETALOL HCL	Y
ORAL	TABLET	LOPRESSOR	METOPROLOL TARTRATE	Y
ORAL	TABLET	METOPROLOL TARTRATE	METOPROLOL TARTRATE	Y
ORAL	TABLET	LOPRESSOR	METOPROLOL TARTRATE	Y
ORAL	TABLET	PROPRANOLOL HCL	PROPRANOLOL HCL	Y
ORAL	TABLET	BETAXOLOL HCL	BETAXOLOL HCL	N
ORAL	TABLET	KERLONE	BETAXOLOL HCL	N
ORAL	TABLET	BISOPROLOL FUMARATE	BISOPROLOL FUMARATE	N
ORAL	TABLET	ZEBETA	BISOPROLOL FUMARATE	N
ORAL	CPMP 24HR	COREG CR	CARVEDILOL PHOSPHATE	N
ORAL	TAB ER 24H	METOPROLOL SUCCINATE	METOPROLOL SUCCINATE	N
ORAL	TAB ER 24H	TOPROL XL	METOPROLOL SUCCINATE	N
ORAL	TABLET	CORGARD	NADOLOL	N
ORAL	TABLET	NADOLOL	NADOLOL	N
ORAL	TABLET	BYSTOLIC	NEBIVOLOL HCL	N
ORAL	TABLET	LEVATOL	PENBUTOLOL SULFATE	N
ORAL	TABLET	PINDOLOL	PINDOLOL	N
ORAL	CAP SA 24H	INDERAL LA	PROPRANOLOL HCL	N
ORAL	CAP SA 24H	PROPRANOLOL HCL ER	PROPRANOLOL HCL	N
ORAL	CAP SA 24H	INDERAL LA	PROPRANOLOL HCL	N
ORAL	SOLUTION	PROPRANOLOL HCL	PROPRANOLOL HCL	N
ORAL	CAP ER 24H	INDERAL XL	PROPRANOLOL HCL	N
ORAL	CAP ER 24H	INNOPRAN XL	PROPRANOLOL HCL	N
ORAL	SOLUTION	HEMANGEOL	PROPRANOLOL HCL	N
ORAL	TABLET	BETAPACE	SOTALOL HCL	N
ORAL	TABLET	BETAPACE AF	SOTALOL HCL	N
ORAL	TABLET	SORINE	SOTALOL HCL	N
ORAL	TABLET	SOTALOL AF	SOTALOL HCL	N
ORAL	TABLET	SOTALOL	SOTALOL HCL	N
ORAL	SOLUTION	SOTYLIZE	SOTALOL HCL	N
ORAL	TABLET	TIMOLOL MALEATE	TIMOLOL MALEATE	N
ORAL	TABLET	BLOCADREN	TIMOLOL MALEATE	N

2

Drug Class Review

Beta Adrenergic Blockers

Preliminary Scan Report #3

February 2015

Last Report: Update #4, July 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.

Scan conducted by:
Brittany Holzhammer, MPH
Kim Peterson, MS

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 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: July 2009 (searches through January 2009)

Dates of Previous Scan Reports

Scan #1: October 2010
Scan #2: October 2013

Scope and Key Questions

Key Questions

1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness?
2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices

Interventions

Interventions include an oral beta blocker compared with another beta blocker, another drug (such as calcium channel blocker), or placebo. (Oral beta blockers: acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, carvedilol phosphate, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol, pindolol, propranolol, propranolol LA, timolol)

Table 1. Effectiveness outcomes

Condition	Measured Outcomes
Hypertension	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance) 4. Quality-of-life
Chronic stable angina (treatment duration ≥ 2 months)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)
Recent myocardial infarction (with and without LV dysfunction)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Symptomatic chronic heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Asymptomatic LV dysfunction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Atrial arrhythmia	1. Rate control 2. Relapse into atrial fibrillation
Migraine	1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment
Bleeding esophageal varices	1. All-cause mortality 2. Fatal/non-fatal rebleeding

Harms

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events reported
- Specific adverse events

Study designs (from last update report)

1. For effectiveness, randomized controlled trials and good-quality systematic reviews
2. For harms, controlled clinical trials and observational studies

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from October 2013 through January 2015 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for identification of new drugs, new populations, and new serious harms. To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. 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 - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials, controlled clinical trials, and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
None.

New Serious Harms

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
None.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan

No new comparative effectiveness reviews were identified that would stand in place of a DERP review in terms of scope.

Identified in previous Preliminary Update Scan(s)

None.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches for this scan resulted in 126 citations. Of those, 3 potentially relevant new trials (Table 2) and 2 companion publications (Table 3) were identified; all of which were head-to-head in design. The 3 newly identified trials and 1 of the companion publications involved the use of carvedilol in populations with heart failure. The second companion publication involved the use of carvedilol in populations with permanent atrial fibrillation.

Together with the trials identified in previous scans, we have identified a total of 20 trials of beta adrenergic blockers (in 22 publications): 11 head-to-head trials (in 13 publications) and 9 placebo-controlled trials. The majority of the head-to-head evidence pertains to the use of carvedilol in populations with heart failure. Among the publications of placebo-controlled trials, all involved patients with heart failure and 7 of 9 provide results from subanalyses of previously included head-to-head trials (Table 2).

Study and population characteristics of primary head-to-head trials (Table 2) and companion head-to-head trials (Table 3) are provided below. Abstracts of head-to-head trials are provided in Appendix A. Abstracts of placebo-controlled trials are available upon request.

Table 2. Characteristics of primary head-to-head trials (N=11)

Author, Year Study Name	Beta Blockers	Population
Hypertension		
Espinola-Klein, 2011	Nebivolol vs metoprolol	Hypertension with intermittent claudication
Coronary Artery Bypass Grafting		
Iliuta, 2009	Betaxolol vs metoprolol	Coronary artery bypass grafting
Shahzamani, 2011	Carvedilol vs metoprolol	Coronary artery bypass grafting
Heart Failure		
Hori, 2014 MAIN-CHF II	Bisoprolol fumarate vs. carvedilol	Japanese patients with chronic heart failure
Lainscak, 2013 CIBIS-ELD	Bisoprolol vs. carvedilol	Elderly patients with heart failure
Jabbour, 2010	Carvedilol vs. metoprolol succinate vs. bisoprolol	Heart failure and chronic obstructive pulmonary disease
Udelson, 2009	Carvedilol vs. carvedilol phosphate	Heart failure
Marazzi, 2011	Carvedilol vs. nebivolol	Hypertensive heart failure
Contini, 2013 CARNEBI	Carvedilol vs. nebivolol vs. bisoprolol	Heart failure
Other Conditions		
Ulimoen, 2013	Carvedilol vs metoprolol	Permanent atrial fibrillation
Sen, 2009	Nebivolol vs metoprolol	Cardiac syndrome X

*Shading indicates trials or publications identified in the present scan

Table 3. Characteristics of companion head-to-head trials (N=2)

Author, Year Study Name	Beta Blockers	Population
Heart Failure		
Scherer, 2013 Sub-analysis of CIBIS-ELD	Bisoprolol vs. carvedilol	Elderly patients with heart failure
Other Conditions		
Ulimoen, 2014	Carvedilol vs. metoprolol	Permanent atrial fibrillation

*Shading indicates trials or publications identified in the present scan

Placebo-controlled trials (N=9)

Bisoprolol

- Hawkins, 2009 (heart failure and moderate to severe chronic obstructive pulmonary disease)
- Castagno, 2010 (companion to CIBIS-II; heart failure and renal impairment)

Metoprolol CR

- Ghali, 2009 (companion to MERIT-HF; heart failure and decreased renal function)

Nebivolol

- Ambrosio, 2011 (ischemic events)
- Cohen-Solal, 2009 (influence of renal dysfunction)
- de Boer, 2010 (influence of diabetes)
- Mulder, 2012 (influence of atrial fibrillation)
- van Veldhuisen, 2009 (influence of impaired and preserved left ventricular ejection fraction)

Propranolol

- Silberstein, 2012 (migraine)

SUMMARY

Since the last update report, we have identified no new drugs, no new serious harms, and no new comparative effectiveness reviews of beta adrenergic blockers. We have identified a total of 20 trials of beta adrenergic blockers (in 22 publications): 11 head-to-head trials (in 13 publications) and 9 placebo-controlled trials. The majority of the head-to-head evidence pertains to the use of carvedilol in populations with heart failure.

APPENDIX A. ABSTRACTS OF POTENTIALLY RELEVANT NEW HEAD-TO-HEAD TRIALS OF BETA ADRENERGIC BLOCKERS*

*Shading indicates studies identified in the current scan

Primary Studies (N=11)

Contini, M., et al. (2013). "Multiparametric comparison of CARvedilol, vs. NEbivolol, vs. BIsoprolol in moderate heart failure: the CARNEBI trial." International Journal of Cardiology **168**(3): 2134-2140.

BACKGROUND: Several beta-blockers, with different pharmacological characteristics, are available for heart failure (HF) treatment. We compared Carvedilol (beta1-beta2-alpha-blocker), Bisoprolol (beta1-blocker), and Nebivolol (beta1-blocker, NO-releasing activity).

METHODS: Sixty-one moderate HF patients completed a cross-over randomized trial, receiving, for 2 months each, Carvedilol, Nebivolol, Bisoprolol (25.6 +/- 12.6, 5.0 +/- 2.4 and 5.0 +/- 2.4 mg daily, respectively). At the end of each period, patients underwent: clinical evaluation, laboratory testing, echocardiography, spirometry (including total DLCO and membrane diffusion), O2/CO2 chemoreceptor sensitivity, constant workload, in normoxia and hypoxia (FiO2=16%), and maximal cardiopulmonary exercise test.

RESULTS: No significant differences were observed for clinical evaluation (NYHA classification, Minnesota questionnaire), laboratory findings (including kidney function and BNP), echocardiography, and lung mechanics. DLCO was lower on Carvedilol (18.3 +/- 4.8*mL/min/mmHg) compared to Nebivolol (19.9 +/- 5.1) and Bisoprolol (20.0 +/- 5.0) due to membrane diffusion 20% reduction (*=p<0.0001). Constant workload exercise showed in hypoxia a faster VO2 kinetic and a lower ventilation with Carvedilol. Peripheral and central sensitivity to CO2 was lower in Carvedilol while response to hypoxia was higher in Bisoprolol. Ventilation efficiency (VE/VCO2 slope) was 26.9 +/- 4.1* (Carvedilol), 28.8 +/- 4.0 (Nebivolol), and 29.0 +/- 4.4 (Bisoprolol). Peak VO2 was 15.8 +/- 3.6*mL/kg/min (Carvedilol), 16.9 +/- 4.1 (Nebivolol), and 16.9 +/- 3.6 (Bisoprolol).

CONCLUSIONS: beta-Blockers differently affect several cardiopulmonary functions. Lung diffusion and exercise performance, the former likely due to lower interference with beta2-mediated alveolar fluid clearance, were higher in Nebivolol and Bisoprolol. On the other hand, Carvedilol allowed a better ventilation efficiency during exercise, likely via a different chemoreceptor modulation. Results from this study represent the basis for identifying the best match between a specific beta-blocker and a specific HF patient.

Espinola-Klein, C., G. Weisser, et al. (2011). "-Blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial." Hypertension **58**(2): 148-154.

The use of -receptor blockers in peripheral arterial disease is controversial for their impact on vasomotor tone. The -blocker nebivolol possesses vasodilating, endothelium-dependent, NO-releasing properties that might be beneficial in peripheral arterial disease. The aim of the study was to evaluate the effects and tolerability of nebivolol in comparison with metoprolol in these patients. A total of 128 patients with intermittent claudication and essential hypertension were included and double-blind randomized to receive 5 mg of nebivolol (N=65) or

95 mg of metoprolol (N=63) once daily. End points were changes in ankle-brachial index, initial and absolute claudication distance, endothelial function assessed by flow-mediated dilatation of the brachial artery, blood pressure, and quality of life using the claudication scale questionnaire. End point analysis was possible in 109 patients (85.2%). After the 48-week treatment period, ankle-brachial index and absolute claudication distance improved significantly in both patient groups (P<0.05 for both), with no difference across treatments. A significant increase of initial claudication distance was found in the nebivolol group. Adjusted mean change of initial claudication distance was 33.9% after nebivolol (P=0.003) and 16.6% after metoprolol (P=0.12) treatment. Quality of life was not influenced by either treatment, and there was no relevant change in flow-mediated dilatation in patients treated with nebivolol or metoprolol (P=0.16). Both drugs were equally effective in lowering blood pressure. In conclusion, -blocker therapy was well tolerated in patients with intermittent claudication and arterial hypertension during a treatment period of 1 year. In the direct comparison, there was no significant difference between nebivolol and metoprolol.

Hori, M., et al. (2014). "Efficacy and safety of bisoprolol fumarate compared with carvedilol in Japanese patients with chronic heart failure: results of the randomized, controlled, double-blind, Multistep Administration of bisoprolol IN Chronic Heart Failure II (MAIN-CHF II) study.[Erratum appears in Heart Vessels. 2014 Mar;29(2):248]." Heart & Vessels **29**(2): 238-247.

Bisoprolol fumarate (bisoprolol) is a beta-blocker widely used to treat chronic heart failure (CHF). However, few studies have compared its efficacy and safety with those of the widely used beta-blocker carvedilol in Japanese patients with CHF. We designed a confirmatory trial of bisoprolol using carvedilol as a control drug; however, the trial was discontinued after an off-label use of bisoprolol was approved during the study. Bisoprolol and carvedilol were administered for 32 weeks in 31 and 28 patients, respectively. The mean maintenance doses of bisoprolol and carvedilol were 3.3 and 13.6 mg/day, respectively, and the mean durations of treatment were 188.2 and 172.9 days, respectively. Heart-rate changes were similar in both groups. The mean changes from baseline to Week 32 in left ventricular (LV) ejection fraction (EF) (bisoprolol vs carvedilol groups; 11.7 % +/- 8.6 % vs 10.1 % +/- 10.5 %), LV end-diastolic volume (-37.5 +/- 48.7 vs -24.7 +/- 29.4 ml), and LV end-systolic volume (-41.9 +/- 43.0 vs -29.3 +/- 25.9 ml) revealed a decrease in LV volume and an increase in LVEF in both groups. The cumulative event-free rate for a composite of cardiovascular death or admissions to hospital for worsening of CHF was 92.4 % and 94.7 % in the bisoprolol and carvedilol groups, respectively. Overall, 90.3 % and 85.7 % of patients were titrated up to the maintenance doses of bisoprolol and carvedilol, respectively. Bisoprolol, at half the dose used in other countries, is well tolerated and is as effective as carvedilol for treating Japanese patients with mild to moderate CHF.

Iliuta, L., R. Christodorescu, et al. (2009). "Prevention of perioperative atrial fibrillation with betablockers in coronary surgery: betaxolol versus metoprolol." Interactive Cardiovascular & Thoracic Surgery **9**(1): 89-93.

In this study, we tried to compare the efficacy and safety of betaxolol vs. metoprolol immediately postoperatively in coronary artery bypass grafting (CABG) patients and to determine whether prophylaxy for atrial fibrillation (AF) with betaxolol could reduce

hospitalization and economic costs after cardiac surgery. Our trial was open-label, randomized, multicentric enrolling 1352 coronary surgery patients randomized to receive betaxolol or metoprolol. The primary endpoints were the composites of 30-day mortality, in-hospital AF (safety endpoints), duration of hospitalization and immobilization, quality of life, and the above endpoint plus in-hospital embolic event, bradycardia, gastrointestinal symptoms, sleep disturbances, cold extremities (efficacy plus safety endpoint). At the end of the study the incidence and probability of early postoperative AF with betaxolol was lower than with metoprolol in coronary surgery (P<0.0001). In the two study groups minor side effects were similar and no major complication was reported (P<0.001). Patient compliance was good and the general condition improved due to shortened hospitalization and immobilization with subsequent improvement in the psychological status, less arrhythmias and lack of significant side effects. In conclusion, because of its efficacy and safety, betaxolol was superior to metoprolol for the prevention of the early postoperative AF in coronary surgery.

Jabbour, A., P. S. Macdonald, et al. (2010). "Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial." Journal of the American College of Cardiology **55**(17): 1780-7.

OBJECTIVES: The purpose of this study was to determine the respiratory, hemodynamic, and clinical effects of switching between beta1-selective and nonselective beta-blockers in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD). BACKGROUND: Carvedilol, metoprolol succinate, and bisoprolol are established beta-blockers for treating CHF. Whether differences in beta-receptor specificities affect lung or vascular function in CHF patients, particularly those with coexistent COPD, remains incompletely characterized. METHODS: A randomized, open label, triple-crossover trial involving 51 subjects receiving optimal therapy for CHF was conducted in 2 Australian teaching hospitals. Subjects received each beta-blocker, dose-matched, for 6 weeks before resuming their original beta-blocker. Echocardiography, N-terminal pro-hormone brain natriuretic peptide, central augmented pressure from pulse waveform analysis, respiratory function testing, 6-min walk distance, and New York Heart Association (NYHA) functional class were assessed at each visit. RESULTS: Of 51 subjects with a mean age of 66 +/- 12 years, NYHA functional class I (n = 6), II (n = 29), or III (n = 16), and left ventricular ejection fraction mean of 37 +/- 10%, 35 had coexistent COPD. N-terminal pro-hormone brain natriuretic peptide was significantly lower with carvedilol than with metoprolol or bisoprolol (mean: carvedilol 1,001 [95% confidence interval (CI): 633 to 1,367] ng/l; metoprolol 1,371 [95% CI: 778 to 1,964] ng/l; bisoprolol 1,349 [95% CI: 782 to 1,916] ng/l; p < 0.01), and returned to baseline level on resumption of the initial beta-blocker. Central augmented pressure, a measure of pulsatile afterload, was lowest with carvedilol (carvedilol 9.9 [95% CI: 7.7 to 12.2] mm Hg; metoprolol 11.5 [95% CI: 9.3 to 13.8] mm Hg; bisoprolol 12.2 [95% CI: 9.6 to 14.7] mm Hg; p < 0.05). In subjects with COPD, forced expiratory volume in 1 s was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 [95% CI: 1.67 to 2.03] l/s; metoprolol 1.94 [95% CI: 1.73 to 2.14] l/s; bisoprolol 2.0 [95% CI: 1.79 to 2.22] l/s; p < 0.001). The NYHA functional class, 6-min walk distance, and left ventricular ejection fraction did not change. The beta-blocker switches were well tolerated. CONCLUSIONS: Switching between beta1-selective beta-blockers and the

nonselective beta-blocker carvedilol is well tolerated but results in demonstrable changes in airway function, most marked in patients with COPD. Switching from beta1-selective beta-blockers to carvedilol causes short-term reduction of central augmented pressure and N-terminal pro-hormone brain natriuretic peptide. (Comparison of Nonselective and Beta1-Selective Beta-Blockers on Respiratory and Arterial Function and Cardiac Chamber Dynamics in Patients With Chronic Stable Congestive Cardiac Failure; Australian New Zealand Clinical Trials Registry, ACTRN12605000504617). Copyright (c) 2010 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Lainscak, M., et al. (2013). "Self-rated health predicts adverse events during beta-blocker treatment: the CIBIS-ELD randomised trial analysis." International Journal of Cardiology **163**(1): 87-92.

BACKGROUND: Self-rated health (SRH) predicts outcome in patients with heart failure. Beta-blockers are known to improve health-related quality of life and reduce mortality in such patients. We aimed to evaluate the relation between SRH and adverse events during titration of beta-blockers in elderly patients with heart failure.

METHODS: The cardiac insufficiency bisoprolol study in the elderly (CIBIS-ELD) is a multicentre, double-blind trial, in which 883 patients aged > 65 years with chronic heart failure (73 +/- 6 years, 38% women, left ventricular ejection fraction [LVEF] 42% +/- 14%) were randomised to bisoprolol or carvedilol. SRH was assessed at baseline and after 12 weeks, using a 5-grade descriptive scale: excellent, very good, good, fair, and poor.

RESULTS: Median SRH at baseline and follow-up was good, but more patients reported fair/poor SRH at baseline (36% vs. 30%, p = 0.012). Women, beta-blocker-naive patients, patients in NYHA class III/IV and those with PHQ-9 score > 12 were more likely to report fair/poor baseline SRH (p < 0.001 for all). During follow-up, SRH improved in 34% of patients and worsened in 8% (p < 0.001). Adverse events were experienced by 64% patients and 38% experienced > 1 adverse event or serious adverse event, with higher prevalence in lower SRH categories. In a multivariate logistic regression model, SRH, age, distance achieved on the 6-min walk test and LVEF >45% predicted adverse events (p < 0.05 for all).

CONCLUSIONS: SRH is an independent predictor of adverse events during titration of beta-blockers and correlates with the proportion and number of adverse events per patient.Copyright 2011 Elsevier Ireland Ltd. All rights reserved.

Marazzi, G., M. Volterrani, et al. (2011). "Comparative long term effects of nebivolol and carvedilol in hypertensive heart failure patients." Journal of Cardiac Failure **17**(9): 703-709.

BACKGROUND: Beta-blockers improve left ventricular (LV) systolic function and prognosis in patients with chronic heart failure (CHF), but their different pleiotropic properties may influence their cardiovascular effects. This open-label study compared the effects of long-term treatment with nebivolol versus carvedilol on LV ejection fraction (LVEF), in hypertensive CHF patients. Secondary end points were to assess the effect of the 2 beta-blockers on exercise capacity and clinical outcome.

METHODS AND RESULTS: A total of 160 hypertensive CHF patients, with LVEF <40% and in New York Heart Association (NYHA) functional class I, II, or III, were randomly

assigned to receive nebivolol or carvedilol for 24 months. At baseline and at the end of treatment, all patients underwent clinical evaluation, echocardiography, and 6-minute walking test. The target doses were 10 mg/d for nebivolol and 50 mg/d for carvedilol. Compared with baseline values, LVEF increased by a similar extent in the carvedilol (C) and nebivolol (N) groups (C from 36.1% (SD 1.5%) to 40.9% (SD 1.9%), P < .001; N from 34.1% (SD 1.8%) to 38.5% (SF 2.2%), P < .001). Heart rate and NYHA functional class decreased significantly in both groups, and the 6-minute walking distance increased (C from 420 m (SD 104 m) to 490 m (SD 115m), P < .001; N from 421 m (SD 118 m) to 487 m (SD 138 m), P < .001). During 24 months, 21 carvedilol recipients (26%) and 18 nebivolol recipients (22%) had cardiac events, including 3 and 4deaths, respectively.
CONCLUSION: In the long term, nebivolol and carvedilol appear to be similarly effective in the treatment of hypertensive patients with CHF. Copyright 2011 Elsevier Inc. All rights reserved.

Sen, N., Y. Tavil, et al. (2009). "Nebivolol therapy improves endothelial function and increases exercise tolerance in patients with cardiac syndrome X." Anadolu Kardiyoloji Dergisi **9**(5): 371-9.

OBJECTIVE: We sought to determine whether nebivolol affects coronary endothelial function and exercise induced ischemia in patients with cardiac syndrome X (CSX). METHODS: The study protocol undertaken was based on a single-blind randomized controlled prospective study. After a 2-week washout period, 38 patients with cardiac syndrome X were randomized to receive either nebivolol 5 mg daily (n=19) or metoprolol 50 mg daily (n=19) in a single- blind design for 12 weeks. The control group under study was consisted of 16 age- and gender-matched subjects with negative treadmill exercise tests. Plasma endothelial nitric oxide (NOx), L-arginine, and asymmetric dimethylarginine (ADMA) were measured in all patients at baseline and after 12 weeks of treatment. Statistical differences among groups were tested by one-way analysis of variance and unpaired samples t test for parametric; Kruskal-Wallis and Mann-Whitney U tests for non-parametric variables, respectively. A paired samples t test was used to compare continuous variables before and after drug therapy. RESULTS: At baseline, plasma level of NOx, L-arginine, and L-arginine/ADMA ratio were lower ($p<0.001$ for all) in patients with CSX than in the control patients. Whereas, the plasma ADMA levels were increased in the patient group ($p<0.001$). After 12 weeks of drug therapy, the patients taking nebivolol had increased levels of plasma NOx , plasma L-arginine, the L-arginine/ADMA ratio and decreased levels of plasma ADMA compared to those of the patients taking metoprolol ($p<0.001$). In addition, exercise duration to 1-mm ST depression and total exercise duration significantly increased after treatment in the nebivolol group compared to the metoprolol group ($p<0.01$). In the nebivolol group, Canadian Cardiovascular Society (CCS) angina classification improved by one or more categories in 12 (70%) patients, whereas it deteriorated or remained in the same category in 5 (30%) patients. Meanwhile, in the metoprolol group, the CCS angina classification improved by one or more categories in 7 (41%), whereas it deteriorated or remained in the same category in 10 (59%) patients. CONCLUSION: Circulating endothelial function parameters (plasma ADMA, L-arginine, NOx levels) were impaired in patients with CSX. Nebivolol treatment was associated with better improvements in both circulating endothelial function and exercise stress test parameters than metoprolol. We believe that

further studies are needed to evaluate the effects of nebivolol treatment on long-term clinical outcomes in patients with CSX.

Shahzamani, M., A. Ghanavati, et al. (2011). "Carvedilol compared with metoprolol on left ventricular ejection fraction after coronary artery bypass graft." Journal of PeriAnesthesia Nursing **26**(6): 384-387.

A number of elective coronary artery bypass graft (CABG) surgery patients have impaired underlying left ventricular function (poor ejection fraction). This study was performed to compare the effect of postoperative oral carvedilol versus metoprolol on left ventricular ejection fraction (LVEF) after CABG compared with metoprolol. In a double-blind clinical trial, 60 patients with coronary artery disease, aged 35 to 65 years, who had an ejection fraction of 15% to 35% were included. Either carvedilol or metoprolol was administered the day after CABG. The patients were evaluated by the same cardiologist 14 days before and 2 and 6 months after elective CABG. The results demonstrated better improvements in LVEF in the carvedilol group. No difference regarding postoperative arrhythmias or mortality was detected. The results suggest that carvedilol may exert more of an improved myocardial effect than metoprolol for the low ejection fraction patients undergoing CABG in the early postoperative months.

Udelson, J. E., S. J. Pressler, et al. (2009). "Adherence with once daily versus twice daily carvedilol in patients with heart failure: the Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial." Journal of Cardiac Failure **15**(5): 385-93.

BACKGROUND: Suboptimal compliance in taking guideline-based pharmacotherapy in patients with chronic heart failure (HF) potentially increases the burden of hospitalizations and diminishes quality of life. By simplifying the medical regimen, once-daily dosing can potentially improve compliance. The Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial was designed to measure differential compliance, satisfaction, and quality of life in chronic HF patients taking carvedilol immediate release (IR) twice daily versus the bioequivalent carvedilol controlled-release (CR) once daily. METHODS AND RESULTS: CASPER was a prospective multicenter, 3-arm, parallel-group, randomized clinical trial for a 5-month period. The primary objective of the study was to evaluate and compare compliance with carvedilol IR twice daily (BID) and carvedilol phosphate CR once daily (QD) in patients with chronic HF who were taking carvedilol IR. Secondary objectives included comparisons of quality of life (Kansas City Cardiomyopathy Questionnaire), satisfaction with medication, and brain natriuretic peptide levels between subjects taking the two formulations. A total of 405 patients with chronic HF and left ventricular dysfunction were randomized to: (A) carvedilol IR twice daily, given double blind; (B) carvedilol CR taken in the morning and placebo in the afternoon, given double blind; or (C) carvedilol CR once daily, open label. Compliance was measured using the medication event monitoring system that captures time of bottle opening. The primary end point was a comparison of taking compliance (doses taken divided by total number of prescribed doses over the actual duration of the study) between the double-blind carvedilol IR BID

versus the open-label carvedilol CR QD groups. Sample size estimates were based on assumptions of 75% compliance with BID dosing and 90% compliance with QD dosing. Mean compliance with carvedilol IR BID was 89.3% compared with 88.2% for carvedilol CR QD, and differential mean compliance was 1.1% (95% CI -4.4%, 6.6%; ie, not significant). There were no statistically significant differences in compliance between any of the 3 groups, nor differences in quality of life, treatment satisfaction, or physiologic measures among the 3 study arms. There were also no significant differences in adverse events or side effects among patients switching from carvedilol IR to carvedilol CR in arms B or C over the 5-month study duration compared with patients remaining on carvedilol IR. CONCLUSIONS: Compliance among chronic HF patients in the CASPER trial was high at baseline and unaffected by QD versus BID dosing. Over the 5-month follow-up period, there were no differences in adverse events among patients switching from carvedilol IR to CR.

Ulimoen, S. R., S. Enger, et al. (2013). "Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation." American Journal of Cardiology **111**(2): 225-230.

Rate control of atrial fibrillation (AF) is a main treatment modality. However, data are scarce on the relative efficacy of calcium channel blockers and blockers or between drugs within each class. The purpose of the present study was to compare the effect of 4 rate-reducing, once-daily drug regimens on the ventricular heart rate and arrhythmia-related symptoms in patients with permanent AF. We included 60 patients (mean age 71 +/- 9 years, 18 women) with permanent AF in an investigator-blind cross-over study. Diltiazem 360 mg/day, verapamil 240 mg/day, metoprolol 100 mg/day, and carvedilol 25 mg/day were administered for 3 weeks in a randomized sequence. The 24-hour heart rate was measured using Holter monitoring, and arrhythmia-related symptoms were assessed using the Symptom Checklist questionnaire before randomization and on the last day of each treatment period. The 24-hour mean heart rate was 96 +/- 12 beats/min at baseline (no treatment), 75 +/- 10 beats/min with diltiazem, 81 +/- 11 beats/min with verapamil, 82 +/- 11 beats/min with metoprolol, and 84 +/- 11 beats/min with carvedilol. All drugs reduced the heart rate compared to baseline ($p < 0.001$ for all). The 24-hour heart rate was significantly lower with diltiazem than with any other drug tested ($p < 0.001$ for all). Compared to baseline, diltiazem significantly reduced both the frequency ($p < 0.001$) and the severity ($p = 0.005$) of symptoms. In contrast, verapamil reduced symptom frequency only ($p = 0.012$). In conclusion, diltiazem 360 mg/day was the most effective drug regimen for reducing the heart rate in patients with permanent AF. Arrhythmia-related symptoms were reduced by treatment with the calcium channel blockers diltiazem and verapamil, but not by the blockers.

Companion Publications (N=2)

Scherer, M., et al. (2013). "Determinants of change in quality of life in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD)." European Journal of Internal Medicine **24**(4): 333-338.

OBJECTIVE: Little is known about parameters that lead to improvement in QoL in individual patients. We analysed the data of the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) in order to answer the question of how and to what extent change

in health-related QoL during up-titration with bisoprolol vs. carvedilol is influenced by clinical and psychosocial factors in elderly patients with heart failure.
METHODS: This is a QoL analysis of CIBIS-ELD, an investigator-initiated multi-center randomised phase III trial in elderly patients (65 years or older) with moderate to severe heart failure. Clinical parameters such as New York Heart Association functional class, heart rate, left ventricular ejection fraction (LVEF), 6-min walk distance, as well as the physical and psychosocial component scores on the short-form QoL health survey (SF36) and depression were recorded at baseline and at the final study visit.
RESULTS: Full baseline and follow-up QoL data were available for 589 patients (292 in the bisoprolol and 297 in the carvedilol group). Mean physical and psychosocial QoL improved significantly during treatment. In regression analyses, changes in both SF36 component scores from baseline to follow-up were mainly predicted by baseline QoL and depression as well as change in depression over time. Changes in cardiac severity markers were significantly weaker predictors.
CONCLUSION: Mean QoL increased during up-titration of bisoprolol and carvedilol. Both baseline depression and improvement in depression over time are associated with greater improvement in QoL more strongly than changes in cardiac severity measures.

Ulimoen, S. R., et al. (2014). "Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation." European Heart Journal **35**(8): 517-524.
AIMS: Rate control of atrial fibrillation (AF) has become a main treatment modality, but we need more knowledge regarding the different drugs used for this purpose. In this study, we aimed to compare the effect of four common rate-reducing drugs on exercise capacity and levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with permanent AF.
METHODS AND RESULTS: We included 60 patients (mean age 71 +/- 9 years, 18 women) with permanent AF and normal left ventricular function in a randomized, cross-over, investigator-blind study. Diltiazem 360 mg, verapamil 240 mg, metoprolol 100 mg, and carvedilol 25 mg were administered o.d. for 3 weeks. At baseline and on the last day of each treatment period, the patients underwent a maximal cardiopulmonary exercise test and blood samples were obtained at rest and at peak exercise. The exercise capacity (peak VO2) was significantly lower during treatment with metoprolol and carvedilol compared with baseline (no treatment) or treatment with diltiazem and verapamil ($P < 0.001$ for all). Compared with baseline, treatment with diltiazem and verapamil significantly reduced the NT-proBNP levels both at rest and at peak exercise, whereas treatment with metoprolol and carvedilol increased the levels ($P < 0.05$ for all).
CONCLUSION: Rate-reducing treatment with diltiazem or verapamil preserved exercise capacity and reduced levels of NT-proBNP compared with baseline, whereas treatment with metoprolol or carvedilol reduced the exercise capacity and increased levels of NT-proBNP.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project – Literature Scan Summary

Date of Current Review: May 2015 **Date of Last Review:** March 2014
PDL Class: Overactive Bladder Drugs

Current Status of PDL Class:
See **Appendix 1**.

Conclusions and Recommendations:

- There is no significant new comparative evidence supporting a difference in efficacy or serious harms between drugs.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:

- There is no significant new comparative evidence supporting a difference in efficacy or harms between drugs.

Research Questions:

1. What is the evidence on the efficacy and effectiveness of the overactive bladder drugs in adults?
2. What is the evidence on the harms of overactive bladder drugs in adults?
3. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one overactive bladder drug is more effective or associated with fewer harms?

Methods:
The DERP scan was used to identify any new comparative research that has emerged since the last P&T review.

Summary:
No new overactive bladder drugs, new indications, new formulations or new serious harms were identified in the literature scan. No new comparative high-quality systematic reviews have been performed. Since the previous DERP literature scan report, four were potentially relevant new trials were identified, all of which were placebo-controlled trials of mirabegron, each with a tolterodine active-controlled arm. With the exception of one small trial in women (n=77), which compared darifenacin with solifenacin, all new head-to-head trials identified since the last original DERP report on this drug class compared the newer overactive bladder drugs with tolterodine, oxybutynin and/or placebo. Outcomes studied primarily involved the tolerability of these antimuscarinic agents with efficacy endpoints as secondary outcomes. However, no new trials demonstrate significant evidence of differences in serious harms between drugs for overactive bladder.

References:

1. Holzhammer B. Drug Class Review on Overactive Bladder Drugs, Preliminary Scan Report #2, March 2015. Drug Effectiveness Review Project. Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University.

Appendix 1: Current Status on Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	TAB ER 24H	TOVIAZ	FESOTERODINE FUMARATE	Y
ORAL	ELIXIR	HYOSCYAMINE SULFATE	HYOSCYAMINE SULFATE	Y
ORAL	ELIXIR	HYOSYNE	HYOSCYAMINE SULFATE	Y
ORAL	TAB RAPDIS	ANASPAZ	HYOSCYAMINE SULFATE	Y
ORAL	TAB RAPDIS	ED-SPAZ	HYOSCYAMINE SULFATE	Y
ORAL	TAB RAPDIS	HYOSCYAMINE SULFATE	HYOSCYAMINE SULFATE	Y
ORAL	TAB RAPDIS	NULEV	HYOSCYAMINE SULFATE	Y
ORAL	TAB RAPDIS	OSCIMIN	HYOSCYAMINE SULFATE	Y
ORAL	TAB RAPDIS	SYMAX	HYOSCYAMINE SULFATE	Y
ORAL	SYRUP	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	Y
ORAL	TABLET	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	Y
ORAL	TAB ER 24	DITROPAN XL	OXYBUTYNIN CHLORIDE	Y
ORAL	TAB ER 24	OXYBUTYNIN CHLORIDE ER	OXYBUTYNIN CHLORIDE	Y
ORAL	TAB ER 24	DITROPAN XL	OXYBUTYNIN CHLORIDE	Y
ORAL	TAB ER 24	OXYBUTYNIN CHLORIDE ER	OXYBUTYNIN CHLORIDE	Y
ORAL	TAB ER 24	DITROPAN XL	OXYBUTYNIN CHLORIDE	Y
TRANSDERM	PATCH TDSW	OXYTROL	OXYBUTYNIN	Y
ORAL	TAB ER 24H	ENABLEX	DARIFENACIN HYDROBROMIDE	N
ORAL	TABLET	FLAVOXATE HCL	FLAVOXATE HCL	N
ORAL	TAB MPHASE	SYMAX DUOTAB	HYOSCYAMINE SULFATE	N
ORAL	TAB RAPDIS	MAR-SPAS	HYOSCYAMINE SULFATE	N
ORAL	CAP ER 12H	CYSTOSPAZ-M	HYOSCYAMINE SULFATE	N
ORAL	CAP ER 12H	LEVSINEX	HYOSCYAMINE SULFATE	N
ORAL	TABLET	HYOSCYAMINE SULFATE	HYOSCYAMINE SULFATE	N
ORAL	TABLET	LEVSIN	HYOSCYAMINE SULFATE	N
ORAL	TABLET	OSCIMIN	HYOSCYAMINE SULFATE	N
ORAL	TABLET	SPASDEL	HYOSCYAMINE SULFATE	N
ORAL	TABLET	DONNAMAR	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 12H	HYOSCYAMINE SULFATE	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 12H	HYOSCYAMINE SULFATE ER	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 12H	HYOSCYAMINE SULFATE SR	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 12H	LEVBID	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 12H	OSCIMIN SR	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 12H	SYMAX-SR	HYOSCYAMINE SULFATE	N
ORAL	DROPS	HYOSCYAMINE SULFATE	HYOSCYAMINE SULFATE	N
ORAL	DROPS	HYOSYNE	HYOSCYAMINE SULFATE	N
ORAL	DROPS	SPASDEL	HYOSCYAMINE SULFATE	N
ORAL	TAB ER 24H	MYRBETRIQ	MIRABEGRON	N
TRANSDERM	GEL MD PMP	GELNIQUE	OXYBUTYNIN	N
TRANSDERM	PATCH TD 4	OXYTROL FOR WOMEN	OXYBUTYNIN	N
TRANSDERM	GEL PACKET	GELNIQUE	OXYBUTYNIN CHLORIDE	N
ORAL	TABLET	VESICARE	SOLIFENACIN SUCCINATE	N
ORAL	TABLET	DETROL	TOLTERODINE TARTRATE	N
ORAL	TABLET	TOLTERODINE TARTRATE	TOLTERODINE TARTRATE	N
ORAL	TABLET	TOLTERODINE TARTRATE	TOLTERODINE TARTRATE	N
ORAL	CAP ER 24H	DETROL LA	TOLTERODINE TARTRATE	N
ORAL	CAP ER 24H	TOLTERODINE TARTRATE ER	TOLTERODINE TARTRATE	N
ORAL	CAP ER 24H	DETROL LA	TOLTERODINE TARTRATE	N
ORAL	TABLET	TROSPIUM CHLORIDE	TROSPIUM CHLORIDE	N
ORAL	CAP ER 24H	TROSPIUM CHLORIDE ER	TROSPIUM CHLORIDE	N

Drug Class Review

Overactive Bladder Drugs

Preliminary Scan Report #2

March 2015

Last Report: Summary Review, June 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.

Scan conducted by:
Brittany Holzhammer, MPH

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 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 Previous Report

Summary Review: June 2013 (searches through May 2013)

Date of Previous Scans

Scan #1: February 2014

Scope and Key Questions

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 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 evidence on the efficacy and effectiveness of the overactive bladder drugs in adults?

2. What is the evidence on the harms of overactive bladder drugs in adults?

3. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one overactive bladder drug is more effective or associated with fewer harms?

Inclusion Criteria

Populations
Adults with symptoms of urge incontinence/overactive bladder (urgency, frequency, leakage, and dysuria).

Drugs
Darifenacin, fesoterodine fumarate, flavoxate hydrochloride, mirabegron, oxybutynin chloride, solifenacin succinate, tolterodine tartrate, and trospium chloride.

Comparators
The primary comparison is one of the included overactive bladder drugs with another included overactive bladder drug.

Effectiveness Outcomes
- Change in mean number of incontinence episodes per 24 hours
- Change in mean number of micturitions per 24 hours
- Change in mean number of pads per 24 hours
- Subjective patient assessments of symptoms (severity of "problems" caused by bladder symptoms, severity of urgency, and global evaluation of treatment)

Harms Outcomes
- Overall adverse effects
- Withdrawals due to overall adverse effects
- Serious adverse events reported
- Specific adverse events or withdrawals due to specific adverse events (dry mouth, effects on cognition, blurred vision, and cardiac conduction abnormalities

Study Designs (from previous report)

For effectiveness:
- Controlled clinical trials
- Recent, good quality systematic reviews
- Comparative observational studies of at least 1 year's duration and reporting functional outcomes

For harms:
- Controlled clinical trials
- Comparative observational studies (cohort or case-control) with a well-defined neuropathic pain population
- Non-comparative observational studies only if the duration is 1 year or longer, and if serious harms are reported; a serious harm is one that results in long-term health effects or mortality

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations February 2014 through February 2015 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for identification of new drugs, new populations, and new serious harms. To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. 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 - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials, controlled clinical trials, and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan
None.

New Uses

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan
None.

New Serious Harms

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan
None.

New Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan
No new comparative effectiveness reviews were identified through searches of the AHRQ, CADTH, VA, and CRD websites.

Randomized Controlled Trials

Identified in this Preliminary Update Scan
Medline searches for this scan resulted in 11 citations. Of those, 4 were potentially relevant new trials, all of which were placebo-controlled trials of mirabegron each with a tolterodine active-controlled arm. One trial was a phase II proof-of-concept study, one trial was a phase II dose-ranging study, one trial was a post-hoc analysis of a previously conducted European-Australian phase III trial (NCT00689104) in patients with and without prior antimuscarinic therapy for overactive bladder, and the last trial was a phase III study in Japanese patients. All trials studied the change in mean number of micturitions per 24 hours.

Identified in previous Preliminary Update Scan
Eleven potentially relevant new trials were identified in the previous preliminary update scan. An additional 13 trials were previously reported in the Summary Review as published since the search dates of the included systematic reviews. Together, with the 4 trials identified in the current preliminary update scan, we have identified a total of 28 new trials (9 head-to-head trials and 19 placebo-controlled trials). Characteristics of head-to-head studies are included in Table 1 and abstracts are available in Appendix A. Placebo-controlled studies are listed by drug of study, below, and abstracts are available upon request. Existing new head-to-head evidence compares: solifenacin with darifenacin; mirabegron, fesoterodine, solifenacin and trospium with tolterodine; and trospium, solifenacin, and tolterodine with oxybutynin.

Table 1. New head-to-head trials of overactive bladder drugs (N=9)

Author, Year	N	Drug A	Drug B	Population Details
But, 2012	77	Solifenacin 5 mg	Darifenacin 7.5 mg	Open label, all women, Slovenian patients
Chapple, 2013	2,444	Mirabegron 50 or 100 mg	ER Tolterodine 4 mg	Patients with OAB symptoms for at least 3 months
Corcos, 2011	1,013	Fesoterodine 4 mg	ER Tolterodine 4 mg	Patients with OAB symptoms for at least 3 months
Dede, 2013	90	Tolterodine Trospium	Oxybutynin	Women with urge urinary incontinence
Herschorn, 2011	132	Solifenacin 5 mg	IR Oxybutynin 15 mg	Patients with OAB symptoms for at least 3 months
Hsiao, 2011	48	Solifenacin 5 mg	ER Tolterodine 4 mg	Women, post-marketing study
Kaplan, 2011	2,417	Fesoterodine 8 mg	ER Tolterodine 4 mg	Subjects with >1 urgency incontinence episode and ≥ 8 micturitions per 24 hours
Konstantinidis, 2013	47	Fesoterodine plus Tamsulosin	Tamsulosin	Men > 50 with lower urinary tract symptoms
Khullar, 2013	1,978	Mirabegron 50 or 100 mg	ER Tolterodine 4 mg	Patients with OAB symptoms for at least 3 months

New placebo-controlled trials of overactive bladder drugs (N=19)

Fesoterodine
- Kaplan, 2012
- Staskin, 2011
- Wagg, 2013
- Weiss, 2013

Mirabegron
- Chapple, 2013a
- Chapple, 2013b
- Herschorn, 2013
- Khullar, 2013
- Nitti, 2013a
- Nitti, 2013b
- Yamaguchi, 2014

Oxybutynin
- Sand, 2012

Solifenacin
- Cardozo, 2013
- Oreskovic, 2012
- Yokoyama, 2011

Solifenacin + Tamsulosin
- Kaplan, 2013a
- Kaplan, 2013b
- Yamaguchi, 2011

Tolterodine SR + Doxazosin
- Lee, 2011

*Shading indicates trials identified in the current preliminary update scan.

SUMMARY

Cumulatively, we have identified no new drugs, new uses, new serious harms, and new comprehensive comparative effectiveness reviews of overactive bladder drugs since the Summary Review. We have identified a total of 28 new trials, including 9 head-to-head trials. With the exception of one small trial in women (N=77), which compared darifenacin with solifenacin, the new trials compared the newer overactive bladder drugs with tolterodine, oxybutynin and/or placebo.

APPENDIX A. ABSTRACTS OF POTENTIALLY RELEVANT NEW TRIALS OF OVERACTIVE BLADDER DRUGS

Head-to-head trials (N=9)

But, I., M. S. Goldstajn, et al. (2012). "Comparison of two selective muscarinic receptor antagonists (solifenacin and darifenacin) in women with overactive bladder--the SOLIDAR study." Collegium Antropologicum **36**(4): 1347-1353.

Overactive bladder (OAB) is a common, often debilitating, condition defined as urgency and urge incontinence, usually with frequency and nocturia. The use of muscarinic receptor antagonists are the mainstay of treatment, but their non-selectivity can result in unacceptable adverse effects that limit their usefulness. The purpose of this study was to evaluate 2 of the newer antimuscarinic agents, solifenacin and darifenacin, which demonstrate greater selectivity, in order to compare their tolerance and effectiveness. This was a multicentre, prospective, randomised, comparative (1:1) open-label study conducted in 4 centres comprising Slovenian gynaecologists and urologists. A total of 77 female patients with OAB were enrolled who received either solifenacin 5 mg or darifenacin 7.5 mg once daily. Study measurements consisted of changes in OAB symptoms and quality of life (QOL) evaluations after 1 and 3 months of treatment. Both treatment groups showing a reduction in all OAB symptoms but with no notable difference being seen between the 2 groups. Solifenacin though showed statistically greater improvements in QOL, better overall treatment satisfaction, and a decreased incidence of dry mouth after 3 months of treatment compared to the darifenacin group. This study demonstrates interesting initial results and indicates that these 2 drugs have a different profile that may confer an advantage to patients, but further methodologically rigorous studies comparing the use of solifenacin and darifenacin in OAB are required to establish the differences between these drugs over longer periods of treatment.

Chapple CR. Kaplan SA. Mitcheson D. Klecka J. Cummings J. Drogendijk T. Dorrepaal C. Martin N. European Urology. 63(2):296-305, 2013 Feb. "Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. "

BACKGROUND: Despite several antimuscarinic treatment options for overactive bladder (OAB), there is still a need for distinct treatment approaches to manage this condition. Mirabegron, a beta(3)-adrenoceptor agonist, has demonstrated efficacy and tolerability for up to 12 wk in phase 3 trials.

OBJECTIVE: To assess the 12-mo safety and efficacy of mirabegron.

DESIGN, SETTING, AND PARTICIPANTS: Patients > 18 yr of age with OAB symptoms for > 3 mo.

INTERVENTIONS: After a 2-wk single-blind placebo run-in, patients with eight or more micturitions per 24h and three or more urgency episodes in a 3-d micturition diary were randomized 1:1:1 to once-daily mirabegron 50mg, mirabegron 100mg, or tolterodine extended release (ER) 4 mg for 12 mo.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Primary variable: incidence and severity of treatment-emergent AEs (TEAEs). Secondary variables: change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms.

RESULTS AND LIMITATIONS: A total of 812, 820, and 812 patients received mirabegron 50mg, mirabegron 100mg, and tolterodine ER 4 mg, respectively. Baseline demographic and OAB characteristics were similar across groups. TEAEs were reported in 59.7%, 61.3%, and 62.6% of patients, respectively; most were mild or moderate. Serious TEAEs were reported in 5.2%, 6.2%, and 5.4% of patients, respectively. The most common TEAEs were similar across groups. Dry mouth was reported by 2.8%, 2.3%, and 8.6% of patients, respectively. Adjusted mean changes from baseline to final visit in morning systolic blood pressure were 0.2, 0.4, and -0.5mm Hg for mirabegron 50mg, 100mg, and tolterodine ER 4 mg, respectively. Mirabegron and the active control, tolterodine, improved key OAB symptoms from the first measured time point of 4 wk, and efficacy was maintained throughout the 12-mo treatment period. The study was not placebo controlled, which was a limitation.
CONCLUSIONS: The safety and tolerability of mirabegron was established over 1 yr, with sustained efficacy observed over this treatment period.

Corcos, J., J. C. Angulo, et al. (2011). "Effect of fesoterodine 4 mg on bladder diary and patient-reported outcomes during the first week of treatment in subjects with overactive bladder." Current Medical Research & Opinion **27**(5): 1059-1065.

OBJECTIVE: To assess the onset of efficacy of fesoterodine 4 mg compared with placebo in subjects with overactive bladder (OAB) symptoms.
RESEARCH DESIGN AND METHODS: Subjects who reported OAB symptoms for >= 3 months and recorded >= 8 micturitions and >= 1 urgency urinary incontinence (UUI) episode per 24 hours in 3-day baseline diaries were randomized to fesoterodine 4 mg, tolterodine extended release (ER) 4 mg, or placebo. This is an analysis of first week data from a 12-week, double-blind trial. ClinicalTrials.gov unique ID: NCT00444925.
MAIN OUTCOME MEASURES: Baseline to week 1 changes in 3-day bladder diary variables, Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) scores reported by subjects receiving fesoterodine 4mg or placebo.
RESULTS: By week 1, fesoterodine 4 mg (n = 679) was associated with significantly greater improvements compared with placebo (n = 334) in micturitions, urgency, severe urgency and UUI episodes, frequency-urgency sum, and MVV per 24 hours and 3-day diary-dry rate (all $p < 0.05$), but not nocturnal micturitions per 24 hours ($p = 0.273$). These differences were significant as early as day 5 of treatment (i.e., day 1 of the 3-day diary) for all diary endpoints except nocturnal micturitions and MVV. Changes in PPBC scores were significantly more favorable with fesoterodine 4mg versus placebo ($p = 0.0143$); changes in UPS scores were not significantly different ($p = 0.077$).
CONCLUSION: The results provide evidence that patients receiving fesoterodine 4 mg for their OAB symptoms may expect to experience a response as early as 1 week after initiating treatment. One limitation is that, although 65% of subjects had received treatment with antimuscarinics before the study, whether subjects were dissatisfied with previous treatment and reasons for dissatisfaction were not collected. This might affect the magnitude of outcome improvements. Also, it is not known whether the UPS is sensitive enough to detect treatment differences as early as week 1.

Dede H. Dolen I. Dede FS. Sivaslioglu AA. What is the success of drug treatment in urge urinary incontinence? What should be measured? Archives of Gynecology & Obstetrics. 287(3):511-8, 2013 Mar.

PURPOSE: The aim of this study is to evaluate the efficacy and the tolerability of three classic antimuscarinic drugs used in the treatment of over active bladder syndrome using clinical data and quality of life tests, and to evaluate the parameters affecting the success of these drugs.
METHODS: A total of 90 patients with urge urinary incontinence were randomly allocated into three groups either to receive tolterodine (group A), trospium chloride (group B) or oxybutynin (group C). Urogenital distress inventory short form (UDI-6) and Incontinence impact questionnaire short form (IIQ-7) of the Turkish Urogynecology and Pelvic Reconstructive Surgery Association were performed to each patient before and after treatment to evaluate the effectiveness and tolerability of the antimuscarinic drugs. Adverse events were also recorded during treatment.
RESULTS: Improved urodynamic test values were recorded after 6 weeks of treatment in each group. Similarly, statistically significant differences were observed in UDI-6 and IIQ-7 test scores before and after treatment. Complete cure was achieved in 86 % of patients in group A; however, complete cure rates were 67 and 80 % in group B and C, respectively. Although, patients reported comparable tolerability against trospium chloride (77 %) and tolterodine (80 %), only 23 % of patients using oxybutynin considered the drug as tolerable. The most common side effect was dry mouth, followed by insomnia. Both dry mouth and insomnia was highest in group C (50 %). One patient (0.3 %) in group B and two patients (0.7 %) in group C reported that they did not want to continue to use the drug.
CONCLUSION: Antimuscarinic medications are very successful in the treatment of urge urinary incontinence; however, the success of treatment is not only limited to clinical improvement. Patients do not regard a drug as successful unless it is tolerable, easy to adapt to the daily life and improve the quality of life even it has very successful clinical outcomes.

Herschorn, S., P. Pommerville, et al. (2011). "Tolerability of solifenacin and oxybutynin immediate release in older (> 65 years) and younger (<= 65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study." Current Medical Research & Opinion **27**(2): 375-382.

OBJECTIVE: Overactive bladder (OAB) is a common condition whose prevalence increases with age. Antimuscarinic agents are the pharmacologic treatment of choice, but adverse events such as dry mouth may lead to early discontinuation. The purpose of this analysis was to compare the incidence and severity of dry mouth and other adverse events with solifenacin 5 mg/day and oxybutynin immediate release (IR) 15 mg/day in patients <= 65 years and >65 years in the Canadian VECTOR study (VEsicare in Comparison To Oxybutynin for oveRactive bladder patients).
RESEARCH DESIGN AND METHODS: VECTOR was a randomized, multicentre, prospective, double-blind, double-dummy study in 132 subjects with >= 1 urgency episode per 24 h, with or without urgency incontinence, and >= 8 micturitions per 24 h for >= 3 months. After a 2-week washout, patients received solifenacin 5 mg once daily or oxybutynin IR 5 mg tid for 8 weeks. For the current post-hoc analysis, adverse events were evaluated in subgroups of patients <= 65 years and >65 years, using a full logistic regression model, multinomial logit regression model and reduced model.
RESULTS: The incidence and severity of dry mouth and other adverse events with solifenacin were similar between younger and older patients. In both age subgroups,

solifenacin 5 mg/day was associated with fewer episodes and lower severity of dry mouth, and a lower discontinuation rate, compared with oxybutynin IR 15 mg/day. CONCLUSIONS: Solifenacin 5 mg/day was better tolerated than oxybutynin IR 15 mg/day in younger (<= 65 years) and older (> 65 years) subgroups. Solifenacin was equally well tolerated in both age subgroups. Limitations of the analysis were that the study was not preplanned to perform post-hoc subgroup analysis, patients knew that dry mouth was a primary outcome, and the study used fixed doses of each drug.

Hsiao, S.-M., T.-C. Chang, et al. (2011). "Comparisons of urodynamic effects, therapeutic efficacy and safety of solifenacin versus tolterodine for female overactive bladder syndrome." Journal of Obstetrics & Gynaecology Research **37**(8): 1084-1091.

AIM: To evaluate the urodynamic effects, therapeutic efficacy and safety of solifenacin versus tolterodine treatment for women with overactive bladder syndrome. METHODS: Patients were randomized to receive either solifenacin 5 mg or tolterodine ER 4 mg once a day for 12 weeks at each four-week visit in a post-marketing study. Only women (solifenacin [n = 26] vs. tolterodine [n = 22]) were included in this subgroup analysis. Adverse events and changes of urodynamic values and clinical data were compared between the solifenacin and tolterodine groups.
RESULTS: The volume voided per micturition increased in the solifenacin group (n = 21) (P = 0.04). The strong desire to void and pad-test result improved in the tolterodine group (n = 21; P = 0.02 and 0.03, respectively). There were no between-group differences in changes of any urodynamic data, voiding diary values or adverse events after treatment; however, changes of heart rate differed between the two groups (P = 0.0004), especially at visit 2 (solifenacin vs. tolterodine, -4.3 vs. 3.8, P = 0.02) and visit 3 (-3.2 vs. 4.8, P = 0.03).
CONCLUSIONS: Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy and adverse events in treating women with overactive bladder syndrome; however, tolterodine had a greater effect in increasing heart rate than solifenacin. 2011 The Authors. Journal of Obstetrics and Gynaecology Research 2011 Japan Society of Obstetrics and Gynecology.

Kaplan, S. A., T. Schneider, et al. (2011). "Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial." BJU International **107**(9): 1432-1440.

OBJECTIVE: * To show the superior efficacy of fesoterodine over tolterodine extended release (ER) in a placebo-controlled overactive bladder (OAB) trial with predefined treatment comparisons for both diary measures and patient-reported outcomes.
MATERIALS AND METHODS: * In this 12-week, double-blind, double-dummy trial, subjects reporting >1 urgency urinary incontinence (UUI) episode and >=8 micturitions per 24 h at baseline were randomized to fesoterodine (4 mg for 1 week, 8 mg for 11 weeks), tolterodine ER 4 mg, or placebo. * Subjects completed 3-day bladder diaries, the Patient Perception of Bladder Condition (PPBC) and the Urgency Perception Scale (UPS) at baseline and weeks 1, 4 and 12 and the OAB Questionnaire at baseline and week 12.
RESULTS: * A total of 2417 subjects were randomized. At week 12, fesoterodine 8 mg showed superiority over tolterodine ER 4 mg and placebo on UUI episodes (primary endpoint), micturitions, urgency and most other diary endpoints, and on the PPBC, UPS and all OAB Questionnaire scales and domains (all P < 0.05). * Superiority of

fesoterodine 8 mg over tolterodine ER 4 mg was seen as early as week 4 (3 weeks after escalation to fesoterodine 8 mg). At week 1, fesoterodine 4 mg was superior to placebo on most diary variables, the PPBC and the UPS (all P < 0.05). Dry mouth and constipation rates were 28% and 4% with fesoterodine, 13% and 3% with tolterodine ER, and 5% and 2% with placebo. * Discontinuation rates as a result of adverse events were 5%, 3% and 2% for fesoterodine, tolterodine ER and placebo, respectively. CONCLUSIONS: * In this randomized study, which is the largest to compare antimuscarinic efficacy performed to date, fesoterodine 8 mg was superior to tolterodine ER 4 mg for UUI episodes, micturitions and urgency episodes, as well as for self-reported patient assessments of bladder-related problems, urgency, symptom bother and health-related quality of life. *The superiority of fesoterodine 8 mg over tolterodine ER 4 mg was observed as early as 3 weeks after escalation from fesoterodine 4 mg for most outcomes.

Konstantinidis C. Samarinas M. Andreadakis S. Xanthis S. Skriapas K. "Lower urinary tract symptoms associated with benign prostatic hyperplasia: combined treatment with fesoterodine fumarate extended-release and tamsulosin-a prospective study."Urologia Internationalis. 90(2):156-60, 2013.

OBJECTIVE: To evaluate the efficacy and safety of fesoterodine extended-release (ER) plus tamsulosin in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).
PATIENTS AND METHODS: Men aged >50 years, with LUTS, prostate volume <60 ml and International Prostate Symptom Score (IPSS) >13 were enrolled in this study. 173 consecutive patients were treated initially with tamsulosin (0.4 mg) for 1 week. At the second visit, 47 patients out of the sample of 173 who were still experiencing inconvenient LUTS were randomized into two groups. The first group received a therapy with tamsulosin and fesoterodine combination (group 1, n = 24) while the second continued the therapy with the single administration of tamsulosin (group 2, n = 23) for an additional 4-week period.
RESULTS: There was no statistically significant difference in age, prostate volume, Q, and postvoid residual urine between the two groups. A statistical significance appeared in the combination group regarding the storage and the total IPSS values among the second and third visits (10.5 + 1.4 to 8.5 + 1.3 and 16.1 + 1.8 to 13.7 + 1.5 respectively).
CONCLUSION: Regarding bothersome LUTS and storage symptoms, fesoterodine ER and tamsulosin combination was significantly more effective than the single administration of tamsulosin.

Khullar V. Amarenco G. Angulo JC. Cambronero J. Hoye K. Milsom I. Radziszewski P. Rechberger T. Boerrigter P. Drogendijk T. Wooning M. Chapple C. Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. European Urology. 63(2):283-95, 2013 Feb.

BACKGROUND: Mirabegron, a beta(3)-adrenoceptor agonist, has been developed for the treatment of overactive bladder (OAB).
OBJECTIVE: To assess the efficacy and tolerability of mirabegron versus placebo.
DESIGN, SETTING, AND PARTICIPANTS: Multicenter randomised double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial conducted in 27 countries in Europe and Australia in patients > 18 yr of age with symptoms of OAB for > 3 mo.

INTERVENTION: After a 2-wk single-blind placebo run-in period, patients were randomised to receive placebo, mirabegron 50mg, mirabegron 100mg, or tolterodine extended release 4 mg orally once daily for 12 wk.
OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Patients completed a micturition diary and quality-of-life (QoL) assessments. Co-primary efficacy end points were change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24h. The primary comparison was between mirabegron and placebo with a secondary comparison between tolterodine and placebo. Safety parameters included adverse events (AEs), laboratory assessments, vital signs, electrocardiograms, and postvoid residual volume.
RESULTS AND LIMITATIONS: A total of 1978 patients were randomised and received the study drug. Mirabegron 50-mg and 100-mg groups demonstrated statistically significant improvements (adjusted mean change from baseline [95% confidence intervals]) at the final visit in the number of incontinence episodes per 24h (-1.57 [-1.79 to -1.35] and -1.46 [-1.68 to -1.23], respectively, vs placebo -1.17 [-1.39 to -0.95]) and number of micturitions per 24h (-1.93 [-2.15 to -1.72] and -1.77 [-1.99 to -1.56], respectively, vs placebo -1.34 [-1.55 to -1.12]; $p<0.05$ for all comparisons). Statistically significant improvements were also observed in other key efficacy end points and QoL outcomes. The incidence of treatment-emergent AEs was similar across treatment groups. The main limitation of this study was the short (12-wk) duration of treatment.
CONCLUSIONS: Mirabegron represents a new class of treatment for OAB with proven efficacy and good tolerability.