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 29th, 2014 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

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

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

II. DUR ACTIVITIES
- a. Quarterly Utilization Reports — R. Citron (OSU)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Oregon State Drug Reviews — K. Sentena (OSU)
  1. Strategies for Effective Monitoring and Management of Psychotropics in Children
  2. Evidence Based Review of Fish Oil: Going Beyond the Headlines
- e. FDB Drug File Update — T. Williams (OSU)
  1. List of Drugs
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

III. DUR OLD BUSINESS
- a. Multivitamin PA Criteria — M. Herink (OSU)
  1. PA Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- b. Hepatitis C “Readiness to Treat” — M. Herink (OSU)
  1. Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS
- a. Botulinum Toxins — M. Herink (OSU)
  1. Abbreviated Class Review
  2. Public comment
  3. Discussion of Clinical Recommendations to OHA

b. ADHD DUE — T. Williams (OSU)
1. DERP Policy Report
2. Proposed Safety Edit
3. Public Comment
4. Discussion of Clinical recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

a. Cystic Fibrosis Abbreviated Update — M. Herink (OSU)
1. Abbreviated Update
2. Kalydeco PA Criteria
3. Public Comment
4. Discussion of Clinical recommendations to OHA

b. Antidepressants Class Update — A. Meeker (OSU)
1. Vortioxetine New Drug Evaluation
2. Levomilnacipran New Drug Evaluation
3. Class Review
4. Public Comment
5. Discussion of Clinical recommendations to OHA

c. Inflammatory Bowel Agents — M. Herink (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical recommendations to OHA

d. Phosphate Binders — B. Fouts (OSU)
1. Velphoro New Drug Evaluation
2. Class Update
3. Public comment
4. Discussion of Clinical recommendations to OHA

e. Antiepileptic Class Update — K. Ketchum (OSU)
1. Class Update
2. Eslicarbazepine New Drug Evaluation
3. Public comment
4. Discussion of Clinical recommendations to OHA

f. Drug Class Scans — M. Herink/K. Ketchum (OSU)
1. Bone Metabolism
2. Erythropoiesis Stimulating Agents
3. Hepatitis B Antivirals
4. BPH
5. Overactive Bladder
6. Triptans
7. Public Comment
8. Discussion of Clinical Recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 27, 2014 1:00-5:00 PM
Wilson Training Center
29353 SW Town Center
Wilsonville, OR 97070

MEETING MINUTES

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

Members Present: Cathy Zehrung, RPh; Phillip Levine, PhD; William Origer, MD; Zahia Esber, MD; Stacy Ramirez, PharmD; James Slater, PharmD

Members Present by Phone: David Pass, MD

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

Staff Present by Phone: Kathy Sentena, PharmD, Bing-Bing Liang, PharmD, Brandy Fouts, PharmD; Sherri Willard-Argyres, PharmD

Audience: Stuart O'Brochta (Gilead)*; Richard McLeod; Ralph Magrish (Mercer), Steve Faloon (Otsuka); Kim Laubmeier (Otsuka); Bob Snediker (J & J Stock)*; Theresa Lane (Trillium); Steven Hill (Daiichi Sankyo); Bob Gustafson (Lundbeck); David Barba (Forest); Paul Bonham (Novo Nordisk); Darlene Halverson (Novartis); Mai Duong (Novartis)*; Lance Swanson (Gilead); Kim Clark, PharmD (Grifols); Jason Wideland, PharmD (Gilead); Jamie Damm (Raptor); Connie Brooks (Vertex); Emily Lein, student; Ruby Doan, student; Jeana Colabianchi, PharmD (Sunovion); D.R. McCale (Baxter)*; Kim Clark, PharmD (Grifols); Laura Hill, PharmD (Abbvie); Jim Graves (BMS); David Balhoum (Genentech); Kimberly Blood (WVP); Michelle Bice (Gilead); Matt Willett (Pfizer); B Benson (Merck); Mark Pledger (Novartis); Dr. Walter Shaffer (DMAP); Anne Marie Licos (Med Immune); Dr Kent Benner (OHSU) by phone; Kenneth Ingram, PA (OHSU) by phone;

(*) Provided verbal testimony

I. CALL TO ORDER

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

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

c. Approval of agenda and minutes presented by Dr. Origer (pages 1 - 8)

ACTION: Approved as is.

d. Department updates presented by Dr. Trevor Douglass.
Introduction of Dee Weston to Pharmacy Policy.

II. DUR OLD BUSINESS

a. Benzodiazepine Drug Use Evaluation Follow-up (pages 9 – 12)
Ms. Ketchum presented the following information:
    1. Edit or delete the 3 mg diazepam dose equivalent from the criteria

    2. To avoid false positive identification of new patients from mail order claims, extend the look back period from 100 days to 120 days

    3. Send out provider education letters to prescriber when a patient is identified as a new patient to avoid unnecessary gaps in therapy for appropriate patients.

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

b. Lovaza PA Criteria (page 13)
Dr. Herink presented the following information:

Approve Omega-3 Fatty acid PA criteria including documentation of the following:

1. Clinically diagnosed hypertriglyceridemia with triglyceride levels > 500

2. Failure or contraindication to a fibric acid derivative and niacin OR

3. The patient is taking a statin and is unable to take a fibric acid derivative or niacin due to an increased risk of myopathy.

4. Add gemfibrozil to table 1.

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

III. DUR NEW BUSINESS

a. Antipsychotic Adherence Monitoring RetroDUR Proposal (pages 20 – 35)
Dr. Williams presented the following proposal:

1. Create a weekly RetroDUR provider fax notification campaign of potentially non-adherent patients with a recent diagnosis of schizophrenia with the following reporting metrics:

    a. Provider satisfaction responses.
    b. HEDIS 2013 Adherence to Antipsychotic Medications for individuals with Schizophrenia (SAA).
    c. Hospitalization rates by antipsychotic adherence level.
    d. Pre/post hospitalization and prescription utilization rates for patients identified by program for intervention.

2. Outreach

    a. Collaborate with CCO Pharmacy Directors regarding initiative content and timing and inclusion of CCO patient's providers.
    b. Start with targeting a specific pharmacy and asking providers what information would be most helpful to them (utilization of other mental health related medications including seizure medications, benzodiazepines, and antidepressants).
    c. Evaluate use of injectable antipsychotics to determine if adherence rates differ between injectable and oral agents.
    d. Add schizoaffective disorder as inclusion criteria.

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

b. Zolpidem Drug Use Evaluation (pages 36 – 42)
Ms. Ketchum presented the following information:

1. Limit Zolpidem monthly consumption to 15 units / 30 days by prior authorization to discourage continuous daily use.

2. Place a prior authorization for women on Zolpidem 10 mg and 12.5 mg.

3. Evaluate the approved sedative benzodiazepine continuous therapies for frequently approved comorbidities and include those as approved step therapy edits for zolpidem.

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

c. Immunoglobulin Abbreviated Class Review (pages 43 – 55)
Dr. Fouts presented the class review and the following recommendations:

1. IVIG products are similar in efficacy and should be prescribed based on the risk of adverse events with each formulation, cost, and history of IIG use.

2. The choice of IVIG or SCIG should account for the individual patient's ability to administer IgG at home, compliance, availability and ease of IV access, and comorbid conditions.

3. After executive session, add Sub-Q class to PDL, and designate Gamunex C as only preferred point of sale agent and all other Sub-Q agents as non-preferred.

4. Do not create a PDL class or require PA for PADs at this time.

Public Comment:
D.R. McCale III from Baxter Bioscience presented testimony regarding IG review.

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

d. Immunoglobulin Drug Use Evaluation (pages 56 – 67)
Ms. Lee presented the evaluation and following recommendation:

1. Perform a retrospective quarterly audit and report to P&T for all lgG claims to verify billing accuracy, evidence supporting diagnosis and appropriate dosing.

ACTION: Motion, 2nd, all in favor. Approved.

e. Diclofenac Safety Evaluation (14 – 19)
Dr. Sentena presented the evaluation and following recommendations:

1. Due to limited evidence on safety data associated with diclofenac therapy and the inherent risks associated with all NSAIDs, no changes to preferred drug list are recommended at this time.

2. Revisit in one year.

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

IV. PREFERRED DRUG LIST OLD BUSINESS

a. Hepatitis C Class Update (pages 68 – 90)
Dr. Herink presented new guidelines and the following recommendations:

1. Revise sofosbuvir PA criteria for more appropriate patient selection, including criteria to avoid in patients with significant renal impairment and those who would be noncompliant for a variety of reasons.

2. Restrict sofosbuvir and simeprevir treatment to Fibrosis stage 3 and 4 patients at this time, consistent with recommendations from the hepatology workgroup.

3. Make telaprevir and boceprevir non-preferred due to increased safety concerns and guideline recommendations.

4. Continue to evaluate new evidence as it comes out for further revisions.

5. Develop and present a Readiness to Treat document at May P&T.

6. Explore opportunity to leverage 340B sole-source contract.

Public Testimony:
Dr. Kent Benner and PA Kenneth Ingram reported the community standard discussed with the Hepatitis C workgroup.

Robert Snediker from J&J Stock provided public comment.

Stuart O'Brochta from Gilead provided public comment.

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

V. PREFERRED DRUG LIST NEW BUSINESS

a. Vitamins Abbreviated Class Review - MVI and Antioxidant Supplements (pages 91-105)
Dr. Herink presented the review and following recommendations:

1. Based on evidence of no benefit on mortality, CVD, or cancer outcomes with multivitamins or antioxidant multivitamin supplements, prior authorize agents and

approve for documented nutritional deficiency or diagnosis associated with nutritional deficiency.

2. For mono vitamin supplements with evidence to support their use or insufficient evidence to make strong conclusions, evaluate comparative costs in executive session due to no evidence of superiority of individual products over another. This includes calcium, vitamin D, folic acid, vitamin B, and the ferrous salt formulations.

3. Bring back a review of other minerals and electrolytes for further decision-making.

4. Bring back as old business to the May P&T meeting and present PA criteria.

5. After review in executive session, make products without AAC and not utilization non-preferred.

6. After executive session, make the following non-preferred and do not grandfather:
   - Nascobal
   - Ferrous Sulfate Oral Susp and Drops
   - Vitamin D3 Wafers, Vitamin D2 & D3 Drops

   Make all other products preferred.

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

b. Inhaled Antibiotics Class Update (Cystic Fibrosis) (pages 106 – 115)
Dr. Herink presented the class update and following recommendations:

1. There is no new clinical evidence of effectiveness or safety resulting in recommended changes to current PDL agents. Maintain tobramycin inhalation solution as a preferred agent and evaluate comparative costs of other agents in executive session.

2. Make tobramycin inhalation powder (Tobi Podhaler) non-preferred and require step therapy with tobramycin inhalation solution before approval.

Public Comment:
Stuart O'Brochta from Gilead gave public comment.
Mai Duong from Novartis gave public comment and presented the Tobi Podhaler.

***ACTION:** After Executive Session, no changes to PDL, all in favor.

c. Procysbi® (delayed release cysteamine bitartrate) (pages 116 – 126)
Dr. Willard-Argyres presented the new drug evaluation and following recommendations:

1. Prior authorize cysteamine DR to limit its use to patients with documentation of nephropathic cystinosis and intolerance or nonadherence to cysteamine IR or inability to achieve a WBC cysteine level <1 nmol ½ cysteine per mg protein, preferably from a physician experienced in managing nephropathic cystinosis.

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

d. Topical Antifungals Class Update (pages 127 – 138)
Dr. Liang presented the new drug evaluation and following recommendations:

1. Maintain luliconazole (Luzu) a non-preferred topical antifungal medication on the PDL due to lack of long term clinical outcomes data and direct comparative data to suggest better tolerability or efficacy than currently available agents.

2. Evaluate comparative costs in executive session.

***ACTION:** After Executive Session, no changes to the PDL, all in favor.

e. Drug Class Scans
Dr. Herink presented the reviews and following recommendations:

1. Smoking Cessation (pages 139 – 146)
   a. No further research or review needed at this time; update PA criteria based on HP feedback.
   b. Evaluate comparative costs in executive session.

***ACTION:** After Executive Session, no changes to the PDL, all in favor.

2. Quick Relief medications for asthma (pages 147 – 160)
   a. No further research or review needed at this time.
   b. Evaluate comparative costs in executive session.
   c. Remove Maxair Autoinhaler as it is no longer manufactured.
   d. Add Ventolin HFA as preferred if it does not jeopardize existing contracts.

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

3. Long acting opioids (pages 161 – 191)
   a. Due to insufficient comparative evidence of efficacy and important safety concerns, maintain hydrocodone ER (Zohydro ER) as non-preferred.
   b. Evaluate comparative costs in executive session.

***ACTION:** After Executive Session, no changes to the PDL, all in favor.

4. Proton Pump Inhibitors (pages 192 – 206)
   a. No further research or review needed at this time.
   b. Evaluate comparative costs in executive session.

***ACTION:** After Executive Session, no changes to the PDL, all in favor.

5. GI – digestive enzymes (pages 207 – 210)
   a. No further research or review needed at this time,
   b. Evaluate comparative costs in executive session.

***ACTION:** After Executive Session, no changes to the PDL, all in favor.

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

Mr. Citron confirmed the next P & T meeting will be held May 29, 2014 at 1:00 pm.

VII. ADJOURN

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DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
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Pharmacy Utilization Summary Report: October 2012 - September 2013

Eligibility	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Total Members (FFS & Encounter)	619,870	618,962	621,328	621,239	624,167	626,033	624,596	625,809	625,937	625,469	626,235	626,504	627,564
FFS Members	101,337	85,412	80,358	76,316	78,706	79,138	75,030	75,828	78,595	75,688	79,105	82,146	89,820
Encounter Members	518,533	533,550	540,970	544,923	545,461	546,895	549,566	549,981	547,342	549,781	547,130	544,358	537,743

Gross Cost Figures for Drugs	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	YTD Sum
Total Amount Paid (FFS & Encounter)	$31,521,365	$29,835,532	$29,804,124	$34,535,803	$31,485,854	$32,591,115	$32,438,620	$33,142,619	$29,943,421	$33,636,556	$33,045,919	$32,360,644	$384,341,572
Mental Health Carve-Out Drugs	$7,687,961	$7,223,159	$6,981,620	$7,672,932	$7,109,959	$7,385,545	$7,690,461	$7,842,627	$7,158,815	$8,018,218	$7,865,708	$7,584,446	$140,908,984
FFS Physical Health Drugs	$3,605,389	$2,716,517	$2,592,539	$2,865,846	$2,379,719	$2,485,163	$2,401,600	$2,400,158	$2,119,226	$2,335,549	$2,231,382	$2,224,912	$47,647,617
FFS Physician Administered Drugs	$1,689,755	$1,434,930	$1,222,412	$1,429,209	$1,062,759	$1,221,540	$1,293,629	$1,364,432	$1,110,378	$1,241,816	$936,143	$1,020,310	$15,027,315
Encounter Physical Health Drugs	$15,305,683	$15,438,460	$15,473,799	$18,440,188	$17,156,744	$17,819,741	$17,518,342	$17,343,358	$16,089,506	$17,718,172	$17,976,828	$17,449,343	$255,337,671
Encounter Physician Administered Drugs	$3,232,576	$3,022,465	$3,533,753	$4,127,629	$3,776,674	$3,679,126	$3,534,588	$4,192,043	$3,465,497	$4,322,801	$4,035,859	$4,081,633	$45,004,642

Quarterly Rebates Invoiced	2012-Q4	2013-Q1	2013-Q2	2013-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$25,592,269	$47,003,213	$51,259,195	$42,267,172	$207,217,221
CMS MH Carve-out	$9,980,744	$11,356,618	$11,511,668	$11,886,020	$56,616,912
SR MH Carve-out					$0
CMS FFS Drug	$4,796,925	$4,625,970	$4,249,034	$4,135,570	$22,004,025
SR FFS	$265,613	$190,429	$163,110	$134,912	$944,627
CMS Encounter	$10,447,011	$30,616,811	$34,974,040	$25,981,322	$126,561,413
SR Encounter	$101,977	$213,385	$361,342	$129,349	$1,090,243

Quaterly Net Drug Costs	2012-Q4	2013-Q1	2013-Q2	2013-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$65,568,751	$51,609,559	$44,265,465	$56,775,947	$259,183,990
Mental Health Carve-Out Drugs	$11,911,997	$10,811,818	$11,180,234	$11,582,351	$57,110,799
FFS Phys Health + PAD	$8,199,006	$6,627,837	$6,277,279	$5,719,631	$29,382,533
Encounter Phys Health + PAD	$45,457,748	$34,169,905	$26,807,952	$39,473,965	$172,690,658

PMPM Drug Costs (Excludes Rebate)	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$50.85	$48.20	$47.97	$55.59	$50.44	$52.06	$51.94	$52.96	$47.84	$53.78	$52.77	$51.65	$51.34
Mental Health Carve-Out Drugs	$12.40	$11.67	$11.24	$12.35	$11.39	$11.80	$12.31	$12.53	$11.44	$12.82	$12.56	$12.11	$12.46
FFS Physical Health Drugs	$35.58	$31.80	$32.26	$37.55	$30.24	$31.40	$32.01	$31.65	$26.96	$30.86	$28.21	$27.08	$30.02
FFS Physician Administered Drugs	$16.67	$16.80	$15.21	$18.73	$13.50	$15.44	$17.24	$17.99	$14.13	$16.41	$11.83	$12.42	$15.53
Encounter Physical Health Drugs	$29.52	$28.94	$28.60	$33.84	$31.45	$32.58	$31.88	$31.53	$29.40	$32.23	$32.86	$32.05	$29.95
Encounter Physician Administered Drugs	$6.23	$5.66	$6.53	$7.57	$6.92	$6.73	$6.43	$7.62	$6.33	$7.86	$7.38	$7.50	$6.90

Last Updated: April 16, 2014

Drug Use Research & Management Program
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Pharmacy Utilization Summary Report: October 2012 - September 2013

Claim Counts	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Total Claim Count (FFS & Encounter)	627,037	600,449	596,011	672,262	601,004	619,508	613,090	607,069	559,657	607,256	600,226	585,729	7,289,298
Mental Health Carve-Out Drugs	105,328	100,288	98,134	102,461	91,859	96,373	97,596	98,005	89,131	96,803	94,055	90,473	1,793,424
FFS Physical Health Drugs	88,148	71,174	67,299	70,146	63,324	65,347	65,134	63,265	58,216	62,384	60,414	59,618	1,198,794
FFS Physician Administered Drugs	10,246	8,544	7,777	9,348	8,414	8,372	8,390	8,468	7,802	8,222	8,201	7,518	101,302
Encounter Physical Health Drugs	390,862	386,809	389,896	450,488	402,894	414,541	406,727	400,093	371,176	403,746	400,576	392,603	5,981,819
Encounter Physician Administered Drugs	32,453	33,634	32,905	39,819	34,513	34,875	35,243	37,238	33,332	36,101	36,980	35,517	422,610

Amount Paid per Claim	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Average Paid / Claim (FFS & Encounter) (Rebates Excluded)	$50.27	$49.69	$50.01	$51.37	$52.39	$52.61	$52.91	$54.59	$53.50	$55.39	$55.06	$55.25	$52.75
Mental Health Carve-Out Drugs	$72.99	$72.02	$71.14	$74.89	$77.40	$76.64	$78.80	$80.02	$80.32	$82.83	$83.63	$83.83	$78.76
FFS Physical Health Drugs	$40.90	$38.17	$38.52	$40.86	$37.58	$38.03	$36.87	$37.94	$36.40	$37.44	$36.93	$37.32	$39.52
FFS Physician Administered Drugs	$164.92	$167.95	$157.18	$152.89	$126.31	$145.91	$154.19	$161.13	$142.32	$151.04	$114.15	$135.72	$147.81
Encounter Physical Health Drugs	$39.16	$39.91	$39.69	$40.93	$42.58	$42.99	$43.07	$43.35	$43.35	$43.88	$44.88	$44.45	$42.69
Encounter Physician Administered Drugs	$99.61	$89.86	$107.39	$103.66	$109.43	$105.49	$100.29	$112.57	$103.97	$119.74	$109.14	$114.92	$106.34

Amount Paid per Claim - Multi Source Drugs	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$23.54	$23.30	$23.04	$22.54	$22.92	$23.02	$23.05	$23.14	$22.77	$23.21	$23.71	$23.89	$23.28
Mental Health Carve-Out Drugs	$36.29	$34.71	$34.08	$34.73	$35.31	$35.13	$35.89	$36.01	$35.34	$38.36	$38.82	$39.20	$35.99
FFS Physical Health Drugs	$22.60	$20.96	$20.42	$20.71	$19.99	$20.61	$20.26	$20.87	$20.12	$20.69	$20.97	$20.57	$20.77
Encounter Physical Health Drugs	$20.36	$20.81	$20.75	$20.10	$20.62	$20.64	$20.50	$20.43	$20.24	$20.07	$20.67	$20.95	$20.54

Amount Paid per Claim - Single Source Drugs	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$289.25	$294.72	$293.75	$309.14	$326.14	$334.47	$341.96	$349.79	$351.67	$358.40	$359.16	$341.43	$332.52
Mental Health Carve-Out Drugs	$432.76	$433.78	$433.89	$460.95	$464.19	$460.79	$463.73	$476.47	$483.89	$485.86	$484.91	$482.67	$477.02
FFS Physical Health Drugs	$240.49	$229.81	$237.95	$256.17	$231.51	$232.00	$225.06	$230.89	$222.23	$222.76	$217.34	$223.92	$246.99
Encounter Physical Health Drugs	$255.95	$264.30	$262.27	$277.66	$302.38	$314.32	$323.03	$328.63	$330.85	$340.89	$342.83	$318.56	$308.25

Multi-Source Drug Use Percentage	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Multi-Source Drug Use Percentage	91.7%	91.8%	91.8%	91.6%	91.8%	92.0%	92.0%	92.0%	92.0%	92.0%	92.0%	91.7%	91.9%
Mental Health Carve-Out Drugs	90.7%	90.7%	90.7%	90.6%	90.2%	90.2%	90.0%	90.0%	90.0%	90.1%	90.0%	89.9%	90.3%
FFS Physical Health Drugs	91.6%	91.8%	91.7%	91.4%	91.7%	91.8%	91.9%	91.9%	91.9%	91.7%	91.9%	91.8%	91.7%
Encounter Physical Health Drugs	92.0%	92.2%	92.2%	91.9%	92.2%	92.4%	92.5%	92.6%	92.6%	92.6%	92.5%	92.1%	92.3%

Preferred Drug Use Percentage	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Avg Monthly
Preferred Drug Use Percentage	86.83%	86.73%	86.59%	86.89%	86.96%	87.02%	87.02%	84.95%	84.95%	84.96%	84.88%	84.67%	85.7%
Mental Health Carve-Out Drugs	70.33%	70.74%	70.77%	73.16%	73.10%	73.02%	73.05%	71.89%	71.16%	71.06%	71.19%	71.20%	72.0%
FFS Physical Health Drugs	94.12%	93.89%	93.66%	92.37%	92.48%	92.18%	92.29%	91.10%	91.37%	91.23%	91.56%	91.77%	92.4%
Encounter Physical Health Drugs	90.09%	90.00%	89.80%	89.58%	89.71%	89.83%	89.98%	87.72%	87.87%	87.87%	87.67%	87.36%	88.5%

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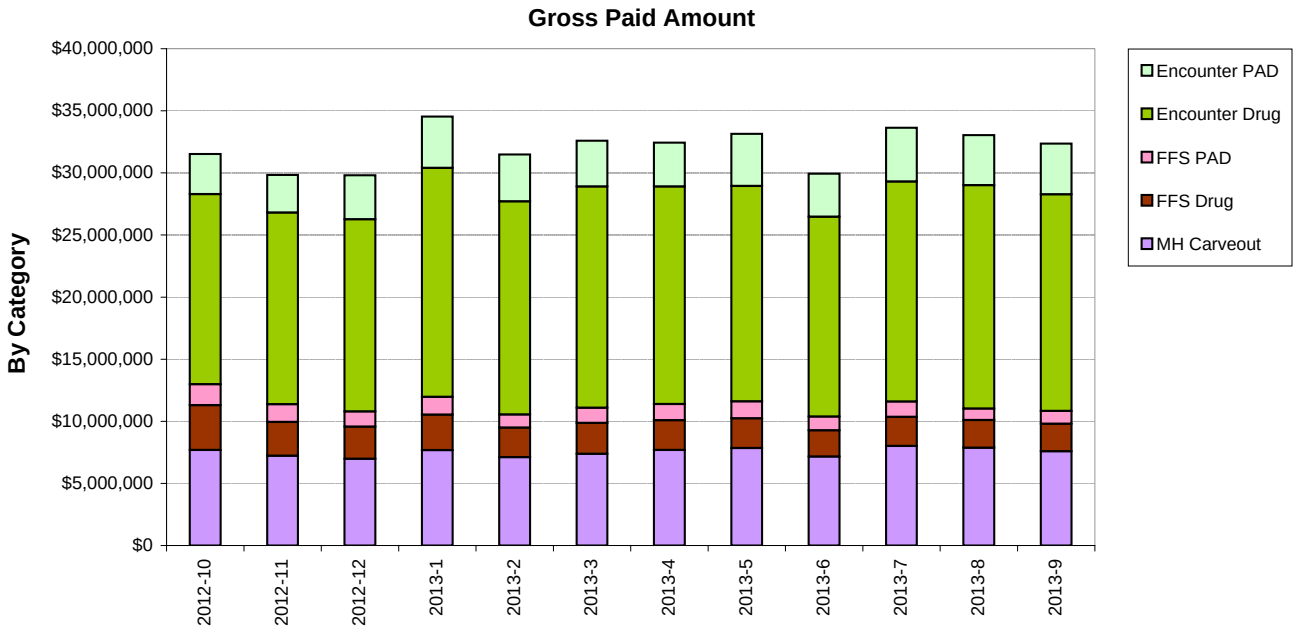
Pharmacy Utilization Summary Report: October 2012 - September 2013



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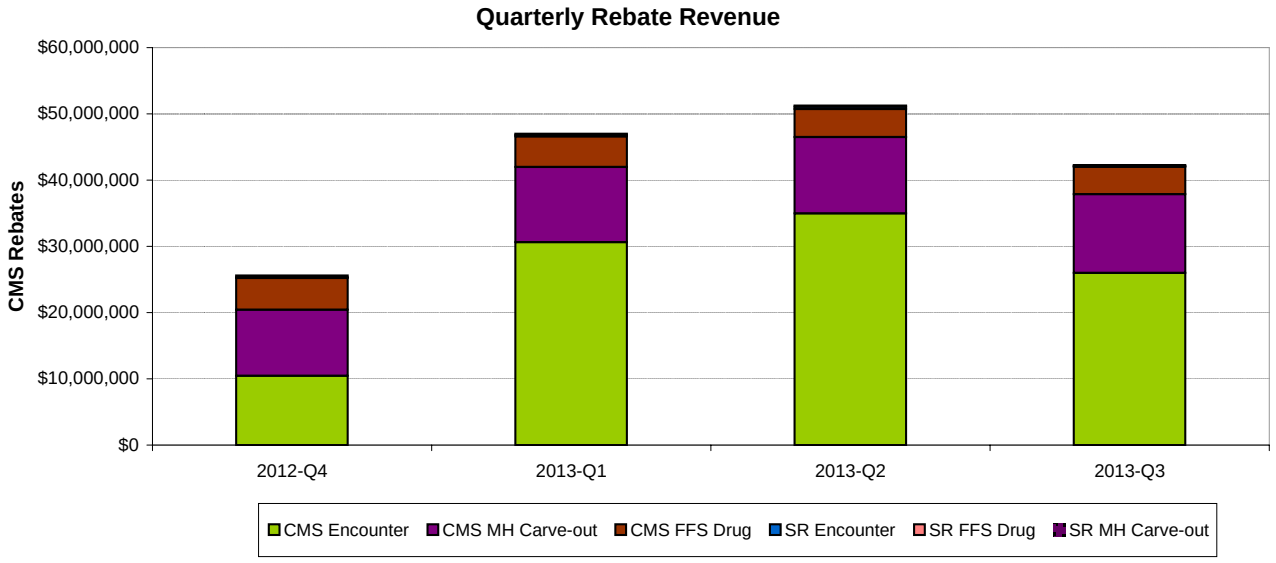
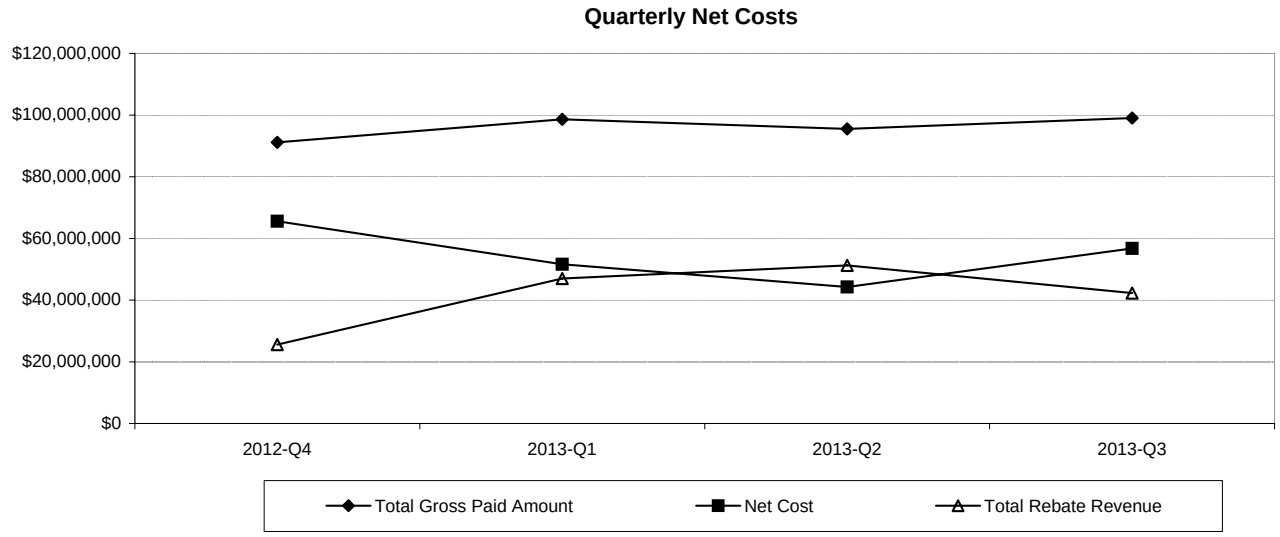
Pharmacy Utilization Summary Report: 2012 Q4 - 2013 Q3





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Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2014

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$8,505,935	21.6%	10,568	$805	V
2	DULOXETINE HCL	Antidepressants - 2nd Gen	$3,258,920	8.3%	14,143	$230	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,358,080	3.5%	2,538	$535	V
4	INTUNIV	ADHD Drugs	$1,351,470	3.4%	5,588	$242	V
5	STRATTERA	ADHD Drugs	$1,095,364	2.8%	4,303	$255	Y
6	LATUDA	Antipsychotics, 2nd Gen	$1,039,714	2.6%	1,538	$676	V
7	INVEGA SUSTENNA	Antipsychotics, 2nd Gen	$817,583	2.1%	641	$1,275	V
8	INVEGA	Antipsychotics, 2nd Gen	$589,361	1.5%	795	$741	V
9	DIVALPROEX SODIUM ER	Antiepileptics	$585,310	1.5%	3,300	$177	Y
10	RISPERDAL CONSTA	Antipsychotics, 2nd Gen	$422,713	1.1%	622	$680	V
11	ZIPRASIDONE HCL	Antipsychotics, 2nd Gen	$398,545	1.0%	3,012	$132	Y
12	TRUVADA	STC 33 - Antivirals	$361,000	0.9%	340	$1,062	
13	MODAFINIL	ADHD Drugs	$355,943	0.9%	601	$592	V
14	ATRIPLA	STC 33 - Antivirals	$343,034	0.9%	193	$1,777	
15	SERTRALINE HCL	Antidepressants - 2nd Gen	$301,348	0.8%	25,726	$12	Y
16	SAPHRIS	Antipsychotics, 2nd Gen	$297,962	0.8%	674	$442	V
17	BUPROPION XL	Antidepressants - 2nd Gen	$284,027	0.7%	10,092	$28	V
18	PRISTIQ ER	Antidepressants - 2nd Gen	$277,695	0.7%	1,319	$211	V
19	FLUOXETINE HCL	Antidepressants - 2nd Gen	$274,159	0.7%	23,459	$12	Y
20	LAMOTRIGINE	Antiepileptics	$267,841	0.7%	926	$289	V
21	TRAZODONE HCL	STC 11 - Psychostimulants, Antidepressants	$264,983	0.7%	28,403	$9	
22	COMPLERA	STC 33 - Antivirals	$228,638	0.6%	146	$1,566	
23	LAMOTRIGINE	Antiepileptics	$221,120	0.6%	15,004	$15	Y
24	LANTUS	Insulins	$219,633	0.6%	830	$265	Y
25	BUPROPION HCL SR	Antidepressants - 2nd Gen	$217,626	0.6%	9,081	$24	Y
26	STRIBILD	STC 33 - Antivirals	$211,521	0.5%	97	$2,181	
27	Factor Viii Recombinant Nos	Physican Administered Drug	$201,471	0.5%	9	$22,386	
28	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$199,180	0.5%	9,263	$22	Y
29	CITALOPRAM HBR	Antidepressants - 2nd Gen	$198,674	0.5%	24,040	$8	Y
30	PROAIR HFA	Asthma Rescue	$195,112	0.5%	3,766	$52	Y
31	CYMBALTA	Antidepressants - 2nd Gen	$192,105	0.5%	1,257	$153	V
32	HUMIRA	Targeted Immune Modulators	$192,040	0.5%	85	$2,259	Y
33	SYNAGIS	STC 33 - Antivirals	$191,503	0.5%	70	$2,736	
34	RISPERIDONE	Antipsychotics, 2nd Gen	$191,322	0.5%	10,875	$18	Y
35	CLOZAPINE	Antipsychotics, 2nd Gen	$190,480	0.5%	2,370	$80	Y
36	LORAZEPAM	Benzodiazepine Anxiolytics	$184,377	0.5%	18,697	$10	
37	Xyntha Inj	Physican Administered Drug	$175,093	0.4%	6	$29,182	
38	METHYLPHENIDATE ER	ADHD Drugs	$172,568	0.4%	1,525	$113	N
39	VENLAFAXINE HCL ER	Antidepressants - 2nd Gen	$169,657	0.4%	9,041	$19	Y
40	VIIBRYD	Antidepressants - 2nd Gen	$166,201	0.4%	1,038	$160	V
		Aggregate	**$39,333,313**		**590,511**	**$296**	

Notes
- FFS Drug Costs only, no rebate excluded
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class

Last updated: April 16, 2014

ProDUR Report for January to March 2014

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	36	17	0	19	0.04%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,248	350	0	898	1.36%
DD (Drug/Drug Interaction)	Set alert/Pay claim	234	59	0	175	0.25%
ER (Early Refill)	**Set alert/Deny claim**	62,472	11,237	37	51,196	67.94%
ID (Ingredient Duplication)	Set alert/Pay claim	16,460	4,182	2	12,262	17.90%
LD (Low Dose)	Set alert/Pay claim	899	188	0	711	0.98%
LR (Late Refill/Underutilization)	Set alert/Pay claim	83	48	0	35	0.09%
MC (Drug/Disease Interaction)	Set alert/Pay claim	1,821	698	0	1,119	1.98%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	565	151	0	414	0.61%
PG (Pregnancy/Drug Interaction)	**Set alert/Deny claim**	2,104	1,354	3	747	2.29%
TD (Therapeutic Duplication)	Set alert/Pay claim	6,033	1,712	0	4,316	6.56%
	Totals	**91,955**	**19,996**	**42**	**71,892**	**100.00%**

ProDUR Report for January to March 2014							
Top Drugs in Each DUR Alerts							
DUR Alert	**Drug Name**	**# Alerts**	**# Overrides**	**# Cancellations & Non-Response**	**# Claims Screened**	**% Alerts/Total Claims**	**% Alerts Overridden**
DC	Haloperidol	170	37	133	2,161	7.9%	21.8%
	Wellbutrin (Bupropion)	361	58	303	28,106	1.3%	16.1%
	Diazepam	62	15	47	10,425	0.6%	24.2%
DD	Geodon (Ziprasidone)	78	23	55	4,163	1.9%	29.5%
	Celexa (Citalopram)	37	3	34	30,809	0.1%	8.1%
ER	Hydrocodone/APAP	322	77	245	8,462	3.8%	23.9%
	Oxycodone	217	87	130	3,348	6.5%	40.1%
	Lorazepam	1,772	386	1,385	24,327	7.3%	21.8%
	Alprazolam	1,238	219	1,019	17,261	7.2%	17.7%
	Lamictal (Lamotrigine)	2,696	549	2,147	21,651	12.5%	20.4%
	Abilify (Aripiprazole)	1,783	299	1,484	14,278	12.5%	16.8%
	Seroquel (Quetiapine)	2,256	473	1,783	16,077	14.0%	21.0%
	Risperdal (Risperidone)	1,988	445	1,543	14,490	13.7%	22.4%
	Wellbutrin (Bupropion)	2,665	380	2,285	28,106	9.5%	14.3%
	Zoloft (Sertraline)	3,550	649	2,901	33,124	10.7%	18.3%
	Celexa (Citalopram)	2,770	367	2,403	30,809	9.0%	13.2%
	Prozac (Fluoxetine)	2,751	427	2,324	28,977	9.5%	15.5%
	Trazodone	3,806	565	3,241	33,966	11.2%	14.8%
	Cymbalta (Duloxetine)	1,927	289	1,638	21,397	9.0%	15.0%
ID	Lamictal (Lamotrigine)	1,019	267	752	21,651	4.7%	26.2%
	Seroquel (Quetiapine)	1,176	334	840	16,077	7.3%	28.4%
	Risperdal (Risperidone)	635	190	445	14,490	4.4%	29.9%
	Zoloft (Sertraline)	878	255	623	33,124	2.7%	29.0%
	Prozac (Fluoxetine)	727	156	571	28,977	2.5%	21.5%
PG	Lorazepam	225	177	48	24,327	0.9%	78.7%
	Alprazolam	163	127	36	17,261	0.9%	77.9%
	Ibuprofen	507	378	129	4,395	11.5%	74.6%
TD	Lamictal (Lamotrigine)	482	137	344	21,651	2.2%	28.4%
	Depakote (Divalproex Sodium)	332	96	236	11,476	2.9%	28.9%
	Seroquel (Quetiapine)	571	155	416	16,077	3.6%	27.1%
	Zyprexa (Olanzapine)	214	75	199	9,726	2.2%	35.0%
	Risperdal (Risperidone)	320	95	225	14,490	2.2%	29.7%

ProDUR Report for January to March 2014

Top Drugs in Early Refill

DUR Alert	Drug Name	CC-3 Vacation Supply	Unique recipient ID's for VS	CC-4 Lost Rx	Unique recipient ID's for Lost	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	4	4	9	8	41	3	57	1
	Hydrocodone Bit/APAP	1	1	1	1	40	0	18	0
	Oxycodone HCl	4	4	2	2	44	4	34	0
	Lorazepam	9	9	14	14	144	4	110	1
	Alprazolam	9	7	12	12	96	1	61	0
	Diazepam	5	5	2	2	54	1	46	0
	Buspar (Buspirone)	3	3	8	8	61	0	52	0
	Lamictal (Lamotrigine)	15	13	27	15*	176	8	159	0
	Depakote (Divalproex Sodium)	8	8	7	6	81	3	112	0
	Clonazepam	1	1	3	3	23	1	28	0
	Gabapentin	2	1	3	3	45	3	29	0
	Abilify (Aripiprazole)	7	5	12	12	82	9	123	1
	Seroquel (Quetiapine)	15	14	19	19	119	6	160	0
	Risperdal (Risperidone)	10	9	14	14	140	5	300	0
	Zyprexa (Olanzapine)	9	7	12	11	60	3	100	0
	Geodon (Ziprasidone)	4	4	3	2	21	4	33	0
	Albuterol	2	2	3	3	12	1	24	0
	Lithium Carbonate	4	4	5	5	70	1	63	0
	Wellbutrin (Bupropion)	18	15	18	17	83	6	137	0
	Prilosec (Omeprazole)	1	1	3	3	15	0	26	0
	Zoloft (Sertraline)	16	16	39	36	263	9	167	0
	Celexa (Citalopram)	11	10	25	24	109	11	125	0
	Prozac (Fluoxetine)	16	16	30	28	153	6	130	0
	Lexapro (Escitaloprim)	9	9	10	10	55	4	58	0
	Paxil (Paroxetine)	4	4	5	5	32	1	34	0
	Trazodone	27	25	26	26	205	9	207	0
	Cymbalta (Duloxetine)	15	13	11	11	90	2	83	1
	Effexor (Venlafaxine)	11	11	14	14	55	0	72	0
	Amitriptyline	6	6	7	4	93	2	62	0
	Straterra (Atomoxetine)	3	3	3	3	17	1	34	0
	TOTALS	**249**	**230**	**347**	**306**	**2479**	**108**	**2644**	**4**

# Clients with 3+ vacation supplies	14	3+ Lost	16
# Clients with 5+ vacation supplies	2	5+ Lost	1

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

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Apr - Jun
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified		59	10	
		Profiles Sent		31	6	
		Responses Received		9	0	
		Response Rate		29%	0%	
		Information Useful or Will Change Practice		5	0	
		Patient Not With Office		0	0	
		Already Scheduled		4	0	
		Will Not Schedule		0	0	
		Requested No Future Notifications		1	0	
	Antipsychotic Metabolic Monitoring	Members Identified		707	290	
		Profiles Sent		706	290	
		Members With Response		65	15	
		Response Rate		9%	5%	
		Newly Scheduled		36	4	
		Provider Contacted		76	91	
		Provider Responses		5	7	
		Provider Agreed with Recommendation		3	2	
		Patient Not With Office		5	5	
	Polypharmacy	Members Identified		408	66	
		Profiles Sent		390	54	
		Responses Received		185	8	
		Response Rate		47%	15%	
		Information Useful or Will Change Practice		37	0	
		Patient Not With Office		19	2	

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Retro-DUR Intervention History by Quarter FFY 2013 - 2014

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Apr - Jun
Profile Review	Children under age 12 antipsychotic	Profiles Reviewed	122	98	27	
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	33	24	2	
	Children under age 18 on any psychotropic	Profiles Reviewed	195	92	32	
	Children under age 6 on any psychotropic	Profiles Reviewed	5	10	4	
	Lock-In	Profiles Reviewed	41	84		
		Letters Sent To Providers	6	3		
		Provider Responses	0	0		
		Provider Agreed / Found Info Useful	0	0		
		Locked In	17	56		

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2013 - 2014

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

4/15/2014

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

Fee For Service

Fiscal Year 2013 - 2014

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

4/15/2014

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

By Ted D. Williams, Pharm.D., BCPS, Oregon State University College of Pharmacy

Background

There is a growing awareness and diagnosis of mental health disorders in children. The 2003 National Comorbidity Survey Replication – Adolescent Supplement (NCS-A) found in adolescents with at least one diagnosable mental health disorder, 42% meet diagnostic criteria for disorders in two or more major diagnostic classes. According to the Center for Disease Control's report on the results of the National Health Interview Survey from 2004-2006, 8.4% of American children 6-17 had at one point been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).[2] The report also indicated the diagnosis of ADHD was more prevalent in children covered by a Medicaid program (11.6%).

The use of psychotropic medications in children is common. Data from 2001-2002 showed 13.5% of all child welfare patients were receiving psychotropics.[3] As of January 2013, 18.5% of children in the Oregon Child Welfare Program received at least one psychotropic. Of these, 48% received at least one antipsychotic. In the entire Oregon Medicaid program, 29% (3,115 of 10,588) of children receiving any psychotropic received at least one antipsychotic.

A variety of state and national agencies are working to develop practice tools and standards for the monitoring of the treatment of mental health disorders in children. These standards focused on the monitoring of, rather than restrictions to, psychotropic medications. The Oregon Health Authority (OHA) has leveraged the work done by these organizations agencies to develop standardized quality metrics.[4–8]

Oregon Pharmacy and Therapeutics Committee Recommendations

In September 2013, the Oregon Pharmacy and Therapeutics (P&T) Committee recommended three quality improvement initiatives for the use of psychotropics medications in children.[10] Each program has four common elements: actionable, patient-specific information, education on evidence-informed care, and a report card on prescribing and monitoring practices. These report cards are intended to raise the awareness of prescribing practices in the Oregon Medicaid population in general and within different specialties. Each report compares the provider's monitoring or prescribing rates to both the overall Medicaid rate as well as their specialty (e.g. Psychiatrists, Family Practice Nurse Practioners, etc). The intent is not to limit practice, but rather to help inform care decisions.

Program Goals

- Improve the continuity of care for children treated for mental health disorders
- Support timely safety and efficacy monitoring of psychotropics through clinician notifications
- Provide actionable, patient specific information along with evidence informed recommendations
- Provide clinicians comparative data on their health care practices

Program Descriptions

The most intensive and highest profile quality improvement initiative focuses on the ongoing monitoring and management of children on unconventional psychotropic therapy. These therapies include children on 5 or more concurrent psychotropics for at least 90 days, 2 concurrent antipsychotics for at least 90 days, or children under 6 years old receiving psychotropics other than central nervous system stimulants. These three regimens were determined to be indicative of patients with complex mental health conditions requiring greater support and monitoring. For these patients, providers are being asked to complete a 6 question survey on the goals of therapy and barriers they have found to coordination of care. A complete list of the questionnaire can be found in the September 2013 P & T Committee meeting packet, available at: http://pharmacy.oregonstate.edu/drug_policy/meetings. The Division of Medical Assistance Programs (DMAP) will use this information to craft policies and interventions to better support providers caring for the needs of these children. Each week, pharmacy claims will be analyzed to identify patients beginning psychotropic therapy warranting additional monitoring. Non-responding providers will be sent new requests every three months. Annual requests for updated care plans will be sent for all patients.

Implementation Schedule

- ADHD February 12, 2014
- Pediatric Psychotropic Polypharmacy February 26, 2014
- Metabolic Monitoring March 12, 2014

The program with the largest population of patients notifies providers of children receiving antipsychotics who do not have a claim for annual glucose monitoring. Providers will receive a list of all patients for who they have prescribed antipsychotics with a request for the status of glucose monitoring. The date of the most recent medical claim for glucose monitoring is included with the patient's information. The list will only be sent for patients without a claims history indicating a glucose test within the last 12 months. Although more frequent monitoring may be clinically appropriate, annual glucose screening is considered the minimum standard of care for all non-diabetic patients receiving antipsychotic therapy.[11] Educational materials for this program include the American Diabetes Association recommended monitoring schedule,

comparison of the metabolic effects of five common antipsychotics, the criteria for metabolic syndrome in children, and an evidence summary of strategies for mitigating the metabolic risks of antipsychotics in children. Recommendations for the monitoring of metabolic effects of antipsychotics was discussed in a 2013 newsletter, available at: http://pharmacy.oregonstate.edu/drug_policy/newsletter.

The project with the smallest scope sends clinicians a reminder to schedule an initial follow up visit within 30 days for fee-for-service patients receiving their first ADHD medication. This is a new Healthcare Effectiveness Data and Information Set (HEDIS) measure and a CCO incentive measure. Educational materials for this program include the American Academy of Pediatrics 2011 recommendations for the treatment of ADHD in children and an assortment of internet links, including the AHRQ Parent's guide to ADHD. Due to the time sensitive nature of this program, faxes will be sent on a weekly basis for all newly identified patients. Providers will only receive one notification for a patient. These educational materials are available in the September 2013 P & T agenda packet, available at: http://pharmacy.oregonstate.edu/drug_policy/meetings.

In addition to centralized DMAP monitoring and management of psychotropic pharmacotherapy, these data are available to the CCOs via an online dashboard. This allows the CCOs to develop strategies customized to their local provider needs and preferences. DMAP has presented these initiatives to the CCO pharmacy directors meeting to promote coordinated messaging. Nonetheless, providers may receive message from DMAP as well as CCOs regarding these patients. If this should occur, providers should respond to both messages with the requested information.

Program Goals & Implementation Timeline

The overarching goal of the program is to raise awareness of the importance of careful management of psychotropics in children, without restricting access to therapy. The "carving out" of many mental health medications may cause barriers to the coordination of care. The quality and consistency of care is expected to improve with the collection and dissemination of care across both providers and health plans. Further improvements can be achieved by raising provider's awareness of current evidence based practices and the practice patterns of other clinicians. The inclusion of actionable, patient specific information allows providers to make meaningful improvements in the care of patient immediately, further reinforcing best practices.

The program roll out will be staggered to minimize the disruption for providers and maximize response rates. The ADHD program will be the first program due to the small number of patients and providers impacted (5-10 patients per week). February 12, 2014 is the anticipated start date for the ADHD program. The pediatric polypharmacy reports will follow approximately 2 weeks later. This program requests detailed clinical information from a smaller group of providers (approximately 300 providers). Finally the metabolic monitoring program will send faxes affecting over 1,000 children to approximately 500 providers. The anticipated start date for this program is March 12, 2014.

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Evidence Based Review of Fish Oil: Going Beyond the Headlines

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Omega-3 fatty acids are postulated to have beneficial effects in patients at risk for vascular disease, including the prevention of stroke, sudden cardiac death and heart failure; adjunctive therapy for the treatment mood disorders such as major depression and bipolar disorders; prevention of cognitive decline and dementia in Alzheimer's patients and in cancer prevention. Over the years, headlines of fish oil have been covered widely in the media with conflicting claims of its benefit or harm.[1–4] This review will summarize the evidence reviewed and conclusions drawn from the high quality meta-analyses and systematic reviews evaluating the therapeutic effects of fish oil supplementation on the previous identified outcomes.

Summary of the Evidence

The high quality meta-analysis and systematic reviews published in the past 10 years were examined. These reviews had high confidence that the evidence reflects the true effect; and further research is very unlikely to change our confidence in the estimate of effect. See Table 1 for the grading definitions and Table 2 for the summary of these reviews.

Cardiovascular Disease (CVD)

- Omega -3 fatty acids do not reduce cardiovascular (CV) events (primary and secondary prevention of myocardial infarction, stroke and cardiovascular death).[5–9] (*Level of Evidence: Moderate)*
- Fish oil supplements have no significant beneficial effect in controlling atrial fibrillation (AF).[10–12] (*Level of Evidence: Moderate)*
- Omega – 3 fatty acids improve cardiac function in patients with chronic heart failure (CHF)[13] and lower blood pressure[14], but the changes are too small to make a clinical difference. (*Level of Evidence: Low)*

Cancer

- Fish oil supplements are of no benefit for cancer prevention based on 3 systematic reviews including observational studies.[15–17] (*Level of Evidence: Moderate)*

Cognitive Function and Dementia

- Omega – 3 fatty acids show no benefit on cognitive function in cognitively healthy older people and patients with Alzheimer's disease (AD) but there was a small benefit for immediate recall and attention, and processing speed in subjects with cognitive impairment without dementia.[18] (*Level of Evidence: Moderate)*
- When used for 6-40 months, Omega-3 fatty acids did not prevent dementia in healthy participants over the age of 60 years who were cognitively healthy.[19] (*Level of Evidence: Low)*

Psychiatric Disorders

- Evidence on effectiveness of omega-3 fatty acids for the treatment of bipolar symptoms and depression is inconclusive.[20-23] (*Level of Evidence: Low)*

Safety

- A consistent theme throughout multiple trials was that Omega-3 fatty acids/fish oil supplements are safe and well tolerated.[6,15,18,19] (*Level of Evidence: Moderate)*

Conclusion

The currently available evidence does not support claims of beneficial outcomes from the use of omega-3 fatty acids for any of the following indications: prevention of stroke, sudden cardiac death and heart failure, adjunctive therapy for the treatment of mood disorders such as major depression and bipolar disorders, prevention of cognitive decline and dementia in Alzheimer's patient, and cancer prevention. Ongoing randomized clinical trials are still investigating the benefits in cardiovascular disease and mood disorders.[24-27]

Policy Changes in Response to the Evidence – Implementation 5/1/14

- Retain legend omega-3 acid ethyl ester (i.e. Lovaza™) as non-preferred on Preferred Drug List (PDL) for treatment of hypertriglyceridemia.
- Put all over-the-counter omega-3 fatty acids/fish oil products on the "Excluded Drug List". Products on this list used for funded diagnoses will be approved through the administrative appeals process.

Table 1. Strength of Evidence Grades and Definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

Table 2: Summary of Meta-analyses and Systematic Reviews

Disease	Significant Findings
CV Events	Delgado-Lista J et al:[5] Marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk.
	Kotwal S et al:[6]There was no overall effect of Omega-3 fatty acids on composite cardiovascular events or on total mortality. Adverse events were more common in the treatment group than the placebo group, predominantly because of an excess of gastrointestinal side effects.
	Kwak SM et al:[7] Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events, all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke.
	Larsson SC et al:[8] No association between omega-3 fatty acids intake and stroke, but suggests that women might benefit from a higher intake of omega-3 fatty acids.
	Rizois EC et al:[9] Omega-3 fatty acids are not statistically significantly associated with major cardiovascular outcomes across various patient populations.
Arrhythmias	Armaganijan L et al:[10] The use of omega-3 fatty acids was not associated with a reduction in the occurrence of postoperative AF in the patients undergoing cardiac surgery compared to the untreated patients.
	Leon H et al:[11] Fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of eicosapentaenoic acid (EPA) or docosahexanoic acid (DHA) to reduce these outcomes is insufficient.

	Liu T et al:[12] Omega-3 fatty acids had no significant effect on the prevention of AF.
CHF	Xin W et al:[13] Left ventricular ejection fraction was significantly increased and left ventricular end-systolic volume was significantly decreased in the fish oil group compared with the placebo group, although left ventricular end-diastolic volume was not significantly affected.
Blood Pressure	Campell F et al:[14] There was a statistically significant reduction in systolic and diastolic BP; 2.56 mmHg and 1.47 mmHg respectively in hypertensive participants; non-significant reduction in both systolic and diastolic BP in normotensive participants.
Cancer	Ries A et al:[15]Insufficient evidence to support a net benefit of fish oil in cachexic patients with advanced cancer. Adverse effects were raret with no severe adverse effects.
	Gerber, et al:[16] A probable level of evidence that fish oil is neither a risk factor nor a beneficial factor with regards to cancers.
	Szmanski KM et al:[17] There was no strong evidence of protective association of fish consumption with prostate cancer incidence but there is a significant 63% reduction on prostate cancer-specific mortality.
Cognition/ Dementia	Mazereeuw G et al:[18] Omega-3 fatty acid treatment was associated with a small, but significant benefit for immediate recall and attention and processing speed in subjects with cognitive impairment and no dementia, but not in healthy subjects or those with AD.
	Sydenham E et al:[19] Omega-3 fatty acids when used for 6-40 months did not prevent dementia in healthy participants over the age of 60 years who were cognitively healthy. Minor adverse events were reported by fewer than 15% of participants.
Bipolar Disorder	Turnbull T et al:[20] Studies using an omega-3 combination of EPA and DHA demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single agent did not. Side effect profile is benign.
	Bloch MH et al:[21] There is limited evidence for omega-3 fatty acids supplementation being an effective acute treatment for depression.
Depression	Sublette ME et al:[22] Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores.
	Appleton KM et al:[23] The were increased effects of omega-3 fatty acids on improvements in depressed mood, but it remains difficult to summarize because of considerable heterogeneity.

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Recent Additions to the First DataBank (FDB) Drug File

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

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

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

Week of:	Generic	Brand	FDA Approved Indication(s)	ICD9 Code	HERC Funding Line
3/16/14	TASIMELTEON	Hetlioz	Non-24-Hour Sleep-Wake Disorder	327.3	636
4/20/14	DROXIDOPA	Northera	Neurogenic Orthostatic Hypotension	458.0	555
4/28/14	METRELEPTIN	Myalept	Congenital generalized or acquired generalized lipodystrophy	272.6	688

Multi-Vitamins and Antioxidant Multivitamin Combinations

Goal(s):

- Approve only for documented nutritional deficiency or diagnosis associated with nutritional deficiency (i.e. Cystic Fibrosis)

Length of Authorization: 12 months

Requires PA: All multi-vitamins in HIC3 = C6Z, C6I and C6G

Covered Alternatives: Upon PA approval, only vitamins generically equivalent to those listed below will be covered:

GSN	Generic Name	Example Brand
002532	MULTIVITAMIN	DAILY VITE or TAB-A-VITE
039744	MULTIVITS,TH W-FE,OTHER MIN	THEREMS-M
002523	MULTIVITAMINS,THERAPEUTIC	THEREMS
064732	MULTIVITAMIN/IRON/FOLIC ACID	CEROVITE ADVANCED FORMULA
048094	MULTIVITAMIN W-MINERALS/LUTEIN	CEROVITE SENIOR
002064	VITAMIN B COMPLEX	VITAMIN B COMPLEX
058801	MULTIVITS-MIN/FA/LYCOPENE/LUT	CERTAVITE SENIOR-ANTIOXIDANT
047608	FOLIC ACID/VITAMIN B COMP W-C	NEPHRO-VITE
022707	BETA-CAROTENE(A) W-C & E/MIN	PROSIGHT
061112	VIT A,C & E/LUTEIN/MINERALS	OCUVITE WITH LUTEIN
066980	MULTIVITAMIN/FA/ZINC ASCORBATE	SOURCECF
067025	PEDIATRIC MULTIVIT #22/FA/ZINC	SOURCECF
058068	MULTIVITAMIN/ZINC GLUCONATE	SOURCECF
068128	PEDIATRIC MULTIVIT #32/FA/ZINC	AKEDAMINS
061991	PEDI MULTIVIT #40/PHYTONADIONE	AQUADEKS
066852	MULTIVITS&MINS/FA/COENZYME Q10	AQUADEKS
068035	MULTIVITS&MINS/FA/COENZYME Q10	AQUADEKS

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh; Deny, (Not covered by the OHP)

Approval Criteria		
2. Does the patient have a documented nutrient deficiency **OR** 3. Does the patient have an increased nutritional need resulting from severe trauma (e.g. severe burn, major bone fracture, etc.) **OR** 4. Does the patient have a diagnosis resulting in malabsorption difficulties (e.g. Crohns disease, Cystic Fibrosis, bowel resection or removal, short gut syndrome, gastric bypass, renal dialysis, dysphagia, achalasia, etc.) **OR** 5. Does the patient have a diagnosis that requires increased vitamin or mineral intake?	**Yes:** Approve up to 1 year	**No:** Pass to RPh; Deny for Medical Appropriateness.

P&T / DUR Action: 3/27/2014 (MH/KK)
Revision(s):
Initiated:

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Hepatitis C Readiness to Treat

Recommendations

- Develop a Hepatitis C readiness to treat assessment to supplement the drug prior authorization process (Appendix 1). The readiness to treat assessment should help identity red flags that may affect treatment adherence and cure rates of hepatitis C virus.
    - Screen Hepatitis C patients to ensure the following:
        - The patient is motivated to start treatment and understand the general goals of therapy
        - Identify any potential barriers to treatment
        - The patient is not homeless or has a high-risk home status.
        - The patient has not had alcohol or drug abuse in the past 6-12 months
        - The patient is getting adequate psychiatric support and treatment if applicable
        - The patient has access to care and a support system, including such things as transportation to appointments
        - The patient meets the criteria in the prior authorization criteria

Background

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

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

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prior to HCV treatment initiation, to optimize treatment adherence and the achievement of sustained virologic response (SVR).

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

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

The PREP-C was used in 50 patients in 2011 being evaluated for HCV treatment at a primary-care based liver clinic. Patients most frequently rated Satisfactory in the Motivation domain and least frequently in the Information domain.[8] The number of domains rated Satisfactory did not differ by sex, race, or by HIV-co-infection status. Twenty one patients (42%) began HCV treatment within 6 months of PREP-C. Specific interview questions as part of PREP-C are included in Appendix 2. The University of Washington, through funding from the Centers for Disease control and Prevention also provides a checklist to use to assess a patient's readiness to start therapy (Appendix 3).[9]

Current prior authorization is in place for medications used in the treatment of HCV (Appendix 4). The criteria include a thorough assessment of disease, significant medical comorbidities, clinical manifestations, liver fibrosis, and history of prior treatment. In general, only patients with advanced fibrosis should be treated at this time. The prior authorization criterion also addresses some of the psychosocial concerns, including: good evidence of adherence, no active drug or alcohol use, and severe or unstable psychiatric disorders. The readiness to treat should include an additional assessment of the psychosocial issues.

Conclusions

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

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Appendix 1: Readiness to Treat Assessment

1. Does the patient have any of the following significant risk factors?

□ Alcohol use in the last 6 months
□ IV Drug use in the last 6 months
□ Active or uncontrolled depression, psychosis, or suicidality
□ Homeless or Home Status at Risk

If any of the above are checked, treatment is not recommended until corrected.

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

Risk Factor	Points
□ Alcohol use in the last 6-12 months	1
□ IV drug use in the last 6-12 months	1
□ Actively treated, but controlled or history of depression	1
□ History of poor compliance with medications	2
□ History of poor compliance with office visits	2
□ ED visit or hospitalization in the last 6 months	2
□ Previous treatment failure in part due to side effects	2
□ A likely or expected major life event expected in the next 6 months (changing jobs, moving, health procedure, etc)	2
□ Please evaluate patient's social support system	0= strong support, no concern 1= mild concern 2=-moderate concern 3= major concern

3. Add the total of points together from question 2.

Points	Treatment Recommended
0	Treatment ready
1-3	Treatment not recommended until other issues corrected
4+	Treatment not recommended

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Appendix 1: PREP-C Interview Questions

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

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

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Appendix 3: Screening Checklist

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

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Appendix 4: PA Criteria

Sofosbuvir (Sovaldi®)

Goal(s) :

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

Length of Authorization

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

Requies PA:

- Sofosbuvir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Is the request for continuation of therapy?	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #3
3. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. If the patient has been treated with peginterferon and ribavirin before, do they have documented noncompliance to their previous treatment?	**Yes:** Pass to RPh, Deny For Appropriateness	**No:** Go to #5
5. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 3 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins). Note: Occasional patients with HCV and hepatocellular carcinoma who do not have advanced fibrosis (Stage 3-4) should be included for treatment. Discuss with physician to confirm these particular cases.	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. Does the patient have a HIV coinfection?	**Yes:** Go to #7	**No:** Go to #8
7. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #8	**No:** Pass to RPh; Deny (medical appropriateness)
8. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes**: Go to #9	**No:** Pass to RPh, Deny for appropriateness
9. Does the patient have significant renal impairment (CrCl < 30 ml/min) or end stage renal disease (ESRD)?	**Yes:** Pass to RPh; Deny for appropriateness	**No:** Go `to #10
10. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #11	
11. Does the patient have genotype 1 or 4 chronic hepatitis C?	**Yes:** Go to # 12	**No:** Go to #15
12. Is the medication being used as triple therapy with both ribavirin and peginterferon alfa?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #13

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13. Is the medication being used with ribavirin or simeprevir?	**Yes:** Go to #14	**No:** Pass To Rph; Deny for Appropriateness
14. Is the patient interferon ineligible defined by having one of the following conditions: • Previous adverse reaction or hypersensitivity to interferon • Decompensated liver disease • Severe or uncontrolled psychiatric disorder in consult with a psychiatrist • Autoimmune hepatitis or other autoimmune disorders • Unstable cardiac disease Note: Patient's or prescribers not wanting to go through treatment with interferon does not meet the criteria for being "interferon ineligible"	**Yes:** Approve initial trial of 12 weeks for total therapy of 12 weeks for sofosbuvir + simeprevir combination **OR** a total of 24 weeks for sofosbuvir + ribavirin therapy	**No:** Pass To Rph; Deny for Appropriateness
15. Does the patient have genotype 2 chronic hepatitis C?	**Yes:** Go to #16	**No:** Go to #17
16. Is the medication being used with ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Pass To Rph; Deny for Appropriateness
17. Does the patient have genotype 3 chronic hepatitis C?	**Yes:** Go to #18	**No:** Pass To Rph; Deny for Appropriateness
18. Is the medication being used with both ribavirin and peginterferon alfa?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #19
19. Is the medication being used with only ribavirin and the patient is interferon ineligible as defined by the conditions listed above in #15?	**Yes:** Approve for 12 weeks initial fill for a total 24 weeks of therapy	**No:** Pass To Rph; Deny for Appropriateness

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P&T Board Action: 1/30/13 (MH)

Revision(s): 3/27/13

Initiated:

Continuation of Therapy- Sofosbuvir		
Has the patient been adherent to and tolerated initial therapy?	**Yes**: Approve for additional 12 weeks in genotype 3 patients and genotype 1 patients who are interferon ineligible (refer to dosage and administration table below).	**No:** DENY (Medical Appropriateness)

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Hepatitis C Oral Protease Inhibitors/Triple Therapy

Goal(s) :

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

Length of Authorization

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

Requires PA:

- Telaprevir
- Boceprevir
- Simeprevir

Approval Criteria		
20. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
21. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
22. Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy"	**No**: Go to #4
23. Is the prescription for simeprevir?	**Yes:** Go to #5	**No:** Go to #8
24. Is the request for combination therapy of sofosbuvir (Solvaldi) and simeprevir (Olysio)?	**Yes:** Use Sofosubuvir PA criteria	**No:** Go to #6
25. Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness. Recommend that the screening take place.
26. Does the patient have the genotype 1 Q80K polymorphism virus?	**Yes:** Pass to RPh, Deny for Appropriateness	**No:** Go To #8
27. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 3 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins). Note: Occasional patients with HCV and hepatocellular carcinoma who do not have advanced fibrosis (Stage 3-4) should be included for treatment. Discuss with physician to confirm these particular cases.	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
28. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #10	**No:** Pass to RPh, Deny For Appropriateness
29. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #11	**No:** Pass to RPh, Deny For Appropriateness
30. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #12	**No:** Pass to RPh, Deny For Appropriateness

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31. Does the patient have a HIV coinfection?	**Yes:** Go to #13	**No:** Go to #14
32. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #14	**No:** Pass to RPh; Deny (medical appropriateness)
33. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #15
34. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #16	**No:** Pass to RPh, Deny For Appropriateness
35. Is the request for telaprevir 750mg (two tabs) TID or 1125 mg (three tabs) BID for 12 weeks?	**Yes:** Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #17 (If dose is different pass to RPh for appropriateness)
36. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Go to #18 (If dose is different pass to RPh for appropriateness)
37. Is the request for simeprevir 150 mg once daily for 12 weeks?	**Yes:** Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks	**No:** Pass to RPh; Deny for medical appropriateness if dose is different

Continuation of Therapy- Telaprevir

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

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

***TREATMENT FUTILITY RULES**

Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks)

Week 24: Detectable Discontinue peginterferon and ribavirin.

If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued

Continuation of Therapy- Boceprevir

1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)

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

***TREATMENT FUTILITY RULES**

If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen.

If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

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

***TREATMENT FUTILITY RULES**

If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen.

If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.

P&T Board Action: 1-26-2012

Revision(s): 9-26-2013 (MH), 1-30-3014 (MH), 3-27-2014 (MH)

Initiated: 4/29/2012

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Abbreviated Class Review: Botulinum toxins

Month/Year of Review: May 2014 **End date of literature search:** March 2014
Current PDL Class: None

Drugs included in review

Drug	FDA approved indications*	Evidence available from clinical trials
OnabotulinumtoxinA (Botox®)	Prophylaxis of chronic migraines (≥ 15 days/month) in adults, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, bladder dysfunction (detrusor overactivity associated with a neurologic condition or overactive bladder), blepharospasm, strabismus,	Pharyngoesophageal segment spasm, achalasia
AbobotulinumtoxinA (Dysport®)	Cervical dystonia	Blepharospasm, Neurogenic detrusor overactivity, urinary incontinence, upper limb spasticity, pharyngoesophageal segment spasm
RimabotulinumtoxinB (Myobloc®)	Cervical dystonia	Urinary incontinence, upper limb spasticity
IncobotulinumtoxinA (Xeomin®)	Cervical dystonia, blepharospasm	Upper limb spasticity

***Non-cosmetic indications only**

Research Questions:

- For what indications is there evidence to support the use of botulinum toxin (BoNT)?
- Are there differences in efficacy/effectiveness between the agents and is there evidence to support choosing a specific BoNT based on indication?
- Is BoNT safe for indications with evidence to support its use?
- Are there subpopulations that certain BoNT preparations are more effective or safer than others?

Conclusions:

- There is moderate quality evidence and support from clinical guidelines that BoNT A is recommended first line for cervical dystonias due to increased efficacy compared to standard therapies. [1,2] BoNT B is recommended for BoNT A resistant dystonias. There is low quality evidence of no difference between abobotulinumtoxinA (ABO) and onabotulinumtoxinA (ONA) in the treatment of cervical dystonia.
- There is low quality evidence demonstrating efficacy of BoNT A for the treatment of blepharospasm. However, open-label studies have demonstrated a significant effect size and clinical guidelines recommend BoNT should be a treatment option for blepharospasm.[1] There is low quality evidence of no difference between ABO and ONA and no difference between ABO and incobotulinumtoxinA (INC) in the treatment of blepharospasm.[1]
- There is moderate quality evidence that ABO, ONA and rimabotulinumtoxinB (RIM) reduces muscle tone and improves passive function for upper limb spasticity and low quality evidence for lower limb spasticity.[10,]There is insufficient evidence for an effect on active function.[11]
- There is low quality evidence that unspecified BoNT A products may be associated with benefit in the prophylaxis of chronic daily headaches (≥15 days a month), but results are inconsistent.[3,4,5] In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headache per month.[3] There is moderate quality evidence of no benefit of prophylaxis with BoNT A in patients with intermittent migraine attacks (less than 15 headache days per month) or chronic tension type headache.[6,5,7]
- There is high quality evidence of no difference between BoNT injections and placebo in neck pain.[8] There is insufficient evidence to support the use of BoNT injections to improve pain or function in patients with lower back pain.[7,9]
- There is low quality and inconsistent evidence for the use of BoNT for increasing healing of anal fissure and appears less effective than sphincterotomy.
- In the treatment of strabismus, there is very low quality evidence, based on a systematic review with limited data that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia, but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus.
- There is low quality evidence of clinical efficacy of BoNT in the treatment of axillary hyperhidrosis and palmar hyperhidrosis. There is insufficient comparative evidence. Aluminum chloride preparations are the most widely used first line agents.
- There is moderate quality evidence that BoNT A injections in the detrusor are the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity that is unresponsive to more conservative therapies
- There is moderate to high quality evidence that pneumatic dilation (PD) and surgical myotomy are more effective on long term remission that BoNT for the treatment of achalasia. BoNT is effective short term, but response diminishes at 2 years. It is a reasonable treatment approach for patients who are not candidates for surgical therapy.

Recommendations:

- Prior Authorize BoNT agents to ensure it is only used where there is evidence to support its use (for all FDA-approved indications, when used in a manner consistent with the evidence) and limit in appropriate patient populations.
- For the prophylaxis of migraine, limit use to patients that meet the following criteria:
    - The patient has chronic migraines (at least 15 days per month with headache lasting 4 hours per day or longer)
    - In consultation with a neurologist or headache specialist
    - An inadequate response with a 3 month trial or contraindication to least two prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, or antiepileptic agents)
    - Do not approve for chronic tension type headaches or for prophylaxis of intermittent migraine attacks.

- Approve for two injections (given 3 months apart) and then require additional documentation regarding migraines after therapy
- Limit BoNT for the treatment of urinary incontinence to patients' refractory to behavioral modification and antimuscarinic therapy.
- Limit BoNT for the treatment of chronic anal fissure for those unresponsive to conservative therapy with topical nitroglycerin or calcium channel blockers.
- Limit BoNT for hyperhidrosis to patients who have failed topical aluminum chloride.
- Limit BoNT for achalasia to patients who have failed or are not candidates for pneumatic dilation and surgical myotomy.

Background:

There are seven serologically distinct forms of botulinum toxin (BoNT), A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain. [10] All serotypes interfere with neural transmission by blocking acetylcholine release at the neuromuscular junction, causing muscle paralysis.[11] Each neurotoxin works at a distinct site.[10] Botulinum toxins now play a role in the management of a variety of medical conditions. Three distinct serotype A botulinum toxin (BoNT A) products, abobotulinumtoxinA (ABO), incobotulinumtoxinA (INC), onabotulinumtoxinA (ONA), and one serotype B botulinum toxin (BoNT B) product, rimabotulinumtoxinB (RIM), have been approved by the U.S. Food and Drug Administration (FDA). The most recent preparation approved is INC in 2010. Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each BoNT product and cannot be compared or converted into units of another product. In addition, there are no universally accepted safe dose conversion ratios. [10] BoNTs are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, where the goal of therapy is to reduce contraction of striated or smooth muscle. All of the products have a black box warning in their labeling regarding the risk of BoNT spreading beyond the site of injection, resulting in adverse events and death in some cases. BoNT A has become first line therapy for cervical dystonia.[12] Not all patients respond well to BoNT A though, and 5 to 10% become resistant to it.[13] In these cases, BoNT B is an alternative to BoNT A. [12] Head to head studies comparing the efficacy and safety of different BoNT formulations are limited.[14]

The use of BoNT has also been evaluated for prophylaxis treatment of migraines. Prophylactic treatment for migraines is often considered for patients who have two or more migraines with three or more days of disability per month or use of acute medication more than twice per week. Common prophylactic treatments for migraines include beta-blockers, tricyclic antidepressants, calcium channel blockers, antiepileptic drugs, and lifestyle management. The reported range of efficacy for these drugs varies from modest (effect size, 0.5-0.8) for most drugs to large (effect size, >0.8) for amitriptyline and valproate.[3] Due to the lack of proven differences in efficacy between different prophylactic medications, a medication is often selected based potential side effects, the presence of other disorders which may be coexistent with migraine, patient disability, and patient preferences in a given patient. OnabotulinumtoxinA is the only BoNT approved by the FDA for the prophylactic treatment of chronic migraine. None of the BoNT formulations are approved for the prophylactic treatment of chronic tension-type headache.

Methods:

A Medline literature search ending March 2014 for new systematic reviews, clinical guidelines, and head to head randomized controlled trials (RCTs) for all of the BoNT products was conducted. Cosmetic indications were excluded, as they are not covered by the Oregon Health Plan (OHP). The focus of the review is on non-cosmetic indications only. 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. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Cervical Dystonia and Blepharospasm:

Cervical dystonia is the most common form of focal dystonia and also referred to as spasmodic torticollis. It is a neurologic condition that causes abnormal movements and/or postures of the neck.[15] Botulinum toxin is considered first-line therapy for cervical dystonia to decrease the severity of associated abnormal head position and neck pain.[16] According to DynaMed, there is level 1 evidence that BoNT (6 trials used ONA, 4 trials used abobotulinumtoxinA and 3 trials used RIM) reduced pain in patients with cervical dystonia and is effective and safe. There is level 2 evidence that abobotulinumtoxinA may be more effective than anticholinergic drugs and that unspecified BoNT A may have fewer adverse events than BoNT B with similar efficacy. [16] BoNT B may be useful for patients refractory to BoNT A. Blepharospasm is a focal dystonia involving the periocular muscles. Clinical signs include increased blinking and spasms of involuntary eye closure. BoNT A is the current first line medication therapy for blepharospasm.[17] Other treatments include surgery, psychological support, and biofeedback.

Systematic Reviews:

A Cochrane Collaboration systematic review of all blinded RCTs of BoNT A versus placebo evaluated the effectiveness and safety of BoNT for cervical dystonia.[18] A literature search up to June 2003 identified 13 studies for inclusion; most of which were published in the early 1990s and included only small numbers of participants. Eight trials evaluated ONA and five evaluated abobotulinumtoxinA. Techniques and administration methods varied significantly between the studies. In general, the quality of the studies was good. There was limited data on objective outcomes. Data from 3 studies (n=121) demonstrated a significant improvement of at least one point (OR 8.16; 95% CI 4.03-16.5) and at least 3 points (OR 4.25; 95% CI 2.00-9.05) in the Tsui scale (demonstrating improvement) compared to placebo. The patient subjective assessment of any improvement was also significantly better with treatment than placebo (OR 6.58; 95% CI 4.55-9.54; 11 studies; n=510). Adverse effects were transient and either mild to moderate or intermittent. Events that occurred more frequently with BoNT than placebo were neck weakness, dysphagia, dry mouth, voice changes, and local pain. There did not appear to be any significant differences between ONA and ABO in efficacy or safety.

In addition, the authors of the Cochrane systematic reviews compared the clinical efficacy and safety of BoNT A versus BoNT B in cervical dystonia.[12] However, at the time of the literature search, only two ongoing trials were identified and there were no preliminary results or interim analysis available for them. The authors were able to make any conclusions on the comparative efficacy or safety of BoNT A versus BoNT B. Since this systematic review, two randomized trials have been published comparing BoNT types A and B.[19,20] The first study was a randomized, double-blind, noninferiority trial in patients cervical dystonia who were toxin-naïve (n=111).[19] The primary outcome was change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), which is a summation of motor severity, pain, and disability. Results demonstrated that BoNT B was noninferior to BoNT A in change in baseline in TWSTRS score (mean difference 02.2 points; 90% CI -4.9 to 0.6), with no difference in duration of effect or adverse events. The second trial was a randomized, double-blind, parallel-arm study in subjects with cervical dystonia who had a previous response from BoNT A (n=139).[20] Both serotypes of BoNT were found to be equivalent at week 4 in terms of efficacy. The BoNT B group had an increase in frequency and severity of dysphagia and dry mouth after treatment compared to BoNT A (dysphagia: ONA 19% vs. RIM 48%; dry mouth: ONA 41% vs. RIM 80%). In clinical responders, BoNT A was associated with a slightly longer duration of benefit than BoNT B (ONA 14 weeks, RIM 12.1 weeks; p=0.033). [20]

Another Cochrane systematic review evaluated RCTs to determine how effective and safe BoNT A is for the treatment of blepharospasm.[17] Overall, the authors found no high quality, randomized, controlled efficacy data to support the use of BoNT A for blepharospasm. Because none of the studies met their inclusion criteria, only a descriptive analysis was provided for the trials excluded that were controlled. However, open-label studies demonstrate a significant effect size (90% of patients benefit), making it difficult to justify new placebo-controlled trials and it appears that BoNT A is indeed effective and safe in blepharospasm. Most of the trials evaluated ONA; two trials included ABO.

An evidence-based review and meta-analysis attempted to evaluate which treatments for dystonia have proven efficacy and which of them have unproven results.[21] A literature search was performed through 2003 and all types of articles were comprised, including case reports. A random effects meta-analysis confirmed positive results for BoNTA efficacy in patients with cervical dystonia (RD 0.46; 95% CI 0.25-0.67; p<0.0001; I2=82.1%) based on 6 double-blind, placebo-controlled trials, all comparing ONA to placebo. Similar results were seen in one RCT evaluating ABO in 75 patients. Two RCTs compared ONA to ABO and one found no differences in degree of improvements between the two preparations, while the second study showed abobotulinumtoxinA to be superior to ONA for impairment and pain, but with a higher incidence if minor side effects. Three double-blind and one single-blind study (n=73) showed a positive effect of BoNT A (nonspecific) on blepharospasm lasting more than 2-3 months (Level A data). A meta-analysis included two placebo controlled studies using BoNT A to treat writer's cramp that resulted in C-level data (RD 0.31; 95% CI 0.10-0.52; p=0.004; I2=0%). The authors concluded that BoNT is possibly effective for writer's cramp. Treatment efficacy was found to be unproven for the following indications: Oromandibular dystonia and laryngeal dystonia. No controlled studies were found in laryngeal dystonia and a single placebo-controlled study showed improvement in only 37.5% of a total of 8 patients with oromandibular dystonia with BoNTA injections.

Clinical Guidelines:

The American Academy of Neurology performed an evidence-based review of the safety and efficacy of BoNT in the treatment of movement disorders.[1] They concluded that BoNT is established as safe and effective for the treatment of cervical dystonia based on seven Class 1 (RCT with masked or objective outcome assessment in a representative population) rated studies. Due to no effective alternative medical therapies, the academy concludes the following:

- BoNT should be offered as a treatment option to patients with cervical dystonia (Level A).
- BoNT is probably more efficacious and better tolerated in patients with cervical dystonia than treatment with trihexyphenidyl (Level B).
- There are no data to compare BoNT with surgical treatment of cervical dystonia.
- From the available evidence there is no proven superiority for a single BoNT product.

Recommendations for additional movement disorders are also included:

- BoNT injection should be considered as a treatment option for blepharospasm (Level B).
    - This is based on two studies demonstrating that BoNT is probably effective with minimal side effects. OnabotulinumtoxinA and INC have been shown to be probably equivalent, and ONA and ABO as possibly equivalent.
- BoNT may be considered as a treatment option for hemifacial spasm (Level C).
- BoNT should be considered as a treatment option for focal upper extremity dystonia (Level B). However, the data are insufficient to provide a recommendation for lower extremity dystonia.
- BoNT should be considered as a treatment option for adductor spasmodic dysphonia (Level B).
- There is insufficient evidence to support or refute the use of BoNT in abductor spasmodic dysphonia (Level U).
- BoNT may be considered as a treatment option for motor tics (Level C). There are insufficient data to determine the effectiveness of BoNT in phonic tics.

- BoNT should be considered as a treatment option for essential hand tremor in those patients who fail treatment with oral agents (Level B).

The European Federation of Neurological Societies also recommend botulin toxin as a treatment option for patients with cervical dystonia.[2] Based on a systematic review from the American Academy of Neurology that established botulinum toxin as an effective treatment for cervical dystonia, blepharospasm, focal upper extremity dystonia, and laryngeal dystonia (probably effective). A lower level of evidence was found for focal lower limb dystonia (possibly effective). The following recommendations are provided:

- BoNT A (or BoNT B if there is resistance to BoNT A) is recommended as first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia (Level A).
- BoNT A is probably effective for adductor-type laryngeal dystonia, but there is insufficient evidence to support efficacy in abductor-type laryngeal dystonia and in muscular tension dysphonia.

Spasticity:

Spasticity results from many etiologies including stroke, trauma, multiple sclerosis, cerebral palsy and neoplasm involving the CNS. Reduction in function is related to at least muscle weakness, soft tissue contracture, and muscle overactivity**.** A recent systematic review and meta-analysis evaluated the efficacy of any preparation of BoNT A for spasticity and pain in adults.[22] Trials including both ONA and ABO were included, although the comparative efficacy and safety of the different BoNT A preparations was not addressed. Specifically, data was evaluated for spasticity and spasticity-related pain in the upper and lower limbs in adults. Results showed that BoNT A may improve spasticity but may not reduce spasticity-related pain in adults.[22] A literature review through April 2013 identified 27 studies and 10 were used for quantitative analysis of pain. Significant heterogeneity was found (I2=83%) for the studies evaluating spasticity-related pain in the upper limb. There was a non-significant effect slightly in favor of BoNT A (standardized mean difference [SMD] 0.44; 95% CI -0.02 to 0.90; p=0.06). Removing the two studies that were thought to cause significant heterogeneity due to different patient populations confirmed a non-significant result (p=0.35). Three studies evaluated pain in the lower limb and also showed no significant effect with BoNT A (RR 1.01; 95% CI 0.19-5.36; p=0.99) with significant heterogeneity (I2=87%). There was moderate quality evidence that BoNT A did demonstrate a statistically significant improvement of spasticity of the upper limb with compared to placebo (RR 1.30; 95% CI 1.11-1.52; p=0.001). There was moderate quality evidence of a significant effect on spasticity in the lower limb as well (RR 2.42; 95% CI 1.60-3.65; p<0.0001).

The American Academy of Neurology also performed an evidence-based review of the safety and efficacy of BoNT (serotypes A and B) in the treatment of adult and childhood spasticity.[23] The review evaluated the use in the following indications: adult spasticity and spasticity in pediatric cerebral palsy. A literature search identified 11 class I efficacy trials in adult upper extremity spasticity, 6 of which used ABO, 4 used ONA and 1 used RIM. All of these studies showed that BoNT is safe and reduced tone in a dose-dependent manner. There was insufficient evidence to evaluate the outcome of active functional gains. Three trials evaluated lower extremity spasticity, most of which focused on reduction in muscle tone with demonstrated efficacy. The authors concluded that BoNT is established as effective in the treatment of adult spasticity in the upper and lower limb in reducing muscle tone and improving passive function. However, few studies examined active function. There were no RCTS comparing BoNT to other treatments for spasticity. In addition, BoNT is established as effective in the treatment of spastic equinus in patients with cerebral palsy. The AAN recommends that:

- BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (level A), and should be considered to improve active function (Level B).
- There is insufficient information to recommend an optimum technique for muscle localization at the time of injection (Level U).

- BoNT injections of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy (level A).
- BoNT should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery (Level B).
- BoNT should be considered as a treatment option in children with upper extremity spasticity (level B).

The Royal College of Physicians developed national guidelines on the management of BoNT in spasticity in adults.[24] The guideline panel notes that local intramuscular injection of BoNT is an established, well-tolerated treatment in the pharmacological management of focal spasticity and there is a strong body of evidence for its effectiveness in the management of upper and lower limb spasticity. The guideline recommends that it be used for focal or multi-focal spasticity in demonstrable muscle overactivity.

The international cerebral palsy institute released a consensus statement for lower limb spasticity in children with cerebral palsy.[25] Based on a literature review and appraisal, the committee recommends the following:

- BoNT A is established as effective in the treatment of spastic equinus to improve gait (level A).
- BoNT A is probably effective to improve goal attainment and function in the management of spastic equinus (level B).
- BoNT A injections to the adductor muscles do not improve gross motor function (level A).
- BoNT A injections to the adductor muscles may delay hip displacement, but does not affect long-term outcomes (level A).
- BoNT A injections to multiple lower limb muscles have inadequate and conflicting data in respect of gait, goal attainment and function (level U).

Migraine:

DynaMed reports that BoNT injections appear ineffective for patients with episode migraine headache (< 15 days/month) based on level 2 evidence, but they may reduce frequency in adults with chronic migraine headache (≥15 days/month).[26]

Systematic Reviews:

A systematic review of trials was conducted through 2012 to assess BoNT A (specific products were not reported) for the prophylactic treatment of headaches in adults.[3] Only RCTs that evaluated BoNT A in association with the reduction in frequency or severity of headaches that were at least 4 weeks induration were included. The Cochrane Risk of Bias tool was used to assess study quality and disagreements were resolved by consensus. A total of 27 placebo-controlled RCTs and 4 active comparator trials were included. Among the placebo controlled trials, 10 evaluated episodic migraines, 5 assessed chronic migraines, 8 evaluated patients with chronic tension-type headaches, and 3 studied chronic daily headaches. Different protocols were followed for botulinum injections, including fixed injection plans and follow-the-pain approached. BoNT A was associated with a reduction in headaches per month for both chronic daily headaches (-2.06 headaches per month; 95% CI -3.56 to -0.56; I^2=28.2%; p=0.25) and chronic migraine (-2.30 headaches per month; 95% CI -3.66 to -0.94; I2=32.2%; p=0.21). There was no association of BoNT A with a reduction in the number of episodic migraine headaches per month or chronic tension-type headaches. Eight studies reported on the likelihood of achieving 50% improvement in headache and BoNT A was associated with improvement in chronic migraine headaches (2 studies; RR 2.21; 95% CI 1.30-3.78). Compared with placebo, there was no association of BoNT A with improvement in chronic daily headaches, episodic migraine headaches, or chronic tension-type headaches. [3]

Only 4 trials compared BoNT A with other treatments. In single trials, BoNT A was not associated with a reduction in headache frequency compared with topiramate (1.4 headaches per month; 95% CI -2.5 to 1.3) or amitriptyline (2.1 headaches per month; 95% CI -1.2 to 5.4) for prophylaxis against chronic migraine

headaches. It was also not associated with reduction in headache frequency compared to valproate in patients with chronic and episodic migraines or in patients with episodic migraines. [3] These trials were not designed as equivalence trials and all were underpowered to show even modest differences. Overall, there was moderate heterogeneity between trials and variability in overall study quality. There was also evidence of a favorable improvement in headaches in the placebo-treated groups, with patients reporting a substantial improvement in headaches over time. The authors concluded that there may be an association between BoNT A and improvement in the frequency of chronic migraine and chronic daily headaches, but not with improvement in the frequency of episodic migraine, chronic tension-type headaches, or episodic tension-type headaches. Also, the effect size was small with a reduction seen in number of headaches per month from 19.5 to 17.2 for chronic migraine and from 17.5 to 15.4 for chronic daily headaches. Although there is insufficient direct evidence to make definitive conclusions comparing BoNT A to other medications, it appears that BoNT A may be associated with less benefit than other common prophylactic medications for migraine headaches.

A 2011 systematic review evaluated the evidence from double-blind, RCTs that had at least 100 patients from a literature search through August 2011.[4] Studies including both BoNT A and BoNT B in the treatment of migraine were included in the search criteria; however, all 10 trials identified evaluated BoNT A (eight with ONA and 2 with ABO). One trial compared BoNT A to histamine and the other nine versus placebo. The primary outcome included the difference in the number of headache episodes and the mean change in number of headache days or headache-free days. The largest available study evaluated ONA and found a small but statistically significant decrease in the mean number of headache days per month (-8.4 vs. -6.6; $p<0.001$) and in mean number of migraine days per month (-8.2 versus -6.2, $p<0.001$) in the treatment group. The small effect size suggests that this may not be clinically significant. Eight additional trials reported on migraine frequency. With the exception of one trial, there were no significant differences in migraine medication use or migraine severity or duration in any of these 8 trials. Only one trial compared BoNT A to another active treatment (histamine), and found no statistical difference between the two groups in the number of headache attacks, or in any of the secondary outcome measures. Common adverse events occurred in 20% to 67% of patients, and included muscular weakness, headache, pain, neck rigidity, blepharoptosis, skin tightness, hypertonia, dysphagia, asthenia, and eyelid edema or ptosis. Overall, the evidence for the effectiveness of BoNT A is inconsistent, and suggests that if there is a benefit, it is small and the clinical significance is unknown. In addition, it does not appear effective for improving quality of life. There was insufficient evidence to evaluate if there was a difference in efficacy among serotypes and the various products. In addition, this review combines the results of trials in chronic migraine and episodic migraine.

Another systematic review evaluated BoNT A use in chronic tension-type headache.[4] A literature search identified 9 RCTs with outcome measures including headache severity and/or intensity, headache frequency, medication use, measures of mood, and quality of life. Six trials evaluated ONA and three evaluated ABO. Seven of the nine found no significant difference in most or all headache outcomes compared to placebo. One trial (n=300) found significantly more headache free days in the placebo group compared to the highest dose of ONA (150U), but no differences in any of the lower dose groups (50U-100U). The only trial to show a statistically significant improvement in multiple headache symptoms was small (n=28) and found fewer headache days, lower headache severity, and shorter duration in the treatment group (ONA) compared to placebo. There were no studies comparing BoNT A to another active treatment for chronic tension-type headache. Overall, the evidence suggests that BoNT is ineffective for the use in chronic tension-type headache.

Clinical Guidelines:

The Canadian Headache Society released high quality clinical guidelines for migraine prophylaxis in March 2012 with an overall goal to assist the practitioner in choosing an appropriate prophylactic medication for an individual with episodic migraine (headache on ≤ 14 days a month), based on current evidence and expert consensus.[6] A comprehensive literature search and systematic review was done by the guideline panel to inform the recommendations regarding medications for migraine prophylaxis. The initial review found eight studies on the use of BoNT A for the prophylaxis of migraine and five fair-quality trials were negative with respect to the primary outcome on migraine frequency. The following are the main recommendations included:

Starting and stopping prophylactic therapy (Based on Expert Consensus only)

- Migraine prophylactic therapy should be considered in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management (Expert Consensus)
- Migraine prophylactic therapy should be considered when the frequency of migraine attacks is such that reliance on acute medications alone puts patients at risk of medication overuse headache. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, NSAIDs) on 15 days a month or more (Expert Consensus).
- Migraine prophylaxis should be considered for patients with greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective.
- Migraine prophylaxis may be considered according to patient preference and physician judgment, for example in patients with hemiplegic migraine.
- A prophylactic medication trial should consist of at least two months at the target or optimal dose before it is considered ineffective.
- A prophylactic medication is usually considered effective if migraine attack frequency or the number of days with headache per month is reduced by 50% or more.
- After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the medication in many patients, although others may benefit from a much longer duration of therapy.

Botulinum Toxin Type A

- A strong recommendation based on high quality evidence against BoNT A for the prophylaxis of episodic migraine in patients with less than 15 headache days per month. The evidence indicates that BoNT A is no better than placebo for prophylaxis of migraine in such patients.

Other medications (for the treatment of episodic migraine)

- A strong recommendation based on high quality evidence supports the use of topiramate, propranolol, metoprolol, and amitriptyline for migraine prophylaxis.
- A strong recommendation based on moderate quality evidence supports the use of nadolol, gabapentin, candesartan, and butterbur.
- A strong recommendation based on low quality evidence and minimal side effects for riboflavin, coenzyme Q10, and magnesium citrate.
- A weak recommendation based on high quality evidence for efficacy of divalproex sodium, flunarizine, and pizotifen primarily because of frequent and significant side effects.
- Propranolol, nadolol, and metoprolol are good initial prophylactic drug choices for many patients with migraine. (Expert Consensus)
- Amitriptyline is a good initial drug and may be particularly useful in patients with insomnia or associated tension-type headache. (Expert Consensus)
- Magnesium is considered the safest migraine prophylactic during pregnancy.

The National Institute for Health and Clinical Excellence (NICE) produced a technology appraisal guidance for BoTN A for the prevention of headaches in adults with chronic migraine.[5] Efficacy was established based on a systematic review of RCTs comparing BoTN A with placebo. Although the clinical trial evidence demonstrated statistically significant benefits of BoTN A compared with placebo for a number of outcomes, the absolute numerical differences were small. Further, there was a large placebo effect seen in trials. The guidance includes the following:

- BoTN A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):
    - That has not responded to at least three prior pharmacological prophylaxis therapies
      AND
    - Whose condition is appropriately managed for medication overuse
- Treatment with BoTN A that is recommended should be stopped in people whose condition:
    - Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles)
      OR
    - Has changed to episodic migraine (fewer than 15 headache days per month) for three consecutive months.

The American Academy of Neurology evaluated the evidence for using BoNT in episodic migraine, tension-type headache, and chronic daily headache.[7] Analysis of data resulted in conclusions that BoNT is probably ineffective for episodic migraine and tension-type headache (Grade B Recommendation) and that there is insufficient evidence for use in chronic daily headache. However, this was performed before the FDA approval of ONA for the use of prophylaxis of headaches in adult patients with chronic migraine.

Chronic Neck/Back Pain:
A Cochrane Database systemic review of BoNT A for subacute/chronic neck pain did not find a statistically or clinically difference between BoNT A and placebo injections.[8] Randomized and quasi-randomized controlled trials were included. Nine trials with 503 participants were included; only BoNT type A was used in these studies. High quality evidence showed little or no difference in pain between BoNT A and saline injections at 4 weeks (standardized mean difference [SMD] -0.07; 95% CI -0.36 to 0.21) and six months for chronic neck pain. Very low quality evidence suggests no difference in pain in those with cervicogenic headache (SMD 0.16; 95% CI -0.53 to 0.86; NNT 264). There was also no benefit seen for disability and quality of life at four weeks and six months.

Another Cochrane Database systematic review evaluated BoNT for treating non-specific lower back pain and did not find sufficient evidence to reach a conclusion regarding its effectiveness.[9] Only 3 trials met inclusion criteria, but only one had a low risk of bias and evaluated patients with non-specific lower back pain (N=31). The two other studies examined specific subpopulations. Heterogeneity of the studies prevented meta-analysis. The one study with a low risk of bias did demonstrate that BoNT A injections were significantly better than control injections on pain intensity and improved function. There is no evidence for long-term improvement in pain intensity. The authors concluded that the evidence in favor of BoNT injections is only of low or very low quality and further research is very likely to change the estimate of effect.

The American Academy of Neurology found only one class II study that demonstrated that BoNT is possibly effective for the treatment of chronic predominantly unilateral low back pain.[7] Although they give a Level C recommendation that it may be considered as a treatment option for patients with chronic predominantly unilateral low back pain, it is difficult to diagnose the precise origin of pain.

Hyperhidrosis:
Hyperhidrosis is a chronic idiopathic disorder of excessive sweating which usually affects the axillae, palms, soles, and forehead. Overall, there is a lack of high quality evidence and clinical guidelines to guide management of the disease.[27] Aluminum chloride topical preparations are the most widely used first line agent. When topical agents have not worked, BoNT (most commonly BoNT A) is often recommended. Effects are reported to last for 6 to 9 months with high reported

levels of patient satisfaction.[27] However, treatment is potentially lifelong. A small quasi-randomized trial (n=10) found ONA and ABO to be equally effective in reducing sweat rate and no difference in duration of benefit.[28] Patients were randomized based on date of birth which adds a significant risk of bias. Another double-blind trial compared ONA and INC in 46 patients with axillary hyperhidrosis using patient reported outcomes.[29] Both groups were equally effective, with a total of 89% reported the overall therapeutic effect as excellent. According to DynaMed, BoNT A intradermal injections are effective for up to 16 weeks and for improving quality of life (level 1 evidence) and BoNT B is reported to reduce sweating and improve quality of life based on poor quality evidence (level 3 evidence).[30]

In the American Academy of Neurology (AAN) assessment of BoNT for the treatment of autonomic disorders and pain, a subcommittee recommended that BoNT should be offered as a treatment option to patients with axillary hyperhidrosis (Level A; Established as effective).[7] Two Class I studies were identified in axillary hyperhidrosis. A RCT double-blind study showed that patients receiving BoNT had a higher response rate (more than 50% reduction of sweat production) at all time points than those receiving placebo (P<0.001). The panel also recommended it should be considered as a treatment option for palmar hyperhidrosis and drooling (Level B; Probably effective). There are no head to head comparisons of BoNT with other treatment options in hyperhidrosis or drooling.

The Canadian Hyperhidrosis Advisory Committee created guidelines for the treatment of primary focal hyperhidrosis.[31] These guidelines recommend using the Hyperhidrosis Disease Severity Scale (HDSS) to measure disease severity before evaluating for treatment. A HDSS score of 2 is defined as underarm sweating is tolerable but sometimes interferes with daily activities. A score of 3 and 4 correlates with underarm sweating frequently interferes with daily activities to always interferes with daily activities. The following recommendations are provided:

Axillary Hyperhidrosis

HDSS Score of 2:

- For mild or moderate axillary hyperhidrosis, topical aluminum chloride is the first choice of therapy. An initial concentration of 10-2% may be tried to minimize irritation. Euhidrosis may not be achieved until a 35% solution is used.
- If a patient fails to respond to topical therapy after 1 month, intradermal injection of BoNT A may be administered. Treatment is repeated on average every 4 to 6 months when the patient has a change in HDSS score that warrants treatment.

HDSS Score of 3 or 4:

- For severe axillary hyperhidrosis, aluminum chloride or BoNT A is first line therapy.
- If a patient fails to respond, consider using both in combination.

Palmer and Plantar Hyperhidrosis

HDSS Score of 2:

- For mild or moderate axillary hyperhidrosis, aluminum chloride hexahydrate in absolute ethanol or in a salicylic acid gel is the therapy of first choice of therapy.
- If a patient fails to respond to topical therapy, intradermal injection of BoNT A may be administered or iontophoresis therapy initiated.

HDSS Score of 3 or 4:

- For severe palmer hyperhidrosis, aluminum chloride, iontophoresis or BoNT A are considered first line therapy.
- If a patient fails to respond, consider using both in combination.

Neurogenic Bladder Dysfunction and Overactive Bladder Syndrome:

Urinary symptoms can arise due to neurological disease in the brain, the spinal cord, or the peripheral nervous system. Damage within these areas can produce characteristic patterns of bladder and sphincter dysfunction. Conditions such as cerebral palsy, stroke, multiple sclerosis, Parkinson's disease, dementia, spinal cord injury, and peripheral neuropathy can cause dysfunction of the lower urinary tract system. [32] Detrusor overactivity is defined as an urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. Detrusor overactivity is subdivided into idiopathic detrusor overactivity (IDO), or overactive bladder syndrome, and neurogenic detrusor overactivity (NDO). Overactive bladder syndrome is a symptom complex of urgency with or without urge incontinence. Overactive bladder symptoms may occur with or without NDO.[33] There are limited high quality systematic reviews evaluating BoNT for NDO. Oral antimuscarinic agents are recommended as first line treatment for neurogenic bladder dysfunction.[33] There is evidence that ONA reduces urinary incontinence but increases urinary tract infections in patients with NDO. [33,34] A prospective, double-blind study demonstrated that ONA injection was associated with decreased incontinence episodes in patients with NDO due to multiple sclerosis.[35]

A 2011 systematic review from the Cochrane Collaboration evaluated BoNT injections for adults with overactive bladder syndrome, both NDO and IDO.[36] A total of 19 unique studies met the inclusion criteria. The majority of studies included participants with NDO, often due to spinal cord injury or multiple sclerosis (MS). The majority also had symptoms refractory to antimuscarinics or did not tolerate the medication as an inclusion criteria. Two studies used BoNT B and the other 8 used BoNT A (two used ABO). Three studies compared intravesical BoNT A versus placebo in change in urinary frequency. At 4-6 weeks results favored BoNT A in reducing episodes per day (mean difference [MD] -6.50; 95% CI -8.92 to -4.07; $p<0.001$; $I2=0\%$). The meta-analysis for incontinence episodes also favored BoNT A at both 4-6 weeks (MC -1.58; 95% CI -2.16 to -1.01; p=0.00001) and 12 weeks (MD -2.74; 95% CI -4.47 to -1.01; p=0.002) of follow-up. However, the results for post-void residual volume (PVR) favored placebo with an increase of PVR of 10.22 ml (95% CI 30.63 to 109.81) in the BoNT group (p=0.00005). Due to different tools used, no pooling of quality of life data could be performed. There were no trials that looked at if one formulation of BoNT is better than another, but it seems that BoNT A has a more durable effect than BoNT B which seems to be limited to less than 10 weeks. In addition, the optimally safe and effective dose is still undetermined. One small studied suggested that a lower dose may have comparable efficacy to and improved safety over high doses. The authors concluded that BoNT injections appear to have an effective effect on refractory overactive bladder symptoms, but little controlled data exist on benefits and safety compared with other interventions, or with placebo. Further data is needed on long term outcomes, safety, and optimal dose.

Another systematic review evaluated the evidence of ONA and ABO in the treatment of NDO, including IDO, painful bladder syndrome, bladder outflow obstruction and detrusor sphincter dyssynergia.[37] The authors reviewed articles between 1985 and December 2010 and the results were compiled into high level and low level data. High level data were RCTs or well-designed quasi-experimental studies. Low level data included non-experimental, correlation or comparative studies. A total of 43 articles met the inclusion criteria. The authors noted that ONA has been studied more widely than ABO or the other preparations. ONA had high level data to support its use in all 5 conditions included; while ABO only had high level data for use in NDO. The evidence for use in detrusor sphincter dyssynergia is very limited, with most of the data coming from open label studies. There are no head to head comparisons of the two preparations.

Guidelines:

The American Urological Association (AUA) provides guidelines for the diagnosis and treatment of non-neurogenic overactive bladder, or IDO.[38] The primary evidence source was an AHRQ review of the treatment of overactive bladder in women.[39] Studies focusing on males were added to the database. The AUA performed its own analysis of the data. The panel notes that overactive bladder is not a disease but a symptom complex that generally is not life-threatening.

Based on expert opinion, no treatment is an acceptable choice made by some patients and caregivers. Treatment is focused on quality of life and symptom improvements. Further recommendations are as followed:

- First line therapy is behavioral therapies including bladder training, bladder control strategies, pelvic floor muscle training, and fluid management. (Grade B Evidence)
    - The literature indicates that behavioral treatments are generally either equivalent to or superior to medications in reducing incontinence episodes, improving frequency, and improving quality of life
- Oral anti-muscarinics, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium, are recommended as second-line therapy (Grade B Evidence), followed by transdermal oxybutynin (Grade C Evidence)
- If patients experience inadequate symptom control or adverse events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried.
- Third line treatment includes sacral neuromodulation or ONA to the carefully selected patient who has failed behavioral and anti-muscarinic therapy or who is not a candidate for these therapies (Grade C Evidence)
    - If prescribed ONA, the patient must be able and willing to return for frequent PVR evaluation and to perform self-catheterization.

The Obstetricians and Gynecologists of Canada also released guidelines for the treatment of unspecified overactive bladder.[40] These guidelines are consistent with AUA guidelines in recommending behavioral therapy as first line treatment, followed by anti-muscarinics as second line. BoNT A is only recommended for refractory overactive bladder due to the high rate of urinary retention. Studies have shown that up to 43% of patients needed clean intermittent self-catheterization. The guidelines recommend that intravesical BoNT A is a clinically effective option for patients unresponsive to conservative options, anticholinergics, or vaginal estrogen.

The European Association of Urology guidelines on neurogenic lower urinary tract dysfunction recommends that the mainstay of treatment for NDO anticholinergic drug therapy (Grade A recommendation), which is a non-invasive conservative treatment. [41] In regards to minimal invasive treatments, the guidelines state that BoNT injection in the detrusor is most effective minimally invasive treatment to reduce NDO.[41] BoNT causes a long-lasting but reversible chemical denervation that lasts for about 9 months. Generalized muscular weakness is an occasional adverse effect. The Consortium for Spinal Cord Medicine clinical practice guidelines recommend considering ONA injections into detrusor for patients with intermittent catheterization with detrusor overactivity.[42]
A NICE clinical guideline for NDO was published in August 2012 based on the best available evidence.[32] BoNT injections are not included in the recommendations for stress incontinence or for the treatment to improve bladder emptying. The following recommendations are given to improve bladder storage:

- Offer bladder wall injection with BoNT A to adults and consider in children:
    - With spinal cord disease AND
    - Symptoms of an overactive bladder or urodynamic investigations showing impaired bladder storage AND
    - In whom antimuscarinic drugs have proven to be ineffective or poorly tolerated
- Before offering bladder wall injection with BoNT A:
    - Explain that a catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, AND
    - That they are able and willing to manage such a regimen should urinary retention develop after the treatment.

The American Academy of Neurology evaluated the literature for the treatment of neurogenic bladder from detrusor overactivity and detrusor sphincter dyssynergia with BoNT.[7] The review found that BoNT is established as safe and effective for the treatment of NDO in adults (3 studies) and data on the use of BoNT for detrusor sphincter dyssynergia are conflicting. BoNT is probably safe and effective for the treatment in patients with spinal cord injury. However, one class I study did not show significant benefit in the treatment of detrusor sphincter dyssynergia in patients with MS. The following recommendations are provided:

- BoNT should be offered as a treatment option for NDO (Level A).
- BoNT should be considered for detrusor sphincter dyssynergia in patients with spinal cord injury (Level B).

A NICE clinical guideline for the management of urinary incontinence in women was issued in September 2013.[43] These guidelines recommend injection of BoNT A to women with overactive bladder caused by proven detrusor overactivity that has not responded to conservative management (including drug therapy with antimuscarinics). They also recommend discussing the risk and benefits, including the risk of intermittent catheterization and the increased risk of urinary tract infection. Treatment should only be started in women who have been trained in clean intermittent catheterization and have performed the technique successfully, and are able and willing to perform this on a regular basis for as long as needed. The recommended dose is 200 units of BoNT-A, or 100 units for women who would prefer a lower dose. BoNT-B should not be offered to women with proven NDO

Anal Fissure: Chronic Anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter, and is treated surgically with an internal sphincterotomy. According to DynaMed, BoNT has inconsistent evidence for increasing healing of anal fissure but appears less effective than sphincterotomy**.**[44]

Based on a Cochrane Collaboration systematic review limited by heterogeneity, authors concluded that medical therapy for chronic anal fissure, including topical glyceryl trinitrate, BoNT (unspecified serotype) or topical calcium channel blockers for fissure in children may be applied with a chance of cure that is marginally better than placebo. [45] For chronic fissure in adults, all medical therapies were found to be far less effective than surgery. Glyceryl trinitrate was found to be marginally but significantly better than placebo in healing anal fissure (48.9% vs. 35.5%/ $p<0.0009$). Studies identified showed that BoNT injection was found in combined analysis to be no better or worse than topical glyceryl trinitrate (OR 0.56; 95% CI 0.20-1.57; $p=0.27$; $I2=71\%$), and also no better than placebo (OR 0.29; 95% CI 0.02-3.61; $p=0.34$; $I2=89\%$). BoNT has also not been shown to do as well as surgery in curing fissure (OR 7.20; 95% CI 3.97-13.07; $p<0.001$; $I2=47\%$). There was no difference seen in one study between ONA and ABO in non-healing of fissure (OR 1.36; 95% CI 0.29-6.43; $p=0.70$), and the authors concluded that the type of BoNT has not been found to affect healing rates. Overall, there was high quality evidence of a significantly higher risk of non-healing (persistence or recurrence) in any medical therapy compared to any surgery (OR 0.11; 95% CI 0.06 to 0.23; $p<0.001$; $I2=62\%$).

The American Society of Colon and Rectal Surgeons released practice guidelines for the management of anal fissures based on a literature search and evidence grading.[46] The following recommendations are provided:

- Nonoperative measures including sitz baths, psyllium fiber and bulking agents with or without the addition of topical anesthetics of anti-inflammatory ointments is recommended first line (strong recommendations; moderate quality evidence).
- Topical nitrates may be used, although they are only marginally superior to placebo in regard to healing (strong recommendation; high quality evidence).
- Anal fissures may be treated with topical calcium blockers, which have a lower incidence of adverse effects than topical nitrates. There are insufficient data to conclude whether they are superior to placebo in healing anal fissures (strong recommendation; moderate quality evidence).

- BoNT has been associated with healing rates superior to placebo. There is inadequate consensus on dosage, site of administration, number of injections or efficacy (Strong recommendation; low quality evidence).
- Surgery is consistently superior to medical therapy and may be offered without a pharmacological treatment failure (Strong recommendation; high quality evidence).

Achalasia

Achalasia is enlargement of the esophagus. Treatment is focused on relieving the obstruction in the distal esophagus created by the incompletely relaxed lower esophageal sphincter. Pharmacological therapy, BoNT injection, pneumatic dilatation (PD), and surgical myotomy are the primary treatment strategies in management of achalasia. BoNT injections are recommended for patients who are poor candidates for other more effective treatment options, such as surgery or dilation.[47] BoNT has been shown to be effective in the short term, but has a high rate of relapse and efficacy quickly and dramatically decreases by 2 years.[48] A meta-analysis by Campos et al. evaluated 9 studies utilizing BoNT as the primary form of therapy. The percentage of patients with symptomatic improvement after one session of BoNT injection was 78.7% at 1 month, 7% at 3 months, 53.3% at 6 months, and 40.6% at over 12 months. However, at least a second injection was required in almost half of patients (46.6%).

A 2006 Cochrane Collaboration systematic review identified 6 studies comparing PD to BoNT (unspecified serotype), both endoscopic options, in patients with primary achalasia.[49] Results of a meta-analysis demonstrated no significant difference in remission between PD and BoNT treatment (RR 1.15; 95% CI 0.95 to 1.38; p=0.39). There was also no significant difference in the mean esophageal pressures between the groups. At 6 months, more patients were in remission in the PD group compared to the BoNT group (RR 2.90; 95% CI 1.48 to 5.67; p=0.00), as well as at 12 months (RR 2.67; 95% CI 1.58 to 4.52; p=0.0002). The authors concluded that PD is the more effective endoscopic treatment in the long term for patients with achalasia.

Another systematic review by Wang, et al. evaluated remission and relapse rate of BoNT compared to PD and surgical myotomy for the treatment of achalasia.[50] A total of 17 clinical studies were included in the analysis (n=761). Five of the studies compared unspecified BoNT injection with PD, 2 compared BoNT with myotomy. Results demonstrated significant differences in remission rate between PD and BoNT (65.8% vs. 36%; RR 2.20; 95% CI 1.51-3.20, p<0.0001) and relapse rate (16.7% vs. 50%; RR 0.36; 95% CI 0.22-0.58) favoring BoNT at 12 months. The authors concluded that PD remains more efficacious that BoNT for the treatment of achalasia. They also found that myotomy had superior efficacy to BoNT in remission rate (83.3% vs. 64.9%; RR 1.28; 95% CI 1.02-1.59; p=0.03). However, there were also more adverse events with BoNT compared to PD (4.5% vs. 18.8%). There was insufficient data to perform a meta-analysis on adverse events and withdrawals. The authors concluded that laproscopic myotomy is the preferred method in the management of achalasia and BoNT can offer dysphagia control, but it is temporary and reversible.

The American College of Gastroenterology recommends PD or laparoscopic surgical myotomy as first line therapy (strong recommendation; moderate quality evidence).[51] BoNT (ONA) is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy (strong recommendation, moderate quality evidence). Lastly, pharmacologic therapy (smooth muscle relaxants) is recommended for patients who have failed BoNT therapy. The primary disadvantage with BoNT for this use is that repeat injections after 6 to 12 months are commonly needed, and the long-term efficacy and safety are not well studied beyond 2 years. Although the initial response rate is high (>75%), the effect eventually wears off and repeat injection is required in a significant portion of the patients. Approximately 50% of patients relapse and require repeat treatments at 6-24 month intervals. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) conducted a literature search to also provide guidelines for the treatment of esophageal achalasia.[52] They are consistent that a single injection of BoNT has been shown to be quite effective, but its long term effectiveness remains limited. They recommend that BoNT can

be administered safely, but its effectiveness is limited especially in the long-term. It should be reserved for patients who are poor candidates for other more effective treatment options, such as surgery or dilation (strong recommendation).

Under the rein of the International Society for Diseases of Esophagus, the Kagoshima consensus on esophageal achalasia was released in 2010.[53] The statement discusses that the clinical response at 2 years is only 3%, decreasing from 90% as an initial clinical response. However, the panel noted that because of its safety, it may be a good option for elderly patients with comorbidities, but it also carries an increased risk of subsequent myotomy, due to fibrosis at the injection sites.

A randomized controlled trial compared the efficacy and tolerability of two BoNT formulations in treating achalasia (ONA and ABO).[54] After BoNT injection was given, 90% of the ONA group and 83.5% of the ABO group reported a symptomatic response to the treatment. No differences were seen between the two formulations in any clinical variables and side effects were similar. At the end of the follow-up period, symptom relapse was documented in 12% of ONA patients and 24% of ABO patients. This was reported as non-significant although p values were not provided.

Strabismus:
Strabismus is the misalignment of 2 eyes so that both cannot be directed toward an object. Comitant strabismus occurs in children <6 years old and noncomitant has an onset later in life. A 2012 Cochrane Collaboration systematic review evaluated the efficacy of any BoNT in the treatment of strabismus compared with alternative treatment options.[55] A literature search was done to identify RCTs and a total of 4 met inclusion criteria (3 with ONA and 1 with ABO). Two trials found that there was no difference between BoNT and surgery for infantile esotropia. There was no evidence for a prophylactic effect of BoNT in a treatment trial of acute onset sixth nerve palsy. BoNT had a poorer response than surgery in a trial of patients with horizontal strabismus. Trials included both ONA and ABO and there was insufficient evidence to establish a dose effect. The American Academy of Ophthalmology concludes that there is insufficient evidence to make treatment recommendations for BoNT treatment for exotropia.[56]

Sialorrhea
Sialorrhea is excessive drooling commonly seen in patients with neurological disorders, such as cerebral palsy, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).[57] Treatment approaches include anticholinergics, antireflux medications, radiation and surgery. More recently, BoNT has become a potential treatment option in these patients. Vashishta, et al conducted a meta-analysis on the available evidence for the use of BoNT A and BoNT B in the treatment of sialorrhea. There were eight studies (three utilizing ONA or ABO and five using RIM) with 181 patients that were included in the analysis. Four studies were in children with cerebral palsy, 2 with adults with Parkinson's disease, and 1 in ALS. The use of BoNT was found to significantly decrease the severity of drooling when compared to placebo using an outcome measure of drooling severity and frequency scales. Both BoNT A and BoNT B preparations were effective in productin similarly significant reductions in drooling severity. [57] Advantages over alternate treatments include a more acceptable safety profile than transdermal scopolamine, fewer drug interactions than scopolamine and glycopyrrolate and a safer alternative to systemic anticholinergic therapy.

An international consensus statement was released for the care of patients with drooling as a result of a neurological problem or anatomical abnormality of the jaw. [58] Literature was searched and appraised to make recommendations. Based on expert opinion only, it is recommended that injection of BoNT A into the salivary glands is given under ultrasound guidance. Due to acquired resistance to BoNT therapy, it is recommend that BoNT B be tried after treatment failure with BoNT A.

Tremor

According to a systematic review of the evidence for BTP for essential tremor (Ferreira and Sampaio, 2003), there is evidence of short-term reduction of tremor but no consistent improvement in disability and function. The review noted that BTP injections cause hand weakness, resulting in a "trade off" between benefits and harms. The review concluded that BTP versus placebo found short term improvement of clinical rating scales, but no consistent improvement of motor task performance or functional disability. The AAN concluded that "the effect of BTA on limb tremor in ET [essential tremor] is modest and is associated with dose-dependent hand weakness and may reduce head tremor and voice tremor associated with ET, but data are limited. When used to treat voice tremor, botulinum toxin A may cause breathiness, hoarseness, and swallowing difficulties."

The AAN's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson et al, 2008) stated that botulinum neurotoxin should be considered a treatment option for essential hand tremor in those patients who fail treatment with oral agents. On the other hand, there is insufficient evidence to draw a conclusion on the use of BTP in the treatment of head and voice tremor.

Other Indications:

BoNT has been studied in a number of other disorders where this is insufficient evidence to recommend its use. Several open-label studies have evaluated BoNT in gastroparesis and observed mild improvements in gastric emptying and modest improvement in symptoms.[59–61] Two double-blind placebo-controlled trials have showed no difference in improvement in symptoms compared with placebo.[62] BoNT injection into the pylorus is not recommended as a treatment for gastroparesis. BoNT A has also been evaluated for use in restless legs syndrome; however, there is insufficient evidence to support the use, with one double-blind, RCT showing no significant benefit with BoNT A compared to placebo.[63,64] A recent systematic review from the Cochrane Collaboration were unable to identify any controlled clinical trials assessing the efficacy and safety of BoNT for masseter hypertrophy.[65]

Other areas in which larger, well-designed studies are needed to demonstrate effectiveness include cricopharyngeal dysphagia, gustatory epiphora (crocodile tears), Sphincter of Oddi dysfunction,pancreas divisum, anismus, , pelvic floor spasticity, chronic prostaticpain, severe paradoxical vocal cord movement, postparotidectomy sialoceles, severe bruxism,temporomandibular disorders, myofascial pain syndrome, brachial plexus palsy, thyroid associatedophthalmopathy, esophageal spasm, post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia, trismus and stridor in amyotrophic lateral sclerosis, proctalgia fugax, nasal hypersecretion, gastroparesis (including diabetic gastroparesis), Lichen simplex, lateral epicondylitis, Stiff-person syndrome, benign prostatic hyperplasia, traumatic sixth nerve palsy, Tourette's syndrome, and pain and/or wound healing after hemorrhoidectomy. Only small and uncontrolled open-label studies have been performed for these conditions.

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Appendix A: Dosing for BoNT Preparations

Indication	Abobotulinumtoxin A	Incobotulinumtoxin A	Onabotulinumtoxin A	Rimabotulinumtoxin B
Cervical dystonia	500 units IM divided among affected muscles	120 units IM divided among affected muscles	198 units – 300 units IM divided among affected muscles, max 50 units per site	2,500 units – 5,000 units IM divided among affected muscles
Upper limb spasticity	500 units – 1,500 units IM divided among affected muscles	80 units – 435 units IM divided among affected muscles	75 units – 360 units IM divided among affected muscles, max 50 units per site	1,000 units – 5,000 units IM divided among affected muscles
Blepharospasm	40 units – 120 units as divided injections	1.25 units – 2.5 units injected into medial and lateral pretarsal orbicularis oculi of the upper lid and lateral pretarsal orbicularis oculi of the lower lid	1.25 units – 2.5 units injected into medial and lateral pretarsal orbicularis oculi of the upper lid and lateral pretarsal orbicularis oculi of the lower lid	
Axillary hyperhidrosis	200 units intradermally per axilla		50 units intradermally per axilla	
Overactive Bladder/Urinary			100 units divided into 20 intradetrusor injections	5,000 units divided into 10 intradetrusor injections sparing

Incontinence			sparing the trigone	the trigone
Neurogenic detrusor overactivity	500 units divided into 20 intradetrusor injections sparing the trigone		200 units divided into 30 intradetrusor injections sparing the trigone	
Chronic migraine prophylaxis			155 units IM divided in 31 sites	
PES	200 units injected into the PES musculature		100 units injected into the PES musculature	

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Attention Deficit Hyperactivity Disorder (ADHD) Drug Use Evaluation

Recommendations

- Create a safety edit for:
  - Prescribing of ADHD medications by non-psychiatrists when regimen is:
    - Outside of the standard ages
    - Outside the standard doses
    - Non-standard polypharmacy
  - Adults 18 or older receiving ADHD medications
- Require informed consent, controlled substance contract, or similar risk mitigation tool for adults prescribed CNS stimulants

Background

Attention deficit hyperactivity disorder (ADHD) has been characterized as the most commonly diagnosed mental health disorder in children and is increasingly diagnosed in adults.[1,2] Pharmacotherapy, in conjunction with psychosocial interventions, is a core treatment modality for ADHD. As discussed previously, pharmacotherapy options include traditional stimulants (e.g. amphetamine and methylphenidate derivatives), non-traditional stimulants (e.g. modafinil), and non-stimulants (e.g. guanfacine, clonidine, and atomoxetine).[3,4] Current recommendations from the American Academy of Pediatrics (AAP) and the 2011 Drug Effectiveness Review Project (DERP) indicate different pharmacotherapy options for different age groups.[5,6] A 2013 DERP report evaluated state Medicaid program policies managing the use of stimulants for the treatment of ADHD.[1] These finding were compared to the current Oregon Fee-For-Service (FFS) policies[7] and the following areas for improvement were identified:

1. Promote age-specific therapy
2. Verify indications for pharmacotherapy
3. Limit the use of non-standard polypharmacy regimens
4. Develop specific policies for patients with a history of substance abuse
5. Develop an informed consent process

A drug use evaluation (DUE) was performed to determine if policy changes in these areas would impact current pharmacy utilization.

DUE Goals

- Determine the prevalence of members prescribed ADHD treatments according to best practice guidelines (age, indication & polypharmacy)[1,5,6,8]
- Determine the prevalence of substance misuse in adolescents 12-17 and adults receiving ADHD medications

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Methods

Inclusion and Exclusion Criteria

The DUE evaluated claims from 8/1/2011 until 2/13/2013. Members were selected based on the presence of at least one paid Fee-For-Service (FFS) pharmacy claim between 8/1/2012 and 11/30/2012 for a medication used in the treatment of ADHD (Table A1). The Index Event (IE) was defined as the first claim for an ADHD medication during this timeframe. Patients with dual Medicare eligibility during the study period were excluded, as were members enrolled in a coordinated care organization (CCO). Members with a gap in eligibility exceeding 25% during the study period were excluded. Patients with a recent history of hypertension without a diagnosis of ADHD (ICD9 314.xx), only receiving prescriptions for clonidine immediate release were excluded due to the likelihood that clonidine is being used for hypertension, not ADHD. Hypertension was identified by diagnosis codes (ICD9 40x.xx) or outpatient pharmacy claims for common antihypertensive medications (Table A2). Patients with a diagnosis of drug withdrawal (ICD9 292.0) and no ADHD diagnosis receiving only immediate release clonidine were also excluded.

Baseline Characteristics

Baseline characteristics of age, gender and ethnicity were assessed at the IE. Age groups were defined to correspond to age-specific variations in treatment and monitoring recommendations. ADHD diagnosis was assessed based on the presence of medical claims between the IE-365 days and IE+30 days with an ICD9 code of 314.xx.

Measures

Standard therapy definitions were based on the findings and recommendations of the AAP and DERP.[5,8] The term "standard" therapy has been used in recognition that individualized therapy outside of guidelines may be clinically appropriate based on factors not readily available from claims data. Standard therapy is defined as meeting all recommendations for age, dose, indication, and presence of other medication therapies (i.e. polypharmacy). Drug therapy was considered age-standard if the patient's age was within the range listed in table A1 on the first claim date for a given medication during the study period. The dose for a particular prescription was considered standard if the total daily dose was less than or equal to the maximum daily dose listed in table A1. If at least one claim exceeded the maximum daily dose, the member was categorized as receiving non-standard dosing. The daily dose was calculated based on the day supply, quantity dispensed, and strength as indicated on the paid claim.

Polypharmacy was evaluated during the 90 days following the IE. Polypharmacy was defined as at least 60 days covered by each agent, with a minimum overlap of 60 days and a gap in therapy not exceeding 32 days.[9] The use of a long acting stimulant in conjunction with an immediate release stimulant was not considered polypharmacy. Polypharmacy was categorized as non-standard in children under 6 years old, regardless of the combination, per AAP guidelines.[5] Polypharmacy was considered a standard therapy in children 6-17 when a stimulant was used in combination with clonidine, or guanfacine. All other combinations were considered non-standard in children 6-17. All polypharmacy in adults was considered non-standard.[6,10]

Therapy was considered standard for the indication if there was a history of ADHD (ICD9 314.xx) at baseline. Member receiving stimulants for narcolepsy (ICD9 347.xx) were categorized has receiving standard therapy. The presence of obstructive sleep apnea (ICD9 327.xx) and the use of modafinil or armodafinil were considered standard indications.

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Patients without any of these indications were considered as treated for non-standard indications. A second aggregate measure of non-standard regimens, excluding standard indication, was also reported.

Substance misuse was identified by medical claims with a diagnosis contained in Table A3 or outpatient prescriptions listed in table A4. Recent history of substance misuse was defined as the presence of at least one claim between 365 days before the IE and 30 days after the IE. Any history of misuses includes members with any claim prior to the IE + 30 days. Substance misuse was only evaluated in adolescents and adults as these are the two highest risk groups for misuse and diversion.[6]

Results

The majority of members receiving ADHD therapy were under 18 years old, male, and white (Table 1). Of the 2,355 member included 1,045 (44%) had a claims history suggesting non-standard pharmacotherapy (Table 2). Non-standard polypharmacy was uncommon (5%, n=126). Overall the most common type of non-standard therapy was non-standard indication (37%). In children 3-5 years old, non-standard regimens were most commonly characterized as inappropriate for this age group (94%). Of the 83 members receiving pharmacotherapy outside standard doses, 48 (59%) were receiving medications for which there are no current PA criteria (atomoxetine, clonidine, guanfacine, and modafinil).

In adults receiving ADHD pharmacotherapy, 19% had a recent history of substance misuse and 34% have a history of substance misuse (Table 3). Of the 172 adult members with a any history of substance misuse, 110 (64%) were receiving traditional CNS Stimulants. Of the 85 adolescents with a history of substance misuse, 59 (70%) were receiving traditional stimulants.

Table 1. Baseline Characteristics

	n=2355	
	#	%
Age		
Under 3 years	1	0%
3-5 years	50	2%
6-11 years	858	36%
12-17 years	944	40%
18 years and older	502	21%
Ethnicity		
Non-White	455	19%
White	1,900	81%
Gender		
F	845	36%
M	1,510	64%

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Table 2. ADHD Pharmacotherapy Descriptions

	Overall		Under 3 years		3-5 years		6-11 years		12-17 years		18 years and older	
	n=2355		n=1		n=50		n=858		n=944		n=502	
	#	%	#	%	#	%	#	%	#	%	#	%
Non-Standard Prescribing - Overall	1,045	44%	1	100%	47	94%	299	35%	402	43%	296	59%
Outside Standard Age	184	8%	1	100%	47	94%	0	0%	4	0%	132	26%
Outside Standard Dose	83	4%	0	0%	1	2%	17	2%	37	4%	28	6%
No Standard Indication	870	37%	1	100%	18	36%	253	29%	347	37%	251	50%
Non-Standard Polypharmacy	126	5%	0	0%	3	6%	52	6%	44	5%	27	5%

Table 3. Substance Misuse History

	12-17 years		18 years and older	
	n=944		n=502	
	#	%	#	%
Recent History of Substance Misuse				
Any	54	6%	95	19%
Stimulants	8	1%	21	4%
Other Drugs	46	5%	75	15%
Any History of Substance Misuse				
Any	85	9%	172	34%
Stimulants	14	1%	53	11%
Other Drugs	77	8%	152	30%

Discussion

A significant proportion (44%) of FFS members receiving ADHD pharmacotherapy were identified as being treated with non-standard prescribing. There was a high prevalence (37%) of no documented standard indication for ADHD therapy but past experience has shown that administrative claims may underreport the prevalence of a disorder. The use of non-standard doses was low (4%), likely due to the current PA criteria indicating CNS stimulants exceeding maximum doses must be prescribed by a psychiatrist.

The prevalence of substance abuse history in adult ADHD patients was high (recent 19%, any 34%). Published reports indicate diversion and misuse issues are also significant in adolescents with 5% to 8% reporting misusing and high incidence of giving them away (15% to 24%) or selling them (7%-19%). The 1% rate of stimulant misuse in adolescents is significantly lower than other published rates. This could be a function of underreporting in claims data.

There is currently no mechanism to ensure patients with treatment-resistant ADHD symptoms are receiving specialty psychiatric care. Neither is there a process to support increased monitoring for members receiving CNS stimulants with an increased risk of substance misuse.

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Recommendations

Multiple states have implemented prior authorizations to monitor and manage non-standard prescribing practices (Table 4). Several state (Delaware, Idaho, Utah, and Missouri) require screening and monitoring for efficacy and safety of ADHD medications in patients with a history of substance abuse.[1] Idaho is the most restrictive and does not approve the use of CNS stimulants in adults with a history of substance abuse. There is no clear evidence supporting a particular approach.

Appendix B contains a safety edit designed to promote specialized care for patients receiving non-standard ADHD pharmacotherapy. The safety edit be triggered for:

- ADHD medications prescribed by non-psychiatrists when regimen is:
  - Outside of the standard ages
  - Outside the standard doses
  - Non-standard polypharmacy

Table 4. Prior Authorization Policies for Non-Standard Prescribing[1]

	Age Restrictions	Dose Limits	Polypharmacy
Arkansas	✓	✓	✓
Colorado		✓	
Delaware	✓		
Idaho	✓		
Illinois	✓		
Missouri			✓
New York	✓		
Oregon		✓	
Tennessee		✓	
Texas		✓	✓
Utah	✓		

There are client confidentiality regulations constraining targeted safety edits in patients with a history of substance misuse. Certain types of substance abuse treatment history cannot be disclosed without written patient consent. Therefore a prior authorization policy based on this information is not practical. Requiring prior authorizations for all adults could unnecessarily restrict access to physician or pharmacy services. A provider survey and education campaign represents a low-impact option to determine current strategies and opportunities for DMAP to provide additional resources (e.g. sample documents). Providers who prescribed CNS stimulants to FFS members during the prior 12 months would be a reasonable target audience. Results of this survey and further policy recommendations will be brought to the P & T committee.

A risk associated with any utilization control is the unintended discontinuation of therapy.[12] This can occur when patient do not understand the process or the prescriber does not complete the request. A retrospective drug use review will monitor patients for claims denied due to the PA requirement without either a PA requested or an alternative prescription. The retrospective review will also monitor for denied claims, a proxy for prescriptions paid for with cash.

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Appendix A

Table A1 ADHD Medications[5,6,8]

Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (mg)
armodafinil	18		250
atomoxetine	6		100
clonidine*	6	17	0.4
dexmethylphenidate	6		20
dextroamphetamine sulfate	6		40
dextroamphetamine/amphetamine	6		60
guanfacine	6	17	4
lisdexamfetamine dimesylate	6		70
methamphetamine	6		60
methylphenidate immediate release	3		90
methylphenidate sustained release	6		90
methylphenidate transdermal	6		30
modafinil	18		200

*Prescriptions for transdermal clonidine we excluded, as these are only indicated for cardiovascular indications.
Bupropion and desipramine were excluded due to their common use in the treatment of affective disorders.

Table A2 – Antihypertensive agents

Drug Class	Generic name
ACE, ARB, DRI Drugs	ALISKIREN HEMIFUMARATE
ACE, ARB, DRI Drugs	AZILSARTAN MEDOXOMIL
ACE, ARB, DRI Drugs	BENAZEPRIL HCL
ACE, ARB, DRI Drugs	CANDESARTAN CILEXETIL
ACE, ARB, DRI Drugs	CAPTOPRIL
ACE, ARB, DRI Drugs	ENALAPRIL MALEATE
ACE, ARB, DRI Drugs	EPROSARTAN MESYLATE
ACE, ARB, DRI Drugs	FOSINOPRIL SODIUM
ACE, ARB, DRI Drugs	IRBESARTAN
ACE, ARB, DRI Drugs	LISINOPRIL
ACE, ARB, DRI Drugs	LOSARTAN POTASSIUM
ACE, ARB, DRI Drugs	MOEXIPRIL HCL
ACE, ARB, DRI Drugs	OLMESARTAN MEDOXOMIL
ACE, ARB, DRI Drugs	PERINDOPRIL ERBUMINE
ACE, ARB, DRI Drugs	QUINAPRIL HCL
ACE, ARB, DRI Drugs	QUINAPRIL HCL/MAG CARB
ACE, ARB, DRI Drugs	RAMIPRIL
ACE, ARB, DRI Drugs	TELMISARTAN
ACE, ARB, DRI Drugs	TRANDOLAPRIL
ACE, ARB, DRI Drugs	VALSARTAN
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	ALISKIREN/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	AZILSARTAN MED/CHLORTHALIDONE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	BENAZEPRIL/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	CANDESARTAN/HYDROCHLOROTHIAZID
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	CAPTOPRIL/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	ENALAPRIL/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	EPROSARTAN/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	FOSINOPRIL/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	IRBESARTAN/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	LISINOPRIL/HYDROCHLOROTHIAZIDE

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Drug Class	Generic name
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	LOSARTAN/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	MOEXIPRIL/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	OLMESARTAN/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	QUINAPRIL/HYDROCHLOROTHIAZIDE
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	TELMISARTAN/HYDROCHLOROTHIAZID
ACE-HCTZ, ARB-HCTZ, DRI-HCTZ Drugs	VALSARTAN/HYDROCHLOROTHIAZIDE
Beta-Blockers	ACEBUTOLOL HCL
Beta-Blockers	ATENOLOL
Beta-Blockers	BETAXOLOL HCL
Beta-Blockers	BISOPROLOL FUMARATE
Beta-Blockers	CARTEOLOL HCL
Beta-Blockers	CARVEDILOL
Beta-Blockers	CARVEDILOL PHOSPHATE
Beta-Blockers	LABETALOL HCL
Beta-Blockers	METOPROLOL SUCCINATE
Beta-Blockers	METOPROLOL TARTRATE
Beta-Blockers	NADOLOL
Beta-Blockers	NEBIVOLOL HCL
Beta-Blockers	PENBUTOLOL SULFATE
Beta-Blockers	PINDOLOL
Beta-Blockers	PROPRANOLOL HCL
Beta-Blockers	SOTALOL HCL
Beta-Blockers	TIMOLOL MALEATE
Calcium Channel Blockers - Dihydropyridine	AMLODIPINE BESYLATE
Calcium Channel Blockers - Dihydropyridine	BEPRIDIL HCL
Calcium Channel Blockers - Dihydropyridine	DILTIAZEM MALATE
Calcium Channel Blockers - Dihydropyridine	FELODIPINE
Calcium Channel Blockers - Dihydropyridine	ISRADIPINE
Calcium Channel Blockers - Dihydropyridine	NICARDIPINE HCL
Calcium Channel Blockers - Dihydropyridine	NIMODIPINE
Calcium Channel Blockers - Dihydropyridine	NISOLDIPINE
Calcium Channel Blockers - Non-Dihydropyridine	DILTIAZEM HCL
Calcium Channel Blockers - Non-Dihydropyridine	NIFEDIPINE
Calcium Channel Blockers - Non-Dihydropyridine	VERAPAMIL HCL
Diuretics	AMILORIDE HCL
Diuretics	AMILORIDE/HYDROCHLOROTHIAZIDE
Diuretics	BENDROFLUMETHIAZIDE
Diuretics	BENZTHIAZIDE
Diuretics	BUMETANIDE
Diuretics	CHLOROTHIAZIDE
Diuretics	CHLORTHALIDONE
Diuretics	EPLERENONE
Diuretics	ETHACRYNIC ACID
Diuretics	FUROSEMIDE
Diuretics	HYDROCHLOROTHIAZIDE
Diuretics	HYDROFLUMETHIAZIDE
Diuretics	INDAPAMIDE
Diuretics	METHYCLOTHIAZIDE
Diuretics	METOLAZONE
Diuretics	POLYTHIAZIDE
Diuretics	SPIRONOLACT/HYDROCHLOROTHIAZID
Diuretics	SPIRONOLACTONE
Diuretics	TORSEMIDE
Diuretics	TRIAMTERENE
Diuretics	TRIAMTERENE/HYDROCHLOROTHIAZID
Diuretics	TRICHLORMETHIAZIDE

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Table A3 Diagnosis Codes and Categories

ICD9 Code	Description	Stimulant Related
291	ALCOHOL-INDUCED MENTAL DISORDERS	
2910	Alcohol withdrawal delirium	
29100	DSM ALCOHOL WITHDRAWAL DELIRIU	
2911	Alcohol-induced persisting amnestic disorder	
29110	DSM ALCOHOL AMNESTIC SYNDROME	
2912	Alcohol-induced persisting dementia	
29120	DSM OTHER ALCOHOLIC DEMENTIA	
2913	Alcohol-induced psychotic disorder with hallucinations	
29130	DSM ALCOHOL WITHDRAWAL HALLUCI	
2914	Idiosyncratic alcohol intoxication	
29140	DSM IDIOSYNCRATIC ALCOHOL INTO	
2915	Alcohol-induced psychotic disorder with delusions	
2918	OTHER SPECIFIED ALCOHOL-INDUCED MENTAL DISORDERS	
29180	DSM OTHER SPEC ALCOHOL PSYCHOS	
29181	Alcohol withdrawal	
29182	Alcohol induced sleep disorders	
29189	Other alcohol-induced mental disorders	
2919	Unspecified alcohol-induced mental disorders	
292	DRUG-INDUCED MENTAL DISORDERS	
2920	Drug withdrawal	
29200	DSM DRUG WITHDRAWAL SYNDROME	
2921	PARANOID &OR HALLUCINATORY STATES INDUCED DRUGS	
29211	Drug-induced psychotic disorder with delusions	
29212	Drug-induced psychotic disorder with hallucinations	
2922	Pathological drug intoxication	
2928	OTHER SPECIFIED DRUG-INDUCED MENTAL DISORDERS	
29281	Drug-induced delirium	
29282	Drug-induced persisting dementia	
29283	Drug-induced persisting amnestic disorder	
29284	Drug-induced mood disorder	
29285	Drug induced sleep disorders	
29289	Other specified drug-induced mental disorders	
2929	Unspecified drug-induced mental disorder	
29290	DSM UNSPECIFIED DRUG INDUCED O	
30016	Factitious disorder with predominantly psychological signs and symptoms	
303	ALCOHOL DEPENDENCE SYNDROME	
3030	ACUTE ALCOHOLIC INTOXICATION	
30300	Acute alcoholic intoxication in alcoholism, unspecified	
30301	Acute alcoholic intoxication in alcoholism, continuous	
30302	Acute alcoholic intoxication in alcoholism, episodic	
30303	Acute alcoholic intoxication in alcoholism, in remission	
3039	OTHER AND UNSPECIFIED ALCOHOL DEPENDENCE	
30390	Other and unspecified alcohol dependence, unspecified	
30391	Other and unspecified alcohol dependence, continuous	
30392	Other and unspecified alcohol dependence, episodic	
30393	Other and unspecified alcohol dependence, in remission	
304	DRUG DEPENDENCE	
3040	OPIOID TYPE DEPENDENCE	
30400	Opioid type dependence, unspecified	
30401	Opioid type dependence, continuous	
30402	Opioid type dependence, episodic	
30403	Opioid type dependence, in remission	
3041	SEDATIVE HYPNOTIC OR ANXIOLYTIC DEPENDENCE	
30410	Sedative, hypnotic or anxiolytic dependence, unspecified	
30411	Sedative, hypnotic or anxiolytic dependence, continuous	
30412	Sedative, hypnotic or anxiolytic dependence, episodic	
30413	Sedative, hypnotic or anxiolytic dependence, in remission	
3042	COCAINE DEPENDENCE	
30420	Cocaine dependence, unspecified	
30421	Cocaine dependence, continuous	
30422	Cocaine dependence, episodic	
30423	Cocaine dependence, in remission	
3043	CANNABIS DEPENDENCE	
30430	Cannabis dependence, unspecified	
30431	Cannabis dependence, continuous	
30432	Cannabis dependence, episodic	
30433	Cannabis dependence, in remission	
3044	AMPHETAMINE AND OTHER PSYCHOSTIMULANT DEPENDENCE	Yes
30440	Amphetamine and other psychostimulant dependence, unspecified	Yes
30441	Amphetamine and other psychostimulant dependence, continuous	Yes
30442	Amphetamine and other psychostimulant dependence, episodic	Yes

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ICD9 Code	Description	Stimulant Related
30443	Amphetamine and other psychostimulant dependence, in remission	Yes
3045	HALLUCINOGEN DEPENDENCE	
30450	Hallucinogen dependence, unspecified	
30451	Hallucinogen dependence, continuous	
30452	Hallucinogen dependence, episodic	
30453	Hallucinogen dependence, in remission	
3046	OTHER SPECIFIED DRUG DEPENDENCE	
30460	Other specified drug dependence, unspecified	
30461	Other specified drug dependence, continuous	
30462	Other specified drug dependence, episodic	
30463	Other specified drug dependence, in remission	
3047	COMB OPIOID DRUG W/ANY OTH DRUG DEPENDENCE	
30470	Combinations of opioid type drug with any other drug dependence, unspecified	
30471	Combinations of opioid type drug with any other drug dependence, continuous	
30472	Combinations of opioid type drug with any other drug dependence, episodic	
30473	Combinations of opioid type drug with any other drug dependence, in remission	
3048	COMB DRUG DEPENDENCE EXCLUDING OPIOID DRUG	
30480	Combinations of drug dependence excluding opioid type drug, unspecified	
30481	Combinations of drug dependence excluding opioid type drug, continuous	
30482	Combinations of drug dependence excluding opioid type drug, episodic	
30483	Combinations of drug dependence excluding opioid type drug, in remission	
3049	UNSPECIFIED DRUG DEPENDENCE	
30490	Unspecified drug dependence, unspecified	
30491	Unspecified drug dependence, continuous	
30492	Unspecified drug dependence, episodic	
30493	Unspecified drug dependence, in remission	
305	NONDEPENDENT ABUSE OF DRUGS	
3050	NONDEPENDENT ALCOHOL ABUSE	
30500	Alcohol abuse, unspecified	
30501	Alcohol abuse, continuous	
30502	Alcohol abuse, episodic	
30503	Alcohol abuse, in remission	
3052	NONDEPENDENT CANNABIS ABUSE	
30520	Cannabis abuse, unspecified	
30521	Cannabis abuse, continuous	
30522	Cannabis abuse, episodic	
30523	Cannabis abuse, in remission	
3053	NONDEPENDENT HALLUCINOGEN ABUSE	
30530	Hallucinogen abuse, unspecified	
30531	Hallucinogen abuse, continuous	
30532	Hallucinogen abuse, episodic	
30533	Hallucinogen abuse, in remission	
3054	NONDEPENDENT SEDATIVE HYPNOTIC/ANXIOLYTIC ABUSE	
30540	Sedative, hypnotic or anxiolytic abuse, unspecified	
30541	Sedative, hypnotic or anxiolytic abuse, continuous	
30542	Sedative, hypnotic or anxiolytic abuse, episodic	
30543	Sedative, hypnotic or anxiolytic abuse, in remission	
3055	NONDEPENDENT OPIOID ABUSE	
30550	Opioid abuse, unspecified	
30551	Opioid abuse, continuous	
30552	Opioid abuse, episodic	
30553	Opioid abuse, in remission	
3056	NONDEPENDENT COCAINE ABUSE	
30560	Cocaine abuse, unspecified	
30561	Cocaine abuse, continuous	
30562	Cocaine abuse, episodic	
30563	Cocaine abuse, in remission	
3057	NONDEPEND AMPHET/REL ACTING SYMPATHOMIMET ABS	Yes
30570	Amphetamine or related acting sympathomimetic abuse, unspecified	Yes
30571	Amphetamine or related acting sympathomimetic abuse, continuous	Yes
30572	Amphetamine or related acting sympathomimetic abuse, episodic	Yes
30573	Amphetamine or related acting sympathomimetic abuse, in remission	Yes
3058	NONDEPENDENT ANTIDEPRESSANT TYPE ABUSE	
30580	Antidepressant type abuse, unspecified	
30581	Antidepressant type abuse, continuous	
30582	Antidepressant type abuse, episodic	
30583	Antidepressant type abuse, in remission	
3059	OTHER MIXED/UNSPECIFIED NONDEPENDENT DRUG ABUSE	
30590	Other, mixed, or unspecified drug abuse, unspecified	
30591	Other, mixed, or unspecified drug abuse, continuous	
30592	Other, mixed, or unspecified drug abuse, episodic	
30593	Other, mixed, or unspecified drug abuse, in remission	
9650	POISONING BY OPIATES AND RELATED NARCOTICS	
96500	Poisoning by opium (alkaloids), unspecified	

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ICD9 Code	Description	Stimulant Related
96501	Poisoning by heroin	
96502	Poisoning by methadone	
96509	Poisoning by other opiates and related narcotics	
9654	Poisoning by aromatic analgesics, not elsewhere classified	
967	POISONING BY SEDATIVES AND HYPNOTICS	
9670	Poisoning by barbiturates	
9671	Poisoning by chloral hydrate group	
9672	Poisoning by paraldehyde	
9673	Poisoning by bromine compounds	
9674	Poisoning by methaqualone compounds	
9675	Poisoning by glutethimide group	
9676	Poisoning by mixed sedatives, not elsewhere classified	
9678	Poisoning by other sedatives and hypnotics	
9679	Poisoning by unspecified sedative or hypnotic	
9694	Poisoning by benzodiazepine-based tranquilizers	
9695	Poisoning by other tranquilizers	
9696	Poisoning by psychodysleptics (hallucinogens)	
9697	POISONING BY PSYCHOSTIMULANTS	Yes
96970	Poisoning by psychostimulant, unspecified	Yes
96971	Poisoning by caffeine	
96972	Poisoning by amphetamines	Yes
96973	Poisoning by methylphenidate	Yes
96979	Poisoning by other psychostimulants	Yes
97081	Poisoning by cocaine	
97089	Poisoning by other central nervous system stimulants	Yes
9779	Poisoning by unspecified drug or medicinal substance	
E8500	Accidental poisoning by heroin	
E8501	Accidental poisoning by methadone	
E8502	Accidental poisoning by other opiates and related narcotics	
E851	Accidental poisoning by barbiturates	
E852	ACCIDENTAL POISONING OTHER SEDATIVES&HYPNOTICS	
E8520	Accidental poisoning by chloral hydrate group	
E8521	Accidental poisoning by paraldehyde	
E8522	Accidental poisoning by bromine compounds	
E8523	Accidental poisoning by methaqualone compounds	
E8524	Accidental poisoning by glutethimide group	
E8525	Accidental poisoning by mixed sedatives, not elsewhere classified	
E8528	Accidental poisoning by other specified sedatives and hypnotics	

ICD9 Code	Description	Stimulant Related
E8529	Accidental poisoning by unspecified sedative or hypnotic	
E8532	Accidental poisoning by benzodiazepine-based tranquilizers	
E8541	Accidental poisoning by psychodysleptics [hallucinogens]	
E8543	Accidental poisoning by central nervous system stimulants	Yes
E860	ACCIDENTAL POISONING BY ALCOHOL NEC	
E8600	Accidental poisoning by alcoholic beverages	
E8601	Accidental poisoning by other and unspecified ethyl alcohol and its products	
E8602	Accidental poisoning by methyl alcohol	
E8603	Accidental poisoning by isopropyl alcohol	
E8604	Accidental poisoning by fusel oil	
E8608	Accidental poisoning by other specified alcohols	
E8609	Accidental poisoning by unspecified alcohol	
E9500	Suicide and self-inflicted poisoning by analgesics, antipyretics, and antirheumatics	
E9501	Suicide and self-inflicted poisoning by barbiturates	
E9502	Suicide and self-inflicted poisoning by other sedatives and hypnotics	
E9503	Suicide and self-inflicted poisoning by tranquilizers and other psychotropic agents	
V652	Person feigning illness	
V6520	DSM PERSON FEIGNING ILLNESS	
V681	Issue of repeat prescriptions	

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Table A4 – Outpatient Medications Associated with Substance Misuse/Abuse

Generic Name
ACAMPROSATE CALCIUM
BUPRENORPHINE HCL
BUPRENORPHINE HCL/NALOXONE HCL
DISULFIRAM
NALTREXONE HCL
NALTREXONE MICROSPHERES

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Appendix B Safety Edit

Attention Deficit Hyperactivity Disorder (ADHD)

Goal(s):

- Cover ADHD medications only for OHP covered diagnoses consistent with current best practices
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines
- Promote preferred drugs in class

Length of Authorization:

- Up to 12 months

Triggers:

- Regimens prescribed by a non-psychiatrist which are:
  - Outside of standard age (Table 2)
  - Outside standard dose (Table 2)
  - Non-standard polypharmacy (Table 3)
- Adults 18 years or older
- Non-preferred drugs on the enforceable preferred drug list. Preferred alternatives listed at www.orpdl.org

Table 1. Approved and Funded Indications for ADHD Medications

Indication	Methylphenidate and derivatives	Amphetamines	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Atomoxetine (Strattera™)	Clonidine ER (Kapvay™)	Guanfacine ER (Intuniv™)
ADHD	Six and Older	Three and older	Not approved	Not approved	Six and older	Children 6-17 only	Children 6-17 only
Narcolepsy	Six and older	Three and older	Adults 18 and older	Adults 18 and older	Not approved	Not approved	Not approved
Drug Induced Sedation	Six and older	Three and older	Not approved	Not approved	Not approved	Not approved	Not approved
Obstructive sleep apnea	Not approved	Not approved	Adults 18 and older	Adults 18 and older	Not approved	Not approved	Not approved

Table 2. Standard Age and Dose Ranges for ADHD Medications

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose
Non-Traditional Stimulant	armodafinil	18		250mg
Non-Stimulant	atomoxetine	6		100mg
Non-Stimulant	clonidine	6	17	0.4mg
CNS Stimulant	dexmethylphenidate	6		20mg or 2mg/kg/day if under 18yrs
CNS Stimulant	dextroamphetamine	6		40 mg or 0.5mg/kg/ day if under 18yrs
CNS Stimulant	dextroamphetamine/amphetamine	6		60 mg or 0.5mg/kg/ day if under 18yrs
Non-Stimulant	guanfacine	6	17	4mg
CNS Stimulant	lisdexamfetamine	6		70mg or 0.5mg/kg/ day if under 18yrs
CNS Stimulant	methylphenidate immediate release	3		90mg or 2mg/kg/ day if under 18yrs
CNS Stimulant	methylphenidate sustained release	6		90mg or 2mg/kg/ day if under 18yrs
CNS Stimulant	methylphenidate transdermal	6		30mg
Non-Traditional Stimulant	modafinil	18		200mg

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Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Under 6 years old*	Combination therapy not recommended
6-17 years old*	CNS Stimulant + Guanfacine CNS Stimulant + Clonidine
18 and older**	Combination therapy not recommended

* As recommended by the American Academy of Pediatrics 2011 Guidelines
**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project 2011

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the treated diagnosis an OHP funded condition?	Yes: Go To #3	No: Pass to RPh. Deny
3. Is the requested agent a non-preferred agent?	Yes: Go To #4	No: Go To #5
4. Is the provider willing to switch to a preferred agent?	Yes: Inform the provider of preferred alternatives	No: Go To #5
5. Is the request for an approved indication? (Table 1)	Yes: Go To #6	No: Pass to RPh. Deny. Medical Appropriateness. May approve continuation of existing therapy once up to 90 days to allow time to appeal.
6. Is the request from a psychiatrist or was the regimen developed in consultation with a psychiatrist?	Yes: Approve 12 months	No: Go To #7
7. Are the age and the dose within the limits in Table 2? Note: For children under 18, the maximum dose for some medications may require a recent weight.	Yes: Go To #8	No: Pass to RPh. Deny. Medical Appropriateness. Doses exceeding defined limits are only approved when prescribed by a psychiatrist or in consultation with a psychiatrist. May approve continuation of existing therapy once up to 90 days to allow time to schedule appointment with a psychiatrist.

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Approval Criteria		
8. Is the requested agent the only ADHD treatment that has been filled within the last 30 days?	Yes: Approve 12 months	No: Go To #9
9. Have all other recent ADHD medications been discontinued or are they in the process of being discontinued / tapered?	Yes: Approve 12 months	No: Go To #10
10. Is the request for a single short acting CNS stimulant and a single long acting CNS stimulant?	Yes: Approve 12 months	No: Pass to RPh. Deny. Medical Appropriateness. Non-standard polypharmacy regimens are only approved when prescribed by a psychiatrist or in consultation with a psychiatrist. May approve continuation of existing therapy once up to 90 days to allow time to schedule appointment with a psychiatrist.

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Abbreviated Class Update: Medications for Cystic Fibrosis (CF)

Month/Year of Review: May 2014 **End date of literature search:** April 2014

Current PDL Class:

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

Current PA Criteria: Appendix 1: PA in place to ensure appropriate drug use and limit to patient populations in which ivacaftor has been shown to be effective and safe.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of ivacaftor?
- Are there unique patients or situations where ivacaftor may be more effective or safer than currently available agents?

Previous Recommendations:

- There is 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 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. Due to the robust nature of the results and benefits that outweigh the risks, use in this population is also recommended
- 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 are unknown.
- It is recommended to use clinical prior authorization criteria (Appendix) 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.

Conclusions:

- 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.
- There is low quality evidence that tobramycin 300mg/4ml is superior to placebo in lung function as measured by FEV_1 and noninferior to tobramycin 300mg/4ml.

Recommendations:

- Update PA criteria (appendix 1) to include additional CFTR mutations ivacaftor recently became approved for.
- Evaluate comparative cost of tobramycin 300mg/4ml (Bethkis®) in executive session.

Reason for Review:

In February, 2014, the FDA approved ivacaftor who have one of eight additional CF mutations. This review will evaluate the new indication and supporting evidence. This update will also evaluate the newer formulation of inhaled tobramycin 300mg/4ml (Bethkis®).

Background:

Cystic Fibrosis (CF) is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality.[1] Most available treatments for CF focus on symptom management, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[2] Many different mutations have been identified in the gene that causes GF. Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator approved in 2012 for the treatment of CF in patients 6 years and older who have the G551D mutation in the CFTR gene (approximately 4% of CF patients).[3] Ivacaftor is meant to treat the underlying cause of cystic fibrosis, by influencing the basic CF defect.[4] Two additional medications that target the defects in CFTR production are currently being studied.

Ivacaftor has demonstrated superiority to placebo in patients 6 years of age and older with the G551D mutation, as illustrated by an increase in FEV_1.[5–7] There are no head to head trials comparing ivacaftor to other CF treatments and changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. Another study was done in homozygous patients for the F508del-CFTR mutation which showed no benefit

in lung function or patient-reported outcomes; ivacaftor should not be used in this population.[8] Currently, ongoing studies are evaluating ivacaftor monotherapy in new disease populations, including children less than 6 years of age and additional mutations.

Methods:
A Medline literature search ending April 2014 Week 4 for meta-analyses or randomized active-controlled trials (RCT's) evaluating ivacaftor in patients with CF was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
A systematic review and cost-effectiveness analysis was done by NICE to evaluate ivacaftor for the treatment of patients with CF and the G551D mutation.[1] There were insufficient data to conduct a formal meta-analysis. Three studies were identified: a RCT in adults, a RCT in children, and an open-label extension study of the two RCTs. Both RCTs demonstrated significantly greater changes from baseline in lung function in patients on ivacaftor than placebo (10.5 mean difference, 95% CI 8.5 to 12.5 in adults and 10.0, 95% CI 4.5 to 15.5 in children). The number and severity of pulmonary exacerbations were also significantly reduced in the adult study (RR 0.60; 95% CI 0.41 to 0.85) at 48 weeks. Adverse events were minor and comparable across treatment groups. The most common adverse events were pulmonary exacerbation, cough, headache, upper respiratory tract infection and oropharyngeal pain. In addition, the high cost of ivacaftor may make it difficult for uptake of treatment. Long-term effectiveness research is still needed.

New Guidelines:
The CF Foundation's Pulmonary Clinical Practice Guidelines Committee updated their guideline for Chronic Medications for Maintenance of Lung Health in 2012.[2] However, these were completed before the additional mutations were included in the indication. Overall, the committee rated the certainty of net benefit for ivacaftor in patients with at least one G551D CFTR mutation as high and the net benefit as substantial. At the time of these guidelines, the committee concluded there was insufficient information ot make a recommendation for additional mutations.

New FDA Approved Indications:
In February 2014, the FDA approved ivacaftor for people with CF ages 6 and older who have one of eight additional mutations in the CFTR gene in addition to the previous approved G551D mutation. The additional mutations include G178R, S549N, S549R, G551S, S1251N, S1255P, and G1349D. In the United States, approximately 150 people have one of the additional eight mutations.

The expanded use is based on results of one unpublished two-part phase III clinical trial in people with $FEV_1 > 40\%$ with these mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or G970R (KONNECTION trial).[3,9] Part 1 was a randomized, double-blind, placebo-

controlled cross-over study (8 weeks), and Part 2 was an open-label period where all patients received ivacaftor. The use of hypertonic saline was not permitted. Data did not support approval of the drug in patients with the G970R mutation. The primary endpoint was improvement in lung function, measured by the change from baseline in percent predicted FEV_1 at 8 weeks of treatment. For the overall population of the 9 mutations, ivacaftor resulted in a significant improvement in percent predicted FEV_1 (10.7;95% CI 7.3 to 14.1 p<0.0001) with a high degree of variability of response between the different mutations, with mean change from baseline ranging from 3 to 20. Efficacy in patients with the G970R mutation could not be established. This study has not been published and therefore cannot be assessed for quality. Results are not available from clinicaltrials.gov.

Randomized Controlled Trials: After exclusion of studies due to study design, only 2 RCTs were identified.

Study	Comparisons	Patient Population	Primary Objective	Results
Davies, et al.[7] RCT, DB, PC	Ivacaftor 150 mg every 12 hours vs. placebo	Patients with CF aged 6-11 years with a G551D CFTR mutation on at least one allele (n=52)	Absolute change from baseline through week 24 in percent predicted FEV_1	Mean change from baseline in FEV_1: Ivacaf: 12.5% Placebo: 0.1% P<0.001
Flume, et al.[8] RCT, DB, PC	Ivacaftor 150 mg every 12 hours vs. placebo	Patients with CF aged 12 or older, homozygous for the F508del-CFTR mutation (n=140)	Absolute change from baseline through week 16 in percent predicted FEV_1	Mean change from baseline in FEV_1 compared to placebo: 1.7% (95% CI -0.6 to 4.1) P=0.15

New Formulations:
Tobramycin inhalation solution has been available in a 300mg/5ml preparation since 1997. In late 2012, a higher concentrated formulation of 300mg/4ml solution of tobramycin (Bethkis®) was approved by the FDA for management of cystic fibrosis patients.[10,11] Approval was based on two RCTs comparing tobramycin to placebo and one open-label comparative trial of tobramycin 300mg/4ml and tobramycin 300mg/4ml (TOBI®).[11] In the two RCTs, tobramycin 300mg/4ml demonstrated superiority over placebo in change from baseline in FEV_1 percent predicted at week 4 (LS mean difference 11%; 954% CI 3 to 19; p=0.003 in study 1 and LS mean difference 6%; 95% CI 3 to 10; p<0.001).

The poor-quality open-label comparative study evaluated the two formulations in patients aged 6 years and older who were chronically colonized with *Pseudomonas aeruginosa*.[12] Results demonstrated that tobramycin 300mg/4ml was noninferior to tobramycin 300mg/5ml in FEV_1 with a difference of -0.5 (95% CI -2.6 to 1.6) and the lower limit for he 95% CI falling well above the predefined non-inferiority margin. However, there was

no justification provided for the non-inferiority margin in the trial. Pulmonary exacerbations were infrequent and similar between groups (3.8% in the 4ml group and 3.0% in the 5 ml group.

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. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. 2014.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. De Boeck K, Paskavitz J, Chen X, Higgins M. M. Ivacaftor, a CFTR potentiator, in cystic fibrosis patients who have a non-G551D-CFTR gating mutation: Phase 3, Part 1 results. Pediatr. Pulmonol. 2013;48(S36):292. Abstract 241.

10. FDA Center for Drug Evaluation and Research. Bethkis (Tobramycin 300mg/4ml inhalaion solution) Summary Review. Application Number: 201820Orig1s000. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/201820_bethkis_toc.cfm.

11. Cornerstone Therapeutics. Bethkis (tobramycin inhalation solution 300mg/4ml) prescribing information. Available at: http://bethkis.com/wp-content/uploads/2013/11/BETHKIS-Tobramycin-Inalation-Solution-Full-Prescribing-Information-Web.pdf.

12. Mazurek H, Chiron R, Kucerova T, et al. Long-term efficacy and safety of aerosolized tobramycin 300 mg/4 ml in cystic fibrosis. *Pediatr Pulmonol*. 2014. doi:10.1002/ppul.22989.

Ivacaftor (Kalydeco®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which ivacaftor has been shown 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? • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a mutation.	**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 or has had an adequate trial, if indicated and/or tolerated of the following medications below: - 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 the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**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 response to therapy? Document response (e.g. improvement in FEV_1, weight gain, reduction in exacerbations or sweat test).	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical 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 the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**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 studied in other populations of patients with Cystic Fibrosis.

P &T Action: 6/28/12 (KS), 4/26/12 (MH/KS)
Revision(s): 5/29/2014
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

Abbreviated Class Update: Ivacaftor (Kalydeco®) for Cystic Fibrosis

Month/Year of Review: May 2014 **End date of literature search:** April 2014
Last Reviewed: June 2012

Current PA Criteria: Appendix 1: PA in place to ensure appropriate drug use and limit to patient populations in which ivacaftor has been shown to be effective and safe.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of ivacaftor?
- Are there unique patients or situations where ivacaftor may be more effective or safer than currently available agents?

Previous Recommendations:

- There is 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 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. Due to the robust nature of the results and benefits that outweigh the risks, use in this population is also recommended
- 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 are unknown.
- It is recommended to use clinical prior authorization criteria (Appendix) 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.

Conclusions:

- 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.

Recommendations:

- Update PA criteria (appendix 1) to include additional CFTR mutations ivacaftor recently became approved for.

Reason for Review:

In February, 2014, the FDA approved ivacaftor who have one of eight additional CF mutations. This review will evaluate the new indication and supporting evidence.

Background:

Cystic Fibrosis (CF) is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality.[1] Most available treatments for CF focus on symptom management, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[2] Many different mutations have been identified in the gene that causes GF. Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator approved in 2012 for the treatment of CF in patients 6 years and older who have the G551D mutation in the CFTR gene (approximately 4% of CF patients).[3] Ivacaftor is meant to treat the underlying cause of cystic fibrosis, by influencing the basic CF defect.[4] Two additional medications that target the defects in CFTR production are currently being studied.

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Methods:

A Medline literature search ending April 2014 Week 4 for meta-analyses or randomized active-controlled trials (RCT's) evaluating ivacaftor in patients with CF was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was

searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
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New Guidelines:
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The expanded use is based on results of one unpublished phase III clinical trial in people with these mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or G970R (KONNECTION trial).[3] Data did not support approval of the drug in patients with the G970R mutation. A two-part, randomized, double-blind, placebo-controlled crossover trial in 30 patients age 6 years of age or older with FEV_1 > 40% evaluated ivacaftor or placebo for 8 weeks. The use of hypertonic saline was not permitted. The primary endpoint was improvement in lung function, measured by the change from baseline in percent predicted FEV_1 at 8 weeks of treatment. For the overall population of the 9 mutations, ivacaftor resulted in a significant improvement in percent predicted FEV_1 (10.7; $p<0.0001$) with a high degree of variability of response between the different mutations, with mean change from baseline ranging from 3 to 20. Efficacy in patients with the G970R mutation could not be established. This study has not been published and therefore cannot be assessed for quality. Results are not available from clinicaltrials.gov.

Randomized Controlled Trials: After exclusion of studies due to study design, only 2 RCTs were identified.

Study	Comparisons	Patient Population	Primary Objective	Results
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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.

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4. 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.

5. 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.

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7. 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.

8. 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.

Appendix 1 – Current PA Criteria:

Ivacaftor (Kalydeco®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which ivacaftor has been shown 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? • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a mutation.	**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 or has had an adequate trial, if indicated and/or tolerated of the following medications below: - 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 the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**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 response to therapy? Document response (e.g. improvement in FEV_1, weight gain, reduction in exacerbations or sweat test).	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical 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 the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**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 studied in other populations of patients with Cystic Fibrosis.

P &T Action: 6/28/12 (KS), 4/26/12 (MH/KS)
Revision(s): 5/29/2014
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: Second Generation Antidepressant Medications

Month/Year of Review: May 2014
PDL Classes: Psychiatric: Antidepressants
New drug(s): vortioxetine (Brintellix®)
levomilnacipran extended-release (Fetzima®)

Last Oregon Review: April 2012
Source Document: OSU College of Pharmacy
Manufacturer: Takeda & Lundbeck/Forest
Dossier Received: Yes/Pending

Current Status of Voluntary PDL Class:

- **Preferred Agents:** BUPROPION HCL TABLET/TABLET ER, CITALOPRAM TABLET/SOLUTION, FLUOXETINE CAPSULE/SOLUTION/TABLET, FLUVOXAMINE, MIRTAZEPINE TAB RAPDIS/TABLET, PAROXETINE TABLET, SERTRALINE ORAL CONC/TABLET, VENLAFAXINE TABLET, VENLAFAXINE ER
- **Non-Preferred Agents:** BUPROPRION XL, DESVENLAFAXINE (PRISTIQ ER), DULOXETINE (CYMBALTA®), ESCITALOPRAM, FLUOXETINE DF (PROZAC® WEEKLY), NEFAZODONE, PAROXETINE HCL (PAXIL CR®), SELEGILINE PATCH (ENSAM®), VILAZODONE (VIIBRYD®), OLANZAPINE/FLUOXETINE (SYMBYAX®)

Status of the Voluntary Mental Health Preferred Drug List

Currently, all antidepressants are available without prior authorization for non-preferred placement. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs. Second generation antidepressants have been reviewed for clinical efficacy and safety and specific agents were chosen as clinically preferred; this eliminates a copay. Oregon's Medicaid program currently charges no copayment for preferred PDL drugs.

Research Questions:

- Is there any new evidence of effectiveness or harms that will support changes to the voluntary PDL antidepressant class?
- Is there any evidence that vortioxetine is more effective or safer than currently available antidepressants for relapse or remission in the treatment of depression or in the treatment of anxiety?
- Is there any evidence that levomilnacipran is more effective or safer than currently available antidepressants for relapse or remission in the treatment of depression?
- Are there any subpopulations of patients with depression or anxiety for which vortioxetine or levomilnacipran is more effective or associated with less harm?

Conclusions:

- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder (MDD).

- There is moderate quality evidence that vortioxetine is safe and effective for the treatment of MDD based on short-term placebo-controlled trials. There is insufficient evidence to determine the most effective treatment dose.
- There is moderate quality evidence that vortioxetine is not superior to duloxetine 60 mg daily or venlafaxine XR 225 mg daily in efficacy.
- There is low quality evidence that levomilnacipran is safe and effective for the treatment of MDD based on short-term placebo-controlled trials.
- There is insufficient evidence to determine the effectiveness of either vortioxetine or levomilnacipran in the maintenance treatment of MDD, as well as in pediatric patients or patients with severe hepatic impairment.
- There is moderate quality evidence that fluoxetine, paroxetine, sertraline, topiramate and venlafaxine improve post-traumatic stress disorder (PTSD) symptoms. There is insufficient evidence to determine if there are any differences in effectiveness or whether any treatment approach was more effective for victims of particular trauma types.
- There is low quality evidence that there is no difference between treatment strategies in patients who fail to respond to SSRIs as first-line treatment in response and remission rates. These strategies include monotherapy (dose escalation, increased duration or switching drugs) or a combination of therapies.

Recommendations:
- Evidence does not support superiority of vortioxetine or levomilnacipran over other agents in this drug class. Recommend that both be listed as non-preferred agents.
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

Previous P&T Conclusions and Recommendations (April 2012):
- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder (MDD). These findings pertain to patients in the acute, continuation, and maintenance phases; those with accompanying symptom clusters; and subgroups defined by age, sex, ethnicity, or comorbid conditions, although only sparse evidence for these findings exists for subgroups.
- Citalopram causes dose-dependent QT interval prolongation. The FDA recommends that citalopram should no longer be prescribed at doses greater than 40 mg per day
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.
- Include a dose limit of 40mg/day for citalopram.
- Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
    - As an example, academic detailing can be used to promote appropriate utilization

Reason for Review: This class was last reviewed in April 2012. Since the last review, two antidepressants were approved. In addition, new guidelines, systematic reviews and head-to-head trials have been published.

Background:

Before the late 1980s, the pharmacologic treatment of Axis I psychiatric disorders (such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual disorders) was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[1] TCAs and MAOIs are often referred to as traditional or first-generation antidepressants. These drugs are often accompanied by multiple side effects that many patients find intolerable. TCAs tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation and MAOIs have the potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine.[1] Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters.[1] In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine.[1] Since then, five other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, and escitalopram.[1] The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine.[1] Other agents used for treatment of MDD include, nefazodone, mirtazapine, and bupropion.[1]

In randomized clinical trials (RCTs) of antidepressants, the FDA accepts a primary success criterion that is determined by measuring the difference between a baseline score and a post-treatment score for a primary effectiveness endpoint (measured via widely used scales). The most widely used observer-administered depression rating scales are the Hamilton Depression Rating Scale (HAMD), 24-item and 17-item versions (HAMD24 and HAMD17, respectively), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinician Global Impressions-Severity of Illness (CGI-S) scale. The MADRS measures core symptoms of major depression on 10 items; each item is scored on a scale from 0 to 6. The HAMD assesses up to 24 items associated with major depression; each item is scored from 0 to 5. The CGI-S measures disease severity on a 7-point scale which scores the clinician's global assessment of the patient rather than individual aspects of the disease state. Limited information is available defining a clinically meaningful change in these scales.

Consensus definition of outcomes has been described.[2,3] Response refers to a clinically significant degree of depressive symptom reduction following treatment initiation.[2,3] Remission is the virtual absence of depressive symptoms.[2] The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).[2] The criteria for response and remission rates vary by trial, but the most widely accepted cutoffs for response is a ≥50% reduction from baseline (both MADRS and HAMD), and a specific threshold for remission. A score of ≤7 on the HAMD17 is widely accepted, with some suggesting a score of ≤5 be used, but there are differing recommendations for remission using MADRS.[3] A HAMD17 score of ≤7 corresponds to a MADRS score of ≤9, but others recommend a MADRS score of ≤5 to define remission, while most clinical trials use a score of ≤10.[3]

In PTSD, the most widely used measure is the Clinician-Administered PTSD Scale (CAPS).[4] This scale is often referred to as the "gold-standard" measure for PTSD.[4] CAPS is a semistructured interview that measures the 17 symptoms of PTSD and assesses each using two questions (34 total items) to measure symptom frequency of occurrence and symptom intensity. [4] The drawback of using this scale is the time of administration due to its large number of items; it can take 40-60 minutes to administer the scale. [4] A decrease of 15 points in this scale is considered clinically significant. [4]

An Agency for Healthcare Research & Quality (AHRQ) comparative effectiveness report on this class indicates that overall, 37% of patients with MDD do not achieve a treatment response and 53% do not achieve remission in short-term trials.[1] There is moderate quality evidence that all second-generation antidepressants have similar efficacy in MDD, and statistically significant differences for some head-to-head comparisons are not likely to be clinically relevant.[1] There was moderate quality evidence of no difference in health-related quality of life, although this is rarely measured as a primary outcome measure.[1] There is moderate quality evidence that mirtazapine may have statistically significantly faster onset of action than citalopram, fluoxetine, paroxetine and sertraline (NNT to yield one additional responder after 1 or 2 weeks of treatment is 7).[1] There is moderate quality evidence that active treatment is favored over placebo in relapse prevention

and recurrence prevention trials and moderate quality evidence of no difference in efficacy of maintaining remission between antidepressants.[1] There is insufficient evidence available to evaluate whether switching from one medication to another increases the number of patients who remain in remission.[1]

Recently, two antidepressants were approved for use in MDD. The first to be approved, levomilnacipran, is the active enantiomer of milnacipran (Savella®), an SNRI approved for use in fibromyalgia.[5] Vortioxetine (Brintellix®) is a multimodal antidepressant believed to work through a unique mix of serotonin (5-HT) subtype 5-HT_3 and 5-HT_7 receptor antagonism, 5-HT_{1B} receptor partial agonism, 5-HT_{1A} receptor agonism and inhibition of the 5-HT transporter.[6] The FDA approved vortioxetine with a target dose of 20 mg daily due to a lack of efficacy in smaller doses in the US population despite trials showing benefit in other populations.[6] The FDA-accepted primary endpoint of trials evaluating both drugs for efficacy was change in baseline in either MADRS or HAMD total score.[5,6]

Methods:
A Medline literature search ending March 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, bupropion, and mirtazapine. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, two systematic reviews[7,8], one guideline[9], three head-to-head trials[10–12], and two new drugs were identified[5,6].

Systematic Reviews:

Agency for Healthcare Research and Quality:

An AHRQ comparative effectiveness review by Jonas et al.[7] evaluated the efficacy, effectiveness and harms of psychological and pharmacological treatments for adults with PTSD with a literature search through May 2012. After review, 92 RCTs were included in the analysis. There is moderate strength of evidence (SOE) supporting the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms; effect sizes were small or medium (e.g., 4.9- to 15.5-point reduction in CAPS compared with placebo), and low SOE for risperidone in reducing PTSD symptoms. Evidence was insufficient evidence to determine if other medications improve symptoms. There is moderate SOE for paroxetine (NNT 8) and venlafaxine (NNT 9) supporting their efficacy for inducing remission and insufficient evidence for other medications. Evidence supports paroxetine's efficacy for improving depression symptoms and functional impairment (moderate SOE) and venlafaxine's efficacy for improving depression symptoms, quality of life, and functional impairment (moderate SOE). There was little direct comparative evidence to determine if there are any differences in treatments in effectiveness or whether any treatment approached were more effective for victims of particular trauma types.. Network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to be more effective than most medications for reducing PTSD symptoms, but analysis was based largely on indirect evidence and limited to one outcome measure (low SOE). Overall, evidence was insufficient to compare adverse events for various interventions or to draw conclusions about withdrawals due to adverse events, mortality, suicide, suicidal ideation, or self-harmful behaviors. .

A second AHRQ comparative effectiveness review by Santaguida et al. was undertaken to evaluate treatment strategies in patients who failed to respond to SSRIs as first-line treatment.[8] The efficacy (benefits and harms) of monotherapy approaches (dose escalation, increased duration, or switch) or combined therapies were

evaluated. From a literature search through April 2011, 44 studies and 27 clinical practice guidelines (CPGs) were identified. There is low strength of evidence evaluating relative differences for any monotherapy or combination therapy approach. Based on 12 studies comparing monotherapy interventions relative to other monotherapies, there is no certainty of any advantage between different monotherapies for either response to treatment or remission. The exception was one single study that demonstrated that low-dose sertraline had small improvement in response. There is also insufficient evidence to conclude that a dose escalation or a switch to another antidepressant is equivalent or superior to any comparator treatment in patients with inadequate response to initial SSRI.. Thirty three studies evaluated monotherapy compared to combined therapies, in which the majority showed no clear difference for any monotherapy, relative to combined therapy, in response and remission. The exception was with atypical antipsychotics. Two studies with limited sample sizes and using risperidone as an augmenting agent showed benefit compared to combined therapy. The majority of studies were not designed to assess superiority of the strategies.

Authors also evaluated the range of recommendations following the failure of a SSRI based on CPGs published between 2004 and 2011. There were significant differences between the CPGs and variability in quality. For adults, increasing the dose or duration was frequently recommended, but the interval or change in dose was not specific. The majority did not recommend any specific type of antidepressant when switching.

New Guidelines:

National Institute for Health and Care Excellence (NICE)
NICE issued a new guideline regarding social anxiety disorder in May 2013 based on a review of the evidence.[9] These guidelines recommend that if drug treatment is needed, an SSRI should be offered.[9] Specifically, escitalopram or sertraline are recommended first line.[9] If the first SSRI is not effective, recommendations include using an alternative SSRI (fluvoxamine or paroxetine) or SNRI (venlafaxine), taking into account the efficacy, side effect profile, risk of early activation symptoms and tendency of drugs to produce a withdrawal syndrome.[9] Patients should be carefully monitored for side effects, including suicidal thinking and self-harm and follow up visits should be conducted every 2-4 weeks during the first 3 months of treatment and every month thereafter; patients under 30 who are prescribed an SSRI or SNRI should be monitored every week for the first month of use for suicidal thinking and self-harm.[9] For adults whose symptoms have not responded to an alternative SSRI or an SNRI, a monoamine oxidase inhibitor is recommended.

Randomized Controlled Trials: After the literature review, a total of 3 head to head RCTs were identified. Other studies were excluded because they had the wrong outcome, were placebo-controlled, or were not randomized. The abstracts of these can be found in Appendix 3.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Bose et al. (2012).[10] Parallel group, double-blind randomized	Escitalopram vs duloxetine	Patients with severe depression (n=571)	Time to all cause premature study discontinuation	There was no difference in time to all-cause discontinuation between groups (hazard ratio escitalopram/duloxetine = 0.95 [95% CI 0.64, 1.41]; p = 0.727). Treatment with escitalopram compared with duloxetine resulted in significant improvement in MADRS total score at the end of week 8 (least squares mean difference = -1.87 [95% CI -3.60, -0.14]; p = 0.034

				Significantly more escitalopram (54%) than duloxetine (42%) patients achieved remission (MADRS ≤10) by week 8 (p = 0.013). Adverse events were similar between the two treatment groups.
Raskin et al. (2012).[11] Double-blind, double-dummy, randomized, parallel group	Duloxetine vs escitalopram	Patients with MDD (n=483)	LS mean change from baseline in the Apathy Evaluation Scale, Clinician (AES-C) total score after 8 weeks of treatment	There was a statistically significant change from baseline in AES-C score for both duloxetine (-13.9) and escitalopram (-13.5) (p<0.001 for both). When compared to each other, there was no difference in the primary outcome (95% CI: -1.87 to 1.10; p= 0.612) There were no significant differences between the two groups on any measure (apathy, depression and functional outcomes).
Richard et al. (2012).[12] Double-blind, double-dummy, placebo controlled	Venlafaxine XR vs paroxetine vs placebo	Parkinson's disease patients with depression (n=115)	Change from baseline in HAM-D score after 12 weeks	There was no difference in the primary outcome between the paroxetine group (-6.2 points; 97.5% CI: 2.2 to 10.3) and the venlafaxine XR group (-4.2 points; 97.5% CI 0.1 to 8.4) (p=0.28). There were no significant differences between the two active groups in response or remission rates.

New Safety Alert/Indications: None

Horizon Scan: One antidepressant was identified on the AHRQ Healthcare Horizon Scanning Report. Amitifadine is a serotonin-norepinephrine-dopamine reuptake inhibitor in phase IIb/IIIa trials for the treatment of treatment-resistant MDD.[13]

New Drug Evaluations:

Vortioxetine (Brintellix®)
FDA approved indications: Treatment of Major Depressive Disorder (MDD)
Potential off-label use: Generalized Anxiety Disorder (has been studied in four short-term efficacy studies, but is not approved for this use)

Clinical Efficacy Data:

The approval of vortioxetine was based off of 10 short-term studies and 1 relapse-prevention study in adults to support the indication of treatment of major depressive disorder.[6] The trials included a total of 6,184 adult patients (ages 18-70 years) meeting DSM-IV-TR criteria for MDD, single episode or recurrent.

Table 2 provides a summary of the evidence findings for these studies. The primary outcome measure used to evaluate efficacy was the Montgomery-Asberg Depression Rating Scale (MADRS). Five of the short-term studies evaluated were conducted exclusively in the US[6]. Seven of the evaluated studies have been published[14–20]. Three longer-term studies have been published, the 24-week relapse-prevention study[21] and two open-label extension studies[22,23]. The manufacturer's dossier includes data for 12 short-term efficacy studies; 8 have positive results, 3 have negative results, and 1trial failed (neither vortioxetine nor the active control separated from placebo).[24] Results for one unpublished failed trial are not available.[24] Approval was based on the least squares (LS) mean change from baseline of MADRS or HAMD-24 scores compared to placebo. In US trials, only the 20 mg daily dose demonstrated statistical significance over placebo in change from baseline scores, although a trend toward efficacy was noted at lower doses in included studies.[6] The FDA recommends that patients are started at 10 mg daily and increased to a target daily dose of 20 mg as tolerated.[25] Non-US data shows statistical significance for lower doses of vortioxetine.[6] Of the published trials, only one studied the 20 mg daily dose.[6,20,24] Response and remission continue to be the most important clinical outcomes for patients.

Overall, vortioxetine appears to improve rates of response and remission when measured with MADRS or HAMD compared to placebo and the effect does not appear to be dose-dependent. Trials do not show a dose-response relationship. As an example, Henigsberg et al[15] studied three doses of vortioxetine and response rates were similar in all arms (1.90, 1.79, and 2.00 for 1 mg, 5 mg, and 10 mg, respectively). Remission rates were also similar at 1.55, 1.74, and 1.61 for the 1 mg, 5 mg and 10 mg groups, respectively. Of the published short-term efficacy studies, 2 had an overall quality rating of good, 4 were rated fair and one was of poor-fair methodological quality. Three of the four unpublished studies had a vortioxetine 20 mg arm, and two of these studies did not show that the 20 mg dose was statistically different than placebo in MADRS response or remission.

The baseline MADRS score of patients enrolled in short-term trials were in the low 30s on average, indicating moderate-to-severe MDD. A high percentage of participants were Caucasian, and a majority was female. In all but one study in elderly patients, the average age of participants was in the mid-40s. Extensive exclusion criteria included patients at risk of suicide, concurrent psychiatric disorders or medical illnesses and patients with treatment-resistant depression. These characteristics of study participants make it hard to generalize these findings to a broader population.

One longer-term efficacy study evaluating relapse prevention was also conducted.[21] Patients were enrolled in a 12-week open-label, flexible dose treatment period and continued to the double-blind period if they were in remission (MADRS total score $\leq$10) at weeks 10 and 12 of the open-label treatment period.[21] During the double-blind period, included patients were randomized 1:1 to continue their stabilized dose (5 mg or 10mg) or switched to placebo. [21] A majority of the vortioxetine patients were on 10 mg daily.[21] The primary efficacy variable was time to relapse of depressive symptoms.[21] The proportion of patients who relapsed was lower in the vortioxetine group (15%) than the placebo group (30%) with a hazard ratio (HR) of 2.09 (95% CI: 1.35-3.23, p=0.0010).[21] This result may be biased toward vortioxetine because only patients who responded to vortioxetine during the single-blind run-in period were included in the double-blind treatment phase. There was a high rate of attrition in both groups.

While this drug is being promoted as having a new and novel mechanism of action, there is no evidence that it is more efficacious than other second generation antidepressants that are on the market. In the six trials where there was an active comparison (venlafaxine XR or duloxetine), vortioxetine did not have higher rates of response and remission than the active comparison. At low doses, there were no differences in response rates between vortioxetine and the active comparison, but when compared to 15 and 20 mg doses of vortioxetine, MADRS response rates were higher in the active control arms. There were no differences in remission rates at any dose of vortioxetine compared to the active control. There is a need for more head-to-head trials to truly understand vortioxetine's comparative effectiveness in this class.

Clinical Safety:

In the prescribing information, the most common adverse events are nausea, diarrhea and dry mouth; the most common serious adverse events are serotonin syndrome, abnormal bruising or bleeding, hypomania, or hypernatremia. It does not appear that side effects are dose-related; however there is an increase in withdrawals due to adverse events as the dose increases.

Two year-long open-label, single-arm extension studies evaluating a total of 1369 patients have been published.[22,23] In Alam et al, 70.6% of patients experienced a treatment-related adverse event, the most common being nausea (15.2%), headache (12.4%) and nasopharyngitis (9.8%).[23] Similar results were seen in the second extension study with 72.7% of patients experiencing an adverse event, the most common being nausea (19.8%), headache (15.3%) and nasopharyngitis (10.5%).[22] Serious adverse events occurred in 3.4% of patients in Baldwin et al and 3.5 % of patients in Alam et al.[22,23]

In the clinical program, all 6 deaths occurred in the vortioxetine treatment group.[6] The causes of death included 2 cancers, 1 suicide, 1 morphine toxicity, 1 road traffic accident, and 1 accidental death (an accidental fall from a balcony). [6] For the death from morphine toxicity and the accidental death, suicide could not be ruled out as a cause, according to the sponsor, due to limited information available.[6] All deaths were considered by the investigators as unrelated to vortioxetine treatment.[6]

Vortioxetine has not been studied in pediatric patients or patients with severe hepatic impairment. No subgroup analyses studying gender, race or ethnicity have been published.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Response*
2) Remission*
3) Relapse
4) Hospitalization
5) Quality of Life
6) Withdrawals due to adverse events
7) Major adverse events

*Secondary endpoints in vortioxetine trials

Primary Study Endpoint:

1) Change in baseline MADRS total score
2) Change in baseline HAMD total score

Table 2. Vortioxetine Comparative Evidence Table

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

Alvarez et al, 2012[14] MC, R, DB, PG, PC 6-week Non-US	V5: Vortioxetine 5mg daily V10: vortioxetine 10mg P: placebo VEN: venlafaxine XR 225mg	Demographics: adults 18-65, mean age: 43 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; 18-65 years old; MADRS total score ≥30 at baseline visit Exclusion Criteria: Current psychiatric disorder other than; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; any substance abuse disorder within the previous 6 months, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or any Axis II disorder; suicide risk; cognitive behavioral therapy (CBT); pregnant/breastfeeding; known hypersensitivity or were non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004	ITT: V5: 10 V10: 100 P: 105 D: 112 Attrition: V5: 10 (9.3%) V10: 1 (18.0% P: 18 (16.7% VEN: 19 (16.9%	<u>Mean change from baseline in MADRS:</u> V5: -20.4* V10: -20.2* P: -14.5 VEN: -20.9* *difference from placebo p-value: <0.0001 <u>MADRS Response Rate:</u> V5: 72/108 (66.7%) V10: 68/100 (68%) P: 47/105 (44.8%) VEN: 81/112 (72.3%) V5 Vs P: RR 1.49, 95% CI (01.15-1.93) p-value 0.002 V10 Vs. P: RR 1.52, 95% CI (1.17-1.97) p-value <0.001 VEN Vs P: RR 1.62, 95% CI (1.26-2.063) p-value <0.001 <u>MADRS Remission Rate:</u> V5: 53/108 (49.1%) V10:49/100 (49%) P: 28/105 (26.7%) VEN: 62/112 (55.4%) V5 Vs P: RR 1.84; 95% CI 1.27-2.67; p-value <0.01 V10 Vs P: RR 1.84; 95% CI 1.26-2.67; p-value <0.01 VEN Vs P: RR 1.69; 95% CI 1.12-2.57; p-value <0.001	NA 22%/5 23%/5 17%/6 22.4%/5 22.3%/5 28.7%/4	<u>Withdrawals Due to Adverse Events:</u> V5: 3 (2.8%) V10: 7 (7.0%) P: 4 (3.7%) VEN: 16 (14.3%) V5 Vs P: RR 0.73, 95% CI (0.13-3.78) P-value 0.719 V10 Vs P: RR 1.84, 95% CI (0.50-7.34) p-value 0.365 VEN Vs P: RR 3.75, 95% CI (1.23-13.08) p-value 0.009 <u>Serious Adverse Events:</u> V5: 0 NS V10: 2 (2.0%) NS P: 0 VEN: 1 (<1%) NS	 NS NS 10.6%/10 NS	**Quality Rating:** Good **Internal Validity:** <u>Selection:</u> Patients were randomized according to a computer-generated randomization list and details were contained in sealed opaque envelopes. <u>Performance:</u> Patients, caregivers and investigators were blinded. Patients were given weekly wallet cards containing double-dummy capsules and instructed to take both capsules at the same time every day <u>Detection</u>: Raters were trained to increase inter-rater reliability and training was chaired by an experienced investigator. Patients were assessed by same investigator at each visit, whenever possible. <u>Attrition</u>: a modified intention-to-treat analysis was used for efficacy outcomes and full-analysis set used for safety outcomes. Total attrition was 15%; loss to follow-up very low (n=1) **External Validity:** <u>Recruitment:</u> Advertisements used in Australia, Canada, Finland, Malaysia and Sweden, otherwise unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited non-Caucasian patients which limits the generalizability of results <u>Setting:</u> 49 non-US outpatient sites in Australia, Canada, Asia and Europe <u>Outcomes:</u> The primary endpoint was mean change from baseline in MADRS total score at week 6

Baldwin et al, 2011[15] MC, R, DB, PC 8 weeks Europe, Asia, Africa	V2.5: vortioxetine 2.5 mg V5: vortioxetine 5 mg V10: vortioxetine 10 mg P: placebo DUL: duloxetine 60 mg	Demographics: adults 18-75, mean age: 45 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; 18-65 years old; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder other than; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; any substance abuse disorder within the previous 6 months, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or any Axis II disorder; suicide risk; cognitive behavioral therapy (CBT); pregnant/breastfeeding; known hypersensitivity or were non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004	FAS: V2.5: 155 V5: 15 V10: 151 P: 145 DUL: 149 Attrition: V2.5: 25 (16.1% V5: 33 (21.3% V10: 34 (22.5% P: 22 (15.2% DUL: 36 (24.2%	<u>Mean change from baseline in MADRS:</u> V2.5: -16.2 p-value: 0.219 V5: -16.5 p-value: 0.132 V10: -16.3 p-value: 0.185 P: -14.8 DUL: -16.8 p-value: 0.74 <u>MADRS Response:</u> V2.5: 84/155 (54.2%) V5: 87/155 (56.1%) V10: 88/151 (57.6%) P: 68/145 (46.9%) DUL: 85/149 (57.1%) V2.5 Vs P: RR 1.16 (95% CI 0.92-1.45) V5 Vs P: RR 1.20 (95% CI 0.96-1.49) V10 Vs P: RR 1.24 (95% CI 1.00-1.55) DUL Vs P: RR 1.14 (95% CI 0.87-1.50) <u>MADRS Remission:</u> V2.5: 51/155 (32.9%) V5: 56/155 (36.1%) C: 54/151 (35.8%) P: 49/145 (33.8%) DUL: 52/149 (34.9%) V2.5 Vs P: RR 0.97 (95% CI 0.71-1.34) V5 Vs P: RR 1.07 (95% CI 0.79-1.46) V10 Vs P: RR 1.06 (95% CI 0.77-1.45) DUL Vs P: RR 1.02 (95% CI 0.72-1.46)	NA NS NS NS NS NS NS NS NS	<u>Withdrawals Due to Adverse Events:</u> V2.5: 10 (6.5%) V5: 18 (11.6%) V10: 15 (9.9%) P: 12 (8.3%) DUL: 19 (12.8%) V 2.5 Vs. P: RR 0.80, 95% CI (0.33-1.92), p-value 0.66 V5 Vs P: RR 1.41, 95% CI (0.67-3.04), p-value 0.34 V10 Vs P: RR 1.18, 95% CI (0.54-2.61), p-value 0.691 DULVs P: RR 1.51, 95% CI (0.73-3.22) p-value 0.259 <u>Serious Adverse Events:</u> Not reported	NS NS NS NS	**Quality Rating:** Fair **Internal Validity:** <u>Selection:</u> Patients were randomized according to a computer-generated randomization list and details were contained in sealed opaque envelopes. <u>Performance:</u> Double blind, double dummy <u>Detection:</u> Double-blind; Raters were trained to increase inter-rater reliability and training was chaired by an experienced investigator. Patients were assessed by same investigator at each visit, whenever possible; scales were given in local languages with validated translations <u>Attrition:</u> Overall attrition is 20%; higher in the duloxetine group (28%) due to unknown reasons **External Validity:** <u>Recruitment:</u> Advertisements used in several countries; unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited to mostly Caucasian and some Asian patients which limits the generalizability of results <u>Setting:</u> 100 inpatient and outpatient centers from 20 countries (Australia, Canada, Europe and Asia) <u>Outcomes</u> Primary endpoint was an ANCOVA of the change from baseline in MADRS total score at week 8. Covariates were treatment and site factors and the baseline MADRS total score.

Jain et al, 2012[16] MC, R, DB, PC US 6-weeks US	V: Vortioxetine 5 mg P: placebo	Demographics: adults 18-75, mean age: 42 y/o; 60% female Inclusion Criteria: Patients with MDD major depressive episode of at least 3 months' duration according to DSM-IV-TR criteria; outpatient; baseline MADRS score ≥ 30 at baseline Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), or if current or past history neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or lab values. Concomitant use of any neuroactive medications prohibited 2-5 weeks prior to start of study and throughout treatment period. Patients at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, or had made serious suicide attempt in previous 6 months.	N: V: 300 P: 300 Attrition: V: 56 (18.7% P: 64 (21.3%	<u>Mean change from baseline in MADRS:</u> V: -15.8 P: -15.4 p-value: 0.326 95% CI: -2.19 to 1.55 <u>HAMD24 Response Rate:</u> V: 135/292 (46.2%) P: 132/286 (46.2%) RR: 1.0, 95% CI (0.83-1.19) p-value: 0.984 <u>MADRS Remission Rate:</u> V: 85/292 (29.1%) P: 92/286 (32.2%) RR: 0.90, 95% CI (0.70-1.16) p-value: 0.418	NA NS NS	<u>Withdrawals Due to Adverse Events:</u> V: 9 (3.0%) P: 11 (3.7%) RR 0.82, 95% CI (0.32-2.10) p-value 0.821 <u>Serious Adverse Events:</u> V: 7 (2.3%) P: 4 (1.3%) RR 1.75, 95% CI (0.47-7.06) p-value 0.55	NS NS	**Quality Rating:** Fair **Internal Validity:** <u>Selection:</u> Centralized computer system used for randomization and medication assignment <u>Performance:</u> Study medication was identical in appearance and dispensed using unique identification numbers; double-blind <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability <u>Attrition:</u> Slightly higher attrition in placebo group (21% vs 19%) with more protocol deviations and patients withdrawn in placebo group. Loss to follow up high (n=39) **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria limits generalizability to population <u>Setting:</u> Outpatient sites in the US <u>Outcomes:</u> Primary outcome change from baseline in HAMD total score at week 6 which is difficult to determine the clinical significance of. Response and Remission were included as secondary outcomes.

Henigsberg et al, 2012[17] MC, R, DB, PG, PC 8-weeks Europe, Asia, Africa	V1: Vortioxetine 1 mg V5: Vortioxetine 5 mg V10: vortioxetine 10mg P: placebo	Demographics: adults 18-75, mean age: 46 y/o; 63% female Inclusion Criteria: Patients with MDD major depressive episode of at least 3 months' duration according to DSM-IV-TR criteria; outpatient; baseline MADRS score ≥ 26 at baseline Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), or if current or past history neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or lab values. Concomitant use of any neuroactive medications prohibited 2-5 weeks prior to start of study and throughout treatment period. Patients at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, or had made serious suicide attempt in previous 6 months.	FAS: V1: 140 V5: 140 V10: 140 P: 140 Attrition: V1: 13 (9.3%) V5: 11 (7.8%) V10: 18 (12.8%) P: 13 (9.3%)	Mean change from baseline in MADRS: V1: -14.82 p-value: N/A V5: -15.42 p-value: <0.001 V10: -16.23 p-value: <0.001 P: -11.30 MADRS Response Rate: V1: 65 (46.8%) V5: 61 (43.9%) V10: 68 (48.9%) P: 34 (24.5%) V1 Vs P: RR 1.90 (95% CI 1.35, 2.67); p-value <0.001 V5 Vs P: RR 1.79 (95% CI 1.27, 2.54); p-value = 0.001 V 10 Vs P: RR 2.00 (95% CI 1.43, 2.80); p-value <0.001 HAMD24 Response Rate: V1: 66 (47.5%) V5: 63 (45.3%) V10: 69 (49.6%) P: 32 (23.0%) V1 Vs P: RR 1.71 (95% CI 1.17, 2.55); p-value =0.004 V5 Vs P: RR 1.66 (95% CI 1.13, 2.49); p-value= 0.008 V10 Vs P: RR 1.77 (95% CI 1.21, 2.63); p-value =0.002 MADRS Remission Rate: V1: 36 (25.9%) V5: 40 (28.8%) V10: 37 (26.6%) P: 23 (16.5%) V1 Vs P: RR 1.55 (95% CI 0.97, 2.48); p-value = 0.003 V5 Vs P; RR 1.74 (95% CI 1.10, 2.74); p-value <0.001 V10 Vs P; RR 1.61 (95% CI 1.01, 2.56); p-value = 0.002	NA 22.3%/5 19.4%/6 24.4%/4 24.5%/4 22.3%/5 26.6%/4 9.4%/11 6.3%/16 6.1%/17	Withdrawals Due to Adverse Events: V1: 3 (2.1%) V5: 1 (0.7%) V10: 5 (3.6%) P: 2 (1.4%) Serious Adverse Events: V1: 1 (<1%) V5: 1 (<1%) V10: 5 (3.6%) P: 2 (1.4%)	NS NS	**Quality Rating:** Poor-Fair **Internal Validity:** Selection: Randomization occurred, no details were given. No allocation concealment details were given. Performance: Double-blind, blinding was maintained throughout the study; all study medication was identical in appearance and dispensed using unique identification numbers. Detection: Lack of detail and known inter-rater variability with no details for controlling for variability. Attrition: Stated modified intention to treat analysis conducted, but did not use. <10% total attrition, loss to follow-up low. **External Validity:** Recruitment: Unclear Patient Characteristics: Extensive exclusion criteria Setting: Outpatient sites in Europe, Africa, Asia Outcomes: Primary outcome change from baseline in HAMD total score and MADRS total score at week 8

Mahablesh-warker et al, 2013[18] MC, R, DB, PG, PC US 8-weeks	V2.5: vortioxetine 2.5 mg V5: vortioxetine 5 mg P: placebo DUL: duloxetine 60 mg	Demographics: adults 18-75, mean age: 42 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥22 at baseline visit Exclusion Criteria: Current psychiatric disorder other than; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; any substance abuse disorder within the previous 6 months, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or any Axis II disorder; suicide risk; cognitive behavioral therapy (CBT); pregnant/breastfeeding; known hypersensitivity or were non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004	ITT: V2.5: 146 V5: 15 P: 149 DUL: 149 Attrition: V2.5: 54 (32.3% V5: 31 (20.3% P: 42 (27.3% DUL: 33 (21.6%	Mean change from baseline in HAMD24: V2.5: -12.04 p-value: 0.138 V5: -11.08 p-value: 0.577 P: -10.50 DUL: -13.47 p-value: 0.005 HAMD24 Response Rate: V2.5: 60 (41.1%) V5: 58 (37.9%) P: 48 (32.2%) DUL: 76 (51.0%) V2.5 Vs P: RR 1.28, 95% CI (0.93-1.76) p-value: 0.118 V5 Vs P: RR 1.18, 95% CI (0.85-1.64) p-value: 0.335 DUL Vs P: 1.58, 95% CI (1.18-2.13) p-value: 0.001 MADRS Remission Rate: V2.5: 33 (22.6%) V5: 32 (20.9%) P: 33 (22.1%) DUL: 51 (34.2%) V2.5 Vs P: RR 1.02, 95% CI (0.65-1.61) p-value 0.925 V5 Vs P: RR 0.94, 95% CI 0.60-4.50) p-value 0.794 DUL Vs P: RR 1.55, 95% CI (1.04-2.31) p-value 0.28	NA NS NS 18.8%/6 NS NS NS	Withdrawals Due to Adverse Events: V2.5: 7 (4.5%) V5: 12 (7.8%) P: 7 (4.5%) DUL: 17 (11.2%) Serious Adverse Events: V2.5: 0 V5: 4 (2.6%) P: 2 (1.3%) DUL: 2 (1.3%)	NS NS	**Quality Rating:** Fair **Internal Validity:** Selection: Randomization schedule developed by Takeda and investigators were informed of each patient's coded treatment allocation by an interactive voice-activated system. Performance: Participants and investigators were blinded to treatment allocation for duration of study; identical capsules used Detection: Lack of detail and known inter-rater variability with no details for controlling for variability. Attrition: High attrition. Overall 26% attrition (35.3% on V2.5 group, 27.6% in DUL group). Overall loss to follow-up high (n=43). **External Validity:** Recruitment: advertisement posters, brochures, doctor-to-patient letters and websites Patient Characteristics: Extensive exclusion criteria Setting: 49 outpatient clinics in the US Outcomes: LS Mean change from baseline in HAMD24 total score after 8 weeks

Katona et al, 2012[19] MC, R, BD, PC US and non-US 8-weeks	V: Vortioxetine 5 mg P: Placebo D: Duloxetine 60mg	Demographics: adults ≥65, mean age: 70 y/o; 65% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, any Axis II disorder; suicide risk; known hypersensitivity or non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004; elevated IOP or at risk for acute glaucoma, chronic liver disease, clinically significant unstable illness, MI within previous 6 months, TSH level outside reference range at screening, abnormal vital signs	FAS: V: 154 P: 145 D: 147 Attrition: V: 20 (12.8% P: 17 (11.7% D: 23 (15.2%	<u>Mean change from baseline in MADRS:</u> V: -13.7 p-value: 0.0011 P: -10.3 D: -15.8 p-value: <0.0001 <u>MADRS Response Rate:</u> V: 92 (59.7%) P: 52 (35.9%) D: 104 (70.7%) V Vs P: RR 1.67, 95% CI (1.28-2.17) p-value <0.001 D Vs P: RR 1.97, 95% CI (1.55-2.50) p-value <0.001 <u>HAMD24 Response Rate:</u> V: 82 (53.2%) P: 51 (35.2%) D: 93 (63.3%) V Vs P: RR 1.51, 95% CI (1.15-2.01) p-value <0.01 D Vs P: RR 1.80, 95% CI (1.39-2.33) p-value <0.001 <u>MADRS Remission Rate:</u> V: 52 (33.8%) P: 30 (20.7%) D: 69 (46.9%) V Vs P: RR 1.63, 95% CI (1.09-2.48) p-value <0.05 D Vs P: RR 2.27, 95% CI 1.57-3.34) p-value <0.001 <u>HAMD17 Remission Rate:</u> V: 45 (29.2%) P: 28 (19.3%) D: 51 (34.7%) V Vs P: RR 1.51, 95% CI (0.98-2.37) p-value <0.05 D vs P: RR1.80, 95% CI 1.81-2.77) p-value <0.01	NA 24%/4 35%/3 18%/6 28%/4 13%/8 24%/4 10%/10 15%/7	<u>Withdrawals Due to Adverse Events:</u> V: 10 (6.4%) P: 6 (4.1%) D: 15 (9.9%) V Vs P: RR 1.56, 95% CI (0.34-4.75) p-value: 0.875 D Vs P: RR 2.40, 95% CI (0.90-6.82) p-value 0.16 <u>Serious Adverse Events:</u> V: 1 (<1%) p-value: NS P: 4 (2.8%) D: 1 (<1%) p-value: NS	23%/43 6%/17 NW	**Quality Rating:** Good **Internal Validity:** <u>Selection:</u> Eligible patients assigned to double-blind treatment according to computer-generated randomization list; details of randomization were contained in a set of sealed opaque envelopes. Sequentially enrolled patients were assigned the lowest randomization number available in blocks of six at each site <u>Performance:</u> All investigators, trial personnel and patients were blinded to treatment assignment; double-dummy design used <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall low attrition. Loss to follow-up low (n=2) **External Validity:** <u>Recruitment:</u> Advertisements used to recruit patients in Sweden, Finland; otherwise unknown <u>Patient Characteristics:</u> Extensive exclusion criteria; limited to mostly Caucasian patients which limits the generalizability of results. <u>Setting:</u> 81 outpatient settings in Canada, Finland, France, Germany, Sweden, Ukraine and the US <u>Outcomes</u>: ANCOVA of the mean change from baseline in HAMD24 total score at week 8

Boulenger et al, 2013[21] MC, R, DB, PG, PC Non-US 8-weeks	V15: Vortioxetine 15mg V20: vortioxetine 20mg P: Placebo D: duloxetine 60 mg	Demographics: adults18-75, mean age: 46 y/o; 66% female Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, any Axis II disorder; suicide risk; known hypersensitivity or non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004; elevated IOP or at risk for acute glaucoma, chronic liver disease, clinically significant unstable illness, MI within previous 6 months, TSH level outside reference range at screening	FAS: V15: 149 V20: 151 P: 158 D: 146 Attrition: V15: 3 (23.0% V20: 2 (17.2% P: 25 (15.8% D: 16 (10.9%	<u>Mean change from baseline in MADRS:</u> V15: -17.2 p-value: <0.001 V20: -18.8 p-value: <0.001 P: -11.7 D: -21.2 p-value: <0.001 <u>MADRS Response Rate:</u> V15: 85 (57.0%) V20: 93 (61.6%) P: 51 (32.3%) D: 108 (74.0%) V15 Vs P: RR 1.77, 95% CI (1.35-2.33) p-value <0.0001 V20 Vs P: RR 1.91. 95% CI (1.47-2.45) p-value <0.0001 D Vs P: RR 2.29, 95% CI (1.81-2.89) p-value <0.0001 <u>MADRS Remission Rate:</u> V15: 52 (34.9%) V20: 58 (38.4%) P: 30 (19.0%) D: 79 (54.1%) V15 Vs P: RR 1.84, 95% CI (1.22-2.79) p-value 0.0016 V20 Vs P: RR 2.02, 95% CI (1.54-3.04) p-value 0.0002 D Vs P: RR 2.85, 95% CI (1.99-4.14) p-value <.0001	NA 24.7%/4 29.3%/3 41.7%/2 15.9%/6 19.4%/5 35.1%/3	<u>Withdrawals Due to Adverse Events:</u> V15: 10 (6.7%) V20: 17 (11.3%) P: 7 (4.4%) D: 7 (4.8%) V15 Vs P:RR 1.52, 95% CI (0.55-4.33), p-value 0.382 V20 Vs P: RR 2.54, 95% CI (1.03-6.63), p-value 0.032 D Vs P: RR 1.08, 95% CI (0.35-3.36) p-value 1.0 <u>Serious Adverse Events:</u> V15: 0 V20: 2 (1.3%) P: 0 D: 3 (2.0%) NS	NS 6.9%/15 NS NS	**Quality Rating:** Fair **Internal Validity:** <u>Selection:</u> Patients were randomized according to a computer-generated randomization list and details were contained in sealed opaque envelopes. <u>Performance:</u> double-dummy design used <u>Detection:</u> Double-blind; Raters were trained to increase inter-rater reliability in MADRS, MINI, CGI, HAMA, and DESS scales. <u>Attrition:</u> Attrition overall was acceptable, however the V15 group had a higher level of attrition than other groups, with high numbers of patients withdrawn due to adverse events, lack of efficacy, and undefined. **External Validity:** <u>Recruitment:</u> Advertisements used in some countries, otherwise not described. <u>Patient Characteristics:</u> Extensive exclusion criteria; limited to mostly Caucasian patients which limits the generalizability of results. <u>Setting:</u> Outpatient settings in 13 countries in Europe and South Africa <u>Outcomes:</u> Change from baseline in MADRS total score at week 8

Boulenger et al, 2012[21] MC, R, DB, PC Non-US Period I: 12-weeks Period II: 24-weeks	Period I: Open label, acute Tx V: Vortioxetine 5mg or V10 mg (flexible-dose) Period II: Relapse Prevention V: vortioxetine fixed dose (5 or 10 mg) P: placebo	Demographics: adults ≥65, mean age: 70 y/o; 65% female, 78.2% Caucasian Inclusion Criteria: Patients with MDD presenting with current major depressive episode of at least 3 months according to DSM-IV-TR criteria; outpatient; MADRS total score ≥26 at baseline visit Exclusion Criteria: Current psychiatric disorder; current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, any Axis II disorder; suicide risk; known hypersensitivity or non-response to venlafaxine; depression resistant to two adequate antidepressant treatments of at least 6 week duration, or had previously been exposed to Lu AA21004; elevated IOP or at risk for acute glaucoma, chronic liver disease, clinically significant unstable illness, MI within previous 6 months, TSH level outside reference range at screening	Period I: N=639 Period II: V: 204 P: 192 Attrition: Period I: 37.4% Period II: V: 79 (38.3% P: 88 (41.2%	Period I: MADRS Response Rate: 75.7% MADRS Remission Rate: 68.7% Period II: Relapse Rate: V: 12.7% P: 23.4% HR 2.0, 95% CI 1.26-3.21 P=0.0035	NA NA NA	Withdrawals due to adverse events: Period I: 54/639 (8.4%) Period II: 16/206 (7.8%) vs. 5/194 (2.6%) Serious Adverse Events: Period I: NR Period II: V: 7 (3.4%) P: 4 (2.1%)	NA 0.052/ 20 NA 0.013/ 77	**Quality Rating:** Poor **Internal Validity:** Selection: All patients received open-label vortioxetine for 12 weeks and then were randomized to placebo or vortioxetine for 24 weeks. Patients were randomized based on a computer-generation randomization list, details were unknown to any investigators and contained in a set of sealed opaque envelopes. At each study center, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four Performance: All investigators, trial personnel and participants were blinded to treatment for the duration of the study. Medication was given as encapsulated tablets or matched placebo. Detection: Rater training was undertaken to increase inter-rater reliability and chaired by an experienced investigator. Only those investigators who had actively participated in training sessions prior to inclusion of patients into the study and received certification were allowed to rate patients. Scales were used in local language versions. Attrition: High overall attrition **External Validity:** Recruitment: Advertisements used in 9 countries, otherwise unclear Patient Characteristics: Extensive exclusion criteria Setting: 66 outpatient settings in 17 countries (Europe, Asia, Canada, and Australia Outcomes: Time to relapse of MDD (MADRS score of >10) within the first 24 weeks of the double-blind period.

Baldwin et al 2012[22]	A: vortioxetine 2.5-10 mg	Demographics: adults 18-75, mean age: 46 y/o; 68% female Inclusion Criteria: Patients enrolled in Baldwin et al 2011 if investigator judged that 12 months of therapy was indicated Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), or if current or past history neurological or substance abuse disorder, current clinically significant medical illness or clinically significant abnormalities in vital signs or lab values. Concomitant use of any neuroactive medications prohibited 2-5 weeks prior to start of study and throughout treatment period. Patients at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, or had made serious suicide attempt in previous 6 months.	N=535 Attrition: A: 207 (38.7%	MADRS Response at week 52 (LOCF): 84.3% MADRS Remission at 52 weeks (LOCF): A: 71.2%	NA NA	Withdrawals due to adverse events: A: 42/535 (7.9%) Serious Adverse Events: A: 18/535 (3.4%)	NA NA	**Quality Rating:** Poor As an open-label, single-arm study, this does not constitute an adequate, well-controlled study

Alam et al[23] 2013	A: vortioxetine 2.5-10 mg	Demographics: adults 18-75, mean age: 46 y/o; 68% female; 83% Caucasian Inclusion Criteria: Patients enrolled in Mahableshwarker et a 2013l or Henigsberg et al 2012 and if investigator judged that 12 months of therapy was indicated Exclusion Criteria: Current psychiatric disorder other than MDD (assessed using MINI), at serious risk of suicide or who had score of ≥ 5 on item 10 of MADRS scale, experienced a continuing moderate or severe adverse events related to treatment from the original acute trial, or using disallowed medications	N= 836 Attrition: 310 (37%)	MADRS Response at week 52 (LOCF): 60.2% MADRS Remission at 52 weeks (LOCF): A: 61.7%	NA NA	Withdrawals due to adverse events: A: 49/836 (7.9%) Serious Adverse Events: A: 29/836 (3.5%)	NA NA	**Quality Rating:** Poor As an open-label, single-arm study, this does not constitute an adequate, well-controlled study

levomilnacipran (Fetzima®)

FDA approved indications: Treatment of MDD

Clinical Efficacy Data:

Levomilnacipran is the active enantiomer of milnacipran, an SNRI approved for use in fibromyalgia.[29] The approval of levomilnacipran in July 2013 was based on three 8-week, placebo-controlled RCTs in adults with MDD.[5,26–28] Two additional studies have been published, one short term efficacy study and one longer-term safety study.[28,30]The trials included a total of 2,243 adult patients (ages 18-70 years) meeting DSM-IV-TR criteria for MDD, single episode or recurrent. Table 3 provides a summary of the evidence findings for the two studies. The primary measure used to evaluate efficacy was change from baseline in total MADRS score. Response and remission rates remain the most relevant clinical efficacy endpoints in treating MDD.

Response rates appear to be similar for the 40 mg and 80 mg doses in available studies, but there was an increase in MADRS response with the 120 mg dose. MADRS remission rates were similar among all doses, although data is limited. MADRS response rates were similar between the two doses of levomilnacipran

studied in the Bakish et al study with RRs of 1.43 (95% CI 1.10-1.86) and 1.34 (95% CI 1.05-1.78) for the 40 mg and 80 mg groups, respectively.[27] MADRS remission RRs were 1.67 (95% CI 1.12-2.51) and 1.80 (95% CI 1.22-2.68) for the 40 mg and 80 mg groups, respectively. In Asnis et al, which studied three doses of levomilnacipran, only the 120mg group had a statistically significant MADRS response rate (RR 1.42; 95% CI 1.05-1.94), while no group was statistically significant for MADRS remission rates.[31] A third short-term efficacy study titrated patients from levomilnacipran SR 25 mg daily to either 75 mg or 100 mg daily based on tolerance; both MADRS response (RR 1.34; 95% CI 1.18-1.66)and MADRS remission (RR 1.78; 95% CI 1.40-2.28) outcomes were statistically significant.[30]The flexible-dose study grouped all doses of levomilnacipran together which limits our ability to fully appraise this study for efficacy.[31]

The baseline MADRS score of patients enrolled in Montgomery et al and Bakish et al was 30 (moderate-to-severe MDD). In Asnis et al, the baseline MADRS score was 36, indicating a slightly more sever patient population. A high percentage of participants in all trials were Caucasian, mostly female and in their early 40s. Extensive exclusion criteria included patients at risk of suicide, concurrent psychiatric disorders or medical illnesses and patients with treatment-resistant depression. These characteristics of study participants make it hard to generalize these findings to a broader population.

No head-to-head studies or studies with an active comparator have been published. Levomilnacipran has not been studied in pediatric patients or patients with severe hepatic impairment. Dose adjustments should be made for patients with renal insufficiency. No subgroup analyses studying gender, race or ethnicity have been published.

Clinical Safety:

The most common adverse events seen in trials as compared to placebo were nausea, constipation, hyperhidriosis, tachycardia, erectile dysfunction, increased heart rate and urinary hesitation.[5] The two dose-related adverse reactions were urinary hesitation and erectile dysfunction.[5]

One long-term, open-label extension study of levomilnacipran including 825 patients has been published to examine safety and tolerability.[28] In this study, 13.0% of patients withdrew from the study due to adverse events. The most common adverse events seen were headache (22.2%), nausea (16.2%), upper respiratory tract infection (13.2%), hyperhidrosis (10.9%), constipation (9.6%), nasopharyngitis (8.5%), dizziness (8,1%), insomnia (8.0%), tachycardia (7.6%), dry mouth (7.2%), and erectile dysfunction (5.6% of men). Serious adverse events occurred in 4.0% of patient and no deaths occurred.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Response*
2) Remission*
3) Relapse
4) Hospitalization
5) Quality of Life
6) Withdrawals due to adverse events
7) Major adverse events

*Secondary endpoints in levomilnacipran trials

Primary Study Endpoint:

1) Change in baseline Montgomery-Asberg Depression Rating Scale (MADRS)

Table 3. Levomilnacipran Comparative Evidence Table

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Montgomery et al, 2013[30] MC, DB, PC, PG, RCT 10 weeks	L: levomilnacipran SR 75 mg or 100 mg P. Placebo	Demographics: Adult patients (18-70 yrs); mean age 44.5 y/o; 66.5% female; 91% white Inclusion Criteria: DSM-IV-TR criteria for MDD, current episode of MDD ≥1 month; HAMD17 score >22/SDS score ≥10 with at least 1 subscale ≥6 Exclusion Criteria: abnormal lab tests, clinical findings, or ECG findings; current of history of psychiatric or personality disorders; substance abuse (last 6 months); physical condi39ons; pregnancy; allergy/nonresponse to milnicipran; psychotherapy sessions previous 6 months; ECT (preceding 3 months); concomitant psychotropic medicine	Full Analysis Set (FAS): L: 276 P: 277 Attrition: L: 57 (20.2%) P: 70 (24.9%)	Difference in MADRS total score from baseline vs placebo, LOCF (week 10): LS mean difference: -3.7 95% CI (-5.2 to -2.1) p-value: <0.0001 MADRS Response Rate*: L: 163 (59.1%) P: 117 (42.2%) RR 1.34; 95% CI 1.18-1.66; p-value: <0.0001 MADRS Remission Rate*: L: 128 (46.4%) P: 72 (26.0%) RR 1.78; 95% CI (1.40-2.28); p-value: <0.0001	NA 17%/ 6 20.4%/ 5	Withdrawals Due to Adverse Events: L: 26 (9.4%) P: 18 (6.5%) RR 1.44, 95% CI (0.78-2.69) p-value 0.272 Serious Adverse Events: L: 3 (1.1%) P: 9 (3.2%) RR 0.35, 95% CI (0.08-1.39) p-value 0.143	NS NS	**Quality Rating:** Fair **Internal Validity: RoB** Selection: Patients were randomized by a computer-generated list of numbers that were blindly linked to test drug or placebo; groups in each study center were balanced according to severity of baseline MADRS score (<30 or ≥30). Blinding information was contained in sealed decoding envelopes. Performance: Double-blind design used. During titration, patients received an equivalent number of identical-looking active or placebo capsules. Patients assigned to active treatment were titrated from 25 mg to 75 mg over 11 days. If good tolerance was discerned by telephone assessment, the 100mg active target dose was initiated on day 12 and maintained for the study duration. Detection: Lack of detail and known inter-rater variability with no details for controlling for variability. Attrition: Overall attrition high, more loss in the placebo group due to insufficient therapeutic response and worsening of MDD. **External Validity:** Recruitment: Unclear Patient Characteristics: Extensive exclusion criteria; limited to mostly Caucasian patients which limits the generalizability of results. Setting: 68 sites in Europe, India, and South Africa Outcomes: MADRS total score change from baseline to week 10

Asnis et al, 2013[26]	L40: levomilnacipran SR 40m mg L80: levomilnacipran SR 80m mg L120: levomilnacipran SR 120m mg P: placebo	Demographics: Adult patients (18-65 yrs); mean age 41 y/o; 64% female; 75% white Inclusion Criteria: DSM-IV-TR criteria for MDD, current episode of MDD ≥8 weeks; MADRS score ≥30, BMI ≥18 and ≤40 Exclusion Criteria: abnormal lab tests, clinical findings, or ECG findings; current of history of psychiatric or personality disorders; lifetime history of manic/hypomanic episode; substance abuse (last 6 months); medical conditions; suicide risk; pregnancy; allergy/nonresponse to milnicipran, other SNRIs/ SSRIs; nonresponse to two or more antidepressants after treatment with adequate dose and duration; concomitant psychotropic medicine	mITT: L40: 176 L80: 177 L120: 176 P: 175 Attrition: L40: 48 (27.0%) L80: 58 (32.4%) L120: 63 (35.0%) P: 38 (21.6%)	<u>LS mean change in MADRS total score from baseline, LOCF (week 8):</u> L40: -8.6 (vs. P: p-value NS) L80: -9.7 (vs. P: p-value <0.05) L120: -9.7 (vs. P: p-value <0.05) P: -7.2 <u>MADRS Response Rate*</u>: L40: 64 (36.4%) L80: 66 (37.3%) L120: 73 (41.5%) P: 51 (29.1%) L40 VS P: RR 1.25; 95% CI (0.91-1.72); p-value NS L80 VS P: RR 1.27; 95% CI (0.93-1.76); p-value NS L120 VS. P: RR 1.42; 95% CI (1.05-1.94); p-value 0.019 <u>MADRS Remission Rate*</u>: L40: 38 (21.6%) L80: 37 (20.9%) L120: 36 (20.5%) P: 34 (19.4%) L40 VS P: RR 1.11; 95% CI (0.72-1.73); p-value NS L80 VS P: RR 1.08; 95% CI (0.69-1.68); p-value NS L120 VS P: RR 1.05; 95% CI (0.67-1.65); p-value NS	NA NS NS 12.4%/ 8 NS NS NS	<u>Withdrawals Due to Adverse Events:</u> L40: 13 (7.3%) L80: 26 (14.5%) L120: 12 (6.7%) P: 3 (1.7%) L40 Vs P: RR 4.065, 95% CI (1.112-17.842), p-value 0.020 L80 Vs P: RR 7.620, 95% CI (4.274-31.414), p-value <0.001 L120 Vs. P: RR 3.733, 95% CI (1.007-16.551), p-value=0.033 <u>Serious Adverse Events:</u> L40: 2 (1.1%) L80: 1 (0.6%) L120:0 P: 0 All arms vs. P: NS	5.6%/ 18 12.8%/ 8 5%/ 20 NS	**Quality Rating:** Fair **Internal Validity: RoB** <u>Selection:</u> Patients were randomized by a computer generated list of numbers. <u>Performance:</u> Investigators and patients were blinded to allocation throughout treatment and down-taper periods. Patients were assigned to identically appearing treatment. Blinding was maintained via a secured randomization code list. <u>Detection:</u> Double blind. Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> High attrition in the levomilnacipran groups, especially due to adverse events and withdrawal of consent **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria limits generalizability <u>Setting:</u> 38 US outpatient centers <u>Outcomes</u>: MADRS total score mean change from baseline at week 8

Bakish et al, 2013[27]	L40: Levomilnacipran SR 40 L80: Levomilnacipran SR 80 P: placebo	Demographics: adult patients 18-75 yrs; mean age 43; 63% female; 74% white Inclusion Criteria: DSM-IV-TR criteria for recurrent MDD, current episode of MDD 6 weeks-12 months; 5 or fewer episodes of MDD within previous 5 years; MADRS score ≥26, CGI-S score ≥4; BMI ≥18 and≤40 Exclusion Criteria: abnormal lab tests, clinical findings, or ECG findings; current of history of psychiatric or personality disorders; lifetime history of manic/hypomanic episode; substance abuse (last 6 months); medical conditions; suicide risk; pregnancy; allergy/nonresponse to milnicipran, other SNRIs/ SSRIs, or levomilnicipran; nonresponse to two or more antidepressants after treatment with adequate dose and duration; concomitant psychotropic medicine	ITT: L40: 185 L80: 187 P: 185 Attrition: L40: 40 (21.6%) L80: 45 (24.1%) P: 31 (16.7%)	<u>LS mean change in MADRS total score from baseline, LOCF (week 8):</u> L40: -13.1 (vs. P: p-value = 0.025) L80: -13.1 (vs. P: p-value = 0.024) P: -10.7 <u>MADRS Response Rate*</u>: L40: 90 (49%) L80: 88 (47%) P: 63 (34%) L40 vs P: RR 1.43; 95% CI (1.10-1.86) p-value = 0.004 L80 vs P: RR 1.34; 95% CI 1.05-1.78) p-value = 0.010 <u>MADRS Remission Rate*</u>: L40: 55 (30%) L80: 60 (32%) P: 33 (18%) L40 vs P: RR 1.67; 95% CI (1.12-2.51) p-value = 0.012 L80 vs P: RR 1.80; 95% CI (1.22-2.68) p-value = 0.002	NA 15%/7 13%/ 8 12%/ 8 14%/ 7	<u>Withdrawals Due to Adverse Events:</u> L40: 12 (6.4%) L80: 19 (10.1%) P: 3 (1.6%) L40 Vs. P: RR 3.817, 95% CI (1.029-16.925); p-value: 0.032 L80 Vs. P: RR 5.780, 95% CI 1.668-24.400); p-value: 0.001 <u>Serious Adverse Events:</u> L40: 0 L80: 0 P: 0 All vs. P: NS	4.8%/ 21 8.5%/ 12 Ns	**Quality Rating:** Fair **Internal Validity: RoB** <u>Selection:</u> Allocation was performed using a computer-generated randomization numbers and treatment assignments were made using a web-response system <u>Performance:</u> Identically appearing treatments with labels corresponding to the sequence of treatment assignment were supplied. All study personnel and patients were blinded to treatment for the entire study period. <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall high attrition (23%), with more attrition in the levomilnacipran groups due to more adverse events and more protocol violations **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria limits generalizability <u>Setting:</u> 51 outpatient centers in the US and Canada <u>Outcomes</u>: Change from baseline in MADRS total score at week 8

Sambunaris et al, 2014[31] MC, DB, PC, PG, RCT	L: levomilnacipran SR 40-120 mg P: Placebo	Demographics: Adult patients (18-80 yrs); mean age 45 y/o; 65% female Inclusion Criteria: DSM-IV-TR criteria for MDD, current episode of MDD ≥4 weeks; MADRS score ≥30, BMI ≥18 and ≤40 Exclusion Criteria: current of history of psychiatric or personality disorders; lifetime history of major psychiatric diagnosis;medical conditions; suicide risk; pregnancy; nonresponse to two or more antidepressants after treatment with adequate dose and duration; concomitant psychotropic medicine	mITT: L: 215 P: 214 Attrition: L: 54 (24.9%) P: 54 (20.7%)	<u>LS mean change in MADRS total score from baseline, LOCF (week 8):</u> L: -13.9 P: -11.4 Difference: -2.53; 95% CI: (-4.557, -0.549) p-value: 0.0127 <u>MADRS Response Rate*</u>: L: 90 (41.9%) P: 63 (29.4%) RR 1.42, 95% CI (1.09-1.87) p-value: 0.0083 <u>MADRS Remission Rate*</u>: L: 37 (17.2%) P: 39 (18.2%) RR 0.94, 95% CI (0.61-1.46) p-value: 0.441	NA 12.4%/8 NS	<u>Withdrawals Due to Adverse Events:</u> L: 17 (7.8%) P: 7 (3.2%) RR 2.313, 95% CI (0.926-6.071) p-value 0.059 <u>Serious Adverse Events:</u> L: 2 (<1%) P: 3 (1.4%) NS	NS NS	**Quality Rating: Poor-Fair** **Internal Validity: RoB** <u>Selection:</u> Patients randomized by a computer generated list of numbers <u>Performance</u>: Patients assigned to identically appearing treatment that corresponded to the sequence of randomization numbers; investigators and patients were blinded to treatment assignment. Levomilnacipran was titrated up based on response but no details were given about how placebo was matched when patients were titrated, or if both groups were assess at each time point and medication was adjusted accordingly. <u>Detection:</u> Lack of detail and known inter-rater variability with no details for controlling for variability. <u>Attrition:</u> Overall high attrition. Higher attrition in levomilnacipran group due to more withdrawals due to adverse events **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> No details given <u>Setting:</u> 23 US outpatient centers <u>Outcomes</u>: Change from baseline in MADRS total score at week 8

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Appendix 1: Specific Drug Information: Vortioxetine

CLINICAL PHARMACOLOGY:

PHARMACOKINETICS[25]

Parameter	Result
Oral Bioavailability	75%
Protein Binding	98%
Elimination	Urine (59%); feces (26%)
Half-Life	~66 hours
Metabolism	Hepatic through CYP450, primarily CYP 2D6, and gloconic acid conjugation

DOSE & AVAILABILITY[25]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5 mg, 10 mg, 20 mg	PO	Daily	Initial: 10 mg once daily; increase to 20 mg once daily as tolerated; consider 5 mg once daily for patients who do not tolerate higher doses. Maintenance: 5-20 mg once daily.	None	Mild-to-moderate: no adjustment Severe: Do not use (has not been studied)	Has not been studied	Same as adult	• May be taken without regard to meals • If switiching from MAOI, 14 days should elapse before starting vortioxetine

DRUG SAFETY[25]

Serious (REMS, Black Box Warnings, Contraindications):

Black box warning: Increased risk of suicidal thoughts and behavior in children, adolescents, and young adults **(18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. **Vortioxetine is not approved for use in children.**

Contraindications: Hypersensitivity to vortioxetine or any component; use of MAO inhibitors concurrently or within 21 days of discontinuing vortioxetine or within 14 days of discontinuing the MAO inhibitor; initiation of vortioxetine in a patient receiving linezolid or intravenous methylene blue.

Cautions: use caution in elderly patients; may have higher risk of SIADH or hyponatremia

Warnings and Precautions:

Serotonin syndrome: Potentially life-threatening serotonin syndrome (SS) has occurred with serotonergic antidepressants (eg, SSRIs, SNRIs), particularly when used in combination with other serotonergic agents (eg, triptans, TCAs, fentanyl, lithium, tramadol, buspirone, St John's wort, tryptophan) or agents that impair metabolism of serotonin (eg, MAO inhibitors intended to treat psychiatric disorders, other MAO inhibitors [ie, linezolid and intravenous methylene blue]). Monitor patients closely for signs of SS such as mental status changes (eg, agitation, hallucinations, delirium, coma); autonomic instability (eg, tachycardia, labile blood pressure, diaphoresis); neuromuscular changes (eg, tremor, rigidity, myoclonus); GI symptoms (eg, nausea, vomiting, diarrhea); and/or seizures. Discontinue treatment (and any concomitant serotonergic agent) immediately if signs/symptoms arise.

Discontinuation syndrome: Abrupt discontinuation or interruption of antidepressant therapy has been associated with a discontinuation syndrome. Symptoms arising may vary with antidepressant however commonly include nausea, vomiting, diarrhea, headaches, lightheadedness, dizziness, diminished appetite, sweating, chills, tremors, paresthesias, fatigue, somnolence, and sleep disturbances (eg, vivid dreams, insomnia). Greater risks for developing a discontinuation syndrome have been associated with antidepressants with shorter half-lives, longer durations of treatment, and abrupt discontinuation. For antidepressants of short or intermediate half-lives, symptoms may emerge within 2-5 days after treatment discontinuation and last 7-14 days.

Mania/hypomania: May precipitate a mixed/manic episode in patients at risk for bipolar disorder. Use with caution in patients with a family history of bipolar disorder, mania, or hypomania. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Vortioxetine is not FDA approved for the treatment of bipolar depression.**

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Vortioxetine may be confused with duloxetine, fluoxetine, paroxetine, venlafaxine

Appendix 2: Specific Drug Information : Levomilnacipran

CLINICAL PHARMACOLOGY: Levomilnacipran

PHARMACOKINETICS[5]

Parameter	Result
Oral Bioavailability	92%
Protein Binding	22%
Elimination	Renal (58% excreted unchanged)
Half-Life	12 hours
Metabolism	CYP3A4 (major)

DOSE & AVAILABILITY[5]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
20mg 40mg 80mg 120mg	oral	Daily	Start with 20 mg/day for 2 days, the increase to 40 mg/day, may increase by 40 mg/day every 2 days. Maximum recommended dose is 120mg/day	CrCl 30-59 mL/min: do not exceed 80 mg/day CrCl 15-29 mL/min: do not exceed 40mg/day ESRD: do not use	none	Safety and efficacy not established in patients <18 years old	No dose adjustment	• If switiching from MAOI, 14 days should elapse before starting levomilnacipran • When used with a strong CYP3A4 inhibitor, dose should not exceed 80 mg/day • Not approved for the management of fibromyalgia

DRUG SAFETY[5]

Serious (REMS, Black Box Warnings, Contraindications):

Black box warning: Increased risk of suicidal thoughts and behavior in children, adolescents, and young adults. Monitor all patients started on antidepressants for worsening and emergence of suicidal thoughts and behaviors. This is based on a pooled analysis of 24 short-term studies of 9 antidepressant drugs in children and adolescents on antidepressants. All antidepressants carry this warning.

Contraindications: Known hypersensitivity to any component of the drug; the use of MAOIs within 14 days of starting or 7 days of stopping treatment with levomilnacipran; uncontrolled narrow-angle glaucoma due to increased risk of mydriasis when used concomitantly with levomilnacipran

Warnings and Precautions: There is an increased risk of serotonin syndrome with SSRIs and SNRIs, particularly when used with other serotonergic drugs and with drugs that impair the metabolism of serotonin (MAOIs, linezolid and IV methylene blue). SNRIs, including levomilnacipran, have been associated with increase s in blood pressure; in short-term trials with levomilnacipran, there was a mean increases in systolic BP of 3 mmHg and diastolic BP of 3.9 mmHg, compared to no change in the placebo group. Levomilnacipran was associated with a mean increase in heart rate of 7.4 beats per minute (bpm) in trials compared to a decrease of 0.3 bpm in placebo-treated patients. Urinary hesitation occurred in 4-6% of levomilnacipran patients compared to no patients in the placebo groupin short-term studies. Patients should not abruptly discontinue levomilnacipran due to adverse events following abrupt discontinuation.

Pregnancy/Lactation: Pregnancy Category C. No teratogenic effects were observed when levomilnacipran was administered to pregnant rats or rabbits at doses up to 8 and 16 times the maximum recommended human dose (MRHD). Fetal body weights were reduced in rats, and skeletal ossification was delayed in both rats and rabbits at this dose; these effects were not observed in either species at doses up to 2.5 and 5 times the MHRD. However, no studies have been performed with pregnant women so the drug should be used during pregnancy only if needed. It is not known if levomilnacipran is present in human milk; studies have shown that it

does pass into the milk of lactating rats. Therefore, breastfeeding women should decide to discontinue nursing or discontinue the drug based on the risks and benefits.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Levomilnacipran may be confused with milnacipran, levonunolol, levocarnitine, levocetirizine, levodopa, levofloxacin, levoleucovorin, levonogestrel, levorphanol, levothyroxine, and levomefolate.

Appendix 3: Abstracts of potentially relevant randomized controlled trials and systematic reviews

Bose, A., J. Tsai, et al. (2012). "Early non-response in patients with severe depression: escitalopram up-titration versus switch to duloxetine." Clin Drug Investig **32**(6): 373-85.
BACKGROUND: Comparative evidence for second-step treatment strategies in severe depression is scarce. Up-titrating a well-tolerated selective serotonin reuptake inhibitor (SSRI) versus switching to a serotonin norepinephrine reuptake inhibitor (SNRI) after initial SSRI non-response are possible treatment options. It is often unclear whether relevant tolerability and efficacy differences exist between SSRI up-titration versus switch to an SNRI. OBJECTIVE: The objective of this study was to evaluate tolerability and efficacy of up-titration of escitalopram versus switch to duloxetine in patients who failed to respond to escitalopram 10 mg/day. METHODS: This was an active-controlled, parallel-group, double-blind, randomized study in a general community comparing escitalopram and duloxetine in patients with severe depression; patients who did not respond (<50% Montgomery-Asberg Depression Rating Scale [MADRS] improvement) to 2 weeks of single-blind escitalopram 10 mg/day during the lead-in period were randomized to 8 weeks of double-blind treatment. 571 male and female outpatients aged 18-65 years with severe depression (MADRS total score >/=30) participated in the study and received at least one dose of escitalopram 10 mg/day in the single-blind lead-in phase. During the double-blind randomized phase, 474 patients who did not respond to lead-in escitalopram were randomized and received treatment with escitalopram 20 mg (n = 229) or duloxetine 60 mg (n = 245). Treatment was single-blind escitalopram 10 mg/day during a 2-week lead-in followed by 8-week double-blind escitalopram 20 mg/day or duloxetine 60 mg/day. The main outcome measure was time to all-cause premature study discontinuation. RESULTS: There was no difference in time to all-cause discontinuation between groups (hazard ratio escitalopram/duloxetine = 0.95 [95% CI 0.64, 1.41]; p = 0.727). Treatment with escitalopram compared with duloxetine resulted in significant improvement in MADRS total score at the end of week 8 (least squares mean difference [LSMD] = -1.87 [95% CI -3.60, -0.14]; p = 0.034) using last observation carried forward (LOCF) analysis. Significantly more escitalopram (54%) than duloxetine (42%) patients achieved remission (MADRS </=10) by week 8 (p = 0.013). Adverse events were similar between the two treatment groups. CONCLUSION: In initial non-responders to escitalopram 10 mg/day, dose escalation to 20 mg/day provided better efficacy than switching to duloxetine 60 mg/day, while discontinuations for any reasons and adverse events were similar. CLINICAL TRIAL REGISTRATION: Registered at ClinicalTrials.gov as NCT00384436.

Jonas, D. E., K. Cusack, et al. (2013). *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)*. Rockville MD.
To assess efficacy, comparative effectiveness, and harms of psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). MEDLINE(R), Cochrane Library, PILOTS, International Pharmaceutical Abstracts, CINAHL(R), PsycINFO(R), Web of Science, Embase, U.S. Food and Drug Administration Web site, and reference lists of published literature (January 1980-May 2012). Two investigators independently selected, extracted data from, and rated risk of bias of relevant trials. We conducted quantitative analyses using random-effects models to estimate pooled effects. To estimate medications' comparative effectiveness, we conducted a network meta-analysis using Bayesian methods. We graded strength of evidence (SOE) based on established guidance.

We included 92 trials of patients, generally with severe PTSD and mean age of 30s to 40s. High SOE supports efficacy of exposure therapy for improving PTSD symptoms (Cohen's d -1.27; 95% confidence interval, -1.54 to -1.00); number needed to treat (NNT) to achieve loss of diagnosis was 2 (moderate SOE). Evidence also supports efficacy of cognitive processing therapy (CPT), cognitive therapy (CT), cognitive behavioral therapy (CBT)-mixed therapies, eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy for improving PTSD symptoms and/or achieving loss of diagnosis (moderate SOE). Effect sizes for reducing PTSD symptoms were large (e.g., 28.9- to 32.2-point reduction in Clinician-Administered PTSD Scale [CAPS]; Cohen's d ~ -1.0 or more compared with controls); NNTs were </= 4 to achieve loss of diagnosis for CPT, CT, CBT-mixed, and EMDR. Evidence supports the efficacy of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms (moderate SOE); effect sizes were small or medium (e.g., 4.9- to 15.5-point reduction in CAPS compared with placebo). Evidence for paroxetine and venlafaxine also supports their efficacy for inducing remission (NNTs ~8; moderate SOE). Evidence supports paroxetine's efficacy for improving depression symptoms and functional impairment (moderate SOE) and venlafaxine's efficacy for improving depression symptoms, quality of life, and functional impairment (moderate SOE). Risperidone may help PTSD symptoms (low SOE). Network meta-analysis of 28 trials (4,817 subjects) found paroxetine and topiramate to be more effective than most medications for reducing PTSD symptoms, but analysis was based largely on indirect evidence and limited to one outcome measure (low SOE). We found insufficient head-to-head evidence comparing efficacious treatments; insufficient evidence to verify whether any treatment approaches were more effective for victims of particular trauma types or to determine comparative risks of adverse effects. Several psychological and pharmacological treatments have at least moderate SOE supporting their efficacy: exposure, CPT, CT, CBT-mixed therapies, EMDR, narrative exposure therapy, fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine.

Raskin, J., T. George, et al. (2012). "Apathy in currently nondepressed patients treated with a SSRI for a major depressive episode: outcomes following randomized switch to either duloxetine or escitalopram." J Psychiatr Res **46**(5): 667-74.
Apathy in the context of treated major depressive disorder (MDD) is a common but understudied symptom. This multicenter, double-blind, randomized study investigated whether switching from a selective serotonin reuptake inhibitor (SSRI) to a serotonin-norepinephrine reuptake inhibitor (SNRI), compared with switching to another SSRI, improved apathy symptoms in patients who had been treated with a SSRI for MDD for >/= 3 months, were no longer depressed (Montgomery-Asberg Depression Rating Scale [MADRS] total score </= 15), and continued to have apathy (Apathy Evaluation Scale-- Clinician rated version [AES-C] total score >30). Following 8 weeks of treatment, both the duloxetine (SNRI, 244 patients) and escitalopram (SSRI, 239 patients) groups significantly improved from baseline on the AES-C total score (least squares mean change [standard error]: duloxetine -13.9 [0.54]; escitalopram -13.5 [0.54], both P < 0.001), and on the secondary apathy, depression, and functional outcomes. There were no significant differences between the two groups on any measure, including AES-C total score (least squares mean difference [95% confidence interval]: -0.4 [-1.87 to 1.10], P = 0.612; primary objective). There was a significant within-group improvement in apathy in the subgroup who received escitalopram before and during the study. There were few differences in safety between the two groups. This study did not support the hypothesis that switching from a SSRI to a SNRI has a beneficial effect on apathy symptoms. However, given the study limitations, it is possible that more specific targeting of the noradrenergic pathway would be of benefit.

Richard, I. H., M. P. McDermott, et al. (2012). "A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease." Neurology **78**(16): 1229-36.
OBJECTIVE: To evaluate the efficacy and safety of a selective serotonin reuptake inhibitor (SSRI) and a serotonin and norepinephrine reuptake inhibitor (SNRI) in the treatment of depression in Parkinson disease (PD). METHODS: A total of 115 subjects with PD were enrolled at 20 sites. Subjects were randomized to receive an SSRI (paroxetine; n = 42), an SNRI (venlafaxine extended release [XR]; n = 34), or placebo (n = 39). Subjects met DSM-IV criteria for a depressive disorder, or operationally defined subsyndromal depression, and scored >12 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). Subjects

were followed for 12 weeks (6-week dosage adjustment, 6-week maintenance). Maximum daily dosages were 40 mg for paroxetine and 225 mg for venlafaxine XR. The primary outcome measure was change in the HAM-D score from baseline to week 12. RESULTS: Treatment effects (relative to placebo), expressed as mean 12-week reductions in HAM-D score, were 6.2 points (97.5% confidence interval [CI] 2.2 to 10.3, p = 0.0007) in the paroxetine group and 4.2 points (97.5% CI 0.1 to 8.4, p = 0.02) in the venlafaxine XR group. No treatment effects were seen on motor function. CONCLUSIONS: Both paroxetine and venlafaxine XR significantly improved depression in subjects with PD. Both medications were generally safe and well tolerated and did not worsen motor function. CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that paroxetine and venlafaxine XR are effective in treating depression in patients with PD.

Santaguida, P. L., G. MacQueen, et al. (2012). *Treatment for Depression After Unsatisfactory Response to SSRIs*. Rockville MD.
A comparative effectiveness review was undertaken to evaluate treatment strategies in patients who failed to respond to selective serotonin reuptake inhibitors (SSRIs) as first-line treatment. The efficacy (benefits and harms) of monotherapy approaches (dose escalation, increased duration, or switch) or combined therapies were evaluated. Efficacy in the context of subgroups was also evaluated. Recommendations in Clinical Practice Guidelines (CPGs) from 2004 to April 2011 were compared. MEDLINE(R), Embase(R), CINAHL(R), PsychINFO(R), AMED (Allied and Complementary Medicine), Cochrane Database of Systematic Reviews, and Cochrane Central(R) were searched from 1980 to April 13, 2011. An extensive grey literature search was also undertaken, including publications of drug regulatory agencies. Systematic review methodology was employed.Eligibility criteria included English studies of adults (aged >/=18 years) or adolescents and children (8-18 years) with major depressive disorder, dysthymia, or subsyndromal depression, who had an inadequate response to an SSRI at entry into the study. Comparative study designs were eligible. Publications focusing only on treatment algorithms were not considered to be CPGs. From 46,884 citations, there were 44 studies and 27 guidelines that were eligible. Key Questions 1 and 2 (KQ1-a and KQ2): Forty-one studies included adults and three studies included adolescents; all included subjects with major depressive disorder except for one with adult dysthymia and subsyndromal patients alone. A limited number of studies (n=11) evaluated monotherapy strategies and these showed no differences among approaches. Although there were more studies evaluating monotherapy relative to combined therapies (n=33), the types of add-on agents were numerous and showed no relative differences; the exception was the addition of risperidone to an SSRI. KQ 3: Seven studies evaluated the impact of disease type, disease severity, previous comorbidities, age, gender, and race on treatment outcomes and showed no clear trend. KQ4: From 18 CPGs for adults, the majority did not provide specific recommendations for monotherapy strategies; for combination therapies, although specific agents were specified, there was variability across CPGs when recommending agents and strategies. Recommendations were more consistent for the CPGs for adolescents (n=7). There is low strength of evidence evaluating relative differences for any monotherapy or combination therapy approach. All but 2 of 44 studies showed no relative differences in response and remission rates. Two studies with limited sample sizes and using risperidone as an augmenting agent showed benefit with combined therapy. The majority of studies were not designed to assess superiority of the strategies. Inconsistency and lack of clarity for clinical actions were noted when comparing CPGs.

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Month/Year of Review: May 2014
PDL Class: Inflammatory Bowel Agents

Date of Last Review: September 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: BALSALAZIDE DISODIUM, MESALAMINE SUPPOSITORIES (CANASA®), MESALAMINE CAPSULES ER 24H (APRISO®), MESALAMINE ENEMA, MESALAMINE TABLET DR (LIALDA®), OLSALAZINE SODIUM CAPSULE (DIPENTUM®), SULFASALAZINE TABLET DR, SULFASALAZINE TABLET
- Non-preferred Agents: MESALAMINE TABLET DR (ASACOL®), MESALAMINE TABLETS DR HIGH DOSE (ASACOL HD®), MESALAMINE CAPSULE DR (DELZICOL®), MESALAMINE CAPSULES (PENTASA®), MESALAMINE ENEMAS SULFITE-FREE (SFROWASA®), MESALAMINE WITH CLEANSING WIPES KIT, BALSALAZIDE SODIUM TABLET (GIAZO®)

Current PA Criteria: The generic non-preferred drugs in PDL classes prior authorization criteria is in place to support preferred PDL ulcerative colitis agents and to cover for OHP above the line diagnoses only.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of inflammatory bowel agents?
- Are there unique patients or situations where agents may be more effective or safer than currently available agents?

Previous Conclusions Recommendations:

- Evidence does not support a difference in efficacy/effectiveness between the aminosalicylates.
- Evidence does not support a difference in harms/adverse events between the aminosalicylates.
- Olsalazine can cause secretory diarrhea and is only indicated for maintenance therapy.
- Include different formulations as preferred products on the PDL, including a long-acting and rectal option.

Conclusions:

- There is high quality evidence that 5-aminosalicylic acid is superior to placebo in inducing clinical remission (RR 0.86; 95% CI 0.81 to 0.91; NNT 9) and relapse (RR 0.69; 95% CI 0.62 to 0.77; NNT 5-8). [1,2]
- There is moderate quality evidence of no difference between 5-aminosalicylate products and sulfasalazine in failure to induce clinical remission (RR 0.90; 95% CI 0.77 to 1.04) and high quality evidence of superiority of sulfasalazine in maintaining clinical remission (RR 1.14; 95% CI 1.03 to 1.27), with a higher rate or relapse associated with aminosalicylates. [1,2] However, when including only the studies with

outcomes at 12 months or taking the olsalazine trials out of the analysis, there was no difference between sulfasalazine and aminosalicylic acid in maintenance of clinical remission.

- There is moderate quality evidence of less withdrawals due to adverse events with oral 5-aminosaylciates compared to sulfasalazine (RR 0.40; 95% CI 0.24 to 0.69).[1]
- There is moderate quality evidence of no difference between once daily dosing and conventional dosing in failure to induce clinical remission, maintaining clinical remission or adverse events and withdrawals due to adverse events. [1]
- There is moderate quality evidence of no difference between different formulations of oral aminosayliclates in induction of clinical remission (RR 0.94; 95% CI 0.86 to 1.02) or adverse events and withdrawals due to adverse events (RR 0.94; 95% CI 0.57 to 1.54), and low quality evidence of no difference in maintaining clinical remission (RR 1.01; 95% CI 0.80 to 1.28). [1,2]
- There is evidence that higher doses (≥ 3g/day) of aminosalicylate are more likely to induce clinical remission than lower doses. [1]
- There is low quality evidence of no difference in maintenance of remission between rectal and oral formulations of 5-aminosalicylic acid (RR 1.24; 95% CI 0.92 to 1.66; p=0.15) for distal ulcerative colitis.

Recommendations:

- Continue to maintain topical and oral options as preferred on the PDL.
- No further review of research needed at this time and review comparative costs.

Reason for Review:

Routine scan of the literature for new developments.

Background:

Ulcerative colitis is an inflammatory disorder of the gastrointestinal tract that also affects the colorectum.[3] It is a chronic disease that if untreated has a relapsing and remitting course. The goals of treatment are to induce remission and prevent relapse of disease activity, improving quality of life, and avoiding long term consequences. In addition to remission, endoscopic mucosal healing is commonly used as an endpoint in RCTs due to evidence that it is associated with a lower likelihood of disease relapse or colectomy.[3] Mild to moderate flares are often treated with oral or topical aminosalicylates or oral steroids. Evidence has shown that aminosalicylates can induce remission in mild to moderately active disease (NNT 6) and they are the main drugs used to prevent relapse. It is unclear which preparations are most effective and there is insufficient evidence directly comparing the different formulations. The newer 5-aminosalicylic acid preparations were intended to avoid the adverse effects of the older sulfasalazine therapy while maintaining its therapeutic benefits.[1] Overall, they are safe and well tolerated with the most common side effects being headache, abdominal pain, nausea, vomiting, skin rash, and diarrhea. [3] It has also been demonstrated that doses of 2 g or more are more effective in achieving remission compared to doses under 2 g (NNT 11). In patients whose disease is limited to the rectum, topical aminosalicylates can be a useful approach. Guidelines from……. Recommend topical treatment as first line in patients, however; adherence and patient preference should be part of the decision on treatment modality. More severe disease requires treatment with intravenous glucocorticosteriods and biological agents such as infliximab and adalimumab. [3]

Crohn's disease is another type of inflammatory bowel disease. Aminosalicylates are also used to treat Crohn's disease, although they are not FDA approved for this indication. Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the progression of disease and biologics are a mainstay in treatment.[4] However, there is controversy over when biologics should be introduced in the disease course. A top-down therapy approach starts with immunomodulators and biologics early, as opposed to taking them after use of aminosalicylates and corticosteroids (step-up therapy). Further research is needed to review the benefits and harms of step-up versus top-down treatment strategies.

Methods:

A Medline literature search ending March 2014 Week 4 for meta-analyses or randomized active-controlled trials (RCT's) comparing aminosalicylates to each other or to other drugs for the treatment of ulcerative colitis was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A recent systematic review from AHRQ compared the efficacy and safety of agents in the treatment of Crohn's disease through an evaluation of the literature through June 2011.[4] Most of the data were comparing biologic agents to each other or placebo. Five trials evaluated the effectiveness of aminosalicylates as monotherapy to induce remission and 14 trials compared aminosalicylates to placebo in maintaining remission. Overall, there was low strength evidence that aminosalicylates (mesalamine at least 3.2 g daily or sulfasalazine) were more effective than placebo in inducing remission at weeks 16-17. There was also low strength of evidence of a benefit in remission with sulfasalazine compared to placebo at week 104 (risk difference 14%) and that sulfasalazine was more effective than placebo in healing fistulas. For maintaining remission, there was low strength of evidence that mesalamine at 3 to 4 g daily was more efficacious than placebo to maintain remission, and moderate strength of evidence that mesalamine at 2 g daily was not more efficacious than placebo. There was moderate strength of evidence of no difference between olsalazine and placebo in maintaining remission. A pooled analysis comparing aminosalicylates with placebo in remission at weeks 48 to 54 showed no significant difference between sulfasalazine (RR 1.0; 95% CI 0.8 to 1.2), mesalamine (RR 1.1; 95% CI 1.0 to 1.3), mesalamine controlled-release (RR 1.2; 95% CI 1.0 to 1.5) or olsalazine (RR 1.0; 95% CI 0.9 to 1.2).

There was limited evidence evaluating overall safety. There was moderate strength of evidence favoring a combination of prednisone and sulfasalazine over prednisone along for infections (RR 0.3). Overall, there were a number of medications that were effective in inducing and maintaining remission in Crohn's disease, no single medication or class was found to be most effective, provided the best quality of life, or had the best safety profile. Infliximab was the only medication that was consistently more effective than placebo across a number of outcomes for both induction and maintenance of remission.

Two systematic reviews from the Cochrane Collaboration assessed the efficacy and safety of oral aminosalicylates; one for induction of remission in active ulcerative colitis and the other for maintenance of remission.[1,2] A total of 49 studies were identified that measured induction of remission in RCTs and most were of high methodological quality.[1] A random effects analysis demonstrated high quality evidence that fewer patients in the treatment group failed to enter remission compared to placebo (72% vs. 85%;RR 0.86; 95% CI 0.81-0.91; I2=38%; p<0.001) and there was a trend towards greater efficacy with higher doses with

a statistically significant benefit for the 2 to 2.9 g/day (RR 0.87; 95% CI 0.79 to 0.96) and the 3 g or greater per day (RR 0.81; 95% CI 0.74 to 0.88). There was moderate quality evidence of no difference between 5-aminosalicylates and sulfasalazine in failure to entre remission (RR 0.90; 95% CI 0.77 to 1.04; p=0.15). There was moderate quality evidence of no difference in remission between once daily and conventional dosing (RR 0.95; 95%CI 0.82 to 1.10; p=0.49), and no difference in medication adherence (RR 1.36; 95% CI 0.64 to 2.86; p=0.42). When comparing different preparations, there was no statistically significant difference in failure to enter clinical remission between various formulations of 5-aminosalicylate (Balsalzide, Pentasa, Olsalazine, micropellets) and comparator formulations (Asacol, Claversal, and Salofalk), with a RR of 0.95 (95% CI 0.86 to 1.02; p=0.11).

A total of 37 studies were included in the second analysis evaluating maintenance of remission.[2] Similar to previous results, there was high quality evidence of fewer patients failing to maintain remission in the aminosalicylate group compared to placebo (41% vs. 58%; RR 0.69; 95% CI 0.62 to 0.77; p<0.0001; I^2=15%). Sulfasalazine was significantly superior to 5-aminosalicylic acid in the failure to maintain remission (48% vs. 43%; RR 1.14; 95% CI 1.03 to 1.27; p=0.01; NNT -17), based on high quality evidence. When this analysis was limited to studies that measured at 12 months, there was no significant difference (RR 1.10; 95% CI 0.98 to 1.23). Sulfasalazine was shown to be superior to olsalazine in clinical remission (OR 1.20; 95% CI 1.04 to 1.38). There was moderate quality evidence of no difference between once daily and conventional dosing in failure to maintain clinical remission at 6 months (RR 1.02; 95% CI 0.85 to 1.23) and 12 months (RR 0.92; 95% CI 0.83 to 1.03). There was low quality evidence of no difference between different formulations in maintenance of clinical remission at 12 months (RR 1.01; 95% CI 0.80 to 1.28).

There was no statistically significant difference in the incidence of adverse events between treatment and placebo groups (R 0.97; 95% CI 0.85 to 1.11; p=0.65), and no difference in withdrawals due to adverse events (RR 0.88; 95% CI 0.62 to 1.24; p=0.39). However, 5 trials comparing olsalazine to placebo showed a higher proportion of olsalazine patients withdrawn due to adverse events (8.8% vs. 3.3%; RR 2.58; 95% CI 1.16 to 5.70). Patients taking sulfasalazine were more likely to experience an adverse event compared to those on a 5-aminosalicylate (29% vs. 15%; RR 0.48; 95% CI 0.37 to 0.63) and more likely to withdraw due to adverse events (13% vs. 5%; RR 0.40; 95% CI 0.24 to 0.69). However, in the studies measuring maintenance of remission, there was no difference in adverse events or withdrawals due to adverse events (RR 1.27; 95% CI 0.87 to 1.87). There was no overall difference in adverse events or withdraws due to adverse events between the different formulations of mesalamine.

Another Cochrane Collaboration systematic review assessed the efficacy and safety of rectal 5-aminosalicylic acid for maintaining remission of distal ulcerative colitis.[5] Nine studies met inclusion criteria and 6 were rated as low risk of bias. Three studies were rated as high risk of bias due to blinding. There was low quality evidence that rectal delivery was significantly superior compared to placebo for maintenance of remission over 12 months (62% vs. 30%; RR 2.22; 95% CI 1.26 to 3.90; I2=67%; p<0.01). There was also low quality evidence of no significant difference between rectal and oral 5-aminosalicylic acid for remission over 6 months (RR 1.24; 95% CI 0.92 to 1.66; I2=0%; p=0.15). There was no statistically significant difference in the proportion of patients with at least one adverse event or withdrawals due to adverse events (RR 1.04; 95% CI 0.23 to 4.70; p=0.96). There were no trials available comparing rectal aminosalicylic acid to other therapies such as rectal steroids.

New Guidelines:

In 2013, NICE released a clinical guideline for the treatment of ulcerative colitis in adults, children and young people.[6] The following recommendations related to aminosalicylates were provided:

Inducing remission: step 1 therapy for mild to moderate disease:

- For proctitis or proctosigmoiditis:
  - Topical aminosalicylate alone (suppository or enema)
  - Consider adding an oral aminosalicylate to a topical agent OR
  - Consider an oral aminosalicylate alone, based on the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment
- For left-sided or extensive ulcerative colitis:
  - Offer a high induction dose of an oral aminosalicylate or oral aminosalicylate in children and young people
  - Consider adding a topical aminosalicylate or oral beclometasone

Maintaining Remission:

- Consider a once-daily dosing regimen for oral aminosalicylates when used for maintaining remission.

Recent FDA warnings:
None

New Formulations:
A new delayed release formulation of mesalamine 400mg delayed release capsules (Delzicol®) was approved in February 2013 intended to replace mesalamine delayed release (Asacol®). Delzicol was formulated without dibutyl phthalate (DBP), which is associated with safety concerns. Evidence from animal studies suggests that DBP is associated with external and skeletal malformations and adverse effects on the male reproductive system. There is no relevant human safety information available. Delzicol is approved for the treatment of mild to moderate active ulcerative colitis and for the maintenance of remission. Approval was based on a pharmacokinetic and bioavailability study demonstrating bioequivalence to the old formulation. Postmarketing studies in pediatric patients was requested.[7]

Balsalazide (Giazo®) is a new formulation of the oral product balsalzide approved in February 2012 and indicated for mild to moderately active ulcerative colitis in male patients 18 years of age and older. Safety and effectiveness of giazo beyond 8 weeks in adults have not been established and effectiveness in female patients was not demonstrated in clinical trials.[8] This is the only balsalzide product dosed twice daily. It was approved based on two, randomized, double-blind trials; one placebo-controlled and one non-inferiority trial. These have not been published and cannot be assessed for quality. In the first placebo-controlled trial (n=250), the primary endpoint was clinical improvement at 8 weeks, based on the Modified Mayo Disease Activity Index (MMDAI). Clinical improvement was defined by at least a 3 point improvement in MMDAI. There was a significantly greater number of total patients with clinical improvement in the treatment group compared to placebo (55% vs. 40%; p=0.024). However, there was a higher response rate in the placebo arm when looking at female patients only; 54% of female patients in the balsalazide group achieving clinical response and 58% of females in the placebo group. This was significantly different than the treatment effect seen in males (57% in

balsalzide vs. 30% in placebo group; p<0.001). There was also no improvement seen in clinical remission or mucosal healing in the female subset of patients with balsalazide versus placebo. [8]

A second RCT was a non-inferiority study with mesalamine (Asacol) with the primary endpoint again being a reduction of at least 3 points in MMDAI (clinical improvement). In the per-protocol population, 61.7% of patients in the balsalzide group achieved clinical response at week 6 compared to 60.8% in the mesalamine group; with a difference of 0.9%. Results were similar in the modified Intention to treat population as well. FDA reviewers recommended a post marketing trial of female patients to adequately assess the gender differences observed. [8]

Randomized Controlled Trials:

Study information	Comparison	Patient Population	Primary Outcome	Results
D'Haens et al.[9] RCT, DB, non-inferiority trial	Mesalamine once daily (Lialda) vs. twice daily delayed release mesalamine (Asacol) (n-826)	Patients with ulcerative colitis in remission for ≥ 30 days on a stable dose of mesalamine or equivalent of sulfasalazine	Endoscopic remission at 6 months	Endoscopic Remission: Lialda: 83.7% Asacol: 81.5% 95% CI -3.9% to 8.1% Time to Relapse: Lialda: 12.8% Asacol: 14.6% HR 0.87; p=0.5

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Month/Year of Review: May 2014
PDL Classes: Phosphate Binders
New Drug Evaluation: Sucrofferic Oxyhydroxide (Velphoro®)

Date of Last Review: September 2012
Source Document: Provider Synergies
Dossier Received: Yes

Current Status of PDL Class:

- Preferred Agents: CALCIUM ACETATE
- Non-preferred Agents: SEVELAMER (RENAGEL®), SEVELAMER CARBONATE (RENVELA®), LANTHANUM CARBONATE (FOSRENOL®), CALCIUM CARBONATE/ MAG CARB (MAGNEBIND®)

Previous Conclusions & Recommendations:

1. Pediatric safety and efficacy not yet determined.
2. Calcium based binders (based on evidence) especially in infants and younger children may be OK.
3. Sevelamer and calcium based (opinion based) may be ok in older children and adolescents.
4. Lanthanum long-term effect on bone is unclear.
5. Consider step therapy with calcium acetate first then resin based agents.

Background:

Since the previous review of phosphate binders, a new drug with a novel mechanism of action, sucroferric oxyhydroxide has been approved. It has been studied in a phase 2 dose-finding trial, an open-label phase 3 trial comparing it to sevelamer, and a long-term extension study that is unpublished at this time. The phase 3 study showed is non-inferior to sevelamer at reducing serum phosphorus after 12 weeks of treatment. While pill-burden was lower in patients treated with sucroferric oxyhydroxide, patients in either treatment group had adherence rates >70%, the predefined threshold for adherence. The most common adverse reactions were gastrointestinal and mild to moderate in nature.

This updated review also includes data from a meta-analysis published in 2013. This trial compared calcium-based phosphate binders to non-calcium-based phosphate binders. The authors found a 22% reduction in mortality among patients who used non-calcium-based phosphate binders compared to those using calcium-based phosphate binders. Serum phosphate levels were similar across both groups, so it is unclear how treatment with non-calcium-based phosphate binders leads to improved mortality. Mortality benefits were not observed when the non-calcium phosphate binders were evaluated individually. These results align with an open-label Italian trial, which found that sevelamer had a lower incidence of cardiovascular mortality compared to calcium carbonate, although there were many limitations to this trial and results should be interpreted with caution.

The Kidney Disease International: Global Outcomes Clinical Practice Guidelines (KDIGO) recommendations pertaining to phosphate binders have not been updated at this time. The KDIGO guidelines indicate that the choice of phosphate binder should take into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile.

Conclusions and Recommendation:

1. Phosphate binders should be selected based on each patient's specific clinical needs.
2. Consider adding a non-calcium-based phosphate binder to the preferred class, based on cost. There is no evidence that shows that one agent is more effective or safer than an alternative, however there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide.
3. Evaluate comparative costs in executive session.

PA Criteria/QL: Default prior authorization required for non-preferred drugs to ensure that non-preferred drugs are used for an above-the-line condition

Methods:

A MEDLINE OVID search was conducted using all included drugs and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2012 to current. 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. A search for any new evidence demonstrating a benefit in adult indications was also done. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews (no updates since previous review):

Cochrane Collaboration

A systematic review from the Cochrane Collaboration assessed the benefits and harms of phosphate binders in adults with chronic kidney disease (CKD).[1] From a literature search through March 2010, 60 studies (7631 participants) were identified, comparing phosphate binders to placebo or other phosphate binders. There were two independent reviewers who assessed the risk of bias for the included studies, and concluded overall that the study quality varied among the included studies. The following contributed to the overall quality variance: allocation concealment was adequate in approximately 18% of the studies and unclear in others; participants and investigators were blinded in approximately 17% of the studies and outcome assessors were blinded in none of the studies; 22% were analyzed on an intention-to-treat basis; and lost-to-follow-up ranged from 0-31%, but did not differ between the treatment and control groups of the studies. Overall, there was no significant reduction in all-cause mortality (10 studies, 3,079 participants: RR 0.73, 95% CI 0.46 to 1.16) or serum calcium-phosphorus (Ca x P) product with sevelamer hydrochloride compared to calcium-based agents.[1] The Ca x P product has been shown with limited evidence to increase the risk for development of calcification and possibly increase the risk for lower patient survival in CKD if it is >55 mg^2/dL^2.[2] There was a significant reduction in serum phosphorous (16 studies, 3126 participants: MD 0.23 mg/dL, 95% CI 0.04 to 0.42) and parathyroid hormone (PTH) (12 studies, 2551 participants; MD 56 pg/mL, 95% CI 26 to 84), but a significant increase in the risk of hypercalcemia (12 studies, 1144 participants: RR 0.45, 95% CI 0.35 to 0.59) with calcium-based agents compared to sevelamer hydrochloride.[1] There was a significant increase in the risk of adverse gastrointestinal events with sevelamer hydrochloride in comparison to calcium salts (5 studies, 498 participants: RR 1.58, 95% CI 1.11 to 2.25). Compared with calcium-based agents, lanthanum significantly reduced serum calcium (2 studies, 122 participants: MD -0.30 mg/dL, 95% CI -0.64 to -0.25) and the Ca x P product, but not serum phosphorus levels. There was no significant difference in phosphorus levels with calcium acetate in comparison to calcium carbonate (5 studies, 143 participants, MD -0.19

mg/dL, 95% CI -0.61 to 0.24).[1] Authors concluded that all phosphate binders reduce serum phosphorous when compared to placebo, and there is insufficient data to conclude the comparative superiority of novel non-calcium agents over calcium-containing binders for patient centered outcomes of all-cause mortality and cardiovascular end-points in CKD.[1] The primary advantage of more recently developed phosphate binders (lanthanum carbonate and sevelamer hydrochloride) is a reduction in hypercalcemia.

Another Cochrane review from 2010 investigated the benefits and harms of interventions for the prevention and treatment of bone disease in children with CKD.[3] A total of 15 randomized controlled trials (369 children) were identified, but only four studies included phosphate binders as the intervention. Overall, the quality of the evidence was very low for both the comparison of calcium carbonate versus sevelamer and calcium carbonate versus aluminum hydroxide in all measured outcomes because of small patient numbers, large loss to follow-up and risk of bias in study design.[3] The authors concluded that phosphate binders (aluminum hydroxide, calcium carbonate or acetate and sevelamer) had indistinguishable effects in lowering serum phosphate, reducing PTH and on mean height standard deviation score (SDS) but that hypercalcemia was more common with calcium-containing binders.[3]

Meta-Analyses:

A meta-analysis published in 2013 reviewed the effects of calcium-based versus non-calcium based phosphate binders on mortality and included a total of 18 trials (11 randomized trials) with 3,409 patients receiving non-calcium-based phosphate binders (sevelamer or lanthanum) and 4,026 receiving calcium-based phosphate binders (calcium carbonate or calcium acetate).[4] Trials ranged in size from 42 to 2,103 with median duration of follow up between 5 and 44 months. Five of the studies were rated as having a high risk of bias, due to large losses of follow-up, shortage of documentation in key tool domains, inadequate sequence generation, allocation concealment and/or blinding. The analysis of the 11 randomized trials (4622 patients with 939 deaths) found a reduction in all-cause mortality of 22% in the non-calcium-based binders compared with those who received the calcium-based phosphate binders (risk ratio 0.78, 95% CI 0.61-0.98). The mortality difference was only noted in the five trials that reported outcomes at 24 months. The mortality decrease was not statistically significant when the two non-calcium-based phosphate binders were looked at individually. The relative risk of mortality for sevelamer was 0.89 (95% CI 0.78-1.01) and 0.74 (95% CI 0.49-1.13) for lanthanum when compared to those randomly assigned to calcium-based phosphate binders. The mortality difference was not linked to phosphate reduction, due to the near equal phosphate levels in the two groups. While the authors hypothesized that the mortality difference may be due to the slowing of vascular calcification in the non-calcium-based phosphate binders, this has not been shown in clinical trials. Only two trials reported information on cardiovascular events, showing a RR of 0.85 (95% CI 0.35-2.03) for the non-calcium based phosphate binder sevelamer (lanthanum not studied). The meta-analysis was not able to find mortality difference between the 2 different non-calcium-based binders, sevelamer and lanthanum.

A previously-reviewed meta-analysis compared sevelamer and calcium-based phosphate binders (CBPB) on cardiovascular calcification in hemodialysis (HD) patients.[5] It included 14 trials with a total of 3,271 patients.[5] The duration of the trials ranged from 8 weeks to 45 months. The Jadad score was used to assess the quality of the trials, and six out of 14 trials ended up scoring three or more on the score, which is considered a high quality trial.[6] All 14 trials included statements regarding randomization and five of the trials described the detailed methods used for randomization. Four trials reported changes in the coronary artery calcium (CAC) score from baseline, but taken together, there was no significant difference between the sevelamer group and the CBPB group (weighted mean difference -74.87; 95% CI -159.96 to 10.22). The levels of intact parathyroid hormone were significantly higher in the sevelamer groups than in the CBPB group (weighted mean difference 55.85; 95% CI 14.47-97.24). Overall, the authors concluded that the meta-analysis found no significant differences in cardiovascular calcification between sevelamer and CBPB. Sevelamer-treated patients had higher intact parathyroid hormone levels, lower phosphorus levels, lower calcium-phosphorus product, and fewer episodes of hypercalcemia without altering serum calcium.[5]

Guidelines (no updates since previous review):

Kidney Disease International: Global Outcomes Clinical Practice Guidelines (KDIGO)[7]

The most recent guideline published that discusses the use of phosphate binders in CKD is the KIDGO Clinical Practice Guidelines from 2009. The AGREE II guideline appraisal tool was used to assess the overall quality of the KDIGO guidelines.[8] The overall quality of the guidelines was considered six out of seven for highest possible quality, and would be recommended for use. Areas for improvement included the search method (only the Medline search database was used), the evidence and recommendation connection (some of the recommendations were opinions only due to lack of randomized controlled trials), and there was minimal discussion on the influence of the funding body.

The KDIGO guidelines graded the strength of their recommendations by providing levels (level 1=strong evidence; level 2=weak evidence) and grades (A=high quality; B=moderate; C=low; D=very low) for the quality of evidence used to back up their recommendations. The following are the major recommendations:

- For patients with CKD stages 3-5, maintaining serum phosphorous in the normal range is suggested (2.5-4.5 mg/dL) (level of evidence 2C).
- In patients with CKD stage 5D, lowering elevated phosphorus levels toward the normal range is suggested (2C).
- In patients with CKD stages 3-5 (2D) and 5D (2B), using phosphate-binding agents in the treatment of hyperphosphatemia is suggested. The choice of phosphate binder should take into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile (not graded).
- In patients with CKD stages 3-5D and hyperphosphatemia, it is recommended to restrict the dose of calcium-based phosphate binders in the presence of persistent or recurrent hypercalcemia (1B).
- In patients with CKD stages 3-5D and hyperphosphatemia, restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low is suggested (2C).
- In patients with CKD stages 3-5D, avoiding long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication is recommended (1C).
- In patients with CKD stages 3-5D, limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments is suggested (2D).
- In patients with CKD stages 5D, increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia is recommended (2C).

NEW DRUG: SUCROFERRIC OXYHYDROXIDE (VELPHORO)

Background:

Sucroferric oxyhydroxide was approved in November 2013 for controlling phosphorus levels in patients with chronic kidney disease on dialysis. It's an iron-based phosphate binder and is available as a flavored, chewable tablet that can be taken without water.

INDICATION	DOSAGE FORM	DOSE	MECHANISM OF ACTION
Control of serum phosphorus levels in patients with chronic kidney disease on dialysis	500mg chewable tablets	1,500mg daily (divided with 3 meals). Adjust by 1 tablet per day as needed until an acceptable serum phosphorus level (</= 5.5 mg/dL). Titrate	Ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and the phosphate in the dilate. The bound phosphate is eliminated with feces. Serum phosphorus

		as often as weekly.	and calcium-phosphorus levels are reduced.

Efficacy:

The efficacy and safety of sucroferric oxyhydroxide was evaluated in three clinical trials: a phase 2 dose-finding study, a phase 3 randomized trial, and a long-term extension study.

The Phase 2 dose-ranging study was a parallel-group, randomized, open-label, active-controlled, trial, comparing five dosage regimens of sucroferric oxyhydroxide. Subjects (n=150) were receiving dialysis three times per week for ≥3 months and had a serum phosphorus >5.5mg/dL. Subjects were randomized to receive one of the following regimens: 1.25, 5, 7.5, 10, or 12.5 g/day. Those randomized to the control group received 4.8 g/day of sevelamer. After 6 weeks of treatment, a dose dependent response was observed, with the highest responses observed in patients receiving 10 or 12.5 g/day. The 5 and 7.5mg doses resulted in a response similar to that of sevelamer, but the study was not designed to directly compare the different treatment options. Adverse events were considered mild to moderate and not dose dependent, with a 10.9% discontinuing treatment due to adverse events.[9,10]

A Phase 3, open-label, active controlled trial, compared sucroferric oxyhydroxide to sevelamer in patients with chronic kidney disease, undergoing dialysis. Of the 1,059 subjects included in the trial, 1,041 were included in the full analysis set, as they had received at least one dose of study medication and had at least one post baseline evaluable efficacy assessment. Patients were treated for 24 weeks total (8 weeks of dose titration, 4 weeks with no dose change, 12 weeks maintenance). After 24 weeks, patients were randomized to a maintenance dose (MD) or a low-dose (LD) control of 250 mg/day of sucroferric oxyhydroxide and assessed at week 27. The primary efficacy endpoint was the superiority of MD compared to LD. Change in serum phosphorus after 12 weeks of treatment was evaluated as a secondary endpoint. Adherence was measured, but a formal comparison was not conducted.[9,11]

After 12 weeks of treatment, sucroferric oxyhydroxide was non-inferior to sevelamer for change in serum phosphorus levels (-0.71 mmol/L vs -0.79 mmol/L, respectively). After 24 weeks, mean serum phosphorus concentrations were similar for patients receiving MD and LD sucroferric oxyhydroxide, 1.5 mmol/l and 1.6 mmol/l, respectively. Patients treated with LD sucroferric oxyhydroxide experienced a significantly larger increase in serum phosphorous levels after 3 weeks ($p<0.001$). More patients experienced at least one treatment emergent adverse event TEAE) in the sucroferric oxyhydroxide -treated group, versus those in the sevelamer-treated group (83.2% vs 76.1%). The most commonly reported adverse events were diarrhea, discolored stools, and hyperphosphatemia. Severe TEAE's were infrequent and similar between the two groups (1% vs 1.1%). There was a higher incidence of TEAEs leading to withdrawal in the sucroferric oxyhydroxide group (15.7%) versus the sevelamer group (6.6%). On average, patients in the sucroferric oxyhydroxide group took 3.1 tablets per day, compared to 8.1 in the sevelamer group, and both groups were considered to be adherent (82.6% in the sucroferric oxyhydroxide group vs 77.2% in the sevelamer group), as indicated by the pre-specified threshold of 70%.[9,11]

Aside from the limitation of the open-label trial design, the starting sucroferric oxyhydroxide treatment regimen consisted of twice daily dosing. Patients receiving this treatment were initially experiencing at least one meal without a phosphate binder until the dose was increased to three times daily, the current FDA-approved dose. Many of the patients (38%) had received prior treatment with sevelamer and may have grown accustomed to side effects prior to the study, impacting the perception of TEAEs.

Patients who completed this study were eligible for inclusion in a Phase 3, unpublished, long-term extension study where they were treated for an additional 28 weeks (total of 52-56 weeks). This study enrolled 659 subjects, 83.3% of which completed the study. Subjects continued the same treatment they were initially randomized to, however doses ranged from 5-15 g/day in the sucroferric oxyhydroxide group and 2.4-14.4 g/day in the sevelamer group. After 12 months of treatment, the safety profile was comparable between the two treatment groups. The most common adverse events in the sucroferric oxyhydroxide group were gastrointestinal (52.5% in the sucroferric oxyhydroxide group, 42.8% in the SEV group). No deaths were considered related to study treatment. Serum phosphorus levels were maintained over the 28 weeks and were comparable between the two treatment groups.[9]

OTHER NEW TRIAL(S):

Sevelamer was compared to calcium carbonate in a 466 subject randomized, open-label, multicenter study over a 36 months. The primary outcome was cardiovascular death due to arrhythmias in adult patients with CKD stage 5 on dialysis. Patients were recruited from 18 centers in Italy. Subjects were randomized 1:1 to receive sevelamer (n=232) or calcium-containing phosphate binder (n=234), all of which received calcium carbonate. The average baseline serum phosphorus was higher in the sevelamer group (mean, 5.6± 1.7 [SD] vs 4.8± 1.4 mg/dL). Investigators were allowed to adjust study drug doses in order to reach a target serum phosphorus level of 2.7-5.5 mg/dL. At the end of the study sevelamer had lower serum phosphate levels (4.2± 1.2; -1.37 ± 1.93 change from baseline; p<0.001) compared to calcium carbonate (4.8± 1.1; -0.10± 1.67 change from baseline; p=0.4). The average median dosage of sevelamer was 4,800 mg/d and 2,000 mg/d of calcium carbonate. Subjects in the sevelamer group had a lower incidence of cardiovascular mortality due to cardiac arrhythmias compared to the calcium carbonate group (HR, 0.06; 95% CI, 0.01-0.25; P<0.001). There were 2 cardiovascular deaths due to cardiac arrhythmias in the sevelamer group and 27 in the calcium carbonate group. The study was limited by the fact that there was a much greater drop in serum phosphorous levels in the sevelamer group, the study was open-labeled, there was a higher baseline coronary artery calcification burden in calcium carbonate-treated patients, and there was a lower than expected mortality rate.[12]

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
Wuthrich, et al. RCT, OL, AC, Phase 2[10]	Sucroferric oxyhydroxide (SUC): 1.25 g/day 5 g/day 7.5 g/day 10 g/day 12.5 g/day Sevelamer (SEV): 4.8 g/day	Hemodialysis patients with serum phosphorus concentrations >5.5mg/dL n=154	Serum phosphorus after 6 weeks of treatment	<u>Treatment weeks:</u> <u>Δ in serum phosphorous at 6</u> SUC: 1.25 g/day -0.13 mg/dL (not significant) 5 g/day -1.08 mg/dL (p=0.02) 7.5 g/day -1.25 mg/dL (p=0.003) 10 g/day -2.00 mg/dL (p=0.003) 12.5 g/day -1.69 mg/dL (p=0.003) SEV: 4.8 g/day -1.06 mg/dl (p=0.003)
Floege et al. RCT, OL, AC, Phase 3[11]	Sucroferric oxyhydroxide low dose (LD) vs maintenance dose (MD) sevelamer carbonate studied for secondary endpoint (SEV)	Hemodialysis at least 3x per week or PD for at least 3 months and serum phosphorus concentrations >/= 1.94 mmol/l	Change in serum phosphorous from week 24-27	<u>Δ in serum phosphorous from week 24-27</u> LD: +0.6 mmol/l MD: Not reported in study P<0.001 <u>Δ in serum phosphorous at 12 weeks:</u> SUC: -0.71 mmol/l SEV: -0.79 mmol/l P-value not reported
Di Iorio et al. RCT, OL[12]	Sevelamer Calcium-containing phosphate binder (all patients received calcium carbonate)	Hemodialysis patients that were recruited from 18 centers in Italy.	Cardiovascular death due to cardiac arrhythmias. 24 month intervention phase and patients were followed for 36 months.	<u>CV mortality due to cardiac arrhythmias</u> Sevelamer compared to calcium carbonate (HR, 0.06; 95% CI, 0.01-0.25;P<0.001). <u>Δ in serum phosphorous from baseline:</u> SEV: -1.37 mg/dL P<0.001 Calcium carbonate: -0.1 mg/dL P=0.4

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Abbreviated Update: Oral Antiepileptic Drugs

Month/Year of Review: July 2014
End date of literature search: Week 2, April 2014
New drug(s): Eslicarbazepine (Aptiom™)
Manufacturer: Sunovion Inc.

Current Status of PDL Class: See Appendix 1

Research Questions:

- Is there any new relative evidence from high quality systematic reviews or evidence-based guidelines suggesting recommended changes to the current PDL class?
- Is eslicarbazepine more effective than currently available agents?
- Is eslicarbazepine safer than currently available agents?
- Are there unique patients or situations where eslicarbazepine may be more effective or safer than currently available agents?

Conclusions:

- There were no new comparative systematic reviews or evidence-based guidelines identified on which to recommend changes to the current PDL class.
- FDA safety communications indicate that all valproate products are now contraindicated for pregnant women[1] and ezogabine has a new Boxed Warning about the risk of permanent retinal abnormalities, vision loss and skin discoloration with its use. [2]
- There is insufficient comparative efficacy and safety evidence for eslicarbazepine versus other AEDs.
- There is high level of evidence[3] eslicarbazepine is associated with overall ≥50% reduction in seizure frequency (RR 1.86 95% CI 1.46-2.36) over placebo when added on to current therapy for drug-resistant partial epilepsy but patients on eslicarbazepine were more likely to withdraw for adverse events (RR 2.26 95% CI 0.98 to 5.21).

Recommendations:

- Consider additional safety prior authorization (PA) criteria for ezogabine and pregnancy PA criteria for valproate drugs.
- No further research required at this time. Evaluate comparative costs in executive session.

Reason for Review:
In May 2012, the Oregon Pharmacy & Therapeutic Committee (P&T) evaluated the comparative effectiveness evidence of the oral anticonvulsants. Since this review, the Food and Drug Administration (FDA) approved eslicarbazepine (Aptiom™) as adjunctive treatment of partial-onset seizures.[4] Eslicarbazepine's mechanism of action is theorized to reduce seizures by inhibiting voltage-gated sodium channels.[4]

Previous P&T Conclusions and Recommendations (May 2012[5,6,7]):

- There is insufficient evidence to make comparative conclusions about adjunctive treatments for epilepsy.
- Updated NICE guidelines[8] recommend carbamazepine or lamotrigine as first line agents for focal seizures (moderate to very low quality evidence) and sodium valproate as first line treatment for tonic-clonic seizures (low to very low quality evidence).
- Based on a recent AHRQ review,[9] there is insufficient to low strength of evidence suggesting that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same medication increases the short-term risk of hospitalization and hospital stay duration and increases the short -term risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization.
- Recommendations were to consider inclusion of all the chemical entities for epilepsy diagnoses but prefer generic alternatives and forms where appropriate and "grandfather" stabilized patients rather than force a change to preferred agents.
- Subsequent New Drug Evaluations have recommended second and third line agents be designated non-preferred (i.e. clobazam, perampanel, ezogabine, felbamate).

Background:
Epilepsy is a common neurological disorder characterized by two or more seizures that are not precipitated by other causes.[10] Antiepileptic drugs (AEDs) to prevent recurrence of seizures are the mainstay of treatment.[8] The overall goals of antiepileptic therapy are to prevent seizures. Reduction in seizure frequency of 50% or more is generally accepted as demonstrating efficacy for FDA approval.[4] When initial drugs have failed and adjunctive treatment is used seizure reduction is likely to be the primary aim.[9] Drug selection is based upon epileptic syndrome, seizure type, the adverse effect profile and patient preference.[8] Despite approximately half of newly diagnosed epileptics being successfully treated with the first AED, treatment failure and drug intolerance can occur. Monotherapy is more likely to promote compliance, reduces potential for drug interactions and is less costly but may not keep a patient seizure free. There are no controlled trials comparing different combinations of AEDs.[12]

Methods:
A Medline literature search through April 2014, week 2, for new systematic reviews that compared AEDs head-to-head for the treatment of epilepsy or randomized controlled trials (RCT's) evaluating eslicarbazepine for the treatment of epilepsy was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date 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.

New Guidelines:
None identified.

New Systematic Reviews:
No new comparative systematic reviews were identified.

New Safety Information:

Suicide:
In 2009, the FDA issued an alert warning of increased risk of suicide ideation and behavior in patients treated with selected AEDs.[13] A expert consensus statement on this issue was recently published by the ad hoc task force of the Commission on Neuropsychobiology and the International League Against Epilepsy.[14] It notes that the risk of actual suicide is very low.[14] The FDA reports the rate as: AED 0.43% versus placebo 0.24%.[13] The consensus statement stresses that this low absolute risk be balanced with the risks of refusing or stopping AEDs, though the risk was not quantified.

Valproate:
The FDA issued a safety alert for all valproate related products notifying providers that they are contraindicated and should not be taken by women for migraine prophylaxis because it can cause diminished IQ scores in the children born to these mothers.[1] The labeling now indicates these are pregnancy category "X" (from "D").

Ezogabine:
The FDA approved Boxed Warning labeling changes for ezogabine that emphasize the risk of permanent retinal abnormalities, vision loss and skin discoloration with its use. It is to be limited to patients that have not responded adequately to several alternative therapies. Those on ezogabine should be monitored every 6 months for retinal changes by an ophthalmic professional.

Clobazam:
The FDA issued a safety alert for clobazam warning the public that it can cause rare Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). It can happen at any time during treatment but the likelihood is greater in the first 8 weeks of treatment. All 21 reported cases have resulted in hospitalization, one in blindness and one in death. Nineteen cases were associated with other drugs known to be associated with SJS/TEN; however there was a close temporal relationship to initiation of clobazam.

New Drug Evaluation: Eslicarbazepine:

Eslicarbazepine was approved by the FDA November 8, 2013 for adjunctive treatment of partial-onset seizures in adults (see Appendix 2: Specific Drug Information). It was approved by the European Medicines Agency in 2009 based upon 3 phase III studies.[15,16,17] In 2009, the FDA recommended the application not be approved due to "…profound and extensive deficiencies in the conduct and documentation of the studies,…".[4] For this reason, upon resubmission in 2012, the sponsor dropped 303 [NCT00957372].[4] Three studies (301[NCT00957684],[15] 302[NCT00957047],[18] 304[NCT00988429][4]) were considered supportive for the proposed indication. A pooled analysis of 301, 302 and 303 (the study that was dropped in the FDA submission) was recently published but excluded from this evaluation.[19] No active controlled trials were identified.

Cochrane[3] published a systematic review of RCTs of eslicarbazepine versus placebo for adjunctive therapy for drug-resistant partial epilepsy. It included 4 trials[15,18,16, 17] and 1146 patients. The background AED therapy was not described in the systematic review. The overall RR for ≥50% reduction in seizure frequency was 1.86 95% CI 1.46 - 2.36. Patients on eslicarbazepine were more likely to withdraw for adverse events (RR 2.26 95% CI 0.98 - 5.21). The review concluded that eslicarbazepine reduces seizure frequency when used as add-on for drug-resistant partial epilepsy but that the trials were of short-term duration (12-18 weeks) and included adults only. No additional, blinded and published RCTs were identified. Two open-label extension studies have been published but were excluded from this evalutation.[20,21]

Safety was assessed from a database of 4225 patients who were exposed to eslicarbazepine in 53 studies (n=847 healthy volunteers, n=1553 in patients with partial epilepsy, n=1832 in non-epilepsy patients).[4] Rare serious adverse events are similar to other drugs in the class (i.e. suicidal ideation, SJS/TEN, drug reaction with eosinophilia and systemic symptoms, anaphylaxis, hyponatremia, neurological disturbances and hepatic injury. Patients should be tapered off eslicarbazepine to minimize the risk of seizures. There were dose dependent decreases in T3 and T4 serum test but the changes were not associated with other abnormal thyroid function tests.

The NICE guidelines[8] recommend eslicarbazepine as third-line for partial epilepsy.

There is potential for off-label uses as the FDA noted 36 studies were submitted with the first application and 17 new studies with the approved submission.[4] Clinicaltrials.gov lists 28 studies involving eslicarbazepine (a.k.a. BIA-2093); 3 Phase II for Bipolar I, 3 for diabetic neuropathic pain (1 each Phase I, II, III), 1 Phase II for migraine prophylaxis, 1 Phase II for Fibromyalgia, 2 (1 each Phase I, II), and 2 for post-herpetic neuralgia (1 each Phase II, III) and 18 for Epilepsy or Partial Epilepsy (8 Phase I, 2 Phase II, 9 Phase III, 1 Phase IV and 1 unknown).

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Appendix 1 – Current PDL Status

Preferred	
GENERIC NAME	**FORM**
CARBAMAZEPINE	ORAL SUSP
CARBAMAZEPINE	TAB CHEW
CARBAMAZEPINE	TAB ER 12H
CARBAMAZEPINE	TABLET
DIVALPROEX	CAP SPRINK
DIVALPROEX	TAB ER 24H
DIVALPROEX	TAB DR
ETHOSUXIMIDE	CAPSULE
ETHOSUXIMIDE	SOLUTION
ETHOTOIN	TABLET
GABAPENTIN	CAPSULE
LACOSAMIDE	TABLET
LAMOTRIGINE	TABLET
LEVETIRACETAM	SOLUTION
LEVETIRACETAM	TABLET
METHOSUXIMIDE	CAPSULE
OXCARBAZEPINE	ORAL SUSP
OXCARBAZEPINE	TABLET
PHENOBARBITAL	ELIXER
PHENOBARBITAL	TABLET
PHENYTOIN	ORAL SUSP
PHENYTOIN	TAB CHEW
PHENYTOIN EXTENDED	CAPSULE
RUFINAMIDE	TABLET
TIAGABINE	TABLET
TOPIRAMATE	TABLET
VALPROIC ACID	CAPSULE
VALPROIC ACID	SOLUTION
ZONISAMIDE	CAPSULE

Non-Preferred	
GENERIC NAME	**FORM**
CARBAMAZEPINE	CPMP 12 HR
CLOBAZAM	ORAL SUSP
EZOGABINE	TABLET
FELBAMATE	ORAL SUSP
FELBAMATE	TABLET
GABAPENTIN	SOLUTION
GABAPENTIN	TABLET
LACOSAMIDE	SOLUTION
LEVETIRACETAM	TAB ER 24H
OXCARBAZEPINE	TAB ER 24H
PERAMPANEL	TABLET
PREGABLIN	SOLUTION
PREGABLIN	CAPSULE
RUFINAMIDE	ORAL SUSP
TOPIRAMATE	CAP ER 24H
TOPIRAMATE	CAP SPRINK
VIGABATRIN	POWD PACK
VIGABATRIN	TABLET
LAMOTRIGINE	TAB ER 24H
LAMOTRIGINE	TAB RAPIDIS
LAMOTRIGINE	TB CHW DSP
LAMOTRIGINE	TB ER DSPK
LAMOTRIGINE	TB RD DSPK
VALPROIC ACID	CAPSULE DR

Appendix 2: Specific Drug Information[4]

CLINICAL PHARMACOLOGY: Eslicarbazepine is a novel, once daily AED thought to reduce seizures by inhibition of the voltage-gated sodium channels. It is chemically related to carbamazepine and oxcarbazepine but does not inhibit most P450 enzymes, thus has reduced risk of drug-drug interactions. Clearance is dependent on renal function.

PHARMACOKINETICS:

Parameter	Result
Oral Bioavailability	91% after first-past metabolism to active form
Protein Binding	<40%
Elimination	90% & glucoronide conjugates excreted in urine; other 10% of minor metabolites excreted in urine
Half-Life	13-20 hours; steady-state in 4-5 days
Metabolism	hydrolytic first-pass to active metabolite (eslicarbazepine from acetate salt)

DOSE & AVAILABILITY:

AVAILABLE STRENGTH	FORM	FREQUENCY	RENAL ADJ	HEPATIC ADJ	PED DOSE	GER DOSE	OTHER
200MG 400MG 600MG 800MG	TABLET (DO NOT CRUSH)	Initiate at 400mg QD x 7 days then increase to 800mg QD. Maximum: 1200mg QD (after minimum of 1 week at 800mg QD)	CrCl <50ml/min: Initiate at 200mg QD x 14 days then increase to 400mg (recommended maintenance)	NA	NA	NA	Taper required for discontinuance. Pregnancy Category: C

DRUG SAFETY:

Serious (REMS, Black Box Warnings, Contraindications): None.

Warnings and Precautions: Suicidal Behavior and Ideation, Serious Dermatologic Reactions, Drug Reaction with Eosinophilia and Systemic Symptoms, Anaphylactic Reactions and Angioedema, Hyponatremia, Neurological Adverse Reactions (e.g. dizziness, disturbance of gait, somnolence, etc.), Drug Induced Liver Injury.

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Month/Year of Review: May 2014
PDL Class: Bone Metabolism Agents for Osteoporosis or Paget's Disease

Date of Last Review: September 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: ALENDRONATE TABLET, IBANDRONATE TABLET, RISEDRONATE TABLET
- Non Preferred: CALCITONIN INH, CALCITONIN SQ/IM, ETIDRONATE, IBANDRONATE (IV), RISDRONATE DR, TERIPARATIDE SQ, RALOXIFENE, DENOSUMAB, ZOLEDRONIC ACID IV, TILUDRONATE

Current PA Criteria: Appendix 1: Non-preferred drugs require PA to ensure appropriate drug use and safety of bone resorption suppression agents by authorizing utilization in specified patient populations.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of bone metabolism agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Previous Recommendations:

- Consider inclusion of denosumab, zoledronic acid, risedronate, alendronate in various routes and dosing schedules for osteoporosis treatment based upon cost.
- Include at least one nitrogen-containing bisphosphonate for Paget's Disease **(**zoledronic acid, pamidronate, risedronate, alendronate or ibandronate).
- Make calcitonin, raloxefene and teriparatide non-preferred due to limited evidence to reduce non-vertebral and hip fracture risk in post-menopausal women. Calcitonin has limited evidence for Paget's Disease.
- Make tiludronate non-preferred as it is only indicated for Paget's, is not a nitrogen containing bisphosphonate and it has insufficient evidence for osteoporosis treatment.
- Consider a RetroDUR intervention of bisphosponates to notify clinicians to re-evaluate patient FRAX score after 5 years of therapy.

Conclusions:

- There is no new comparative evidence that changes the previous conclusions.
- No further review of research needed at this time and review comparative costs.

Previous Conclusions:

- The comparative efficacy and safety of treatments has not been assessed for men with osteoporosis.
- There is high strength evidence that specific bisphosphonates (zoledronic acid, risedronate, alendronate) and denosumab reduce the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. No other drugs reduce all three fracture risks.
- There is insufficient or no data to distinguish superiority of any bisphosphonate, or bisphosphonates superior to other drugs for reduction in vertebral fracture risk in postmenopausal women. Evidence for etidronate, ibandronate, pamidronate have not been shown to reduce non-vertebral fractures in post-menopausal women. There is insufficient evidence for tilundronate for osteoporosis treatment.
- There was high strength evidence that the incidence of osteonecrosis of the jaw in patients taking bisphosphonates was low (<1-28 cases in 100,000 person years). Low strength evidence associated bisphosphonate use with atypical femur fractures and insufficient evidence associated bisphosphonate use to esophageal cancer and atrial fibrillation.
- There is high strength evidence of increased risk of infection with denosumab compared to placebo.
- There is high strength evidence that raloxifene increases the odds of pulmonary embolism, thromboembolic events and cerebrovascular accidents compared to placebo.
- Nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate are ibandronate) are considered first-line therapy for Paget's Disease treatment. There is insufficient evidence to distinguish superiority of any nitrogen-containing bisphosphonate.

Reason for Review:

Routine scan of the literature for new developments.

Background:

Osteoporosis is a skeletal disease of decreasing bone mass resulting in diminished bone strength and increased risk of fractures.[1] Multiple mechanisms are responsible including old age, sex steroid deficiency, lipid oxidation, decreased physical activity and use of glucocorticoids. Throughout life, older bone is resorbed by osteoclasts and replaced with new bone made by osteoblasts.[1] This process is known as remodeling and is orchestrated and targeted to a particular site that is in need for repair by osteocytes.[1] When this system is out of balance, bone loss occurs.[2] In the past decade, the master signals that regulate this process have been defined. The receptor activator of nuclear factor kappa-B ligand (RANKL) is a key signal that increases bone loss and has become a prime target for the treatment of osteoporosis.[3]

Bone mineral density (BMD) assessed with dual x-ray absorptiometry (DXA) is a surrogate marker used to diagnose osteoporosis. A patient is considered to have osteoporosis with a BMD T-score of less than 2.5 standard deviations below the average of a young adult.[3] BMD can be used in conjunction with the World Health Organization fracture-risk assessment tool (FRAX) to estimate an individual's 10-year risk of sustaining a hip fracture or other osteoporotic fractures.[3] The life-time fracture risk of a patient with osteoporosis is as high as 40% and fractures of the hip, spine or wrist the most common locations.[3] The National Osteoporosis Foundation estimates more than 10 million people have osteoporosis with 50% of Caucasian women with a lifetime risk of fracture and 20% of men.[2] The primary goal of osteoporosis management is to reduce fracture risk.

Drugs to treat osteoporosis fall into two groups, the anti-resorptive drugs, which slow down bone resorption, and anabolic drugs, which stimulate bone formation. The anti-resorptive drugs include bisphosphonates, raloxifene, calcitonin and the new IgG2 monoclonal antibody, denusomab, which suppresses the RANKL pathway. Parathyroid hormone increases bone formation and is the only anabolic drug. All drugs require adequate serum levels of calcium and vitamin D for optimum effect. Bisphosphonates are considered first line[4] therapy but short-term tolerability and potential long-term risk of atypical femur fracture, osteonecrosis of the jaw and esophageal cancer have left patients and clinicians looking for other options.[5]

Paget's Disease is a disorder of bone metabolism that includes an accelerated rate of bone remodeling, resulting in overgrowth of bone at selected sites and impaired integrity of affected bone.[6] It is a fairly common finding in aging bone, with estimates ranging from 2.3 - 9% in older patients within affected populations.[7] Many patients with Paget's Disease are asymptomatic but others exhibit pain and deformities.[6] Fractures, bone tumors, neurologic disease, cardiac disease, and abnormalities in calcium and phosphate balance can also occur.[6] The goals of treatment are to reduce pain, normalize bone remodeling and slow disease progression.[6] The newer nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate and ibandronate) are first-line for the initial treatment of Paget disease.

Methods:
A Medline literature search ending March 2014 Week 4 for meta-analyses or randomized active-controlled trials (RCT's) comparing bisphosphonates to each other or to other osteoporosis drugs for the treatment of osteoporosis or Paget's Disease was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Murad et al.[8] published a network meta-analysis of drug treatments to prevent fragility fractures. The systematic review included RCTs through December 2011 that enrolled patients at risk for fragility fractures treated with bisphosonates, teriparatide, selective estrogen receptor modulators, denosumab or calcium and vitamin D. Studies were evaluated for quality by two independently working reviewers and determined to be of low to moderate risk of bias but imprecise due to the small number of fracture events overall. Teriparatide, bispohosphonates and denosumab were the most effective in reducing the risk of fragility fractures. Raloxifene was less effective. But, differences in efficacy across the drugs was small (e.g. Hip Fracture OR 0.42 95% CI 0.1-1.82 for teriparatide versus 0.45 95% CI 0.27-0.68 for alendronate). Calcium and vitamin D were only effective in combination to reduce hip fracture risk (OR 0.81 95% CI 0.68-0.96).

CADTH published a rapid review of denosumab and zoledronic acid for postmenopausal osteoporosis who have failed or discontinued previous bisphosphonate therapy.[9] The literature search included all study designs published between January 2007 and May 2012. Studies were appraised using established quality appraisal methods. The drugs were found safe and effective for patients who were intolerant or failed bisphosphonates based upon BMD outcomes but they could not rule out residual bisphosphonate activity in all studies.

A non-systematic review of osteoporosis treatment in men identified RCTs evaluating bisphosphonates, denosumab and teriparatide effect on vertebral and non-vertebral fractures.[10] Alendronate, risedronate, zoledronic acid and teriparatide each have evidence of vertebral fracture reduction when used as primary prevention in men with osteoporosis. Denosumab evidence of vertebral fracture reduction is limited to those with secondary osteoporosis from androgen deprivation therapy.

A meta-analysis used adjusted indirect comparisons and mixed treatment comparison methods to compare treatments in the absence of head-to-head trials. It identified RCTs published through November 4, 2009 that evaluated osteoporosis drugs with fracture outcomes. The trials were reviewed for quality using Jadad scoring. Thirty-four studies met inclusion criteria. The authors compared denosumab to individual bisphosphonates, raloxifene and teriparatide. It was not statistically different than any comparator for clinical vertebral or non-vertebral fractures. It was statistically better than raloxifene, alendronate, risedronate and bisphosphates as a group if the outcome was restricted to new vertebral fractures. The clinical significance of this statistically determined difference is limited by the assumptions of the model and the selection of studies for inclusion and should be interpreted cautiously.

New Guidelines:

The American College of Obstetricians and Gynecologists published a Practice Bulletin on osteoporosis management in September 2012.[11] This is a comprehensive treatment guideline for women. Bisphosphonates are recommended first line but raloxifene is an alternative for younger postmenopausal women also wanting breast cancer protection. It is recommended that bisphosphonate selection be based only patient preference for route of delivery and insurance coverage. Denosumab is recommended for high risk patients unable to tolerated bisphosphonates. Teriparatide is reserved for severe osteoporotic patients who have experienced fractures. Calcitonin is not recommended except for lower risk patients unable to tolerate bisphosphonates. Combination therapy is not recommended. Bisphosphonate treatment interruption should be considered after 5-10 years of use.

Osteoporosis International published the European Guidelines in October 2012.[12] Much of the guideline focuses on fracture risk assessment. The guidelines identify alendronate, risedronate, zoledronic acid and denosumab with evidence of reducing vertebral and non-vertebral fracture. Alendronate is recommended first-line based upon cost.

The Endocrine Society published clinical guidelines for Osteoporosis in Men in June 2012.[13] The guidelines recommend selection of and FDA approved agent for men (alendronate, risedronate, zoledronic acid or teriparatide) be individualized based upon severity of osteoporosis, comorbid conditions and cost. Men with recent hip fracture are recommended zoledronic acid. Denosumb is recommended only for men receiving androgen deprivation therapy.

Recent FDA warnings:

In April 2013[14] all bisphosphonate drugs underwent labeling changes to include the risk of osteonecrosis of the jaw may increase with duration of exposure and that there has be post-marketing reports of asthma exacerbations. There have been fatal cases of anaphylaxis reported with the use of ibandronate injection.

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Appendix 1 – Current PA Criteria:

Bone Resorption Suppression and Related Agents

Goal(s):

- To ensure appropriate drug use and safety of bone resorption suppression agents by authorization utilization in specified patient populations.

Initiative:

- Prior Authorization

Length of Authorization: Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPH; Deny, (Not covered by the OHP)

Approval Criteria		
3. 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 Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform provider of covered alternatives in class.	No: Go to #4.
4. Is the request for raloxifene (Evista)?	Yes: Go to #5.	No: go to #6.
5. Is the patient pregnant and/or at increased risk of thromboembolism or stroke?	Yes: Deny (Medical Appropriateness). Inform provider of pregnancy category X and black box warning of thromboembolism and stroke risk.	No: Approve for shorter of 1 ear or length of prescription.
6. Is the request for teriparatide (Forteo) and is the patient at high risk for fractures? Examples include: • Postmenopausal women with osteoporosis • Men with primary or hypogonadal osteoporosis • Osteoporosis associated with sustained glucocorticoid therapy	Yes: Go to #7	No: Go to #8
7. Is the patient also taking a bisphosphonate, a pediatric or young adult patient with open epiphyses, at increased risk of osteosarcoma or a history of skeletal malignancies, metabolic bone disease, underlying hypercalcemic disorders, or unexplained elevations of alkaline phosphatase?	Yes: Deny, (Medical Appropriateness)	No: Approve for shorter of 1 year or length of prescription
8. RPH Only All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.	If above the line and clinic provides supporting literature: approve for length of treatment	If below the line: Deny (Not covered by the OHP).

P&T / DUR Action: 9/16/10 (KS)
Revision(s):
Initiated: 1/1/11

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Month/Year of Review: May 2014 **Date of Last Review:** June 2012
PDL Class: Erythropoeiesis Stimulating Agents **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: DARBEPOETIN ALFA, EPOETIN ALFA (EPOGEN® - BRAND ONLY)
- Non Preferred: EPOETIN ALFA (PROCRIT®), PEGINESATIDE (OMONTYS®)

Previous Conclusions:

- For ESA treatment of CKD anemia, there is no target Hb level that is considered at less risk for death, serious cardiovascular events or stroke. Recommendations are to use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions. There are no differences in efficacy or safety between the epoetin and darbepoetin.
- For ESA treatment of chemotherapy induced anemia there is evidence of higher mortality, tumor progression and higher thromboembolic events associated ESA therapy. The majority of these trials targeted Hb targets > 12 g/dl. Both American and European updated treatment guidelines caution that ESA initiation should incorporate patient preferences for risk and benefit. The lowest ESA dose to prevent transfusion should be used. Non-responders should discontinue ESA after 6-8 weeks. There are no differences in efficacy or safety between the epoetin and darbepoetin.
- There is insufficient evidence to assess efficacy and safety of peginesatide relative to epoetin or darbepoetin.

Previous Recommendations:

- There is no evidence of a difference in safety or efficacy between darbepoetin and epoetin and preference can be established on cost.
- Recommend listing peginesatide as non-preferred until more safety and efficacy data are available.
- Recommend modify the initial approval lengths for CKD associated anemia and chemotherapy induced anemia to 12 weeks to assess adequate response in concurrence with the Oregon Health Plan (OHP) list of covered services.
- Recommend the Health Evidence Review Commission reevaluate OHP guideline note 7. FDA labeling and current practice is 12 weeks.

PA Criteria: All ESAs require PA for clinical appropriateness according to OHP guidelines and current medical literature and to preferentially cover preferred products when feasible. Requests are authorized for 12 weeks initially, then up to 12 months with a quantity limit of 30 days per dispense. See Appendix 1.

Conclusions:

- Peginesatide was removed from the market in February 2013 due to 19 reports of anaphylaxis following first dose (including 3 deaths) in patients receiving dialysis. It is recommended it be removed entirely from the PDL.
- There is no new comparative evidence that changes the previous conclusions.
- No further review of research needed at this time and review comparative costs.

Methods:

A Medline literature search ending March Week 4 2014 for meta-analyses, systematic reviews or randomized active-controlled trials (RCT's) comparing erythropoietin to darbepoetin for treatment of anemia. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews and RCTs. The FDA website was searched for background information from advisory committees, new indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. .

New Systematic Reviews and Guidelines

CKD:

The 2012 Kidney Disease Improving Global Outcomes (KDIGO)[1] guidelines recommend initiating ESA only for patients with hemoglobin <10 g/dL and balance the individuals risk of needing transfusion and risks of ESA therapy, as well as the prior response to iron therapy. The guidelines state there is no robust evidence to distinguish one brand ESA from another regulatory agency approved product.

Oncology:

Two new systematic reviews confirm previous conclusions about the risks and benefits of ESA use in oncology. Neither resolves the controversy of whether targeting hemoglobin levels less than 10 g/dl is less risky.

A 2013 AHRQ Comparative Effectiveness[2] update of managing anemia in chemotherapy patients found moderate level evidence that ESAs reduce the proportion of patients that need blood transfusions and there is no meaningful difference between darbepoetin and erythropoietin. Low strength evidence suggested that there was no effect on overall survival but moderate level evidence that ESAs increased on-study (short-term) mortality and thromboembolic events.

A 2012 update[3] of a previously published 2007 Cochrane review of 91 RCTs evaluated erythropoietin or darbepoetin in 20,102 patients with anemia associated with cancer. It found Level 1 [likely reliable] evidence that ESAs reduce the need for blood transfusion (RR 0.65 95% CI 0.62 – 0.68, NNT 7-8). However, it found Level 2 [mid-level] evidence that ESAs may increase thromboembolic complications (RR 1.52 95% CI 1.34 – 1.74, NNH 29-64) and mortality (HR 1.05 95% CI 1-1.11). The morbidity results were limited by trial heterogeneity.

FDA warnings:
On February 24, 2013 the FDA issued a news release noticing health care providers of an immediate recall of all lots of Omontys injection due to 19 cases of anaphylaxis and subsequently, 3 deaths.[4] The drug is no longer marketed in the United States.

New Drugs or formulations:
None.

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Appendix 1: Prior Authorization Criteria

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

- Cover ESAs according to OHP guidelines[1] and current medical literature.
- Cover preferred products when feasible.

Length of Authorization:

- 12 weeks initially, then up to 12 months
- Quantity limit of 30 day per dispense

Requires PA:

- All ESAs require PA for clinical appropriateness.

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis?	Yes: Go to **#Error! Reference source not found.**	No: Pass to RPH; Deny (not covered by the OHP).
3. Is this continuation therapy?	Yes: Go to #12	No: Go to #4
4. Is the requested product preferred?	Yes: Go to #6	No: Go to #5
5. Will the Prescriber change to a preferred product?	Yes: Inform provider of covered alternatives in class. Go to #6	No: Go to **#Error! Reference source not found.**
6. Is the diagnosis anemia due to chronic renal failure[2] or chemotherapy[3,4] ?	Yes: Go to #7	No: Go to #8

Approval Criteria		
7. Is Hb < 10g/dl or Hct < 30% AND Transferrin saturation >20% and/or ferritin >100ng/ml?	Yes: Approve for 12 weeks with additional approval based upon adequate response.	No: Pass to RPH; Deny (not medically appropriate).
8. Is the diagnosis anemia due to HIV[5]?	Yes: Go to #9	No: Go to #10
9. Is the Hb < 10g/dL or Hct < 30% AND Transferrin saturation > 20% AND Endogenous erythropoietin < 500 iu/L AND If on Zidovudine is dose < 4200mg/week?	Yes: Approve for length of Rx or 12 months, whichever is less.	No: Pass to RPh; Deny (not medically appropriate).
10. Is the diagnosis anemia due to ribavirin treatment[6]?	Yes: Go to #11	No: Pass to RPh; Deny, (not medically appropriate).
11. Is the Hb < 10g/dL or Hct < 30% AND Is the transferrin saturation >20% and/or ferritin >100ng/ml AND Has the dose of ribavirin been reduced by 200mg/day and anemia persisted > 2 weeks?	Yes: Approve up to the length of ribavirin treatment.	No: Pass to RPh; Deny (not medically appropriate).
12. Has the patient responded to initial therapy?	Yes: Approve for length of Rx or 12 months, whichever is less.	No: Pass to RPh; Deny (not medically appropriate).

References:

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P&T / DUR Board Action: *11/29/12; 6/28/12(KK); 2/23/12, 09/16/2010 (DO)*
Revision(s): *9/24/12, 5/14/12*
Initiated: *1/1/11*

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Month/Year of Review: March 2014
PDL Classes: Hepatitis B Antivirals

Date of Last Review: February 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:
- Preferred Agents: LAMIVUDINE, TENOFOVIR DISOPROXIL FUMARATE
- Non-Preferred Agents: ADEFOVIR DIPIVOXIL, ENTECAVIR, TELBIVUDINE

Previous Conclusions and Recommendation:
- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Lamivudine has the most robust long term safety data and still has a place in therapy in those with favorable parameters and low risk of resistance. It can also be recommended in clinical situations which a finite prophylaxis course is needed.
- Consensus guidelines recommend either tenofovir or entecavir as first line antivirals for the treatment of hepatitis B. Maintain tenofovir as a preferred hepatitis B antiviral and make entecavir non-preferred based on no clinical evidence of superiority of one agent over the other.
- Establish prior authorization criteria for the non-preferred agents in this class to promote the use of the preferred products.

PA Criteria: Prior authorization criteria are currently in place for all hepatitis B antivirals with criteria to cover only covered diagnoses and for medically appropriate conditions (Appendix 1).

Conclusions and Recommendations:
- No further review or research needed at this time
- Evaluate comparative costs in executive session.

Methods:
A Medline OVID search was conducted with the following search terms: lamivudine, tenofovir**,** adefovir, entecavir, telbivudine, hepatitis B virus. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week one 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:
Zhao et al performed a systematic review and meta-analysis to establish the comparative efficacy of tenofovir versus adefovir for the treatment of hepatitis B. Six studies (n=910) were included in the analysis. The primary endpoint was viral suppression at 48 weeks (HBV-DNA level < 400 copies/mL). ALT normalization and antigen seroconversion were secondary endpoints. After 48 weeks of treatment, the tenofovir cohort had significantly higher HBV-DNA suppression than the adefovir group (RR=2.59; 95% CI 1.01 to 6.67). No difference was found between treatments in ALT normalization rates (RR=1.15; 95% CI 0.96 to 1.37). The difference of HBeAg seroconversion rates at week 48 between the two group was similar (RR = 1.19; 95%CI 0.74 to 1.91). Individual trial quality was measured for adequate sequence generation, allocation concealment, how incomplete outcome data was addressed, and if free of selective reporting or

other bias. Three trials were rated as high quality that adequately addressed all methodological quality concerns. The other three studies were rated as low quality with only the measures addressed incomplete outcome data and free of selective reporting sufficiently answered. All three reported endpoints were graded as low quality recommendations due to overall trial quality.[1]

Su et al conducted a systematic review and meta-analysis to compare the efficacy of telbivudine and entecavir in patients with hepatitis B. Primary outcomes included proportion of patients with undetectable HBV-DNA, HBV antigen loss or seroconversion. Secondary outcomes included percent ALT normalization, drug resistance and adverse outcomes. Thirteen trials (n=3925) were included in the analysis. Treatment duration ranged between four and 72 weeks. At 72 weeks, there was no statistical difference between telbivudine and entecavir in viral undetectability (RR 0.95; 95% CI 0.80 to 1.12). All time points between four weeks to 72 weeks (eight, 12, 24, 36, 48, 52, and 60 weeks) were also nonsignificant for viral nondetect rates for treatment. At weeks four, eight, 60 and 72, there was also no significant difference between the two treatments in antigen seroconversion; however at weeks 12, 24, 48 and 52, there was a significantly higher rate of seroconversion in the telbivudine group than the entecavir group (RR 2.10, 95% CI 1.36 to 3.24; RR 1.71, 95% CI 1.29 to 2.28; RR 1.86, 95% CI 1.36 to 2.54; and RR 1.87, 95% CI 1.21 to 2.90). There was no difference in rates of ALT normalization at any time point between treatment groups. Drug resistance was higher in the telbivudine cohort than the entecavir group at 72 weeks (RR=3.76; 95% CI 1.28 to 11.01). No serious adverse events were reported for either treatment; the most common side effects reported were flu-like symptoms and GI issues (diarrhea, nausea, vomiting). Creatinine kinase levels were significantly higher for the telbivudine group (RR=5.58; 95% CI 2.22 to 13.98). Individual trial quality was measured for adequate sequence generation, allocation concealment, how incomplete outcome data was addressed, and if free of selective reporting or other bias. The thirteen trials were given a grade of unclear for combined methodological quality matrices.[2]

Shi et al performed a meta-analysis evaluating nucleotide and nucleoside analogues in patients with hepatitis B and acute-on-chronic liver failure (ACLF). The primary outcome was three month mortality; HBV-DNA inhibition and ACLF reactivation were secondary endpoints. Five studies were included. Three were retrospective observational studies, and two were prospective randomized controlled trials. Only the end-point of three month mortality measured a head-to-head comparison of nucleotide analogues. Lamivudine and entecavir were compared for mortality rates. Rates were similar between treatment groups (entecavir 36.4% vs. lamivudine 40.5%, RR=0.77; 95% CI 0.45 to 1.32). All nucleotide and nucleoside analogues included (tenofovir, lamivudine and entecavir) were more effective than control at reducing HBV-DNA (70.4% vs. 29%, RR=2.29; 95% CI 1.49 to 3.53) and preventing ACLF reactivation (1.8% vs.18.4%, RR= 0.11; 95% CI 0.03 to 0.43). Individual trial quality was not assessed. Data was taking from observation as well as experimental trials further calling into question the quality of evidence of the findings.[3]

Guidelines:

In 2012, the International Antiviral Society-USA Panel published updated guidelines regarding antiviral treatment for HIV patients. This guideline included recommendations for patients coinfected with hepatitis B virus and HIV. Recommendations were graded for strength of the organization's support; an A grade was defined as having strong support, a B moderate support, and a C grade as having limited support. Recommendations were further classified by quality of evidence. Recommendations derived from evidence from at least one randomized controlled trials (RCT) published in a peer-reviewed journal were given the ranking Ia. Ib recommendations were from evidence from at least one RCT presented in abstract form at a scientific meeting. IIa and IIb recommendations were based on evidence from nonrandomized clinical trials, cohort, or case-control studies either published in journals or presented at a scientific meeting respectively. III recommendations were based on the panel's analysis of the accumulated evidence.[4]

- The ART regimen for HIV- and HBV coinfected persons should include tenofovir and emtricitabine (or lamivudine) as the NRTI background (AIIa).
- In patients with reduced renal function, tenofovir should be avoided, or if treatment for hepatitis B virus (HBV) coinfection is needed, dosing should be adjusted according to the prescribing information (AIIa).

The Consensus guidelines for management of hepatitis B from the Canadian Association for the Study of the Liver were updated in 2012. Recommendations are based on benefit versus risk classification and the quality of evidence to support. In class I recommendations, the benefit of the intervention far outweighs any risk. Class II recommendations are split further into IIa and IIb; for both the benefit outweighs the risk, but class IIa interventions are termed 'reasonable' while IIb interventions are only to be considered. Class III recommendations are classified as having no benefit or possibly harmful. Level A recommendations are derived from data from multiple clinical trials or meta-analyses. Level B recommendations are based on data from a single RCT or nonrandomized studies. Level C recommendations are based on consensus opinion of expert, case studies, or standard of care.[5]

- The consensus guideline committee has recommended that PEG IFN remain one of the first-line treatments for chronic hepatitis B (Class IIa, Level A).
- Tenofovir or entecavir is first-line therapy for treatment-naïve HBV patients because they are the most potent agents available with no (tenofovir) or very low (entecavir) rates of antiviral resistance (Class I, Level A).
- Tenofovir is first-line therapy for lamivudine-resistant HBV. Entecavir should not be used in this setting due to the risk of development of entecavir resistance (Class I, Level A).
- The treatment of choice for lamivudine-resistant HBV infection is tenofovir (Class 2, Level A).
- If a patient requires treatment for HIV alone or for both HIV and HBV, include tenofovir plus either emtricitabine or lamivudine with an appropriate third anti-HIV drug (Class I, Level B).
- The withdrawal of an HBV-active antiviral drug could result in worsening of the HBV infection; it should be avoided if possible, but if done, HBV DNA and ALT need to be carefully monitored (Class I, Level B).
- If tenofovir is stopped and an alternate anti-HBV agent is used, then an appropriate anti-HIV agent should be substituted (Class 1, Level B).
- The recommended first-line treatment during pregnancy is tenofovir (FDA category B), telbivudine should be used if contraindications to tenofovir therapy to lower viral loads and if treatment is not expected to be prolonged postpartum (Class 2, Level B).

In 2012, The United Kingdom's National Institute for Clinical Excellence (NICE) updated its guideline recommendations for management of hepatitis B virus in children, adolescents, and adults.[6] The Guideline Development Group (GDG) for NICE made recommendations based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the supporting evidence. The guideline used 'must' or 'must not' only if there was a legal duty to apply the recommendation or if the consequences of not following the recommendation could be extremely serious or potentially life threatening. The words 'offer', 'refer' or 'advise' were employed when confident that an intervention will do more good than harm, and be cost-effective. The GDG used 'consider' when confident that an intervention will do more good than harm for most patients, and be cost-effective, but other options may be similarly cost-effective.

- Peginterferon alfa-2a (48 weeks) is recommended as first line treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications.
- Entecavir or tenofovir are recommended as second line treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
- Telbivudine is not recommended for the treatment of chronic hepatitis B.
- Do not offer adefovir dipivoxil for treatment of chronic hepatitis B.
- People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir, depending on previous antiviral exposure: Offer tenofovir disoproxil to people with a history of lamivudine resistance.
- If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil. In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.

- Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.
- Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.
- Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby.
- Offer prophylaxis therapy with entecavir or tenofovir if HBV DNA is greater than 2000 IU/ml and lamivude if HBV DNA is less than 2000 IU/ml.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 87 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, six relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Zheng et al compared telbivudine and entecavir for treatment of hepatitis B virus. Adult patients (n=131) were randomized to either 600 mg telbivudine or 0.5 mg entecavir once daily for 24 weeks. The primary endpoint was mean reduction in HBV-DNA serum levels at 24 weeks. Secondary end points included mean reduction from baseline in serum HBV-DNA concentration at week 12, the absence of serum HBV-DNA, absence of serum antigen (HBeAg), HBeAg seroconversion at week 24, the normalization of serum ALT at week 24, and occurrence of adverse events through week 24. The mean reduction in serum HBV-DNA was comparable between telbivudine and entecavir subjects at both weeks 24 (6.00 vs. 5.80 log10 copies) and 12 (4.99 vs. 4.69 log10 copies); for both, $p>0.05$. Rates of undetectable HBV-DNA levels were also similar between treatment groups. At 24 weeks, 67.7% of telbivudine and 57.6% of entecavir subjects were undetectable ($p=0.232$). At 12 weeks, 43.1% telbivudine and 34.8% entecavir patients were undetectable ($p=0.334$). Both absence of antigen and seroconversion rates were also nonsignificant between treatment groups at 24 weeks. Normalization of ALT levels was statistically similar as well at 24 weeks; 78.5% of telbivudine and 74.2% of entecavir subjects had ALT levels within normal limits ($p=0.57$). The most common adverse events were upper respiratory infections, diarrhea, cough, and fatigue. Adverse events were similar between groups with the exception of elevated creatinine; 12.3% of telbivudine patients vs. no entecavir patients had elevated creatinine from baseline at 24 weeks ($p=0.003$). This was a fair quality trial. It was an open label design which can introduce bias. In addition, randomization procedures were not explicitly described.[7]

Ryu et al studied the difference in efficacy of adding adefovir to lamivudine with entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. Patients (n=92) with a history of at least six months lamivudine treatment and current HBV-DNA levels greater than 10^5 log10 copies/mL were randomized to receive either lamivudine 100mg plus adefovir 10 mg or entecavir 1 mg for 12 months. The primary endpoint was the rate of undetectable patients at 12 months of treatment. Secondary endpoints included the reduction of HBV-DNA, the proportion of patients with ALT normalization, HBeAg seroconversion, and nonresponse. At 12 months, 38.3% of lamivudine plus adefovir and 24.4% of entecavir had nondetectable levels of HBV-DNA ($p=0.182$). A greater mean reduction of HBV-DNA log 10 copies occurred in the lamivudine plus adefovir group than the entecavir group (3.80 vs. 2.72 log10 copies; $p<0.001$). More

patients in the entecavir showed no response to treatment (defined as less than 2 log10 copies change from baseline after six months treatment) than the lamivudine/adefovir cohort (28.9% vs. 10.6%; p =0.036). Normalization of ALT levels and antigen seroconversion rates were similar between treatment groups (for both p>0.05). This was a poor quality study. It was an open label design which introduces bias. Treatment groups were not followed for the same amount of time and this was not addressed in the article; all endpoints were set at 12 months. In addition, methodology such as randomization was not described.[8]

Liaw et al conducted a study to compare entecavir with adefovir in patients with chronic hepatitis B with hepatic decompensation. Patients (n=191) with Child-Turcotte-Pugh score of at least seven were randomized to either entecavir 1 mg or adefovir 10 mg once daily for up to 96 weeks. The primary endpoint was the mean reduction in HBV-DNA at week 24. Secondary endpoints included percentage of patients to reach nondetectable serum levels at week 24, improvement in Child-Turcotte-Pugh score at week 48, and rates of adverse events by study end. Entecavir subjects showed a greater reduction in HBV-DNA than the adefovir group by week 24 (treatment difference -1.74 log10 copies; 95% CI -2.30 to -1.18). At week 24, significantly more entecavir patients were nondetectable than adefovir subjects (49% vs. 16%; p<0.0001); this trend continued at week 48 (57% vs. 20%; p<0.0001). Sixty-one percent of entecavir and 67% of adefovir patients showed some improvement or stabilization in Child-Pugh score. Adverse event rates were comparable between groups. Cumulative hepatocellular carcinoma rates were 12% for entecavir and 20% for adefovir. At week 24, mortality rates were 12% for both groups. It was an open label design which can introduce bias. In addition, randomization procedures were not explicitly described.[9]

Ha et al compared the efficacy of three regimens for hepatitis B therapy. Patients (n=91) were randomized to either adefovir 10 mg, adefovir 10 mg plus lamivudine 100 mg, or adefovir 10 mg plus entecavir 1 mg for at least 24 months. All subjects had prior treatment failure with lamivudine monotherapy and developed lamivudine resistance. The primary endpoint was mean reduction in HBV-DNA from baseline. Secondary outcomes included HBV-DNA undetectability (<60 IU/mL) and viral breakthrough. At 24 months, all three treatments showed a mean reduction in HBV-DNA: adefovir -3.78 IU/mL, adefovir plus lamivudine -4.92 IU/mL, and adefovir plus entecavir -5.58 IU/mL. This difference compared with adefovir monotherapy was statistically significant for both the adefovir plus lamivudine (p=0.026) and the adefovir plus entecavir (p=0.012) subjects. Difference in viral undetectability at 24 months, was nonsignificant for the all three treatment groups (adefovir 48.2%, lamivudine plus adefovir 76.7%, entecavir plus adefovir 87.5%). Subjects in the adefovir plus entecavir had not instances of viral breakthrough or mutations; 27.6% of adefovir patients and 13.3% adefovir plus lamivudine had viral breakthrough (for both compared with adefovir plus entecavir p<0.05). This was a low quality study with no description of blinding, randomization, or allocation concealment procedures.[10]

Lok et al evaluated the efficacy of entecavir monotherapy with entecavir plus tenofovir in patients with chronic hepatitis B. Subjects (n=379) were randomized to either entecavir 0.5 mg or entecavir 0.5 mg plus tenofovir 300 mg once daily for 100 weeks. The primary outcome was viral undetectability (<50 IU/mL) at 96 weeks. Both treatment groups had high rates of undetectability (83.2% patients on entecavir plus tenofovir and 76.4% on entecavir patients; p=0.088) with no statistical difference between groups. Adverse events were similar between treatment groups, although mean ALT levels normalized in more entecavir subjects than the dual therapy group (81.9% vs. 69%; p>0.05). This was a poor quality trial. It was open label design which can introduce bias, randomization methods were not described, and there were differences in group baseline characteristics.[11]

Yim et al compared the efficacy of entecavir with adefovir plus lamivudine to treat lamivudine resistant chronic hepatitis B. Subjects (n= 219) were randomized to either entecavir 0.5 mg or adefovir 10 mg plus lamivudine 100 mg for 24 months. The primary outcome was viral undetectability (<60 IU/mL) at 24 months. Rates of virologic breakthrough and genotypic resistance were secondary endpoints. Patients in the dual treatment group were more likely to have nondetectable HBV-DNA levels at 24 months compared with entecavir subjects (56.7% vs. 40%; p= 0.025). Genotypic resistance (9.2% vs. 24.6%, P = 0.005) and combined viral breakthrough (2.0% vs. 17.6%, P < 0.001) were more frequent

in the entecavir group. ALT normalization by treatment end was similar between groups (95.6% for the dual therapy group vs. 88.9% for the entecavir group; p=0.063). There were a couple serious adverse events tracked. Hepatocellular carcinoma developed in four patients from the adefovir plus lamivudine group and in one from entecavir group (p=0.368). Increased serum creatinine (>1.5 mg/dl) occurred in three patients from the combination group. No entecavir patients had elevated creatinine. This was a fair quality trial. It was an open label design which can introduce bias.[12]

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Appendix 1 PA criteria

Hepatitis B Antivirals

Goal(s):

- Cover hepatitis B agents according to OHP guidelines. Cover preferred products when feasible for covered diagnosis.
- Preferred products are selected based on evidence based reviews.

Length of Authorization:

Up to 12 months; quantity limited to a 30 day supply per dispensing.

Requires PA:

- All Hepatitis B antivirals

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Pediatric Age Restrictions:

- lamivudine (Epivir HBV) - 2 years and up
- adefovir dipivoxil (Hepsera) - 12-17 years
- entecavir (Baraclude) - 16 years and up
- telbivudine (Tyzeka) - safety and effectiveness not approved in pediatrics

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for OHP Coverage.
3. Is the request for an antiviral for the treatment of HIV/AIDS?	Yes: Approve for up to 1 year	No: Go to #4
4. Is the request for treatment of Chronic Hepatitis B?	Yes: Go to #5	No: Pass to RPh, Deny for Appropriateness
5. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin."***	Yes: Go to Renewal Criteria	No: Go to #6

Approval Criteria		
6. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	Yes: Document intolerance or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30 day's supply.	No: Go to #7
7. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class.	No: Approve requested treatment for 6 months with monthly quantity limit of 30 day's supply.

Renewal Criteria	
1. Is client compliant with requested treatment (see refill history)?	Yes: Go to 2.
2. Is HBV DNA undetectable?	Yes: Approve for up to 1 year with monthly quantity limit of 30 day's supply

P&T / DUR Action: *4/26/12*
Revision(s):
Initiated: *7/23/12*

Appendix 2: Abstracts of Randomized Control Trials

Zheng M-H, Shi K-Q, Dai Z-J, Ye C, Chen Y-P. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive chronic hepatitis B virus infection in adult Chinese patients. *Clinical Therapeutics*. 2010;32(4):649-658. doi:10.1016/j.clinthera.2010.04.001.

Background: Because drug-resistant strains of hepatitis B virus (HBV) have developed, and because serum HBV-DNA levels may rebound in patients who receive treatment with nucleoside/nucleotide analogues for up to 2 years, there remains a largely unmet clinical need for agents to induce potent virologic suppression in the initial stage of the disease course of HBV infection.

Objective: The aim of this work was to compare the early antiviral effectiveness of telbivudine and entecavir in the treatment of patients with hepatitis B e antigen (HBeAg)-positive HBV.

Methods: In this parallel-group, open-label trial, adult Chinese patients with previously untreated HBeAg-positive HBV (HBV-DNA concentration: ≥6 log10 copies/mL; alanine aminotransferase [ALT] level: ≥2 times the upper limit of normal) were randomized to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks. Blood samples were collected at the baseline and at 12 and 24 weeks after the treatment. The primary end point was the mean reduction from baseline in serum HBV-DNA concentration at week 24. Secondary end points included mean reduction from baseline in serum HBV-DNA concentration at week 12, the absence of serum HBV-DNA, absence of serum HBeAg, HBeAg seroconversion at week 24, the normalization of serum ALT at week 24, and occurrence of adverse events through week 24.

Results: A total of 131 patients were enrolled in the study: 91 men and 40 women, with a mean (SD) age of 32.5 (8.9) years. All patients were ethnic Han Chinese. The baseline demographic characteristics and serum HBV-DNA concentrations in the 2 treatment groups were well matched. Sixty-five patients were randomized to receive telbivudine and 66 to receive entecavir. The mean reductions from baseline in serum HBV-DNA were 4.99 and 4.69 log10 copies/mL at week 12, respectively, and 6.00 and 5.80 log10 copies/mL at week 24 (both time points, *P* = NS between groups). At week 12, HBV-DNA was undetectable in 43.1% (28/65) of the telbivudine group and 34.8% (23/66) of the entecavir group (*P* = NS); at week 24, it was undetectable in 67.7% (44/65) of the telbivudine group and 57.6% (38/66) of the entecavir group (*P* = NS). At week 12, HBeAg absence and seroconversion rates were significantly greater in the telbivudine group than the entecavir group (absence: 20.0% [13/65] vs 3.0% [2/66], respectively [*P* = 0.002]; seroconversion: 13.8% [9/65] vs 3.0% [2/66] [*P* = 0.030]). However, at week 24, HBeAg absence and seroconversion rates were comparable between the telbivudine and entecavir groups (absence: 36.9% [24/65] vs 28.8% [19/66] [*P* = NS]; seroconversion: 24.6% [16/65] vs 13.6% [9/66] [*P* = NS]). In addition, the normalization of ALT levels was observed in 78.5% (51/65) and 74.2% (49/66) of patients treated with telbivudine and entecavir, respectively, at week 24 (*P* = NS). The adverse events were upper respiratory tract infection (12.3% of telbivudine patients vs 9.1% of entecavir patients), fatigue (6.2% vs 7.6%), diarrhea (1.5% vs 3.0%), and coughing (0% vs 1.5%), most of which were mild to moderate. Elevated creatinine phosphokinase was noted in 8 telbivudine-treated patients (12.3%). There were no statistically significant differences in rates of adverse events between groups except for creatinine phosphokinase.

Conclusion: In this study of ethnic Han Chinese adults with previously untreated HBeAg-positive HBV infection, there were no statistically significant differences in effectiveness or tolerability between telbivudine 600 mg and entecavir 0.5 mg at the end of 24 weeks of treatment.

Ryu HJ, Lee JM, Ahn SH, et al. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *Journal of Medical Virology*. 2010;82(11):1835-1842. doi:10.1002/jmv.21898.

No study has reported on the comparative effect of adefovir (ADV) add-on lamivudine (LAM) versus switching to entecavir (ETV) in LAM-resistant patients with chronic hepatitis B. From October 2007 to September 2008, 92 consecutive LAM resistant patients were enrolled (47 LAMþADV and 45 ETV 1mg).All patients were followed for at least 12 months. The parameters assessed included normalization of ALT, HBeAg seroconversion, undetectable HBV DNA, reduction of HBV DNA, and predictors of virologic response. In the LAMþADV and ETV groups, the baseline DNA levels were 7.61 (5.19–9.49) and 7.10 (5.43–9.74) log10 copies/ml, respectively. At month 12, a virologic response occurred in 18/47 (38.3%) and 11/45 (24.4%; P¼0.182) patients; ALT normalization, in 39/41 (95.1%) and 36/40 (90.0%; P¼0.432); HBeAg seroconversion, in 5.1% and 2.4% (P¼0.606); and virologic breakthrough, in 2.1% and 11.1% (P¼0.107), respectively. The mean reduction from the baseline HBV DNA level was greater in the LAMþADV group at month 12 (3.80_1.12 vs. 2.72_1.32 log10 copies/ml; P<0.001). In the multivariate analysis, the independent parameters related to a virologic response at month 12 were baseline ALT (OR¼1.003, 95% CI¼1.000–1.006, P¼0.026) and baseline HBV DNA (OR¼0.495, 95% CI¼0.298– 0.823, P¼0.007). Compared with switching to ETV monotherapy, ADV add-on LAM therapy was more effective at reducing the viral load inpatients with LAM resistance, and the baseline HBV DNA and ALT levels were independent predictors of the virologic response. However, ADV add-on therapy had limitations in patients with a higher baseline HBV DNA in LAM rescue therapy.

Liaw Y-F, Raptopoulou-Gigi M, Cheinquer H, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology*. 2011;54(1):91-100. doi:10.1002/hep.24361.

A randomized, open-label comparative study of entecavir versus adefovir therapy was performed in subjects with chronic hepatitis B who had hepatic decompensation (Child-Turcotte- Pugh score _7). Adult subjects were randomized and treated (n 5 191) with entecavir 1.0 mg or adefovir 10 mg daily for up to 96 weeks from the date of last subject randomization. Subjects were positive or negative for hepatitis B e antigen and experienced or naive for treatment with nucleos(t)ide analogues. The primary efficacy endpoint was the mean reduction in serum hepatitis B virus (HBV) DNA, as determined by polymerase chain reaction, at week 24, adjusted for baseline HBV DNA and lamivudine resistance status by linear regression analysis. Entecavir demonstrated superiority to adefovir for this endpoint (treatment difference 1.74 log10 copies/mL [95% confidence interval 22.30, 21.18]; P < 0.0001). The entecavir group showed a greater change from baseline in HBV DNA at all-time points through week 48 and a higher proportion of subjects who achieved HBV DNA < 300 copies/mL at weeks 24 (entecavir 49%; adefovir 16%; P < 0.0001) and 48 (entecavir 57%; adefovir 20%; P < 0.0001). Approximately two-thirds of subjects in both groups showed improvement/ stabilization in Child-Turcotte-Pugh status. Model for End-Stage Liver Disease score change at week 48 was 22.6 for entecavir and 21.7 for adefovir. Adverse event rates were

comparable between groups. Cumulative hepatocellular carcinoma rates were 12% for entecavir and 20% for adefovir. Cumulative death rates were 23% for entecavir and 33% for adefovir. Week 24 mortality rates were 12% for both groups. Conclusion: Entecavir demonstrated superior virologic efficacy to adefovir in a population of patients with chronic hepatitis B who had hepatic decompensation. Biochemical and clinical benefits were also demonstrated. Entecavir was well tolerated, and early mortality rates were consistent with rates observed in similar populations treated with lamivudine.

Ha M, Zhang G, Diao S, et al. Rescue Therapy for Lamivudine-resistant Chronic Hepatitis B: Adefovir Monotherapy, Adefovir Plus Lamivudine or Entecavir Combination Therapy. *Internal Medicine*. 2012;51(12):1509-1515. doi:10.2169/internalmedicine.51.7329.

Objective We aimed to compare the cumulative efficacy and resistance of ADV monotherapy, ADV add-on LAM (ADV + LAM), ADV and ETV (ADV + ETV) combination therapy in LAM-resistant patients.

Methods Ninety-one adult CHB patients with LAM-resistance mutations (YMDD) were identified. Of these 91, 29 patients were treated with ADV monotherapy, 30 were treated with ADV + LAM and 32 were treated with ADV + ETV combination therapy, for at least 24 months.

Results The mean serum HBV-DNA decreases from baseline at 3, 6, 12, and 24 months were -3.23, -4.41, -5.32, and -5.58 log10IU/mL in the ADV + ETV combination therapy groups, respectively; the most significant among the three treatment groups ($p<0.01$). The rate of HBV-DNA PCR undetectability (<60 IU/mL) at 6 months in ADV + ETV combination therapy was 78.1%; also the most significant among the three treatment groups ($p=0.024$). Viral breakthrough and genotypic mutations were detected in 8 (27.6%) and 4 (13.3%) patients in the ADV monotherapy and ADV+LAM therapy groups, respectively; whereas no case of viral breakthrough and genotypic resistance was detected in the ADV+ETV combination therapy group after24 months ($p<0.05$).

Conclusion ADV + ETV combination therapy demonstrated faster and significantly greater suppression of HBV DNA compared with ADV add-on LAM combination therapy for patients with LAM-resistance mutations. ADV + ETV was superior to ADV + LAM in achieving initial virological response and long-term suppression activity against HBV. ADV + ETV combination therapy was the most effective to refrain from selecting HBV strains with cross-resistance to three NAs (LAM, ADV and ETV) for LAM-resistance patients.

Lok AS, Trinh H, Carosi G, et al. Efficacy of Entecavir With or Without Tenofovir Disoproxil Fumarate for Nucleos(t)ide-Naïve Patients With Chronic Hepatitis B. *Gastroenterology*. 2012;143(3):619-628.e1. doi:10.1053/j.gastro.2012.05.037.

BACKGROUND & AIMS: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent antiviral agents that might have additive or synergistic antiviral activity in treatment of patients with chronic hepatitis B (CHB). We compared the efficacy and safety of ETV monotherapy with those of a combination of ETV and TDF.

METHODS: We performed a randomized, open-label, multicenter, superiority study of 379 nucleos(t)ide-naïve patients with hepatitis B e antigen (HBeAg)-positive (n _264) or HBeAg-negative (n _ 115) CHB. Subjects were given ETV 0.5 mg (n _ 182) or a combination of ETV 0.5 mg and TDF 300 mg (n _ 197) for 100 weeks.

RESULTS: At week 96, comparable proportions of patients in each study arm achieved the primary end point of a level of hepatitis B virus (HBV) DNA _50 IU/mL (83.2% vs 76.4%; *P* _ .088). Among HBeAg-positive patients, a greater proportion given combination therapy achieved levels of HBV DNA _50 IU/mL than those given ETV alone (80.4% vs 69.8%; *P* _ .046). However, this difference was observed only in patients with baseline levels of HBV DNA _108 IU/mL (79% vs 62%) and not in those with baseline levels of HBV DNA _108 IU/mL (83% in both arms). Rates of HBeAg loss and HBeAg seroconversion were comparable between groups, whereas the rate of alanine aminotransferase normalization was greater in the ETV monotherapy group. No HBV variants associated with ETV or TDF resistance were detected. Safety profiles were consistent with previous reports of ETV or TDF monotherapy.

CONCLUSIONS: The antiviral efficacy of ETV monotherapy is comparable to that of ETV plus TDF in a mixed population of nucleos(t)ide-naïve patients with CHB (70% HBeAg positive). The combination therapy could provide an incremental benefit to HBeAg-positive patients with baseline levels of HBV DNA >108 IU/mL.

Yim HJ, Seo YS, Yoon EL, et al. Adding adefovir vs. switching to entecavir for lamivudine-resistant chronic hepatitis B (ACE study): a 2-year follow-up randomized controlled trial. *Liver International*. 2013;33(2):244-254. doi:10.1111/liv.12036.

Background: Management of lamivudine-resistant chronic hepatitis B (CHB) remains challenging, as inappropriate choice of treatment may cause multidrug resistance. Until now, randomized trials directly comparing adding adefovir and switching to entecavir monotherapy have not been reported.

Aims: This multicentre prospective randomized study was designed to compare the efficacy of these two strategies.

Methods: Two hundred and nineteen lamivudine-resistant CHB patients were randomized to either adefovir– lamivudine combination group or entecavir monotherapy group (n = 110 vs. 109), and followed up for 24 months.

Results: One hundred and eighty patients completed this study. At month 24, virological response rate [hepatitis B virus (HBV) DNA <60 IU/ml] was higher in the adefovir– lamivudine combination group compared with entecavir group (56.7% vs. 40%, P = 0.025), although biochemical and serological response rates were not significantly different. Genotypic resistance (9.2% vs. 24.6%, P = 0.005) and combined viral breakthrough (2.0% vs. 17.6%, P < 0.001) were more frequent in the entecavir group. However, by subgroup analysis, virological response rates were not significantly different between the two therapies in HBeAg-positive patients (44.9% vs. 35.7%, P = 0.268) or in patients with high baseline HBV DNA (_7 log IU/ml) (40.7% vs. 31.3%, P = 0.320) at month 24.

Conclusion: This study showed that adefovir–lamivudine combination provides significantly higher antiviral efficacy and the lower resistance rate compared with the entecavir monotherapy in the management of lamivudine- resistant CHB. However, it had limited efficacy in HBeAg-positive patients or in patients with high baseline HBV DNA.

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Month/Year of Review: May 2014
PDL Classes: BPH

Date of Last Review: November 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: DOXAZOSIN MESYLATE, FINASTERIDE, TAMSULOSIN HCL, TERAZOSIN HCL
- Non-Preferred Agents: ALFUZOSIN HCL, SILODOSIN (RAPAFLO), DUTASTERIDE (AVODART), TADALAFIL (ADCIRCA), PRAZOSIN (MINIPRESS), DOXAZOSIN ER (CARDURA XL), DUTASTERIDE/TAMSULOSIN (JALYN)

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Tadalfil demonstrated improvements in urinary symptoms compared to placebo in patients with lower urinary tract symptoms, but demonstrated no difference in post void residual volume or urinary flow rate.
- Tadalafil is also indicated for patients with concurrent BPH and erectile dysfunction. Erectile dysfunction is not a covered diagnosis under the Oregon Health Plan.
- There is insufficient evidence to demonstrate superiority of tadalafil over standard treatment.
- Recommend including at least one Alpha-Blocker and one Alpha Reductase Inhibito as preferred on the PDL.r
- Consider PA criteria to limit cosmetic use

Prior Authorization Criteria: PA criteria are in place to ensure medications are prescribed for OHP covered diagnosis. BPH with urinary obstruction treatment is covered by OPH only when post-void residuals are at least 150 ml (Appendix 1).

Conclusions and Recommendations:

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

Methods:

A Medline OVID search was conducted with the following search terms: doxazosin mesylate, finasteride, tamsulosin HCl, terazosin HCl, alfuzosin HCl, silodosin, dutasteride, tadalafil, BPH, benign prostatic hypertension. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week four 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

Filson et al conducted a meta-analysis and systematic review to compare the efficacy of treating benign prostatic hyperplasia with alpha blockers and anticholinergics with alpha blocker monotherapy. Seven studies were included with a total of 3629 participants. The primary endpoint was improvement in International Prostate Symptom Score (IPSS) and urinary frequency. Secondary outcomes included maximal flow rate and incidence of urinary retention. Alpha blockers studied were tamsulosin or doxazosin. Anticholinergics included tolterodine, oxybutynin, solifenacin, and festerodine. Combination alpha blocker and anticholinergic treatment significantly improved IPSS compared with alpha blocker therapy alone (mean difference -0.73, 95%CI -1.09 to -0.37). Combination therapy also had a significant

decrease in voiding frequency (mean difference -0.69 voids, 95%CI -0.97 to -0.41), a greater reduction in maximal flow rate (mean difference -0.59 mL/s, 95%CI -1.04 to -0.14) and an increase in post-void residual urinary volume (mean difference 11.60 mL, 95%CI 8.50 to 14.70). All studies included were randomized control trials and were analyzed for quality by the authors based on inclusion of allocation concealment, randomization, and blinding methodology. The authors also looked for any evidence of selective reporting, rates of completion of intervention, and what group was used for final analysis. None of the information regarding individual trial quality was published in the review; instead, the authors stated the studies included were deemed as high quality based on their criteria.[1]

Gacci et al performed a meta-analysis and systematic review to compare the effectiveness of combination phosphodiesterase-five inhibitors (PDE5-I) and alpha blockers with alpha blocker monotherapy for improvement in lower urinary tract symptoms in benign prostatic hyperplasia. Trials were included with active or placebo control. In total 12 trials were pooled: seven trials (n=3214) with placebo control and five (n=216) with an alpha blocker combination comparator. The primary endpoint was improvement in the International Index of Erectile Function (IIEF) score, the International Prostate Symptom Score (IPSS) and maximum flow rate. When compared with placebo, subjects on a phosphodiesterase inhibitor showed significant improvement in IIEF (mean difference 5.5, $p<0.0001$) and IPSS (mean difference -2.8, $p<0.0001$). There was no difference between placebo and PDE5-I groups in change in maximal flow rate. When combination alpha blocker and PDE5-I therapy was compared with alpha blocker monotherapy, the combination cohort had significantly improved IIEF score (mean difference 3.6, $p<0.0001$), IPSS (mean difference -1.8, $p=0.05$) and flow rate (mean difference Qmax1.5, $p<0.0001$). The strength of evidence from this meta-analysis could not be determined as individual trial quality was not assessed in the review.[2]

Ding et al conducted a systematic review to compare the efficacy of silodosin with placebo or tamsulosin for treatment of lower urinary tract symptoms in benign prostatic hyperplasia. Four trials (n=2504) were included; three of which included a tamsulosin cohort. All trials were of 12 week duration. The primary outcome was change from baseline in International Prostate symptom Score (IPSS), improvement in quality of life (QoL), and maximum urine flow. When compared with placebo, the silodosin group had a significantly improved IPSS (mean difference -2.78, $p<0.00001$), QoL score (mean difference -0.42, $p=0.004$) and maximum flow rate (mean difference Qmax 1.17 mL/s, $p<0.00001$). Silodosin was also had significant improvement in IPSS (mean difference -1.14, $p=0.02$) and QoL score (mean difference -0.26, $p=0.02$) when compared with tamsulosin. Silodosin was not superior to tamsulosin in improvement in urinary flow rate (mean difference -0.85 mL/s, $p=0.01$). Individual trial quality was measured by the transparency of the allocation concealment, randomization and blinding methodology; as well as the presence of incomplete outcome data, selective outcome reporting and any other sources of bias. By these standards, all four included trials were considered poor quality with unclear sequence generation, allocation concealment, selective outcome reporting and other sources of bias. All four also reported incomplete outcome data.[3]

Yuan et al performed a systematic review to evaluate the safety and efficacy of alpha blockers for benign prostatic hyperplasia (BPH). Fifteen systematic reviews studying five medications (alfuzosin, doxazosin, tamsulosin, terazosin, and naftopidil) were included in the analysis. Primary outcomes were improvement in urinary symptoms using the International Prostate Symptoms Score (IPSS) or Boyarsky scale and improvement in urinary flow rate. Alfuzosin did not show improvement over doxazosin (mean difference 1.7, 95%CI 0.76 to 1.64) or tamsulosin (mean difference 0.30, 95% CI 0.21 to 0.39) in improvement from baseline in urinary symptoms. Terazosin also did not show improvement in symptom score when compared with tamsulosin (0.72, 95% CI -1.51 to 2.94). There was no statistical difference between alfuzosin and terazosin in change of symptom score. Doxazosin significantly improved symptom score when compared with tamsulosin (mean difference -1.60, 95% CI -1.80 to -1.40) but there was no difference between doxazosin and terazosin. Doxazosin showed significant improvement in urinary flow rate compared with tamsulosin (mean difference 0.9 mL/s, $p<0.05$). All other alpha blocker comparisons demonstrated no statistical difference in change in flow rate. There were no significant differences in alpha blockers in total adverse events or rates of withdrawal with the exception of terazosin which had higher adverse event rates (18.00 RR, 95% CI 2.5 to 129.6) and total withdrawals (1.82 RR, 95% CI 1.00 to 3.32) than tamsulosin. Individual systematic reviews were analyzed for

quality using the Assessment of Multiple Systematic Reviews (AMSTAR) and evidence for primary outcomes was evaluated using the GRADE system and presented as high, moderate, and low. All evidence presented between direct comparisons of alpha blockers was graded low or moderate.[4]

Guidelines:

In 2013, the European Association of Urology published updated guidelines regarding the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Recommendations were graded for the strength of the evidence source: an A grade was based on randomized clinical trials, a B on well-conducted but not randomized clinical trials, and a C grade was made despite the absence of directly applicable clinical studies. Recommendations were further classified by quality of evidence. Recommendations derived from evidence from a meta-analysis were given the ranking 1a. 1b recommendations were from evidence from at least one randomized control trial. 2a and 2b recommendations were based on evidence from well-designed nonrandomized clinical trials, or other quasi-experimental studies respectively. Level 3 recommendations were based on well-designed non-experimental studies, such as comparative or correlation studies and case reports and level 4 recommendations were based on expert opinion or clinical experience.[5]

- a1-Blockers can be offered to men with moderate-to-severe LUTS. Recommendation 1a A
- 5a-Reductase inhibitors can be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 ml). 5a-Reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery. Recommendation 1b A
- Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms. Recommendation 1b B
- Phosphodiesterase type 5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction. Recommendation 1b A
- Combination treatment with an a1-blocker together with a 5a-reductase inhibitor can be offered to men with bothersome moderate-to-severe LUTS, enlarged prostates, and reduced Qmax (men likely to develop disease progression). Recommendation 1b A
- Combination treatment with an a1-blocker together with a muscarinic receptor antagonist may be used in patients with bothersome moderate-to-severe LUTS if relief of storage symptoms has been insufficient with the monotherapy of either drug. Recommendation 1b B

The American Urological Association updated its guidelines in 2012 for the management of benign prostatic hyperplasia. Recommendations were based on outcomes data from current clinical literature and by opinion derived from clinical experience of an expert panel. All guideline statements were classified into one of three levels with respect to the degree of flexibility in their application. A "**standard**" had the least flexibility as a treatment policy. A guideline statement was a standard if: the health outcomes of the alternative interventions were sufficiently well known to permit meaningful decisions and there was virtual unanimity about which intervention was preferred. A "**recommendation**" had significantly more flexibility; and an **"option**" was even more flexible. A guideline statement was a recommendation if: the health outcomes of the alternative intervention were sufficiently well known to permit meaningful decisions, and an appreciable but not unanimous majority agrees on which intervention was preferred. A guideline statement was an option if: the health outcomes of the interventions were not sufficiently well known to permit meaningful decisions, or preferences were unknown or equivocal. Options may exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.[6]

- **Option**: Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA-SI score ≥8). Although there are slight differences in the adverse events profiles of these agents, all four appear to have equal clinical effectiveness. As stated in the 2003 Guideline, the effectiveness and efficacy of the four alpha blockers under

consideration appear to be similar. Although studies directly comparing these agents are currently lacking, the available data support this contention.

- **Option**: The older, less costly, generic alpha blockers remain reasonable choices. These require dose titration and blood pressure monitoring. [Based on Panel consensus]
- **Recommendation**: As prazosin and the nonselective alpha-blocker phenoxybenzamine were not reviewed in the course of this Guideline revision, the 2003 Guideline statement indicating that the data were insufficient to support a recommendation for the use of these two agents as treatment alternatives for LUTS secondary to BPH has been maintained. [Based on Panel consensus]
- **Option**: The combination of an alpha-blocker and a 5-alpha reductase inhibitor (5-ARIs) (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate-specific antigen (PSA) level as a proxy for volume, and/or enlargement on digital rectal exam (DRE). [Based on review of the data and Panel consensus]
- **Option**: Finasteride is an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding (i.e., after exclusion of any other causes of hematuria). A similar level of evidence concerning dutasteride was not reviewed; it is the expert opinion of the Panel that dutasteride likely functions in a similar fashion. [Based on review of the data and Panel consensus]
- **Option**: Anticholinergic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated post-void residual and when LUTS are predominantly irritative. [Based on Panel consensus]
- **Recommendation**: Prior to initiation of anticholinergic therapy, baseline PVR urine should be assessed. Anticholinergics should be used with caution in patients with a post-void residual greater than 250 to 300 mL. [Based on Panel consensus]

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 196 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, five relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Haillot et al performed a post hoc analysis of the combination of Avodart and tamsulosin (CombAT) trial focusing solely on the European subgroup. Male subjects with a diagnosis of benign prostatic hypertrophy were randomized to daily tamsulosin 0.4 mg (n=972), dutasteride 0.5 mg (n=970), or both (n=983) and followed for four years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary outcomes included BPH progression, symptoms, or maximum urinary flow rate. At the end of study, AUR or BPH-related surgery had occurred in 3.5% of combination, 11.9% of tamsulosin, and 5.5% of dutasteride subjects. Combination therapy significantly reduced the risk of AUR or BPH-related surgery compared with tamsulosin (RR 72%; 95% CI 58.9 to 80.9%) or dutasteride monotherapy (RR 39.6%; 95% CI 7.6 to 60.6%). When the two primary endpoints were examined separately combination therapy still significantly reduced the risk of AUR compared with tamsulosin (RR 70.3; $p < 0.001$) but not dutasteride (RR 30.1%; $p = 0.23$). Combination therapy significantly reduced the risk of BPH-surgery compared with both tamsulosin (RR 76%; $p<0.001$) and dutasteride monotherapy (RR 47.5%; $p = 0.018$). Combination therapy was

significantly more effective at decreasing BPH clinical progression than tamsulosin (RR 43%; 95% CI 27.7 to 55.1%) or dutasteride (RR 32.1%; 95% 13.2 to 46.9%). Subject symptoms were tracked and measured using the International Prostate Symptom Score (IPSS) tool. Again subjects on the combination therapy experienced a significantly greater decrease in BPH symptoms than either tamsulosin or dutasteride (both p<0.01). Combination therapy significantly increased the urinary flow rate (Qmax) from baseline when compared with tamsulosin (2.5 mL/s vs. 0.8 mL/s; p<0.001) but not with dutasteride (2.5 mL/s vs. 2.2 mL/s; p=0.25). Methodology from the CombAT trial was not reported; trial quality was not able to be assessed.[7]

Yu et al examined whether silodosin was inferior to tamsulosin in treatment of lower urinary tract symptoms related to benign prostatic hyperplasia (BPH). Subjects (n= 209) were randomized to either silodosin 4 mg twice daily or tamsulosin 0.2 mg once daily for 3 months. The primary endpoint was the mean change from baseline in the International Prostate Symptom Score (IPSS) tool. For silodosin to be determined noninferior to tamsulosin, the noninferiority margin for change an IPSS was set at 1.0. Change in maximum urinary flow rate was a secondary endpoint. The difference between the silodosin and tamsulosin groups in change in IPSS score was not significant; 86.2% of silodosin and 81.9% of tamsulosin subjects had a >25% decrease in IPSS score from baseline. The mean difference in IPSS change from baseline was -0.60 (95% CI -2.15 to 0.95) between silodosin and tamsulosin. As this was below the set 1.0, silodosin was found to be noninferior to tamsulosin. There was no difference in change in Qmax between tamsulosin and silodosin (mean change -0.74; 95% CI -2.01 to 0.74). This was a poor quality trial; blinding, randomization and allocation concealment methodology were not described. Tamsulosin dosing was below the standard dose of 0.4 mg while the silodosin dose was the FDA approved daily maintenance dose of 8 mg. [8]

Oelke et al compared the efficacy of tadalafil or tamsulosin with placebo to improve lower urinary tract symptoms in benign prostatic hyperplasia. Male subjects with BPH were randomized to placebo (n=172), tamsulosin 0.4 mg (n=168), or tadalafil 5 mg (n=171) once daily for 12 weeks. The primary outcome was improvement in International Prostate Symptom Score (IPSS) from baseline. Improvement in urinary flow rate as measured by Qmax was a secondary endpoint. Both treatments showed significant improvement in IPSS mean change from baseline compared with placebo (tadalafil -2.1, p<0.001; tamsulosin -1.5, p=0.023). Qmax was also significantly improved in both tamsulosin (2.2mL/s, p=0.014) and tadalafil (2.4 mL/s, p=0.009) compared with placebo. No comparison was made between treatment groups. This was a fair quality trial but without direct comparison between treatments it does not add any new information.[9]

Chung et al conducted a post hoc analysis of the Combination of Avodart and tamsulosin (CombAT) trial to compare any differences in treatment in the subpopulation of Asian (n=325) men. CombAT subjects were randomized to either once daily tamsulosin 0.4 mg (n=112), dutasteride 0.5 mg (n=106), or both (n=107), and followed for four years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary outcomes included BPH progression, symptoms, or maximum urinary flow rate. Although rates of AUR or BPH-related surgery varied greatly between tamsulosin (10.7%) and dutasteride (1.9%), the difference for each was nonsignificant when compared with combination therapy (6.5%, both p>0.05). Symptom progression was significantly improved with combination therapy (18.7%) compared with tamsulosin monotherapy (33%, p<0.05) but not with dutasteride (17.9%). Combination therapy subjects had a significantly greater improvement in IPSS from baseline when compared with tamsulosin (-6.4 vs. -2.2., p<0.05) subjects. There was no significant difference between combination and dutasteride (-6.4 vs. -4.9, p> 0.05). Improvement in urinary flow rate was significantly improved with combination therapy (1.9mL/s) compared with tamsulosin monotherapy (0.3mL/s, p<0.05) but not with dutasteride (1.6mL/s). Methodology from the CombAT trial was not reported; trial quality was not able to be assessed.[10]

Yokoyama et al compared the efficacy of tadalafil with tamsulosin and placebo in improving lower urinary tract symptoms in benign prostatic hyperplasia. Asian men were randomized to either placebo (n=154), tadalafil 2.5 mg (n=151), tadalafil 5 mg (n=155), or tamsulosin 0.2 mg (n=152) for 12 weeks. The primary outcome was improvement from baseline in the International Prostate Symptom Score (IPSS) for tadalafil compared with tamsulosin. Both doses of

tadalafil had significant improvement in IPSS from baseline compared with placebo (for 2.5 mg: -4.8 vs. -3.0, p =0.003; for 5 mg -4.7 mg vs. -3.0, p =0.004). Tamsulosin had an improvement in baseline score of -5.5, but this was not statistically compared with placebo or either tadalafil dose. This was a poor quality trial; no description of blinding, randomization or allocation concealment was provided. Tamsulosin was included in the trial as an active comparator but was not compared with tadalafil or placebo. In addition, tamsulosin was suboptimally dosed. [11]

1. Filson CP, Hollingsworth JM, Clemens JQ, Wei JT. The Efficacy and Safety of Combined Therapy with α-Blockers and Anticholinergics for Men with Benign Prostatic Hyperplasia: A Meta-Analysis. *The Journal of Urology*. 2013;190(6):2153-2160. doi:10.1016/j.juro.2013.05.058.

2. Gacci M, Corona G, Salvi M, et al. A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with α-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *European Urology*. 2012;61(5):994-1003. doi:10.1016/j.eururo.2012.02.033.

3. Ding H, Du W, Hou Z-Z, Wang H-Z, Wang Z-P. Silodosin is effective for treatment of LUTS in men with BPH: a systematic review. *Asian Journal of Andrology*. 2013;15(1):121-128. doi:10.1038/aja.2012.102.

4. Yuan J, Liu Y, Yang Z, Qin X, Yang K, Mao C. The efficacy and safety of alpha-1 blockers for benign prostatic hyperplasia: an overview of 15 systematic reviews. *Current Medical Research and Opinion*. 2013;29(3):279-287. doi:10.1185/03007995.2013.766594.

5. Oelke M, Bachmann A, Descazeaud A, et al. EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction. *European Urology*. 2013;64(1):118-140. doi:10.1016/j.eururo.2013.03.004.

6. American Urological Association. Benign Prostatic Hyperplasia. *auanet.org*. 2010. Available at: http://www.auanet.org/common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf. Accessed April 6, 2014.

7. Haillot O, Fraga A, Maciukiewicz P, et al. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study. *Prostate Cancer and Prostatic Diseases*. 2011;14(4):302-306. doi:10.1038/pcan.2011.13.

8. Yu H-J, Lin AT-L, Yang SS-D, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH): EFFICACY AND SAFETY OF SILODOSIN VS TAMSULOSIN FOR BPH. *BJU International*. 2011;108(11):1843-1848. doi:10.1111/j.1464-410X.2011.10233.x.

9. Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial. *European Urology*. 2012;61(5):917-925. doi:10.1016/j.eururo.2012.01.013.

10. Chung B-H, Lee SH, Roehrborn CG, et al. Comparison of the response to treatment between Asian and Caucasian men with benign prostatic hyperplasia: Long-term results from the combination of dutasteride and tamsulosin study: BPH treatment in Asian and Caucasian men. *International Journal of Urology*. 2012;19(11):1031-1035. doi:10.1111/j.1442-2042.2012.03091.x.

11. Yokoyama O, Yoshida M, Kim SC, et al. Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A randomized placebo- and tamsulosin-controlled 12-week study in Asian men: Tadalafil for BPH-LUTS in Asian men. *International Journal of Urology*. 2013;20(2):193-201. doi:10.1111/j.1442-2042.2012.03130.x.

Date:

Appendix 1: Prior Authorization Criteria:

Benign Prostatic Hypertrophy (BPH) Medications

Goal(s):

- BPH with urinary obstruction treatment is covered by OHP only when post-void residuals are at least 150ml.
- Cosmetic use for baldness is NOT covered.
- Erectile dysfunction is NOT covered.

* Note: Finasteride is also available as Propecia®, which is FDA-approved for alopecia/male pattern baldness. Alopecia and male pattern baldness are not approvable diagnoses for 5-Alpha Reductase (5AR) Inhibitors.

Length of Authorization: 1 year

Preferred Alternatives: All preferred alternatives on PDL list:
http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pdl.pdf
Requires PA: Non-preferred drugs

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code.	
2. Is the request for a phosphodiesterase type 5 inhibitor (e.g. tadalafil or sildenafil)?	**Yes:** Go to #3	**No:** Go to #5
3. Is the diagnosis pulmonary arterial hypertension (PAH)?	**Yes:** Go to Pulmonary arterial hypertension PA criteria	**No:** Go to #4
4. Is the diagnosis erectile dysfunction?	**Yes:** Pass to RPh; Deny (not covered by OHP).	**No:** Go to #5
5. 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). Reports are available at: http://pharmacy.oregonstate.edu/drug_policy/index.php	**Yes:** Inform Provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pdl.pdf	**No**: Go to #6
6. Is the request for renewal of current therapy?	**Yes: Go to "Renewal Therapy"**	**No: Go to #7**
7. Is the request for an alpha blocker, and does client have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction? (592.1, 595.1, 596.0, 596.3-596.5, 596.54, 596.7-596.9, 598, 599.82-	**Yes:** Go to #8	**No:** Go to #9

Date:

599.89)		
8. Has the client tried and failed a 2-month trial of a covered alternative alpha blocker (terazosin, doxazosin, prazosin, tamsulosin)?	**Yes:** Approve an alpha blocker only for 1 year	**No:** Deny until client has tried and failed a covered alternative
9. Does client have a diagnosis of BPH (Benign Prostatic Hypertrophy) or enlarged prostate with obstruction? (600.01, 600.11, 600.21, and 600.91; 788.2 + 600.xx see RPH notes)	**Yes:** Approve for the shorter of 1 year or length of the prescription	**No:** Go to #10
10. Does client have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction? **(599.6, 600.00, 600.10, 600.20, and 600.90**)	**Yes:** Pass to RPH; Deny, (Not Covered by the OHP)	**No:** Pass to RPH; Go to #11
11. RPH Notes only - All other indications need to be evaluated to see if they are above or below the line: **Above the line** covered diagnoses related to prostate may be approved for 1 year **Below the line** diagnoses (e.g. Hair growth, erectile dysfunction) should be denied (Not Covered by the OHP). Alpha Blockers and 5-alpha reductase inhibitors (ARI) may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size. • 788.2 (retention of urine, obstructive); Ask for more specific diagnosis. If along with 600.01, 600.11, 600.21 or 600.91, then may approve. Refer questions of coverage to DMAP.		

Renewal Therapy		
1. Is the request for an alpha blocker, and does client have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction? (592.1, 595.1, 596.0, 596.3-596.5, 596.54, 596.7-596.9, 598, 599.82-599.89)	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient also been taking a 5-alpha reductase inhibitor for the last year?	**Yes:** Recommend against combination therapy exceeding 1 year	**No:** Approve for the shorter of 1 year or length of the prescription
3. Does client have a diagnosis of BPH (Benign Prostatic Hypertrophy) or enlarged prostate with obstruction? (600.01, 600.11, 600.21, and 600.91; 788.2 + 600.xx see RPH notes)	**Yes:** Approve for 1 year	**No:** Go to #4
4. Does client have a diagnosis of unspecified urinary obstruction or	**Yes:** Pass to RPH;	**No:** Pass to RPH;

Date:

benign prostatic hyperplasia without obstruction? **(599.6, 600.00, 600.10, 600.20, and 600.90**)	Deny, (Not Covered by the OHP)	Go to #5
5. RPH only All other indications need to be evaluated as to whether they are above the line or below the line diagnosis. • Alpha Blockers and 5-alpha reductase inhibitors (ARI) may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size. • 788.2 (retention of urine, obstructive); Ask for more specific diagnosis. If along with 600.01, 600.11, 600.21 or 600.91, then may approve.	**If above the line or clinic provides supporting literature:** approve for one year.	**If below the line:** Deny, (Not Covered by the OHP).

DUR Board Action: 9/16/10 (KS), 3/18/10(KK), 5-22-08, 2-23-06
Revision(s): 11/29/12 (MH), 1/1/11, 4/20/10, 5-22-08 (Aebi), 7-1-06, 9-30-05
Effective: 10-14-04 (previously excluded)

Date:

Appendix 2: Abstracts of Randomized Controlled Trials:

Haillot O, Fraga A, Maciukiewicz P, et al. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study. *Prostate Cancer and Prostatic Diseases*. 2011;14(4):302-306.
CombAT (Combination of Avodart and Tamsulosin) was a randomised, double-blind study in men (n=4844) aged > 50 years with a clinical diagnosis of BPH. Patients were randomised to daily tamsulosin 0.4 mg, dutasteride 0.5 mg or both for 4 years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary endpoints included BPH clinical progression, symptoms and maximum urinary flow rate. A post hoc analysis of data from the European subgroup was conducted. A total of 2925 men were randomised to treatment in Europe as part of CombAT (tamsulosin, n=972; dutasteride, n=970; combination, n=983). Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery compared with either monotherapy at 4 years, and also significantly reduced the risk of BPH clinical progression. Combination therapy also provided significantly greater symptom improvement than either monotherapy at 4 years. Safety and tolerability of dutasteride plus tamsulosin was consistent with previous experience of this combination and with the monotherapies. These data provide further evidence to support the use of long-term combination therapy (dutasteride plus tamsulosin) in men with moderate-to-severe lower urinary tract symptoms because of BPH and prostatic enlargement. The results in the European subgroup are generally consistent with those in the overall study population.

Yu H-J, Lin AT-L, Yang SS-D, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH): EFFICACY AND SAFETY OF SILODOSIN VS TAMSULOSIN FOR BPH. *BJU International*. 2011;108(11):1843-1848
OBJECTIVE To test the hypothesis that the efficacy of silodosin would not be inferior to tamsulosin in treating patients with lower urinary tract symptoms associated with benign prostate hyperplasia (BPH).
PATIENTS AND METHODS At nine medical centres, 209 patients with an International Prostate Symptom Score (IPSS) of ≥ 13 were randomized to silodosin (4 mg twice daily) or tamsulosin (0.2 mg once daily) for 12 weeks. The primary efficacy measure was the mean change from baseline to endpoint in IPSS. The non-inferiority margin of the IPSS change was set at 1.0. Secondary efficacy measures included change in maximal urinary flow rate (Q max) and health-related quality of life (HRQL) score.
RESULTS Of the 170 (81.3%) patients who completed the study, 86.2% in the silodosin group vs 81.9% in the tamsulosin group achieved a ≥ 25% decrease in IPSS (=0.53). The mean difference (silodosin minus tamsulosin) in IPSS change from baseline was − 0.60 (95% confidence interval − 2.15, 0.95), inferring the non-inferiority of silodosin to tamsulosin. The mean changes in the Q max and HRQL score from baseline were comparable between the groups (both, *P* >0.05). Although patients receiving silodosin had a significantly higher incidence of abnormal ejaculation (9.7% vs tamsulosin 1.0%, *P*=0.009), only 1.9% discontinued treatment. Tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure (−4.2 mmHg, within-group *P*=0.004) relative to the negligible change of silodosin (−0.1 mmHg, within-group *P*=0.96)
CONCLUSION The trial shows the non-inferiority of silodosin 4 mg twice daily to tamsulosin 0.2 mg once daily in patients with symptomsof BPH.

Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial. *European Urology*. 2012;61(5):917-925.
Background: Tadalafil improved lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH; LUTS/BPH) in clinical studies but has not been evaluated together with an active control in an international clinical study.
Objective: Assess tadalafil or tamsulosin versus placebo for LUTS/BPH.Design, setting, and participants: A randomised, double-blind, international, placebocontrolled, parallel-group study assessed men _45 yr of age with LUTS/BPH, International Prostate Symptom Score (IPSS) _13, and maximum urinary flow rate (Qmax) _4 to _15 ml/s. Following screening and washout, if needed, subjects completed a 4-wk placebo run-in before randomisation to placebo (n = 172), tadalafil 5 mg (n = 171), or tamsulosin 0.4 mg (n = 168) once daily for 12 wk.
Measurements: Outcomes were assessed using analysis of covariance (ANCOVA) or ranked analysis of variance (ANOVA) (continuous variables) and Cochran-Mantel-Haenszel test or Fisher exact test (categorical variables).
Results and limitations: IPSS significantly improved versus placebo through 12 wk with tadalafil (_2.1; p = 0.001; primary efficacy outcome) and tamsulosin (_1.5; p = 0.023) and as early as 1 wk (tadalafil and tamsulosin both _1.5; p < 0.01). BPH Impact Index significantly improved versus placebo at first assessment (week 4) with tadalafil (_0.8; p < 0.001) and tamsulosin (_0.9; p < 0.001) and through 12 wk (tadalafil _0.8, p = 0.003; tamsulosin _0.6, p = 0.026). The IPSS Quality-of-Life Index and the Treatment Satisfaction Scale–BPH improved significantly versus placebo with tadalafil (both p < 0.05) but not with tamsulosin (both p > 0.1). The International Index of Erectile Function–Erectile Function domain improved versus placebo with tadalafil (4.0; p < 0.001) but not tamsulosin (_0.4; p = 0.699). Qmax increased significantly versus placebo with both tadalafil (2.4 ml/s; p = 0.009) and tamsulosin (2.2 ml/s; p = 0.014). Adverse event profiles were consistent with previous reports. This study was limited in not being powered to directly compare tadalafil versus tamsulosin.
Conclusions: Monotherapy with tadalafil or tamsulosin resulted in significant and numerically similar improvements versus placebo in LUTS/BPH and Qmax. However,only tadalafil improved erectile dysfunction.

Chung B-H, Lee SH, Roehrborn CG, et al. Comparison of the response to treatment between Asian and Caucasian men with benign prostatic hyperplasia: Long-term results from the combination of dutasteride and tamsulosin study: BPH treatment in Asian and Caucasian men. *International Journal of Urology*. 2012;19(11):1031-1035.

Date:

The Combination of Avodart and Tamsulosin study was a 4-year, randomized, double-blind study of the efficacy and safety of dutasteride and tamsulosin, alone or in combination, in men with moderate-to-severe benign prostatic hyperplasia. In this post-hoc investigation, we analyzed primary and secondary end-points from the Combination of Avodart and Tamsulosin study in Asian (*n* = 325) and Caucasian men (*n* = 4259). The incidence of acute urinary retention or benign prostatic hyperplasiarelated
surgery did not differ significantly between treatment groups in the Asian subpopulation. In Caucasian men, the incidence of acute urinary retention/benign prostatic hyperplasia-related surgery was significantly lower in the combination therapy group
compared with the tamsulosin monotherapy group ($P < 0.001$), but not compared with dutasteride monotherapy. Combination therapy significantly increased the time to benign prostatic hyperplasia clinical progression and resulted in improved International Prostate Symptom Score, maximum urinary flow rate, quality of life, and reduced prostate volume in Asian and Caucasian men who received combination therapy compared with tamsulosin monotherapy. Combination therapy also significantly improved ($P < 0.05$) time to benign prostatic hyperplasia clinical progression, International Prostate Symptom Score, maximum urinary flow rate and quality of life versus dutasteride in the Caucasian subpopulation. The adverse-event profile was comparable between subpopulations. In conclusion, Asian and Caucasian men respond similarly to these treatments, despite apparent racial differences in 5a-reductase activity.

Yokoyama O, Yoshida M, Kim SC, et al. Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A randomized placebo- and tamsulosin-controlled 12-week study in Asian men: Tadalafil for BPH-LUTS in Asian men. *International Journal of Urology*. 2013;20(2):193-201.

Objectives: To examine the efficacy and safety of tadalafil in Asian men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Methods: Asian men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia were randomized to once-daily placebo (*n* = 154), tadalafil 2.5 mg (*n* = 151), tadalafil 5.0 mg (*n* = 155) or tamsulosin 0.2 mg (active control, *n* = 152) for 12
weeks.

Results: Total International Prostate Symptom Score least-squares mean changes from baseline to end-point significantly improved with tadalafil 2.5 mg (-4.8, $P = 0.003$) and 5 mg (-4.7, $P = 0.004$) versus placebo (-3.0). Significant improvement in the International Prostate Symptom Score versus placebo was observed earlier (week 2) for tadalafil 5.0 mg than for tadalafil 2.5 mg (week 8). Significant improvements ($P < 0.05$) in both tadalafil groups versus placebo were observed for the International Prostate Symptom Score voiding subscore, International Prostate Symptom Score Quality of Life, and for Patient and Clinician Global Impressions of Improvement. Significant improvements versus placebo were observed in the International Prostate Symptom Score storage subscore for tadalafil 5.0 mg (-1.7, $P = 0.021$), but not tadalafil 2.5 mg (-1.5, $P = 0.072$). No significant improvements in benign prostatic hyperplasia Impact Index or improvements in peak urinary flow rates were observed with tadalafil 2.5 mg or 5.0 mg versus placebo. Tamsulosin treatment resulted in significant improvements versus placebo across all efficacy parameters, except for peak urinary flow rates. Safety results were consistent with the known tadalafil and tamsulosin safety profiles.

Conclusions: Tadalafil once daily represents an effective and well tolerated medical treatment for Asian men presenting with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Date:

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Month/Year of Review: March 2014
PDL Classes: Overactive Bladder Drugs

Date of Last Review: January 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: FESOTERODINE FUMARATE (TOVIAZ®), HYOSCYAMINE SULFATE ELIXIR/TAB REDIS, OXYBUTYNIN SYRUP/TAB/TAB ER 24
- Non-Preferred Agents: TROSPIUM TABLET/CAP ER (SANCTURA®/SANCTURA XR®), OXYBUTYNIN GEL (GELNIQUE®), DARIFENACIN TAB ER (ENABLEX®), SOLIFENACIN SUCCINATE TABLET (VESICARE®), TOLTERODINE, TOLTERODINE ER (DETROL LA®), FLAVOXATE, MIRABEGRON (MYRBETRIQ)

Previous Conclusions and Recommendation:

- There is no evidence supporting a difference in efficacy or harms between agents.
- There is low quality evidence that comparisons of extended-release and immediate release formulations tend to find higher rates of adverse events, particularly dry mouth, with immediate release formulations, however no differences in discontinuation rates were found.
- There is low-moderate quality evidence, based on limited published data, that mirabegron improves short term efficacy outcomes including change in mean number of incontinence episodes and micturitions in 24 hours, compared to placebo and is generally well tolerated. Data is from two short term (12 week), published trials (fair-good quality).
- There is insufficient direct evidence comparing mirabegron to other agents for the treatment of OAB. Make mirabegron non-preferred.

PA Criteria: None

Conclusions and Recommendations:

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

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

References:

1. Selph S. Drug Effectiveness Review Porject. Drug Class Review on Overactive Bladder Drugs. Preliminary Scan Report #1. February 2014.

Drug Class Review
on
Overactive Bladder Drugs

Preliminary Scan Report #1

February 2014

Last Summary Review (June 2013)

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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

Scan prepared by Shelley S. Selph, MD

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. 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 FDA since the last report. Other important studies could exist.

Date of Report:

A Summary Review of this topic was completed in June 2013, with searches through May 2013.

Date of Previous Update Scans:

This is the first preliminary update scan since the Summary Review.

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 from existing comparative systematic reviews on the efficacy and effectiveness of the overactive bladder drugs in adults?

2. What is the evidence from existing comparative systematic reviews on the harms of overactive bladder drugs in adults?

3. What is the evidence from existing comparative systematic reviews 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

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
- Noncomparative 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

Literature Search
To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from May 2013 through February Week 1 2014 using terms for included

drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. To identify recent comparative effectiveness reviews, we searched the websites of the US Agency for Healthcare Research and Quality (www.ahrq.gov), 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). and the Canadian Agency for Drugs and Technologies in Health (www.CADTH.ca). We also searched FDA http://www.fda.gov/Drugs/DevelopmentApproval Process/DrugInnovation/ucm336115 .htm and (http://www.centerwatch.com/drug-information/fda-approvals), as well as, (http://www.fda.gov/medwatch/safety.htm) websites for identification of new drugs, indications, and safety alerts.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

No new drugs.

New Indications

No new indications.

Boxed Warnings

No new box warnings

Comparative Effectiveness Reviews

No new comparative effectiveness reviews were identified through searches of the AHRQ, CADTH, VA, and CRD websites.

Randomized Controlled Trials

Medline searches resulted in 36 citations. Of those, 11 were potentially relevant new head-to-head or placebo-controlled trials. An additional 13 trials were previously reported in the Summary Review as published since the search dates of the included systematic reviews for a total of 24 new trials (eight head-to-head studies and 16 placebo-controlled trials). (Table 1). See Appendix A for abstracts of new studies. 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. Potentially relevant overactive bladder trials since summary review

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
Cardozo, 2013	591	Solifenacin 5 mg	Placebo	Patients requesting dose increase were rerandomized at 8 weeks to solfinacin 5 or 10 mg
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
Herschorn, 2013	1,305	Mirabegron 25 or 50 mg	Placebo	Phase III trial, patients > 18 years with OAB symptoms
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
Kaplan, 2012	943	Fesoterodine 4 mg	Placebo	Men with persistent storage after receiving alpha blocker, could increase fesoterodine to 8 mg
Kaplan, 2013a	398	Solifenacin plus Tamsulosin	Placebo plus Tamsulosin	Men with residual urgency and frequency
Kaplan, 2013b	222	Solifenacin 6 or 9 mg plus Tamsulosin	Placebo	Men > 45 with lower urinary tract symptoms with bladder outlet obstruction
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
Lee, 2011	176	SR Tolterodine 4 mg plus Doxazosin	Placebo plus Doxazosin	Men aged 50 or older with BPH
Nitti, 2013a	200	Mirabegron 50 or 100 mg	Placebo	All men with lower urinary tract symptoms and bladder outlet obstruction
Niti, 2013b	1,329	Mirabegron 50 or	Placebo	Patients had PAB symptoms

		100 mg		for at least 3 months
Oreskovic, 2012	171	Solifenacin 5 mg	Placebo	Patients had OAB symptoms for at least 6 months
Sand, 2012	704	Oxybutynin topical gel	Placebo	Phase-3 study enrolling all women with urgency-predominant urinary incontinence
Staskin, 2011	883	Fesoterodine 4 mg with optional increase to 8 mg	Placebo	Post-hoc analysis of 2010 study on effect of voluntary dose escalation
Wagg, 2013	794	Fesoterodine 4 mg with optional increase to 8 mg	Placebo	Patients had OAB symptoms for at least 3 months
Weiss, 2013	963	Fesoterodine 4 mg with optional increase to 8 mg	Placebo	Subjects with 2-8 nocturnal urgency episodes per 24 hours
Yamaguchi, 2011	638	Solifenacin 2.5 or 5 mg plus Tamsulosin	Placebo plus Tamsulosin	Men with lower urinary tract symptoms
Yokoyama, 2011	962	Solifenacin 5 or 10 mg	Placebo	Subgroup analysis, Japanese patients, compared changes in nocturia and sleep

SUMMARY

Twenty-four new trials, including eight head-to-head studies, were identified. With the exception of one small trial in women (n=77) which compared darifenacin with solifenacin, the newer OAB drugs were compared with tolterodine, oxybutynin and/or placebo.

Appendix A. Abstracts of potentially relevant new OAB trials (N=24)

Head-to-head trials (N=8)

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.

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.

Placebo-controlled trials (N=16)

Cardozo L. Amarenco G. Pushkar D. Mikulas J. Drogendijk T. Wright M. Compion G. SUNRISE Study Group. Severity of overactive bladder symptoms and response to dose escalation in a randomized, double-blind trial of solifenacin (SUNRISE). BJU International. 111(5):804-10, 2013 May.

UNLABELLED: WHAT'S KNOWN ON THE SUBJECT? AND WHAT DOES THE STUDY ADD?: Antimuscarinics are effective and well tolerated for treatment of OAB. Studies have found that a flexible dosing strategy can be effective in improving OAB symptoms with minimal impact on tolerability. This study confirms these findings with two doses of solifenacin, and shows that improved outcomes can be achieved by increasing solifenacin dose (from 5 to 10 mg) in patients with more severe symptoms.
OBJECTIVE: To determine the relationship between severity of baseline overactive bladder (OAB) symptoms and requests for solifenacin dose increases, and the efficacy of 5 and 10 mg solifenacin doses in relieving OAB symptoms in patients who requested a dose increase.
PATIENTS AND METHODS: In a 16-week clinical study, patients with OAB were randomized to double-blind treatment with solifenacin or placebo once daily. At week 8, all patients could request a dose increase; these patients entered a second phase of 8 weeks in which those in the solifenacin group were randomized to either 5 or 10 mg doses. The primary efficacy variable was mean change in the number of urgency episodes with or without incontinence per 24 h, measured using the Patient Perception of Intensity of Urgency Scale (PPIUS; grades 3 and 4).
RESULTS: Of 591 patients receiving solifenacin at 8 weeks, 275 (46.5%) requested a dose increase to 10 mg, and were further randomized to receive 10 mg (n = 140) or to remain on 5 mg (n = 135). Patients who requested a dose increase at week 8 generally had more severe OAB symptoms at baseline and a smaller response at week 8 to the initial solifenacin 5 mg dosage than those who did not. Greater reductions in the mean number of severe urgency episodes (PPIUS grades 3 and 4) were observed from week 8 to the end of treatment for patients requesting a dose increase and randomized to 10 mg solifenacin compared with those randomized to remain on 5 mg (mean reductions -0.9 vs -0.4, respectively), although these did not reach statistical significance. Statistically significant reductions were observed in mean total urgency score (TUS; -2.7 vs -0.6; P = 0.010), mean maximum PPIUS urgency rating (-0.3 vs -0.1; P = 0.034) and mean micturition frequency (-0.8 vs -0.1; P = 0.037). For all other OAB variables, greater changes were observed in the solifenacin 10 mg group but these did not reach statistical significance. Of those who requested a dose increase, eight (5.7%) patients randomized to receive 10 mg and one (0.7%) patient randomized to remain on 5 mg reported new or worsening cases of dry mouth.
CONCLUSIONS: Increasing the solifenacin dose to 10 mg further improved OAB symptoms in patients who requested a dose increase after 8 weeks' treatment with 5 mg

solifenacin. The present study supports the view that patients with severe OAB symptoms benefit from a higher antimuscarinic dose.

Herschorn S. Barkin J. Castro-Diaz D. Frankel JM. Espuna-Pons M. Gousse AE. Stolzel M. Martin N. Gunther A. Van Kerrebroeck P. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder.[Erratum appears in Urology. 2013 Dec;82(6):1457] Urology. 82(2):313-20, 2013 Aug.

OBJECTIVE: To assess the efficacy and tolerability of mirabegron 25 mg and 50 mg once-daily vs placebo in patients with overactive bladder (OAB).

MATERIALS AND METHODS: Patients >18 years with OAB symptoms were recruited to a 2-week, single-blind, placebo run-in. Those with >8 micturitions per 24 hours and >3 urgency episodes were randomized 1:1:1 to once-daily mirabegron 25 mg or 50 mg, or placebo for 12 weeks. Primary endpoints were changes to final visit in mean number of incontinence episodes and micturitions per 24 hours. Key secondary endpoints were changes to final visit in mean volume voided or micturition, change to week 4 in mean number of incontinence episodes and micturitions per 24 hours, changes to final visit in mean level of urgency, number of urgency incontinence episodes, and urgency (grade 3 or 4) episodes per 24 hours. Patient-reported outcomes were assessed using the OAB-questionnaire, Patient Perception of Bladder Condition, and Treatment-Satisfaction-Visual Analog Scale.

RESULTS: Both mirabegron groups demonstrated statistically significant improvements in coprimary endpoints vs placebo. Mirabegron 50 mg demonstrated significantly greater improvements vs placebo in the following: change to final visit in mean volume voided per micturition and change to week 4 in mean number of incontinence episodes per 24 hours. Statistically significant improvements vs placebo were demonstrated by mirabegron 50 mg in all patient-reported outcome scales with no increase in the incidence of treatment-emergent adverse events vs placebo.

CONCLUSION: Mirabegron 25 mg and 50 mg were associated with significant improvements in efficacy measures of incontinence episodes and micturition frequency. Mirabegron was well tolerated vs placebo.

Kaplan, S. A., C. G. Roehrborn, et al. (2012). "Add-on fesoterodine for residual storage symptoms suggestive of overactive bladder in men receiving -blocker treatment for lower urinary tract symptoms." BJU International **109**(12): 1831-1840.

UNLABELLED: Study Type - Therapy (RCT) Level of Evidence 1b What's known on the subject? and What does the study add? Male lower urinary tract symptoms are often attributed to bladder outlet obstruction secondary to benign prostatic hyperplasia and treated with drugs targeting the prostate. However, many men with storage lower urinary tract symptoms may not respond adequately to these agents. Antimuscarinics, with or without an -blocker, may be effective for the treatment of the storage symptoms of overactive bladder in some men. Flexible-dose fesoterodine as an add-on treatment significantly improved urinary frequency and symptom bother, but not urgency episodes (primary endpoint), versus add-on placebo and was well tolerated in men with persistent overactive bladder symptoms despite receiving -blocker.

OBJECTIVE: * To evaluate flexible-dose fesoterodine vs placebo in men with persistent overactive bladder (OAB) symptoms despite receiving -blocker treatment

SUBJECTS AND METHODS: * This was a double-blind, 12-week, flexible-dose trial. * Men with persistent storage symptoms (>= 8 micturitions and >= 3 urgency episodes per 24 h) after receiving an -blocker for >= 6 weeks were randomized to add-on fesoterodine 4 mg or placebo, with optional dose escalation to 8 mg at week 4 and reduction back to 4 mg at week 8 (or matching placebo adjustments). * Subjects completed 3-day diaries, International Prostate Symptom Score (IPSS), Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) at baseline and weeks 4 and 12.
RESULTS: * A total of 943 men were randomized and received at least one dose of study treatment (fesoterodine, n= 471; placebo, n= 472). * Among these, 251 (53%) in the fesoterodine group and 300 (64%) in the placebo group requested dose escalation at week 4 and 35 (7%) and 15 (3%) requested dose reduction at week 8. Changes from baseline to week 12 in urgency episodes (primary endpoint) in the fesoterodine (-3.2) and placebo (-2.9) groups were not significantly different (P= 0.196), but improvements in micturitions (P= 0.009) and OAB-q symptom bother score (P= 0.007) were significantly greater with fesoterodine. * At week 4, significantly greater improvements in micturitions (P= 0.006), severe urgency episodes (P= 0.006), IPSS storage score (P= 0.022), OAB-q symptom bother score (P= 0.004), and OAB-q health-related quality of life (P= 0.041), but not urgency episodes (P= 0.062), were observed with add-on fesoterodine. * Dry mouth (fesoterodine, 21%; placebo, 6%) and constipation (fesoterodine, 6%; placebo, 2%) were the most common adverse events. Dysuria and urinary retention were reported by 3% and 2% of subjects, respectively, in the fesoterodine add-on group vs 1% and <1% of subjects, respectively in the placebo add-on group. One subject in each group had acute urinary retention requiring catheterization.
CONCLUSIONS: * Flexible-dose fesoterodine was well tolerated as an add-on treatment in men with persistent storage symptoms. * Changes in urgency episodes at week 12 (primary endpoint) and many secondary endpoints were not significantly different between fesoterodine and placebo add-on treatment; however, improvements in frequency and symptom bother were significantly greater with fesoterodine. * These data suggest that there remains a limited understanding of the optimal evaluation and treatment of men with LUTS.

Kaplan, S. A., K. McCammon, et al. (2013). "Safety and tolerability of solifenacin add-on therapy to -blocker treated men with residual urgency and frequency." Journal of Urology **189**(1 Suppl): S129-134.

PURPOSE: VICTOR was a 12-week, double-blind, placebo controlled trial assessing the safety and tolerability of solifenacin plus tamsulosin in men with residual overactive bladder symptoms after tamsulosin monotherapy. Efficacy of solifenacin plus tamsulosin vs placebo plus tamsulosin was also evaluated.
MATERIALS AND METHODS: A total of 398 men 45 years old or older were randomized to 12 weeks of solifenacin plus tamsulosin or placebo plus tamsulosin once daily. The study population had 8 or more micturitions per 24 hours and 1 or more urgency episode per 24 hours after taking tamsulosin for 4 or more weeks, a total International Prostate Symptom Score of 13 or greater, a Patient Perception of Bladder Condition score of 3 or greater, a post-void residual of 200 ml or less and a peak flow rate of 5 ml per second or greater. Adverse events were monitored throughout the study. The primary efficacy end point was mean change from baseline to week 12 in

micturitions per 24 hours. Secondary measures included mean change in urgency episodes per 24 hours, and changes in Patient Perception of Bladder Condition, Urgency Perception Scale and total International Prostate Symptom Scores.
RESULTS: The most frequent adverse events in the solifenacin plus tamsulosin and placebo plus tamsulosin groups were dry mouth (7% and 3%, respectively) and dizziness (3% and 2%, respectively). Of the patients on solifenacin plus tamsulosin 7 (3%) reported retention and 3 required catheterization. No patients on placebo plus tamsulosin reported retention. Patients on solifenacin plus tamsulosin vs placebo plus tamsulosin showed larger reductions in frequency but not of statistical significance (-1.05 vs -0.67, p = 0.135). However, patients on solifenacin plus tamsulosin vs placebo plus tamsulosin did show statistically significant reductions in urgency (-2.18 vs -1.10, p <0.001). Patient reported outcome measures showed no significant between group differences.
CONCLUSIONS: Solifenacin plus tamsulosin was well tolerated. There was a low incidence of urinary retention requiring catheterization. At week 12 solifenacin plus tamsulosin decreased daily micturitions and urgency episodes. Only urgency reached statistical significance vs placebo plus tamsulosin.

Kaplan SA. He W. Koltun WD. Cummings J. Schneider T. Fakhoury A. Solifenacin plus tamsulosin combination treatment in men with lower urinary tract symptoms and bladder outlet obstruction: a randomized controlled trial. European Urology. 63(1):158-65, 2013 Jan.

BACKGROUND: Alpha blockers are prescribed to manage lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Antimuscarinics are prescribed to treat overactive bladder (OAB).
OBJECTIVE: To investigate the safety of a combination of solifenacin (SOLI) and tamsulosin oral controlled absorption system (TOCAS) in men with LUTS and bladder outlet obstruction (BOO).
DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, parallel-group, placebo-controlled study in men aged >45 yr with LUTS and BOO for >3 mo, total International Prostate Symptom Score (IPSS) >8, BOO index >20, maximum urinary flow rate (Q(max)) <12 ml/s, and voided volume >120 ml.
INTERVENTIONS: Once-daily coadministration of TOCAS 0.4 mg plus SOLI 6 mg, TOCAS 0.4 mg plus SOLI 9 mg, or placebo for 12 wk.
OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Primary (safety) measurements: Q(max) and detrusor pressure at Q(max) (P(det)Q(max)). Other safety assessments included postvoid residual (PVR) volume. Secondary end points included bladder contractile index (BCI) score and percent bladder voiding efficiency (BVE). An analysis of covariance model compared each TOCAS plus SOLI combination with placebo.
RESULTS AND LIMITATIONS: Both active treatment groups were noninferior to placebo at end of treatment (EOT) for P(det)Q(max) and Q(max). Mean change from baseline PVR was significantly higher at all time points for TOCAS 0.4 mg plus SOLI 6 mg, and at weeks 2, 12, and EOT for TOCAS 0.4 mg plus SOLI 9 mg versus placebo. Both treatment groups were similar to placebo for BCI and BVE. Urinary retention was seen in only one patient receiving TOCAS 0.4 mg plus SOLI 6 mg. Limitations of the study were that prostate size and prostate-specific antigen level were not measured.

CONCLUSIONS: TOCAS 0.4 mg plus SOLI 6 mg or 9 mg was noninferior to placebo at EOT for P(det)Q(max) and Q(max) in men with LUTS and BOO, and there was no clinical or statistical evidence of increased risk of urinary retention.

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.

Lee, S. H., B. H. Chung, et al. (2011). "Initial combined treatment with anticholinergics and -blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: a prospective, randomized, multi-center, double-blind, placebo-controlled study." Prostate Cancer & Prostatic Diseases **14**(4): 320-325.

We aimed to evaluate the efficacy and safety of combination treatment using anticholinergics with -blocker for initial treatment of both overactive bladder (OAB) and other lower urinary tract symptoms (LUTS), secondary to BPH. A 12-week, randomized, double-blind, placebo-controlled trial was conducted at four urology clinics in Korea, involving men, aged 50 years or older, with LUTS related to BPH and OAB. A total of 176 patients were randomly assigned to receive doxazosin (4 mg) plus placebo or doxazosin (4 mg) plus tolterodine SR (4 mg), once a day for 12 weeks. Changes from baseline in total International Prostate Symptom Score (IPSS), bladder diary variables, patient perception of bladder condition (PPBC), uroflowmetry, postvoid residual volume and IPSS subscores (voiding and storage) were analyzed. Of the 176 enrolled patients, 91 had doxazosin gastrointestinal therapeutic system (GITS) and placebo, and 85 had combined medication with doxazosin GITS and tolterodine SR. Compared with the doxazosin plus placebo group, the doxazosin plus tolterodine group showed significant reductions in IPSS storage subscore and improvement in the quality of life item, urgency episodes, as well as in micturition frequency at weeks 4 and 12. However, it failed to

improve PPBC at week 4 as well as at week 12. Earlier intervention with anticholinergics plus -blocker was tolerated well, including the questions about urinary retention (n=1) and dry mouth (n=2). Initial combination treatment of anticholinergics plus -blocker showed positive results for men with LUTS related to BPH and OAB symptoms and did not increase the risk of urinary retention.

Nitti VW. Rosenberg S. Mitcheson DH. He W. Fakhoury A. Martin NE. Urodynamics and safety of the beta3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. Journal of Urology. 190(4):1320-7, 2013 Oct.

PURPOSE: Bladder outlet obstruction often presents as storage and voiding symptoms. We investigated urodynamic parameters in men with lower urinary tract symptoms and bladder outlet obstruction treated with the beta3 agonist mirabegron, a new therapy for overactive bladder symptoms.

MATERIALS AND METHODS: A total of 200 men 45 years old or older with lower urinary tract symptoms and bladder outlet obstruction were randomized to receive once daily mirabegron 50 mg (70) or 100 mg (65), or placebo (65) for 12 weeks. The primary urodynamic parameters assessed were change from baseline to end of treatment in maximum urinary flow and detrusor pressure at maximum urinary flow (noninferiority margins -3 ml per second and 15 cm H2O, respectively). We evaluated adverse events and vital signs.

RESULTS: Treatment with mirabegron 50 and 100 mg was noninferior to placebo based on the lower and upper limits of the 95% CI, respectively, for maximum urinary flow and detrusor pressure at maximum urinary flow. The adjusted mean difference vs placebo was 0.40 (95% CI -0.63, 1.42) and 0.62 ml per second (95% CI -0.43, 1.68) for maximum urinary flow, and -5.94 (95% CI -13.98, 2.09) and -1.39 cm H2O (95% CI -9.73, 6.96), respectively, for detrusor pressure at maximum urinary flow. The incidence of adverse events was similar for mirabegron and placebo.

CONCLUSIONS: Mirabegron did not adversely affect voiding urodynamics (maximum urinary flow and detrusor pressure at maximum urinary flow) compared with placebo after 12 weeks of treatment.

Nitti VW. Auerbach S. Martin N. Calhoun A. Lee M. Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. Journal of Urology. 189(4):1388-95, 2013 Apr.

PURPOSE: Many patients with overactive bladder discontinue pharmacotherapy due to suboptimal efficacy or side effects. Mirabegron, a beta3-adrenoceptor agonist, may offer an effective and well tolerated alternative treatment for overactive bladder.

MATERIALS AND METHODS: A randomized, double-blind, placebo controlled trial was conducted in the United States and Canada. After a 2-week placebo run-in period, adults with overactive bladder symptoms for 3 or more months were randomized 1:1:1 to receive placebo, 50 or 100 mg mirabegron once daily for 12 weeks. Efficacy data were collected via patient completed diaries and quality of life assessments. Co-primary efficacy end points were changes from baseline to final visit in mean number of incontinence episodes per 24 hours and micturitions per 24 hours. Key secondary micturition and incontinence end points were also evaluated. Safety assessments included

treatment emergent adverse events, laboratory assessments, vital signs, electrocardiograms and post-void residual volume.
RESULTS: Compared to placebo, 50 and 100 mg mirabegron groups demonstrated statistically significantly greater mean decreases (95% CI) from baseline for incontinence episodes (-1.13 [-1.35, -0.91], -1.47 [-1.69, -1.25] and -1.63 [-1.86, -1.40]) and micturitions (-1.05 [-1.31, -0.79], -1.66 [-1.92, -1.40] and -1.75 [-2.01, -1.48]) per 24 hours ($p < 0.05$). Significant improvements in all key secondary end points were observed for both mirabegron doses vs placebo. The incidence of frequently reported treatment emergent adverse events (hypertension, urinary tract infection, headache, nasopharyngitis) was similar in the mirabegron and placebo groups. Dry mouth was reported for 1.5%, 0.5% and 2.1% of patients in the placebo, 50 and 100 mg mirabegron groups, respectively.
CONCLUSIONS: Once daily mirabegron in a 50 or 100 mg dose is an effective treatment for overactive bladder symptoms with a low occurrence of side effects.

Oreskovic, S., I. But, et al. (2012). "The efficacy and safety of solifenacin in patients with overactive bladder syndrome." Collegium Antropologicum **36**(1): 243-248.

The aim of the randomised, double blind, placebo controlled study was to evaluate the efficacy, tolerability and safety of solifenacin, a once-daily M3 selective receptor antagonist, in patients with overactive bladder syndrome. Following a single blind 2-week placebo run in period, patients who complained from symptoms of OAB for at least 6 months, were randomized to 4 weeks of solifenacin in 5 mg once daily doses or placebo. 171 patients were enrolled in the study and 157 patients completed the study. Patients with solifenacin had significantly improved micturitions per 24 hours after first week of treatment (1.75 +/- 0.63 vs. 2.64 +/- 0.48, $p < 0.001$), and after four weeks (1.56 +/- 0.58 vs. 2.71 +/- 0.45, $p < 0.001$) compared to placebo group. The mean number of urgency episodes per 24 hours had significantly decreased in patients with solifenacin compared to placebo after first week (5.75 +/- 1.43 vs. 6.65 +/- 0.65, $p < 0.001$), and after four weeks of treatment (5.77 +/- 1.33 vs. 6.54 +/- 0.50, $p < 0.001$). Solifenacin was also significantly more effective than placebo in reducing the mean number of episodes of severe urgency from baseline to end point (5.83 +/- 1.16 vs. 6.48 +/- 0.50, $p < 0.001$). Compared with changes obtained with placebo, episodes of urinary frequency were significanlty reduced after first week (0.3 vs. -0.5, $p < 0.001$) and four weeks check up periods in patients treated with solifenacin (0.19 vs. -0.15, $p < 0.001$). Episodes of nocturia was significantly reduced in patients treated with solifenacin after first week (0.3 vs. -0.5, $p < 0.001$), and after four weeks treatment period (0.45 vs. -0.50, $p < 0.001$). The number of incontinence episodes was also significantly decreased in solifenacin group compared to placebo group after first week (1.06 +/- 0.57 vs. 2.74 +/- 0.47, $p < 0.001$) and four weeks check up (0.96 +/- 0.57 vs. 2.75 +/- 0.43, $p < 0.001$). The most common adverse effects with solifenacin were dry mouth and constipation. Adverse effects were mild or moderate severity. The discontinuation rate owing to adverse effects was 4.5%-6.7% with solifenacin and 3.8%-6.1% with placebo, respectively. According to subjective estimation, significant improvement was achieved in 71 (92.21%) of patients treated with solifenacin and in 68 (85%) patients treated with placebo there was no change in OAB symptoms compared to baseline values. UDI score was significantly improved after solifenacin (22.26 +/- 5.91 vs. 29.61 +/- 8.45, $p < 0.001$) compared to placebo. IIQ score was significantly decreased in patients with solifenacin (36.25 +/- 10.34 vs. 46.86 +/-

6.81, p < 0.001) compared to placebo. In conclusion, solifenacin is a safe and effective treatment alternative for patients with overactive bladder symptoms.

Sand, P. K., G. W. Davila, et al. (2012). "Efficacy and safety of oxybutynin chloride topical gel for women with overactive bladder syndrome." American Journal of Obstetrics & Gynecology **206**(2): 168.e161-166.

OBJECTIVE: This subgroup analysis of a phase-3 study evaluated the efficacy and safety of oxybutynin chloride topical gel (OTG) in women with overactive bladder syndrome (OAB).

STUDY DESIGN: Women (n = 704) with urgency-predominant urinary incontinence received OTG or placebo for 12 weeks. The primary endpoint was change from baseline to last observation in number of daily incontinence episodes. Treatments were compared with the use of analysis of covariance.

RESULTS: OTG significantly reduced the number (mean +/- standard deviation) of daily incontinence episodes (OTG, -3.0 +/- 2.8 episodes; placebo, -2.5 +/- 3.0 episodes; P < .0001), reduced urinary frequency (P = .0013), increased voided volume (P = .0006), and improved select health-related quality-of-life domains (P <= .0161) vs placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4%) than with placebo (2.8%; P = .0062).

CONCLUSION: OTG was well tolerated and provided significant improvement in urinary symptoms and health-related quality of life in women with OAB.

Staskin, D., V. Khullar, et al. (2011). "Effects of voluntary dose escalation in a placebo-controlled, flexible-dose trial of fesoterodine in subjects with overactive bladder." Neurourology & Urodynamics **30**(8): 1480-1485.

AIMS: To characterize the response to fesoterodine treatment for overactive bladder (OAB) in subjects who did or did not choose to dose escalate in a flexible-dose study.

METHODS: Subjects were randomized to fesoterodine 4 mg or placebo. At week 2, subjects could remain on 4 mg (non-escalators) or choose to increase to 8 mg (escalators) for the remaining 10 weeks (sham escalation for placebo). Subjects completed 3-day bladder diaries at baseline, week 2 and week 12 noting micturitions, urgency episodes, and urgency urinary incontinence (UUI) episodes.

RESULTS: Sixty-three per cent of 438 subjects randomized to fesoterodine and 73% of 445 randomized to placebo dose escalated. At baseline, fesoterodine escalators had significantly more micturitions and urgency episodes than fesoterodine non-escalators (P<0.001); at week 2, before dose escalation, diary-dry rate and improvement in micturitions and urgency episodes were significantly greater among fesoterodine non-escalators versus escalators (P<0.001); and by week 12, after dose escalation, diary-dry rate and improvements in micturitions and UUI episodes were similar between fesoterodine non-escalators and escalators (P>0.05). The placebo escalator group did not demonstrate a similar response over placebo non-escalators following the dose escalation decision point.

CONCLUSION: A rapid and robust response to fesoterodine 4 mg was demonstrated in non-escalators. Subjects who chose to dose escalate to fesoterodine 8 mg at week 2 showed significant improvement by week 12 versus baseline and week 2 (prior to escalation), as well as versus placebo. Dose escalation to 8 mg fesoterodine provided

subjects with efficacy and tolerability similar to those who were satisfied with the 4-mg dose.

Wagg A. Khullar V. Marschall-Kehrel D. Michel MC. Oelke M. Darekar A. Bitoun CE. Weinstein D. Osterloh I. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. Journal of the American Geriatrics Society. 61(2):185-93, 2013 Feb.

OBJECTIVES: To assess the efficacy and safety of flexible-dose fesoterodine in elderly adults with overactive bladder (OAB).
DESIGN: Twelve-week, randomized, double-blind, placebo-controlled trial.
SETTING: Sixty-one outpatient clinics in Europe, Israel, and Turkey.
PARTICIPANTS: Seven hundred ninety-four individuals aged 65 and older (47% male) with OAB symptoms for 3 months or longer, mean of eight or more micturitions and three or more urgency episodes per 24 hours, at least some moderate problems on Patient Perception of Bladder Condition (PPBC), and Mini-Mental State Examination (MMSE) score of 20 or greater.
INTERVENTIONS: Participants were randomized to fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs < 75) and dosing time (morning vs evening). Participants receiving fesoterodine started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8 (sham escalation for placebo).
MEASUREMENTS: Changes from baseline in bladder-diary variables (primary endpoint, urgency episodes) and patient-reported outcomes including OAB Questionnaire, Treatment Benefit Scale (TBS), PPBC, Urgency Perception Scale (UPS), and OAB Satisfaction Questionnaire (OAB-S); all observed or reported adverse events.
RESULTS: By week 8, 64% of fesoterodine-treated and 71% of placebo-treated participants opted for dose escalation. At week 12, the fesoterodine group had statistically significantly greater improvement than the placebo group in urgency episodes, micturitions, nocturnal micturitions, incontinence pad use, and OAB Questionnaire scores but not urgency urinary incontinence episodes. Responder rates on TBS, PPBC, UPS, and OAB-S were statistically significantly higher with fesoterodine. Improvements in most diary variables and participant-reported outcomes were greater with fesoterodine than placebo in participants in both age groups and when administered in the morning and evening. Rates of dry mouth and constipation were 34% and 9% with fesoterodine and 5% and 3% with placebo, respectively. Rates of adverse events and discontinuations were generally similar in participants in both age groups. There was no change in MMSE score.
CONCLUSION: Fesoterodine was associated with significantly greater improvements in most diary variables and participant-reported outcomes than placebo and was generally well tolerated in older people.

Weiss JP. Jumadilova Z. Johnson TM 2nd. Fitzgerald MP. Carlsson M. Martire DL. Malhotra A. Journal of Urology. 189(4):1396-401, 2013 Apr. Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency.[Erratum appears in J Urol. 2013 Aug;190(2):816]

PURPOSE: Awakening from sleep to urinate is the hallmark of nocturia, a condition that impacts several facets of health related quality of life and for which current therapy is suboptimal. Given the paucity of prospective data on antimuscarinics for the management

of nocturia, we investigated the efficacy and safety of flexible dose fesoterodine for the treatment of nocturnal urgency in subjects with nocturia and overactive bladder.
MATERIALS AND METHODS: Subjects with 2 to 8 nocturnal urgency episodes per 24 hours began a 2-week, single-blind, placebo run-in followed by 1:1 randomization to 12 weeks of double-blind treatment with fesoterodine (4 mg daily for 4 weeks with an optional increase to 8 mg) or placebo using predefined criteria for nocturnal urgency episodes, nocturnal urine volume voided and total 24-hour urine volume voided. The primary end point was change from baseline to week 12 in the mean number of micturition related nocturnal urgency episodes per 24 hours.
RESULTS: Overall 963 subjects were randomized from 2,990 screened, and 82% of subjects treated with fesoterodine and 84% of those treated with placebo completed the study. Significant improvements in the primary end point (-1.28 vs -1.07), in nocturnal micturitions per 24 hours (-1.02 vs -0.85) and in nocturnal frequency urgency sum (-4.01 vs -3.42) were observed with fesoterodine vs placebo (all p <0.01). Health related quality of life measures (overactive bladder questionnaire Symptom Bother -20.1 vs -16.5, sleep 22.3 vs 19.9 and other domains; all p <0.05) were improved with fesoterodine.
CONCLUSIONS: To our knowledge this is the first prospective study to assess antimuscarinic efficacy for reducing nocturnal urgency. Flexible dose fesoterodine significantly reduced nocturnal urgency episodes vs placebo in subjects with overactive bladder.

Yamaguchi, O., H. Kakizaki, et al. (2011). "Solifenacin as add-on therapy for overactive bladder symptoms in men treated for lower urinary tract symptoms--ASSIST, randomized controlled study." Urology **78**(1): 126-133.

OBJECTIVES: To assess the efficacy and safety of solifenacin add-on therapy to tamsulosin in lower urinary tract symptoms (LUTS) men with residual overactive bladder (OAB) symptoms despite tamsulosin monotherapy.
METHODS: In this randomized, multicenter, double-blind study, male LUTS patients aged>=50 years with urgency episodes/24 hours>=2 and micturitions/24 hours>=8 were randomized to 3 groups: 12-weeks tamsulosin plus placebo (TAM+PBO), tamsulosin plus solifenacin 2.5 mg (TAM+SOL), and tamsulosin plus solifenacin 5 mg (TAM+SOL). Changes from baseline to end of treatment in the number of urgency episodes/24 hours (primary endpoint), micturitions, nocturia, urgency incontinence episodes, International Prostate Symptom Scores (IPSS), and Overactive Bladder Symptom Score (OABSS) were compared between the TAM+SOL groups and TAM+PBO. Safety was assessed on adverse events, postvoid residual volume, and maximal urinary flow rate (Qmax.).
RESULTS: Six-hundred thirty-eight men were randomized. Urgency was reduced by 2.2 and 2.4 episodes in the TAM+SOL 2.5 and 5 mg groups, respectively. The TAM+SOL 5 mg group showed significant improvement compared with TAM+PBO (-2.4 vs -1.9, P=.049). The number of micturitions in both TAM+SOL groups were significantly reduced compared with TAM+PBO (both P<.001). IPSS storage symptom score and OABSS significantly improved in both TAM+SOL groups compared with TAM+PBO. Changes in IPSS voiding symptom score and Qmax. were similar in all groups. Four patients (1.9%) in the TAM+SOL 5 mg group had urinary retention, but all recovered after catheterization.

CONCLUSIONS: In male LUTS patients with residual OAB symptoms despite tamsulosin monotherapy, TAM+SOL showed efficacy on urgency, which represents OAB symptoms and was well tolerated.

Yokoyama, O., O. Yamaguchi, et al. (2011). "Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary." Journal of Urology **186**(1): 170-174.

PURPOSE: We compared changes in nocturia and sleep related parameters between the anticholinergic solifenacin and placebo in patients with overactive bladder associated with nocturia.

MATERIALS AND METHODS: We performed subgroup analysis of data from a randomized, controlled trial of solifenacin (5 or 10 mg) in Japan. Men and women 20 years old or older with overactive bladder were eligible for study participation. Patients who voided at least once during the night at baseline and who completed efficacy and quality of life assessment at baseline and 12 weeks (treatment end) were included in analysis. We compared placebo with the posttreatment change in nocturia and daytime frequency, volume voided per micturition, sleeping time, hours of undisturbed sleep and sleep related quality of life.

RESULTS: Subgroup analysis included 962 patients. Solifenacin 10 mg significantly decreased nocturia episodes by 0.46 episodes ($p = 0.0449$). Solifenacin 5 and 10 mg significantly increased nighttime volume voided per micturition by 30 and 41 ml ($p = 0.0033$ and <0.0001, respectively). Compared with placebo (33 minutes) the hours of undisturbed sleep significantly increased by 59 and 60 minutes ($p = 0.0196$ and 0.0195) in patients with solifenacin 5 and 10 mg, respectively. Significant improvement was observed in sleep related quality of life for solifenacin 5 and 10 mg (each $p <0.001$). Results must be interpreted with caution due to the exploratory nature of this analysis.

CONCLUSIONS: Solifenacin 10 mg decreases nocturia episodes. Solifenacin 5 and 10 mg increases nighttime volume voided per micturition and may improve quality of sleep and sleep related quality of life in patients with overactive bladder.

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Month/Year of Review: May 2014
Date of Last Review: July 2013
PDL Classes: Triptans
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: SUMATRIPTAN INJECTION (CARTRIDGE, DISP SYRINGE, PEN, VIAL), SUMATRIPTAN NASAL SPRAY (IMITREX®), NARATRIPTAN TABLET, SUMATRIPTAN TABLET
- Non-Preferred Agents: ELETRIPTAN TABLET (RELPAX®), RIZATRIPTAN TAB RAPIDS (MAXALT MLT®), RIZATRIPTAN TABLET, FROVATRIPTAN TABLET (FROVA®), ALMOTRIPTAN TABLET (AXERT®), SUMATRIPTAN/NAPROXEN (TREXIMET®), ZOLMITRIPTAN SPRAY (ZOMIG®), SUMATRIPTAN TRANSDERMAL (ZECUITY®)

Previous Conclusions and Recommendation:

- In comparing the effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms in adult patients with moderate to severe migraine the oral triptans were similarly efficacious.
- Good strength evidence for reformulated sumatriptan/naproxen versus reformulated sumatriptan 85 mg found the combination superior in pain-free at 2 hours and 24 hours and in normal renal function, overall productivity, and patient satisfaction. There is no evidence comparing the combination product to an available dose of sumatriptan. There is no evidence comparing the combination product to individual component therapy.
- There are no fully published head-to-head trials of frovatriptan.
- Injectable sumatriptan is effective, but there are no acceptable head-to-head studies comparing injectable to the oral form.
- Nasal sumatriptan and zolmitriptan are effective, but there is insufficient data to determine a clinically significant difference for the comparison of zolmitriptan nasal spray vs. the oral form of the drug. There were no head to head trials comparing sumatriptan nasal spray to the oral form of the drug.
- Most of the studies were rated fair quality or below because of variability in endpoints and lack of standard measures for pain relief or time to pain relief.
- Based on poor strength evidence there is no evidence that any one triptan has a particular advantage or disadvantage over others in any subgroups based on age, gender, race, use of prophylactic treatment, or association with menstruation.

PA Criteria: PA criteria is in place to decrease the potential for Medication Overuse Headache through quantity limits and therapeutic duplication denials (Appendix 1).

Conclusions and Recommendations:

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

Methods:

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

References:

1. Holmes R. Drug Effectiveness Review Porject. Drug Class Review: Triptans. Preliminary Scan Report #3. February 2014.

Appendix 1 PA criteria

Antimigraine - Triptans

Goal(s):

- *Decrease potential for Medication Overuse Headache through quantity limits and therapeutic duplication denials.*
- *Promote PDL options.*

Initiative: Anti-migraine PDL, Quantity Limits & Duplicate Therapy.

Length of Authorization: up to 6 months

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

Check the reason for PA request:

- *Non-Preferred drugs will deny on initiation*
- *Preferred drugs will deny only when maximum dose exceeded*
- *Both will deny for concurrent therapy (Concurrent triptans by different routes is allowed.i.e. oral + nasal, oral + injectable, nasal + Injectable)*

Quantity Limits Per Labeling

Generic	Brand	Initial dose	Max. Daily dose	Dosage form	Max # has/Mth	Limit
Almotriptan	Axert	6.25-12.5 mg Rpt in 2hr	25 mg	6.25 mg tab 12.5 mg tab (blister pack, 6, 12)	4	12/45d
Eletriptan	Relpax	20–40 mg Rpt in 2hr	80 mg	20 mg tab 40 mg tab (blister pack, 6, 12)	3	12/60d
Frovatriptan	Frova	2.5-5 mg Rpt in 2hr	7.5 mg	2.5 mg tab (blister pack, 9)	4	9/30d
Naratriptan	Amerge	1-2.5 mg Rpt in 4hr	5 mg	1 mg tab 2.5 mg tab (blister pack, 9)	4	9/30d
Rizatriptan	Maxalt Maxalt MLT	5-10 mg Rpt in 2hr	30 mg	5 mg tab 10 mg tab (blister pack, 6, 12)	4	12/30d
Sumatriptan	Imitrex & generics	25-100 mg po rpt In 2 hr 5-10 mg NS Rpt in 2 hr 3-6 mg SQ Rpt in 2hr	200 mg 40 mg 12 mg	25 mg tab, 50mg tab, 100 mg tab (blister pack, 9) 5 mg, 10 mg NS (box of 6) 6 mg SQ (box 2 syr), kit (2 syr per kit), 6mg/0.5ml vials	4 4 4	9/30d 6/30d 6/30d 3mls/30d

Sumatriptan	Sumavel	6 mg SQ	12 mg	6mg/0.5ml units (package of 6)	4	3ml/30d
Sumatriptan/ Naproxen	Treximent	85mg/ 500mg	170 mg/ 1000 mg	85mg/500mg tab (box of 9)	4	9/30d
Zomitriptan	Zomig Zomig ZMT Zomig NS	1.25-5 mg Rpt in 2hr 5mg NS Rpt in 2hr	10 mg 10mg	2.5 mg tab (blister pack, 6) 5 mg tab (blister pack, 3) 5mg NS (box of 6)	3 4	6/30d 6/30d

Approval Criteria		
1. What is diagnosis being treated?	Record ICD9 code.	
2. Does patient have diagnosis of migraine, ICD-9 346.0-346.9?	**Yes:** Go to #3	**No:** Pass to RPH, Deny, (Medical Appropriateness) There is no evidence to support the use of triptans for non-migraine diagnoses.
3. Is drug requested preferred?	**Yes:** Go to #5.	**No:** Go to #4.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA within recommended dose limits. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the ~~Health Resources Commission (HRC).~~ Pharmacy and Therapeutics (P&T) Committee	**Yes:** Inform provider of covered alternatives in class and dose limits.	**No:** Go to #5.
5. Is request for higher dose than listed in quantity limit chart?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness) • Can recommend use of migraine prophylactic therapy	**No:** Trouble-shoot claim payment (days supply?); Go to #6.

	and reinforce that doses above those recommended by the manufacturer increase the incidence of medication overuse headache (may refer to DUR Board Newsletter above). • One life-time 90-day taper may be approved at pharmacist discretion. • Document.	
6. Is the request for two different oral triptans concurrently?	**Yes:** Go to #7.	**No:** Approve for 6 months
7. Is this a switch in triptan therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Document reason for switch and override for concurrent use for 30 days.	**No:** Go to #8.
8. Does patient request more triptan due to supply lost or stolen or a vacation/travel supply?	**Yes:** Document reason and approve for date of service.	**No:** Pass to RPH, (Medical Appropriateness). There is no evidence to support the use of two different ORAL triptans concurrently.

DUR Board Action: *3/18/10(KK), 9/24/09(DO/KK)11-18-03, 5-13-03*
Revision(s): *3/23/10, 1/1/10, 7-1-06, 5-31-05*

Drug Class Review

Triptans

Preliminary Update Scan #3
February 2014

Last Report: Update #4 (June 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:
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Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
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Marian McDonagh, PharmD, Associate Director

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new controlled clinical trials, comparative effectiveness reviews of relevant 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, June 2009 (searches through January 2009)

Date of Last Preliminary Update Scan Report

April 2013 (searches through March 26, 2013)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine within the following treatment comparisons:
   1a. Monotherapy compared with monotherapy
   1b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
   1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

2. How do the incidence and nature of adverse effects (serious or life-threatening or those that may adversely affect compliance) differ for adult patients with migraine within the following triptan treatment comparisons:
   2a. Monotherapy compared with monotherapy
   2b. Fixed-dose tablets containing a triptan compared with triptan monotherapy

2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

3. Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with any level of migraine (mild, moderate, severe), with or without aura. Definition of migraine must be explicit, to exclude other types of headache (for example, tension headache).

Interventions

Table 1. Included drugs

Active ingredient	Form(s)	Brand name(s)
Almotriptan	Oral tablet	Axert®
Eletriptan	Oral tablet	Relpax®
Frovatriptan	Oral tablet	Frova®
Naratriptan	Oral tablet	Amerge®
Rizatriptan	Oral tablet, orally disintegrating tablet	Maxalt®, Maxalt-MLT®
Sumatriptan	Oral tablet, nasal spray, subcutaneous injection	Imitrex®, Imitrex® StatDose®, Sumavel DosePro®, Alsuma®
Sumatriptan	Iontophoretic transdermal system	Zecuity®[a]
Sumatriptan-naproxen sodium fixed dose combination product	Oral tablet	Treximet®
Zolmitriptan	Oral tablet, nasal spray, orally disintegrating tablet	Zomig®, Zomig-ZMT®

[a]Not in most recent DERP report; FDA approved 1/17/2013

Comparators

- Another triptan
- Triptan and/or analgesic components of fixed-dose tablets
- Placebo

Study designs

- Controlled clinical trial
- Good-quality systematic review

Effectiveness outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, photophobia, phonophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome (for example, change in days of work lost), quality of life, or adverse effect (including drug interactions).

- Measures: Response, time to response, pain-free, sustained response, sustained pain-free, rescue (use of rescue medications), recurrence (reappearance of any degree of symptoms within 24 or 48 hours) after response or becoming pain-free, time to relief, relief of associated symptoms, tablets per attack, and patient satisfaction.

Harms outcomes

- Serious adverse events
- Withdrawals due to any adverse events
- Withdrawals due to specific adverse events (central nervous system effects, chest tightness)

METHODS

Literature Search

To identify relevant clinical trials, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from April 2010 through February 25, 2014 using terms for included drugs. We also searched the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ and http://www.fda.gov/Safety/MedWatch/default.htm) to identify new drugs, indications, and safety alerts (boxed warnings). For this update, we added searches of CenterWatch (http://centerwatch.com), a privately-owned database of clinical trials information, to identify newly-approved drugs and drugs in development.

To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.effectivehealthcare.ahrq.gov) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). For this 2014 update, we added a search of the VA's Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp). We searched the Health Technology Assessment (HTA) Programme using a database from the University of York's Centre for Reviews and Dissemination (CRD) (http://www.crd.york.ac.uk/CRDWeb/). Systematic reviews published in the last three years (2011 and following) were included. All citations were imported into an electronic database (EndNote X4), and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
Zecuity (sumatriptan iontophoretic transdermal system): Approved to treat acute migraine in adults with or without aura (1/17/2013).

New Indications

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
None.

New Safety Alerts

Identified in this Preliminary Update Scan
No new boxed warnings.

Identified in previous Preliminary Update Scans
None.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
For this 2014 update scan we identified one new comparative effectiveness review from Cochrane, which compared sumatriptan and naproxen combination therapy to each component drug as monotherapy and to placebo. The abstract for this review is included in Appendix A, and the citation listed below.

Sumatriptan plus naproxen for acute migraine attacks in adults. Law, Simon. Derry, Sheena. Moore, Andrew R. Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 12, 2013.

Reviews identified in previous Preliminary Update Scans
For earlier scans we identified 2 new comparative effectiveness reviews. One compares acute migraine treatments in emergency settings, and the other is a rapid review of clinical evidence on safety of the triptans. Abstracts of these reviews are attached in Appendix A, and links to the full reports are listed below.

From the AHRQ Effective Healthcare Program:
Acute Migraine Treatment in Emergency Settings. Sumamo Schellenberg E, Dryden DM, Pasichnyk D, Ha C, Vandermeer B, Friedman BW, Colman I, Rowe BH.

Comparative Effectiveness Review No. 84. (Prepared by the University of Alberta Evidence based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12(13)-EHC142-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_20121119.pdf

From CADTH:
Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. Rapid Response Report, Summary with Critical Appraisal. March 2012. Available at: http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches resulted in 71 citations, 24 of these for this 2014 update scan. Of the 71 citations, there were 21 potentially relevant new publications, just two of these new for this 2014 scan. Abstracts of these trials are attached in Appendix B. Since the most recent Update Report, we have identified 5 head-to-head trials (in 9 publications, Table 2) and 12 placebo-controlled trials (Table 3). We identified two placebo-controlled trials of the newly-approved product sumatriptan iontophoretic transdermal system.

Table 2. New head to head trials*

Author Year	Comparison	Focus
Ng-Mak 2009	Almotriptan vs rizatriptan	Time to response
Bartolini 2011 Bartolini 2012	Almotriptan vs frovatriptan	Pain relief, recurrence Menstrual migraine (subgroup analysis)
Savi 2011a Savi 2011b	Frovatriptan vs rizatriptan	Pain relief, recurrence Menstrual migraine (subgroup analysis)
Tullo 2010 Allais 2011a Tullo 2012	Frovatriptan vs zolmitriptan	Pain relief, recurrence, tolerability Menstrual migraine (subgroup analysis) Migraine with aura (subgroup analysis)
Muller 2011	Rizatriptan orally disintegrating tablet vs subcutaneous sumatriptan vs parecoxib	Acute migraine

*Shading indicates trials identified in this scan; others were identified in previous scan(s).

Table 3. New placebo controlled trials*

Author Year	Treatment	Focus
Allais 2011b	Almotriptan	Menstrual migraine
Diener 2011	Eletriptan vs placebo vs an oral CGRP antagonist	Phase II study; pain relief, tolerability
Barbanti 2012	Rizatriptan	Migraine with unilateral cranial autonomic symptoms

Cady 2009	Rizatriptan ODT	Early treatment, combined with patient education
Seeburger 2012	Rizatriptan orally disintegrating tablet	Patients taking topiramate for migraine prophylaxis
Seeburger 2011	Rizatriptan orally disintegrating tablet	Nonresponders to sumatriptan
Goldstein 2012	Sumatriptan transdermal system	Relief of pain, nausea, photo- and phonophobia; tolerability
Schulman 2012	Sumatriptan transdermal system	Migraine patients with baseline nausea
Djupesland 2010	Sumatriptan intranasal powder	Pain relief, tolerability; device (Optinose®) not yet FDA-approved
Mathew 2009	Sumatriptan-naproxen fixed dose combination product	Poor responders to triptan monotherapy
Cady 2011	Sumatriptan-naproxen fixed dose combination product	Menstrual migraine
Derosier 2012	Sumatriptan-naproxen fixed dose combination product vs placebo vs butalbital	Patients with moderate to severe migraine who had used butalbital-containing medications in the past

*Shading indicates trials identified in this scan; others were identified in previous scan(s).

Appendix A. Abstracts of new comparative effectiveness reviews of triptans (N=3)

Sumatriptan plus naproxen for acute migraine attacks in adults. Law, Simon. Derry, Sheena. Moore, Andrew R. Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 12, 2013.
Background Migraine is a common disabling condition and a burden for the individual, health services, and society. Effective abortive treatments include the triptan and non-steroidal anti-inflammatory classes of drugs. These drugs have different mechanisms of action and combining them may provide better relief. Sumatriptan plus naproxen is now available in combination form for the acute treatment of migraine. **Objectives** To determine the efficacy and tolerability of sumatriptan plus naproxen (administered together as separate tablets or taken as a fixed-dose combination tablet) compared with placebo and other active interventions for the acute treatment of migraine headaches in adults. **Search methods** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane LibraryMEDLINE, and EMBASE, together with two online databases (-clinicalstudyregister.com and) for studies to 2 August 2013. We also searched the reference list of included studies and relevant reviews. **Selection criteria** We included randomised, double-blind, placebo- or active-controlled studies, with at least 10 participants per treatment arm, using sumatriptan plus naproxen to treat a migraine headache episode. **Data collection and analysis** Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate risk ratio and numbers needed to treat to benefit (NNT) or harm (NNH) compared with placebo or a different active treatment. **Main results** We included 12 studies using sumatriptan 85 mg or 50 mg plus naproxen 500 mg to treat attacks of mild, moderate, or severe pain intensity: 3663 participants received combination treatment, 3682 placebo, 964 sumatriptan, and 982 naproxen. No studies were considered to be at high risk of bias for any of the criteria evaluated. **Authors' conclusions** Combination treatment was effective in the acute treatment of migraine headaches. The effect was greater than for the same dose of either sumatriptan or naproxen alone, but additional benefits over sumatriptan alone are not large. More participants achieved good relief when medication was taken early in the attack, when pain was still mild. Adverse events were more common with the combination and sumatriptan alone than with placebo or naproxen alone.

Acute Migraine Treatment in Emergency Settings. Sumamo Schellenberg E, Dryden DM, Pasichnyk D, Ha C, Vandermeer B, Friedman BW, Colman I, Rowe BH. Comparative Effectiveness Review No. 84. (Prepared by the University of Alberta Evidence based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12(13)-EHC142-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_20121119.pdf
Structured Abstract
Objectives. To compare the effectiveness and safe y of parenteral pharmacological interventions to treat migraine headaches in adults presenting to the emergency department (ED).
Data sources. In consultation with a librarian, we searched 10 electronic databases, conference proceedings, clinical trials registers, and reference lists.

Methods. Two reviewers independently selected studies, assessed risk of bias, extracted data, and graded the strength of evidence (SOE). Data were pooled using a random-effects model. A mixed-treatment analysis was performed for pain relief and akathisia.
Results. Nine classes of drugs were investigated in 71 controlled trials. Risk of bias was low for 28 percent of the trials, unclear for 61 percent, and high for 11 percent. Overall, active interventions were more effective than placebo for pain relief and headache recurrence. Most head-to-head comparisons for pain reduction were based on single trials resulting in insufficient SOE. The mixed-treatment analysis showed that the most effective treatments were combination therapy (i.e., dihydroergotamine [DHE] added to either neuroleptics or metoclopramide) or neuroleptic monotherapy (low SOE), with a pain reduction of approximately 40 mm on a visual analog scale (VAS). Metoclopramide monotherapy, opioids, and nonsteroidal antiinflammatories (NSAIDs) were the next most effective treatments, with a pain reduction of approximately 24 mm (low SOE). Other agents (e.g., DHE, triptans, orphan agents) were less effective, with a pain reduction of approximately 12-16 mm.
Short-term side effects were infrequent, and considered minor and self-limiting. No two studies reported the same side effects for the same pair of interventions; therefore, the SOE is insufficient to conclude which treatment results in more or fewer adverse effects. Based on the mixed-treatment analysis, the odds of experiencing akathisia symptoms following administration of metoclopramide or neuroleptic agents were 9.4 and 10.7 times greater than with placebo, respectively. The risk of sedation following administration of metoclopramide or neuroleptic agents was 17 percent. The most common short-term side effects for triptans were skin reactions, local reactions, and sedation. For patients receiving DHE, the most common side effects were skin and local reactions, sedation, digestive issues, nausea or vomiting, and chest symptoms. Few side effects were reported for NSAIDS or opioids. In patients receiving magnesium sulfate, high rates of skin flushing and local reactions were reported.
The available evidence failed to identify variable responsiveness based on subgroups.
Migraine relapse can be prevented with intravenous systemic corticosteroids provided in the ED, particularly in patients with prolonged headaches (>72 hours).
Conclusion. Many agents are effective in the treatment of acute migraine headache when compared with placebo. Several treatments provide insufficient evidence for continued use. Neuroleptic monotherapy and DHE in combination with either metoclopramide or neuroleptics appear to be the most effective optionsfor pain relief (VAS). Systemic corticosteroids effectively prevent headache relapse, especially in patients with prolonged headaches. More research is required to identify the most effective parenteral treatments for adults with acute migraine.

Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. Rapid Response Report, Summary with Critical Appraisal. March 2012. Available at: http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf

RESEARCH QUESTION
What is the clinical evidence on the safety and harms of triptans for migraine headaches?
KEY MESSAGE
While no consistent differences were found between triptans in the rates of overall AEs, a small number of studies suggest oral, intranasal and subcutaneous sumatriptan are associated with chest pain and tachycardia. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. One study suggests that providing a clinical limit of 27 rizatriptan ODT 10

mg/month did not reduce the number of migraine days compared with providing a formulary limit of 9 tablets per month. Regardless of quantity, rizatriptan ODT 10 mg was well tolerated as AEs were similar between groups.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A drug class review suggests there are no consistent differences between triptan monotherapies in rates of overall AEs. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. Systematic reviews of sumatriptan and zolmitriptan suggest AEs are transient, mild and increase with dose but there is no significant difference between triptans and comparators for most AEs. Oral, intranasal and subcutaneous sumatriptan were associated with chest pain tachycardia. One in every 44 people treated with oral sumatriptan 100 mg experience chest pain. While no evidence was found regarding AEs as a result of triptan overuse, an observer-blind randomized parallel group study showed that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing 9 tablets/month. Regardless of quantity, rizatriptan was well tolerated as AEs were similar between groups.

Appendix B. Abstracts of potentially relevant new trials of triptans

Head-to-head trials (N=5 new trials and 4 subgroup analyses)

Allais, G., V. Tullo, et al. (2011a). "Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study versus zolmitriptan." Neurological Sciences **32 Suppl 1**: S99-104.

Menstrually related migraine (MRM) is a particularly difficult-to-treat pain condition, associated with substantial disability. Aim of this study was to compare the efficacy and safety of frovatriptan and zolmitriptan in the treatment of MRM attacks, analyzing data from a multicenter, randomized, double blind, cross-over study. We analyzed the subset of 76 regularly menstruating women who participated in one head-to-head multicenter, randomized, double blind, cross-over clinical trial and who took the study drugs to treat MRM attacks. In a randomized sequence, each patient received frovatriptan 2.5mg or zolmitriptan 2.5mg: after treating three episodes of migraine in no more than 3months with the first treatment, the patient had to switch to the other treatment. MRM was defined according to the criteria listed in the Appendix of the last Classification of Headache disorders of the International Headache Society. A total of 73 attacks, classified as MRM, were treated with frovatriptan and 65 with zolmitriptan. Rate of pain relief at 2h was 52% for frovatriptan and 53% for zolmitriptan (p=NS), while rate of pain free at 2h was 22 and 26% (p=NS), respectively. At 24h, 74 and 83% of frovatriptan-treated and 69 and 82% of zolmitriptan-treated patients were pain free and had pain relief, respectively (p=NS). Recurrence at 24h was significantly (p<0.05) lower with frovatriptan (15 vs. 22% zolmitriptan). Frovatriptan proved to be effective in the immediate treatment of MRM attacks, similarly to zolmitriptan, but showed lower recurrence rates, and thus a better sustained relief.

Bartolini, M., M. A. Giamberardino, et al. (2011). "A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine." Journal of Headache & Pain **12**(3): 361-368.

The objective of this study was to evaluate patients' satisfaction with acute treatment of migraine with frovatriptan or almotriptan by preference questionnaire. One hundred and thirty three subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack in the preceding 6months, were enrolled and randomized to frovatriptan 2.5mg or almotriptan 12.5mg, treating 1-3 attacks. The study had a multicenter, randomized, double blind, cross-over design, with treatment periods lasting <3months. At study end patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain free and pain relief episodes at 2 and 4h, and recurrent and sustained pain free episodes within 48h. Of the 133 patients (86%, intention-to-treat population) 114 of them expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (3.1+/-1.3) and almotriptan (3.4+/-1.3). The rates of pain free (30% frovatriptan vs. 32% almotriptan) and pain relief (54% vs. 56%) episodes at 2h did not significantly differ between treatments. This was the case also at 4h (pain free: 56% vs. 59%; pain relief: 75% vs. 72%). Recurrent episodes were significantly (P<0.05) less frequent under frovatriptan (30% vs. 44%), also for the attacks treated within 30min. No significant differences were observed in sustained pain free episodes (21% vs. 18%).

The tolerability profile was similar between the two drugs. In conclusion, our study suggests that frovatriptan has a similar efficacy of almotriptan in the short-term, while some advantages are observed during long-term treatment.

Bartolini, M., M. A. Giamberardino, et al. (2012). "Frovatriptan versus almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study." Journal of Headache & Pain **13**(5): 401-406.

The objective of the study was to compare the efficacy and safety of frovatriptan and almotriptan in women with menstrually related migraine (IHS Classification of Headache disorders) enrolled in a multicenter, randomized, double-blind, cross-over study. Patients received frovatriptan 2.5mg or almotriptan 12.5mg in a randomized sequence: after treating 3 episodes of migraine in no more than 3months with the first treatment, the patient was switched to the other treatment. 67 of the 96 female patients of the intention-to-treat population of the main study had regular menstrual cycles and were thus included in this subgroup analysis. 77 migraine attacks classified as related to menses were treated with frovatriptan and 78 with almotriptan. Rate of pain relief at 2 and 4h was 36 and 53% for frovatriptan and 41 and 50% for almotriptan (p=NS between treatments). Rate of pain free at 2 and 4h was 19 and 47% with frovatriptan and 29 and 54% for almotriptan (p=NS). At 24h, 62% of frovatriptan-treated and 67% of almotriptan-treated patients had pain relief, while 60 versus 67% were pain free (p=NS). Recurrence at 24h was significantly ($p<0.05$) lower with frovatriptan (8 vs. 21% almotriptan). This was the case also at 48h (9 vs. 24%, $p<0.05$). Frovatriptan was as effective as almotriptan in the immediate treatment of menstrually related migraine attacks. However, it showed a more favorable sustained effect, as shown by a lower rate of migraine recurrence.

Muller, T. and L. Lohse (2011). "Efficacy of parecoxib, sumatriptan, and rizatriptan in the treatment of acute migraine attacks." Clinical Neuropharmacology **34**(6): 206-209.

Triptans and analgetic nonsteroidal inflammatory drugs reduce acute pain syndromes in migraine. A further treatment option for an acute headache attack in patients with migraine may be the application of cyclooxygenase-2-specific inhibitors, as they have anti-inflammatory and analgesic properties. The objective of this pilot study was to investigate the effects of an oral fast-dissolving tablet of 10 mg of rizatriptan, an intravenous infusion of 40 mg of parecoxib, and a subcutaneous pen injection of sumatriptan (6 mg/0.5 mL) on pain relief in 3 cohorts of patients with episodic migraine. They were treated owing to the acute onset of a pain attack as a case of emergency. They were randomized to treatment with sumatriptan, rizatriptan, or parecoxib. The participants completed a visual analog scale for pain intensity at baseline before the drug administration and then after intervals of 20, 30, 60, and 120 minutes. Rizatriptan, parecoxib, and sumatriptan reduced pain symptoms. Twenty and 30 minutes after drug intake, rizatriptan was more efficacious than parecoxib and sumatriptan, and parecoxib was more effective than sumatriptan. Only a significant difference between rizatriptan and sumatriptan was found after 60 and 120 minutes. This trial demonstrates the effectiveness of a parecoxib infusion in the treatment of acute migraine and that the circumvention of the first pass effect of the liver by rizatriptan may be beneficial for fast pain relief.

Ng-Mak DS. Hu XH. Bigal M. “Migraine treatment with rizatriptan and almotriptan: a crossover study.” Headache. 49(5):655-62, 2009 May.

BACKGROUND: Rizatriptan and almotriptan are effective and well-tolerated triptans that have not been compared directly. OBJECTIVE: To evaluate the effectiveness of rizatriptan 10 mg and almotriptan for the acute treatment of migraine, in a real-world setting. METHODS: Of a large, multicenter, open-label, crossover study, we conducted a substudy to contrast the effectiveness of rizatriptan 10 mg and almotriptan 12.5 mg for the acute treatment of 2 migraine attacks in a sequential, crossover manner. Time to outcome was assessed using stopwatches. Mean and median times to onset of pain relief (PR) and pain freedom (PF) for rizatriptan and almotriptan were compared. The effect of rizatriptan on times to onset of PR and PF, adjusting for potential confounding factors (treatment sequence, treatment order, and use of rescue medication), was computed via a Cox proportional hazard model. RESULTS: Out of the 146 patients taking almotriptan as their usual care medication, 79 used stopwatch for both attacks. Significantly more patients taking rizatriptan achieved onset of PR within 2 hours after dosing than those taking almotriptan (88.6% vs 73.4%, P = .007). A higher proportion of patients taking rizatriptan achieved PF within 2 hours after dosing than those taking almotriptan (55.7% vs 45.6%, P = .10). Times to onset of PR and PF were significantly shorter with those patients taking rizatriptan than with those taking almotriptan (median time to PR: 45 vs 60 minutes, P = .002; median time to PF: 100 vs 135 minutes, P = .004). The adjusted proportional hazard ratios (rizatriptan vs almotriptan) for times to onset of PR and PF were 1.51 (95% confidence interval 1.20 to 1.88) and 1.42 (95% confidence interval 1.15 to 1.76), respectively. More patients were very satisfied when treating their attacks with rizatriptan than with almotriptan. Rizatriptan was preferred by most patients. CONCLUSIONS: Times to achieve PR and PF were significantly shorter for patients using rizatriptan, as compared with those using almotriptan.

Savi, L., S. Omboni, et al. (2011a). "A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine." Journal of Headache & Pain **12**(2): 219-226.

The objective of this study was to assess patient satisfaction with acute treatment of migraine with frovatriptan or rizatriptan by preference questionnaire. 148 subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack per month in the preceding 6 months, were enrolled and randomized to frovatriptan 2.5 mg or rizatriptan 10 mg treating 1-3 attacks. The study had a multicenter, randomized, double-blind, cross-over design, with treatment periods lasting <3 months. At the end of the study, patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain-free and pain relief episodes at 2 h, and recurrent and sustained pain-free episodes within 48 h. 104 of the 125 patients (83%, intention-to-treat population) expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (2.9+/-1.3) and rizatriptan (3.2+/-1.1). The rates of pain-free (33% frovatriptan vs. 39% rizatriptan) and pain relief (55 vs. 62%) episodes at 2 h were not significantly different between the two treatments. The rate of recurrent episodes was significantly ($p<0.001$) lower under frovatriptan (21 vs. 43% rizatriptan). No significant

differences were observed in sustained pain-free episodes (26% frovatriptan vs. 22% rizatriptan). The number of patients with adverse events was not significantly different between rizatriptan (34) and frovatriptan (25, p=NS). The results suggest that frovatriptan has a similar efficacy to rizatriptan, but a more prolonged duration of action. Springer-Verlag 2010

Savi, L., S. Omboni, et al. (2011b). "Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study versus rizatriptan." Journal of Headache & Pain **12**(6): 609-615.

The objectives of this study are to assess the efficacy and safety of frovatriptan, and rizatriptan in the subgroup of women with menstrually related migraine of a multicenter, randomized, double blind, cross-over study. Each patient received frovatriptan 2.5mg or rizatriptan 10mg in a randomized sequence: after treating 3 episodes of migraine in not more than 3months with the first treatment, the patient had to switch to the other treatment. Menstrually related migraine was defined according to the criteria listed in the Appendix of the last IHS Classification of Headache disorders. 99 out of the 125 patients included in the intention-to-treat analysis of the main study were of a female gender: 93 had regular menstrual cycles and were, thus, included in this analysis. A total of 49 attacks classified as menstrually related migraine were treated with frovatriptan and 59 with rizatriptan. Rate of pain relief at 2h was 58% for frovatriptan and 64% for rizatriptan (p=NS), while rate of pain free at 2h was 31 and 34% (p=NS), respectively. At 24h, 67 and 81% of frovatriptan-treated, and 61 and 74% of rizatriptan-treated patients were pain free and had pain relief, respectively (p=NS). Recurrence at 24h was significantly ($p<0.01$) lower with frovatriptan (10 vs. 32% rizatriptan). Frovatriptan was as effective as rizatriptan in the immediate treatment of menstrually related migraine attacks while showing a favorable sustained effect with a lower rate of migraine recurrence. These results need to be confirmed by randomized, double-blind, prospective, large clinical trials.

Tullo, V., G. Allais, et al. (2010). "Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study." Neurological Sciences 31 Suppl 1: S51-54.

The objective of this study is to assess patients' satisfaction with migraine treatment with frovatriptan (F) or zolmitriptan (Z), by preference questionnaire. 133 subjects with a history of migraine with or without aura (IHS criteria) were randomized to F 2.5 mg or Z 2.5 mg. The study had a multicenter, randomized, double-blind, cross-over design, with each of the two treatment periods lasting no more than 3 months. At the end of the study, patients were asked to assign preference to one of the treatments (primary endpoint). The number of pain-free (PF) and pain-relief (PR) episodes at 2 h, and number of recurrent and sustained pain-free (SPF) episodes within 48 h were the secondary study endpoints. Seventy-seven percent of patients expressed a preference. Average score of preference was 2.9 +/- 1.3 (F) versus 3.0 +/- 1.3 (Z; p = NS). Rate of PF episodes at 2 h was 26% with F and 31% with Z (p = NS). PR episodes at 2 h were 57% for F and 58% for Z (p = NS). Rate of recurrence was 21 (F) and 24% (Z; p = NS). Time to recurrence within 48 h was better for F especially between 4 and 16 h ($p < 0.05$). SPF episodes were 18 (F) versus 22% (Z; p = NS). Drug-related adverse events were significantly ($p < 0.05$) less

under F (3 vs. 10). In conclusion, our study suggests that F has a similar efficacy of Z, with some advantage as regards tolerability and recurrence.

Tullo V, Allais G, Curone M, et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine with aura: a subgroup analysis of a double-blind, randomized, multicenter, Italian study. Neurological Sciences 2012;33 Suppl 1:S61-4.

Migraine with aura affects ~20-30 % of migraineurs and it is much less common than migraine without aura. The aim of this study was to compare the efficacy of frovatriptan 2.5 mg and zolmitriptan 2.5 mg in the treatment of migraine with aura. Analysis was carried out in a subset of 18 subjects with migraine with aura (HIS criteria) out of the 107 enrolled in a multicenter, randomized, double-blind, cross-over study. According to the study design, each patient had to treat three episodes of migraine in no more than 3 months with one drug, before switching to the other treatment. The rate of pain-free episodes at 2 h was significantly ($p < 0.05$) larger under frovatriptan (45.8 %) than under zolmitriptan (16.7 %). Pain free at 4 h, pain relief at 2 and 4 h and recurrent episodes were similar between the two treatments, while sustained pain-free episode was significantly ($p < 0.05$) more frequent during frovatriptan treatment (33.3 vs. 8.3 % zolmitriptan). Our study suggests that frovatriptan is superior to zolmitriptan in the immediate treatment of patients with migraine with aura, and it is capable of maintaining its acute analgesic effect over 48 h.

Placebo-controlled trials (N=12)

Allais, G., G. Bussone, et al. (2011b). "Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study." Cephalalgia **31**(2): 144-151.

BACKGROUND: Menstrually related migraine (MRM) affects more than half of female migraineurs. Because such migraines are often predictable, they provide a suitable target for treatment in the mild pain phase. The present study was designed to provide prospective data on the efficacy of almotriptan for treatment of MRM.

METHODS: Premenopausal women with MRM were randomized to almotriptan (N = 74) or placebo (N = 73), taken at onset of the first perimenstrual migraine. Patients crossed over to the other treatment for the first perimenstrual migraine of their second cycle, followed by a two-month open-label almotriptan treatment period.

RESULTS: Significantly more patients were pain-free at two hours (risk ratio [RR] = 1.81; p = .0008), pain-free from 2-24 hours with no rescue medication (RR = 1.99; p = .0022), and pain-free from 2-24 hours with no rescue medication or adverse events (RR = 1.94; p = .0061) with almotriptan versus placebo. Nausea (p = .0007) and photophobia (p = .0083) at two hours were significantly less frequent with almotriptan. Almotriptan efficacy was consistent between three attacks, with 56.2% of patients pain-free at two hours at least twice. Adverse events were similar with almotriptan and placebo.

CONCLUSION: Almotriptan was significantly more effective than placebo in women with MRM attacks, with consistent efficacy in longer-term follow-up.

Barbanti, P., L. Fofi, et al. (2012). "Rizatriptan in migraineurs with unilateral cranial autonomic symptoms: a double-blind trial." Journal of Headache & Pain **13**(5): 407-414.

The objective and background is to confirm in a double-blind, placebo-controlled study the high triptan response rates we had previously reported in an open study in migraine patients with unilateral cranial autonomic symptoms. In this randomized, double-blind, placebo-controlled study 80 migraineurs with unilateral cranial autonomic symptoms were assigned to receive rizatriptan 10mg wafer or placebo (ratio 1:1) and treated for a single moderate or severe migraine attack. The primary endpoints were pain freedom at 2h and total migraine freedom at 2h. Secondary endpoints included pain relief, no associated symptoms and sustained pain freedom or relief. Significantly more patients reported pain freedom at 2h after taking rizatriptan (54%) than after placebo (8%) (therapeutic gain 46% [28%; 64%]; P<0.001). Similarly, significantly more patients reported total migraine freedom at 2h after rizatriptan (51%) than after placebo (8%) (therapeutic gain 43% [26%; 61%]; P<0.001). Rizatriptan was also more effective than placebo on most secondary endpoints. We confirm in a placebo-controlled study our previous data suggesting that the presence of unilateral cranial autonomic symptoms in migraineurs predicts a positive response to triptans, probably owing to intense trigeminal peripheral afferent activation which strongly recruits peripheral neurovascular 5-HT1B/1D receptors. Acute and preventive pharmacological trials in migraine should focus also on this subset of migraine patients.

Cady, R. K., M. L. Diamond, et al. (2011). "Sumatriptan-naproxen sodium for menstrual migraine and dysmenorrhea: satisfaction, productivity, and functional disability outcomes." Headache **51**(5): 664-673.

OBJECTIVE: To evaluate the impact of a sumatriptan/naproxen sodium combination tablet on patient satisfaction, productivity, and functional disability in menstrual migraine treated during the mild pain phase of a single menstrual migraine attack associated with dysmenorrhea.

BACKGROUND: Menstrual migraineurs with dysmenorrhea represent a unique patient population not previously studied. When health outcomes end points are analyzed alongside traditional efficacy end points in migraine studies, a more comprehensive and robust understanding of the many factors that may influence patients' choice of and adherence to pharmacological treatments for migraine is observed.

METHODS: In 2 replicate, multicenter, randomized, double-blind, placebo-controlled trials, participants with menstrual migraine and dysmenorrhea treated a single menstrual migraine attack with a single fixed-dose tablet of sumatriptan 85mg formulated with RT TechnologyTM and naproxen sodium 500mg (sumatriptan-naproxen sodium) or placebo.

RESULTS: Participants randomized to sumatriptan-naproxen sodium were significantly more satisfied than those randomized to placebo at 24 hours post dose, as demonstrated by higher satisfaction subscale scores for efficacy (P<.001 for both studies), functionality (P=.003 for study 1; P<.001 for study 2), and ease of use (P=.027 for study 1; P=.011 for study 2). There was little bothersomeness of side effects associated with either treatment. Use of sumatriptan-naproxen sodium was also associated with lower reported "lost-time equivalents" in work and leisure time (pooled analysis, P=.003) and lower rates of functional disability (P=.05, study 1; P<.001, study 2) compared with placebo.

CONCLUSION: A fixed-dose combination tablet containing sumatriptan and naproxen sodium significantly improved patient satisfaction, productivity, and restoration of normal functioning in menstrual migraineurs with dysmenorrhea. 2011 American Headache Society.

Cady RK, Martin VT et al. (2009) "Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response." Headache. **49**(5):687-96, 2009 May.
OBJECTIVE: To examine the efficacy of rizatriptan 10-mg orally disintegrating tablet (ODT) for treating migraines of mild intensity soon after onset, with or without patient-specific migraine education.
BACKGROUND: Studies have shown rizatriptan tablet efficacy in early migraine treatment.
METHODS: In this randomized, placebo-controlled, double-blind, factorial design study, adults with a history of migraine were assigned to rizatriptan 10-mg ODT patient education (personalized summary of early migraine signs and symptoms) or placebo patient education in a 1 : 1 : 1 : 1 ratio. Patients were instructed to treat 1 attack at the earliest time they knew that their headache was a migraine, while pain was mild. During the next 24 hours, patients assessed pain severity, associated symptoms, functional disability, use of rescue medication, and treatment satisfaction. The primary endpoint was pain freedom at 2 hours; a key secondary endpoint was 24-hour sustained pain freedom.
RESULTS: Of 207 patients randomized to treatment, 188 (91%) treated a study migraine. Significantly more patients taking rizatriptan reported pain freedom at 2 hours compared with placebo (66.3% vs 28.1%, $P < .001$). Similarly, significantly more patients taking rizatriptan reported 24-hour sustained pain freedom (52.2% vs 17.7%, $P < .001$). A greater proportion of patients in the rizatriptan + education group reported pain freedom at 2 hours compared with those in the rizatriptan + no education group (71.7% vs 60.9%, $P = .430$). Few adverse events were reported.
CONCLUSION: Rizatriptan 10-mg ODT, when taken early, while headache pain is mild, was superior to placebo at providing pain freedom at 2 hours and 24-hour sustained pain freedom.

Derosier, F., F. Sheftell, et al. (2012). "Sumatriptan-naproxen and butalbital: a double-blind, placebo-controlled crossover study." Headache **52**(4): 530-543.
OBJECTIVES: The primary objective was to compare the efficacy of a sumatriptan and naproxen combination medication (SumaRT/Nap-85mg sumatriptan and 500mg naproxen sodium), a butalbital-containing combination medication (BCM-50mg butalbital, 325mg acetaminophen, 40mg caffeine), and placebo when used to treat moderate to severe migraine headache pain in subjects who used BCMs in the past.
BACKGROUND: Despite the lack of Food and Drug Administration approval and the absence of placebo-controlled trials to demonstrate efficacy, butalbital-containing medications are among the most commonly prescribed acute migraine treatments in the United States. Butalbital-containing medications are associated with serious and undesirable side effects, and have been linked to the chronification of migraine and development of medication-overuse headaches. This study compares the relative efficacy, safety, and tolerability of a fixed dose SumaRT/Nap versus a BCM and placebo.
METHODS: Enrolled subjects were required to have treated at least 1 migraine with a butalbital medication in the past. Enrolled subjects treated 3 moderate to severe migraines using

each of the 3 study treatments once in a randomized sequence. The primary endpoint compared SumaRT/Nap versus BCM for sustained pain freedom at 2-24 hours without the use of any rescue medication. This study combines data from 2 identical outpatient, randomized, multicenter, double-blind, double-dummy, 3 attack crossover studies in adult migraineurs (International Classification of Headache Disorders, 2nd edition).

RESULTS: A total of 442 subjects treated at least 1 attack with study medication. The majority of the treated subjects were female (88%) with a mean age 43 years, who reported that their migraines had a severe impact on their lives (78% with Headache Impact Test-6 of >59). At screening, 88% of subjects reported current butalbital use; 68% had used butalbital for more than 6 weeks; and 82% reported satisfaction with butalbital. Across treatment groups, 28-29% of subjects took study medication within 15 minutes of migraine onset, 34-37% of subjects took study medication >15 minutes to 2 hours after onset, and 32-36% of subjects took study medication more than 2 hours after onset. This study did not detect a difference at the nominal 0.05 level in percent sustained pain-free between SumaRT/Nap (8%), BCM (6%), and placebo (3%). SumaRT/Nap was superior to BCM for pain free at 2, 4, 6, 8, 24, 48 hours (P<=.044); pain relief (mild or no pain) at 2, 4, 6, 8, 24, 48 hours (P<=.01); sustained pain relief 2-24 hours (P<.001); migraine free (pain free with no nausea, photophobia, or phonophobia) at 4, 6, 8, 24, 48 hours (P<=.046); and complete symptom free (migraine free with no neck/sinus pain) at 4, 6, 8, 48 hours (P<=.031). Adverse event incidence was similar for all treatments (10%, 12%, and 9% for placebo, SumaRT/Nap, and BCM, respectively). Nausea was the most frequent adverse event (2%, 2%, and <1% for placebo, SumaRT/Nap, and BCM, respectively). Five serious adverse events were reported by 3 subjects: viral meningitis and colon neoplasm (placebo); chest pain and hypertension 17 days postdose (SumaRT/Nap); and breast cancer (BCM). Investigators judged no serious adverse events related to study medication.

CONCLUSIONS: This study primarily included subjects whose migraines significantly impacted their lives. Before the study, these subjects used butalbital-containing medications as part of their current migraine treatment regimen and were satisfied with it, suggesting they were butalbital responders who had found a workable treatment strategy for themselves. When treated with SumaRT/Nap versus BCM in this study, however, a significant proportion of subjects reported better treatment outcomes for themselves for both migraine pain and associated symptoms. Use of SumaRT/Nap was also associated with less rescue medication use and a longer time before use of rescue medication compared with both BCM and placebo. 2011 American Headache Society.

Diener, H.-C., P. Barbanti, et al. (2011). "BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study." Cephalalgia **31**(5): 573-584.

METHODS: Four hundred and sixty-one adult subjects with migraine were randomised to one of five treatments, the oral antagonist at the calcitonin gene-related peptide (CGRP) receptor BI 44370 TA (50mg, 200mg, 400mg), active comparator eletriptan 40mg or placebo. The analysis included 341 subjects who took study medication.

RESULTS: The primary endpoint, pain-free after two hours, was reached by significantly more subjects in the BI44370TA 400mg (20/73=27.4%) and eletriptan 40mg (24/69=34.8%) groups compared to placebo (6/70=8.6%, p=.0016), but not by subjects in the BI 44370 TA 200mg group (14/65=21.5%). The effect of 50mg BI44370TA (5/64=7.8%) was

similar to that of placebo. Analysis of secondary endpoints supported the conclusion from the primary analysis. The frequency of adverse events was low in all groups.
CONCLUSION: Efficacy of BI 44370 TA was shown in a dose-dependent manner in the treatment of acute migraine attacks.

Djupesland, P. G., P. Docekal, et al. (2010). "Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: A randomised, placebo-controlled study." Cephalalgia **30**(8): 933-942.
INTRODUCTION: Intranasal sumatriptan is an option for the treatment of migraine; however, nasal delivery using conventional spray pumps is suboptimal.
METHODS: Adult subjects (n = 117) with migraine were enrolled in a multicentre, randomised, double-blind, parallel group, placebo-controlled study. A single migraine attack was treated in-clinic with sumatriptan 10 mg, sumatriptan 20 mg or placebo administered intranasally by a novel bi-directional powder delivery device when migraine was moderate or severe.
RESULTS: A greater proportion of subjects who received sumatriptan were pain-free at 120 minutes compared with those who received placebo (10 mg/20 mg sumatriptan vs. placebo = 54%/57% vs. 25%, P < .05). Significant benefits were also observed for pain relief at 120 minutes (84%/80% vs. 44%, P < .001/.01) and as early as 60 minutes (73%/74% vs. 38%, P < .01) and for 48 hours sustained pain-free (P < .05). Treatment-related adverse events were rare, with a metallic taste being the most commonly reported (10%/13%).
CONCLUSIONS: Sumatriptan nasal powder administered using the new device during a migraine attack was effective and well tolerated.

Goldstein J, Smith TR, et al (2012). "A sumatriptan iontophoretic transdermal system for the acute treatment of migraine." Headache **52**:1402-10.
OBJECTIVE: Gastrointestinal symptoms, such as nausea and vomiting, occur almost universally at one time or another in patients during a migraine attack. One third of patients who experience migraine-related nausea report that this symptom interferes with their ability to take oral medications. The sumatriptan iontophoretic transdermal system (NuPathe Inc., Conshohocken, PA, USA) uses proprietary technology to circumvent the gastrointestinal tract while delivering triptan therapy. This phase III randomized, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of this system for the acute treatment of migraine.
METHODS: Patients were randomized to treat a single moderate-to-severe migraine attack with the sumatriptan iontophoretic transdermal system or placebo. The primary end point was the proportion of patients who were headache pain-free 2 hours after patch activation. Other end points included the proportions of patients who reported headache pain relief, and freedom from nausea, photophobia, and phonophobia; rescue medication use; and tolerability.
RESULTS: Four hundred sixty-nine patients were treated. Significantly more patients treated with the sumatriptan iontophoretic transdermal system compared with placebo experienced freedom from headache pain, nausea, photophobia, and phonophobia 2 hours after patch activation, experienced rapid and sustained headache pain relief, and used less rescue medication. Treatment-emergent adverse events were reported by 50% and 44% of

patients treated with the sumatriptan iontophoretic transdermal system and placebo, respectively. Most events were transient mild-to-moderate application-site reactions.
CONCLUSIONS: The sumatriptan iontophoretic transdermal system is effective and well tolerated, and may be particularly useful in patients with migraine-related gastrointestinal symptoms such as nausea. 2012 American Headache Society.

Mathew NT, Landy S et al (2009). "Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life." Headache. **49**(7):971-82.
OBJECTIVE: To evaluate efficacy and tolerability of a single, fixed-dose tablet of sumatriptan 85 mg/naproxen sodium 500 mg (sumatriptan/naproxen sodium) vs placebo in migraineurs who had discontinued treatment with a short-acting triptan because of poor response or intolerance.
BACKGROUND: Triptan monotherapy is ineffective or poorly tolerated in 1 of 3 migraineurs and in 2 of 5 migraine attacks. In April, 2008, the Food and Drug Administration approved the combination therapy sumatriptan/naproxen sodium, developed specifically to target multiple migraine mechanisms. This combination product offers an alternative migraine therapy for patients who have reported poor response or intolerance to short-acting triptans.
METHODS: Two replicate, randomized, multicenter, double-blind, placebo-controlled, 2-attack crossover trials evaluated migraineurs who had discontinued a short-acting triptan in the past year because of poor response or intolerance. Patients were instructed to treat within 1 hour and while pain was mild.
RESULTS: Patients (n = 144 study 1; n = 139 study 2) had discontinued an average of 3.3 triptans before study entry. Sumatriptan/naproxen sodium was superior ($P < .001$) to placebo for 2- through 24-hour sustained pain-free response (primary end point) (study 1, 26% vs 8%; study 2, 31% vs 8%) and pain-free response 2 hours post dose (key secondary end point) (study 1, 40% vs 17%; study 2, 44% vs 14%). A similar pattern of results was observed for other end points that evaluated acute (2- or 4-hour), intermediate (8-hour), or 2- through 24-hour sustained response for migraine (ie, pain and associated symptoms), photophobia, phonophobia, or nausea (with the exception of nausea 2 and 4 hours post dose). The percentage of patients with at least 1 adverse event (regardless of causality) was 11% with sumatriptan/naproxen sodium compared with 4% with placebo in study 1 and 9% with sumatriptan/naproxen sodium compared with 5% with placebo in study 2. Only 1 adverse event in 1 study was reported in > or =2% of patients after treatment with sumatriptan/naproxen sodium and reported more frequently with sumatriptan/naproxen than placebo: chest discomfort was reported in 2% of subjects in study 1, and no events met this threshold in study 2. No serious adverse events attributed to study medication were reported in either study.
CONCLUSION: In migraineurs who reported poor response to a short-acting triptan, sumatriptan/naproxen sodium was generally well tolerated and significantly more effective than placebo in conferring initial, intermediate, and sustained efficacy for pain and migraine-associated symptoms of photophobia and phonophobia.

Schulman, E. A. (2012). "Transdermal sumatriptan for acute treatment of migraineurs with baseline nausea.[Erratum appears in Headache. 2012 Jun;52(6):1062]." Headache **52**(2): 204-212.

OBJECTIVE: To evaluate the efficacy and safety of transdermal sumatriptan in migraine patients who have baseline nausea.

BACKGROUND: Migraine-associated nausea and vomiting can limit the effectiveness of acute treatment with oral agents by causing delays, avoidance, or incomplete absorption of medication due to post-dose vomiting.

METHODS: In a multicenter, randomized, double-blind, placebo-controlled study in adult (aged 18-66 years) migraineurs, 530 patients were randomized to receive transdermal sumatriptan or a placebo patch and remained in the study until they had treated a single moderate to severe migraine attack or had gone 2 months without treatment. At baseline (before applying the study patch), patients recorded headache pain intensity and the presence or absence of migraine-associated symptoms, including nausea. The use of analgesic or anti-emetic rescue medications within 2 hours of patch activation was prohibited. Post-hoc analyses were conducted to assess the proportion of patients with nausea at baseline who experienced headache relief and who were free from nausea, photophobia, and phonophobia at 1 and 2 hours post-activation.

RESULTS: A total of 454 patients were included in the intent-to-treat population for efficacy analyses. Baseline demographic and migraine headache characteristics were generally similar between the treatment groups. In the overall study population, transdermal sumatriptan was significantly superior to placebo at 1 hour post-activation for pain relief (29% vs 19%, respectively; P < .0135) and freedom from nausea (71% vs 58%, respectively; P < .05) and at 2 hours post-activation for freedom from pain (18% vs 9%, respectively; P < .009), pain relief (53% vs 29%, respectively; P < .0001), freedom from nausea (84% vs 63% respectively; P < .001), freedom from photophobia (51% vs 36%, respectively; P < .0028), freedom from phonophobia (55% vs 39%, respectively; P < .0002); and freedom from migraine (16% vs 8%, respectively; P < .0135). In the post-hoc analysis, transdermal sumatriptan was markedly superior to placebo for pain relief and freedom from pain, nausea, photo-, and phonophobia at 1 and 2 hours post-activation.

CONCLUSIONS: Transdermal sumatriptan is superior to oral triptans for migraine patients whose baseline nausea causes them to delay or avoid acute treatment. 2012 American Headache Society.

Seeburger, J. L., R. K. Cady, et al. (2012). "Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis." Headache **52**(1): 57-67.

OBJECTIVE: To assess efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treatment of acute migraine in patients using topiramate for migraine prophylaxis.

BACKGROUND: There are limited data from prospective controlled trials demonstrating the benefit of triptans in patients who experience migraine attacks while taking prophylactic medication.

METHODS: This was a worldwide, randomized, placebo-controlled, double-blind, multiple-attack study in adults with a >1-year history of migraine taking a stable dose of topiramate for migraine prophylaxis and experiencing >=2 moderate/severe attacks per month. Participants treated 3 moderate/severe attacks in crossover fashion (2 with

rizatriptan 10-mg ODT, 1 with placebo) following random assignment to 1 of 3 treatment sequences. The primary end point was 2-hour pain relief.

RESULTS: Two-hour pain relief was significantly greater with rizatriptan compared with placebo (55.0% vs 17.4%, P < .001). Response rates also favored rizatriptan for sustained pain relief from 2-24 hours (32.6% vs 11.1%, P < .001), 2-hour pain freedom (36.0% vs 6.5%, P < .001), normal functional ability at 2 hours (42.2% vs 12.7%, P < .001), and overall treatment satisfaction at 24 hours (60.8% vs 33.6%, P < .001). Few participants reported adverse experiences (16 [15.8%] with rizatriptan, 3 [3.2%] with placebo); none were serious.

CONCLUSION: Rizatriptan 10-mg ODT was superior to placebo at all pain end points for treatment of acute migraine in patients using topiramate for migraine prophylaxis. Rizatriptan was generally well tolerated in this population. These results are comparable with those from clinical trials in patients not using prophylaxis, suggesting that the use of topiramate does not affect the efficacy or tolerability of rizatriptan for acute migraine treatment. 2011 American Headache Society.

Seeburger, J. L., F. R. Taylor, et al. (2011). "Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders." Cephalalgia **31**(7): 786-796.

OBJECTIVE: The study was carried out to assess the efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treating acute migraine in patients who are non-responders to sumatriptan.

BACKGROUND: Many migraineurs report dissatisfaction with sumatriptan efficacy. It is unclear whether sumatriptan 100mg non-responders will respond to other triptans.

METHODS: This was a randomized, placebo-controlled, double-blind study in adults with >1-year history of ICHD-II (International Classification of Headache Disorders, second edition) migraine who reported that they generally do not respond to sumatriptan (>=50% unsatisfactory response). In the baseline phase, participants treated a single moderate/severe migraine attack with open-label generic sumatriptan 100mg. Those who continued to experience moderate/severe pain at two hours post-dose were eligible to enter the double-blind treatment phase, during which participants treated three migraine attacks in crossover fashion (two with rizatriptan 10-mg ODT, one with placebo) after being randomly assigned to one of three treatment sequences (1:1:1 ratio). The primary endpoint was two-hour pain relief.

RESULTS: A total of 102 (94%) participants treated at least one study migraine. Pain relief at two hours was significantly greater with rizatriptan compared with placebo (51% vs. 20%, p<.001). Response rates also favored rizatriptan on two-hour pain freedom (22% vs. 12%, p=.013) as well as 24-hour sustained pain relief (38% vs. 14%, p<.001) and sustained pain freedom (20% vs. 11%, p=.036). Treatment was generally well tolerated.

CONCLUSION: Rizatriptan 10-mg ODT was superior to placebo at providing two-hour pain relief and two-hour pain freedom in the treatment of acute migraine in those who do not respond to sumatriptan 100mg. Rizatriptan was generally well tolerated in this population.