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, November 21, 2013 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 — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)
- d. Department Update — T. Douglass (DMAP)
  1. Prescribing Provider Enrollment PA

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. Managing Metabolic Side Effects in Children Receiving Antipsychotics
  2. Updates and Comparisons of Type 2 Diabetes Guidelines

III. PREFERRED DRUG LIST NEW BUSINESS
- a. Vivitrol (naltrexone) New Drug Evaluation — B. Liang (OSU)
  1. New Drug Evaluation
  2. Public comment
  3. Discussion of Clinical recommendations to OHA

IV. HCMB Subcommittee Follow-Up — R. Citron (OSU)
- a. SubCommittee Report
- b. Ampyra (dalfampridine)
- c. Kuvan (sapropterin)
- d. Public Comment
- e. Discussion of Recommendation to OHA

V. DUR OLD BUSINESS
- a. Juxtapid® (lomitapide) & Kynamro® (mipomersen) — K. Ketchum (OSU)
  1. Criteria #5
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA

VI. DUR NEW BUSINESS

a. Benzodiazepine Drug Use Evaluation — K. Ketchum (OSU)
1. Drug Use Evaluation
2. Public Comment
3. Discussion of Clinical recommendations to OHA

VII. PREFERRED DRUG LIST OLD BUSINESS

a. Diabetes Class Clarification — R. Citron (OSU)
1. Oseni®/Kazano®
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

VIII. PREFERRED DRUG LIST NEW BUSINESS (continued)

a. First Generation Antipsychotic Review — M. Herink (OSU)
1. Class Review
2. Public Comment
3. Discussion of Clinical recommendations to OHA

b. Chronic Obstructive Pulmonary Disease (COPD) — A. Meeker (OSU)
1. Breo® Ellipta (vilanterol/fluticasone) New Drug Evaluation
2. Class Update
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

c. Parkinsons Disease — M. Herink (OSU)
1. Neupro® (Rotigotine transdermal) New Drug Evaluation
2. Class Update
3. Public Comment
4. Discussion of Clinical recommendations to OHA

d. Statin Medications — M. Herink (OSU)
1. Class Update
2. Public comment
3. Discussion of Clinical recommendations to OHA

e. Drug Class Scans — M. Herink (OSU)
1. Newer Antiemetics
2. Newer Drugs for Insomnia
3. Nonsteroidal Antiinflammatory Drugs
4. Skeletal Muscle Relaxants

IX. EXECUTIVE SESSION

X. RECONVENE for PUBLIC RECOMMENDATIONS

XI. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 26, 2013 1:00-5:00 PM
HP Corporate Office
4070 27th Court SE
Salem, OR 97302

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or 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.

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

Members Present by Phone: David Pass, MD; Joshua Bishop, PharmD; Stacy Ramirez, PharmD;

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; Kala Berkey, PharmD Candidate

Staff Present by Phone: Kathy Sentena, PharmD, Bing-Bing Liang, PharmD

Audience: Christine Curry, (Genentech)*; Arti Baig (Pfizer)*; Isabel Lloyd, (Vertex); Don Stetcher (Novartis); Cheryl Fletcher, (Abbvie); Laura Hill, (Abbvie)*; Kimberly Blood, (WVP Health Authority); David Barhoum, (Genentech); Lynda Finch, (Biogen Idec)*; Venus Holder, (Lilly); Janet Fox, (Pfizer)*; Patty Harwood, (MedImmune); Kerrie Fowler,(UHA); Michael Estos (Pfizer); Michelle Bice, (Gilead); Laura Litzenberger; (Johnson & Johnson)*; Lori Howarth, (Bayer); Jim Hoover, (Bayer); Brad Peacock, (Gilead); Karen Ward, (Aegerion); Tzeli Triantafillon (VIIV); Paul Barham (NovoNordisk); Mark Cummings, Forest; Deborah Profant, PhD, (Teva)*; Bob Gustafson (Lundbeck); Jamie Damm, (Vertex); Jeana Colabianchi, (Sunovion); Lyle Laird, (Sunovion); Anne Marie Licos, (MedImmune); Bruce Smith (GSK); Caryn McKesin (Western Oregon Advanced Health); Bill Lavia, (MedImmune); Darlene Halverson, (Novartis); Mark Alden, (Genentech); Barry Benson, (Merck); Stephanie Pugh, (Novo Nordisk); Nathan Wood, (Merck)

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:10 pm. Introductions of Committee members and staff.

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

c. The July 25th meeting minutes were reviewed. (pages 4 – 6)

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

ACTION: Approved as is.

d. Department updates by Dr. Trevor Douglass.

II. HCMB Subcommittee Approval

The P & T members agreed to include at least one (1) HERC member, three (3) P & T members, and one (1) Statistician. During the first meeting, the members will elect a chair and vice chair for the committee. Mr. Citron stated they will post and agenda and meeting times on the OSU College website for interested parties.

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

III. DUR OLD BUSINESS

a. Kuvan® (saproterin) (page 7)
Dr. Herink presented modifications to the PA criteria to include clinical target ranges and specification for use in both adults and children.

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

b. Juxtapid® (lomitapide) & Kynamro® (mipomersen) (page 8)
Ms. Ketchum presented to modify the PA criteria to include more details on optimal combination therapy. Added to #4, See Clinical Notes below. Refer to an expert on necessity of #5, allowing coverage if LDL apheresis is not available to them.

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

IV. DUR NEW BUSINESS

a. DUR report: RetroDur for the use of Psychotropic Medications in Children. (pages 32 – 46) Order changed from original agenda. Dr. Williams presented the following:
   1. Send providers an annual request for additional clinical data for children receiving any of the following regimens:
      a. Five or more chronic psychotropics in children
      b. Two or more chronic antipsychotics in children
      c. Psychotropics in children under years old
         i. Non-stimulants under 6 years old
         ii. CNS stimulants under 4 years old
   2. Add the definitions for “chronic” and “concurrent therapy” on provider message that will be faxed.

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

b. DUR report: Metabolic Monitoring of Antipsychotics in Children. (pages 9 – 21) Dr. Williams presented the following updates:
   1. Fax quarterly reports to providers addressing the absence of glucose monitoring in children receiving antipsychotics. Reports to contain the following information:
      a. Dashboard comparing the target provider to other Medicaid providers and providers within their specialty.

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b. Educational materials highlighting recommendations for monitoring and management of metabolic abnormalities in children.
c. List patients without claims for glucose monitoring within the past 12 months.
d. Form indicating the status of metabolic monitoring for each patient for the provider to complete and return to the Medical Assistance Program.

2. Change from annual reminder for children without glucose monitoring to reminder every 6 months.

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

c. DUR report: Follow up for Children prescribed their first ADHD Medication. (page 22 – 31) Dr. Williams presented the following updates:
   1. Fax reports biweekly to promote follow up care for children prescribed their first ADHD medication. Reports to contain the following information
      a. Dashboard comparing the target provider to other Medicaid providers and providers with their specialty.
      b. A list of patients with their first ADHD prescription within the last 2 weeks.
      c. A Form indicating the status of a scheduled follow up visit for each patient for the provider to complete and return to the Medial Assistance Program.
      d. Educational materials highlighting recommendations for monitoring and management of ADHD pharmacotherapy in children.

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

d. Synagis® (palivizumab) Policy Evaluation (pages 47 – 59) Ms. Berkey presented the following updates:
   1. Continue the palivizumab PA for the 2013 – 2014 RSV season with no adjustments.
   2. Follow-up study needed in December or January to ensure safety indicators remain acceptable.

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

V. PREFERRED DRUG LIST (PDL classes will be reviewed for annual pricing update

a. Diabetes Class updates (page 60 – 88)
   Dr. Sentena presented the following updates:
   1. Prior authorize canagliflozin as a third-line treatment option for patients unable to tolerate or have contraindications to metformin and / or sulfonylurea therapy.
   2. Prior authorize alogliptin as a third-line treatment option for patients unable to tolerate or have contraindications to metformin and / or sulfonylurea therapy.
   3. Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.
   4. Evaluate comparative costs in executive session.
   5. * (After executive session) Make canagliflozin and alogliptin non preferred.
   6. * (After executive session) Prior authorize canagliflozin as a fourth-line treatment option for patients unable to tolerate or have contraindications to metformin, sulfonylurea therapy, and other third line treatments.
   7. * (After executive session) Add hypoglycemic risk in Incretin Mimetics PA criteria as a contraindication to sulfonylureas.

Public Comment: Laura Litzenberger, Johnson & Johnson

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

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b. Other Lipotropics (page 89 – 103)
Dr. Herink presented the following updates:
1. Make isocapent ethyl a non-preferred lipotropic agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.
2. Evaluate comparative costs of other agents in executive session for further PDL decisions.
3. * (After executive session) Make Trilipix preferred and brand Tricor preferred over its generic alternatives.
4. * (After executive session) Make Vascepa, Restora, Inositol and Lipogen non-preferred.

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

c. Parkinson's Disease (page 104 – 116)
Dr. Liang presented the following updates:
1. No further research or review needed at this time.
2. Evaluate comparative costs in executive session.
3. Add Neupro to the Parkinson's class and evaluate price in November.
4. * (After executive session) Make carbidopa / levodopa ER preferred.
5. * (After executive session) Fix clerical issues in PA criteria.

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

d. Multiple Sclerosis (page 117 – 136)
Ms. Berkey presented the following updates:
1. Include dimethyl fumarate on the oral MS drug prior authorization criteria to limit to patients who have tried and failed first line agents including beta interferons and / or glatiramer.
2. Include either interferon beta-1a subQ or interferon beta-1b subQ as a preferred option due to evidence demonstrating improved efficacy compared to interferon beta-1a IM in relapse related outcomes.
3. Evaluate costs in executive session for further PDL decision-making.
4. * (After executive session) Make Betaseron and Rebif preferred.
5. * (After executive session) Amend PA criteria to include pathway for Tecfidera.

Public Comment: Dr. Deborah Profant, Teva Pharameuticals; Lynda Finch, Biogen Idec

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

e. Long Acting Opioids (page 137 – 143)
Ms. Ketchum presented the following updates:
1. Evaluate relative cost of tramadol ER in executive session.
2. Set maximum daily dose to 300 mg per drug label.
3. * (After executive session) Make Ultram ER and Conzip non-preferred.

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

f. Hepatitis C Agents (page 144 – 162)
Dr. Herink presented the following updates:
1. Recommended to maintain either one or both of peginterferon alfa-2a and peginterferon alfa-2b as preferred pegylated interferon products.
2. Consider removing criteria #9 of protease inhibitor PA criteria which currently denies for patients with HIV coinfection.
3. Evaluate comparative costs in executive session.
4. * (After executive session) Make Pegasys preferred.
5. * (After executive session) Allow approval of protease inhibitors for patients with HIV / HCV coinfection if under supervision of an HIV specialist.

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Public Comment: Dr. Christine Curry, Genentech
***ACTION:** After Executive Session, all in favor.

g. Drug Class Scans
   1. Topical Androgens (page 163 – 169)
      Dr. Herink presented the following updates:
      a. There is no new evidence that there is a difference in efficacy between the different testosterone products; No further research or review needed at this time.
      b. Evaluate comparative costs in executive session, including relative costs of new formulations (Axiron, Androgel 1.62%, and Fortesta).
      c. * (After executive session) Make Androgel preferred.
      d. * (After executive session) Make Androderm non-preferred and grandfather current patients.

Public Comment: Laura Hill, Abbvie
***ACTION:** After Executive Session, all in favor.

   2. Topical Antiparasites (page 170 – 174)
      Dr. Herink presented the following updates:
      a. No further research or review needed at this time.
      b. Evaluate comparative costs in executive session.
      c. *(After executive session) Make Natroba non-preferred.

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

   3. COPD (page 175 –189)
      Dr. Meeker presented the following updates:
      a. Add Breo Ellipta to the class and bring back more detailed drug review in November.
      b. Evaluate comparative costs in executive session.
      c. * (After executive session) Make both Combivent Respimat and Combivent MDI preferred and remove step edit.

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

   4. Growth Hormones (page 190 – 197)
      Dr. Herink presented the following updates:
      a. No further research or review needed at this time.
      b. Evaluate comparative costs in executive session.
      c. * (After executive session) Make Norditropin preferred.

Public Comment: Janet Fox, Pfizer
***ACTION:** After Executive Session, all in favor.

   5. Alzheimer's Agents (page 198 – 205)
      Dr. Herink presented the following updates:
      a. No further research or review needed at this time.
      b. Evaluate comparative costs in executive session.

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

   6. Public Comment
   7. Discussion of Clinical Recommendations to OHA

h. Classes Under Consideration for Annual PDL Pricing Review.
   1. TIMS
      a. Evaluate comparative costs in executive session
      b. * (After executive session) Make Simponi preferred.

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Public Comment: Arti Baig, Pfizer

2. Antiepileptic Medications
   a. Evaluate comparative costs in executive session
   b. * (After executive session) Make valproic acid solution preferred.
3. Ulcerative Colitis Agents
   a. Evaluative comparative costs in executive session.
   b. * (After executive session) Make Lialda preferred.
4. Public Comment
5. Discussion of clinical recommendations to OHA.

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

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

Mr. Citron confirmed to the public of the next P & T meeting will be held in November.

VII. ADJOURN

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

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Pharmacy Utilization Summary Report: October 2012 - September 2013

	2012			2013									
	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	
Eligibility													**AVG/YTD**
Total Members	619,870	618,962	621,328	621,239	624,167	626,033	624,596	625,809	625,937	625,469	626,235	626,504	623,846
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	80,638
Standard	6,171	4,095	3,486	2,980	3,134	3,076	2,969	2,931	3,120	2,942	3,114	3,133	3,429
Plus	68,720	54,699	50,213	46,670	48,911	49,171	45,574	46,548	48,988	46,194	49,325	52,181	50,600
Medicare Wrap	26,446	26,618	26,659	26,666	26,661	26,891	26,487	26,349	26,487	26,552	26,666	26,832	26,610
Gross Figures													
Total Cost	$12,169,407	$10,743,040	$10,389,680	$11,473,292	$10,334,041	$10,721,675	$10,985,912	$11,032,013	$10,014,655	$11,170,162	$10,873,472	$10,827,888	$130,735,237
FFS Drugs	$4,255,510	$3,301,801	$3,192,087	$3,565,934	$3,000,905	$3,080,474	$3,042,259	$2,913,521	$2,604,279	$2,879,559	$2,769,340	$2,801,545	$37,407,213
Mental Health Carveout Drugs	$7,913,897	$7,441,239	$7,197,593	$7,907,358	$7,333,137	$7,641,201	$7,943,653	$8,118,493	$7,410,376	$8,290,603	$8,104,132	$8,026,343	$93,328,024
Total Rx	192,481	170,617	164,582	171,215	154,478	160,940	161,970	160,470	146,521	158,270	153,364	151,392	1,946,300
FFS Drugs	88,090	71,100	67,202	70,078	63,265	65,235	64,962	63,066	57,967	62,096	59,988	59,834	792,883
Mental Health Carveout Drugs	104,391	99,517	97,380	101,137	91,213	95,705	97,008	97,404	88,554	96,174	93,376	91,558	1,153,417
Cost/Rx	$63.22	$62.97	$63.13	$67.01	$66.90	$66.62	$67.83	$68.75	$68.35	$70.58	$70.90	$71.52	$67.31
FFS Drugs	$48.31	$46.44	$47.50	$50.89	$47.43	$47.22	$46.83	$46.20	$44.93	$46.37	$46.16	$46.82	$47.09
Mental Health Carveout Drugs	$75.81	$74.77	$73.91	$78.18	$80.40	$79.84	$81.89	$83.35	$83.68	$86.20	$86.79	$87.66	$81.04
Generic	$25.80	$24.40	$23.64	$23.77	$23.99	$24.05	$24.23	$24.45	$23.86	$25.38	$25.74	$25.85	$24.60
Brand	$352.24	$357.99	$362.78	$387.73	$383.62	$381.84	$383.62	$388.25	$390.96	$396.12	$396.61	$398.54	$381.69
PMPM Figures													
Cost PMPM	$54.76	$50.68	$51.31	$59.45	$49.88	$51.13	$53.27	$51.40	$44.97	$51.30	$47.95	$46.92	$51.08
Standard	$136.20	$118.76	$126.20	$165.74	$123.19	$139.29	$149.24	$145.18	$128.32	$143.48	$128.35	$117.14	$135.09
Plus	$56.82	$56.81	$57.64	$68.28	$56.64	$58.92	$61.56	$59.60	$51.06	$59.46	$54.38	$54.02	$57.93
Medicare Wrap	$17.84	$13.48	$16.18	$15.74	$14.87	$12.22	$12.66	$11.43	$10.69	$11.72	$11.28	$11.07	$13.27
FFS Drugs	$41.99	$38.66	$39.72	$46.73	$38.13	$38.93	$40.55	$38.42	$33.14	$38.05	$35.01	$34.10	$38.62
Mental Health Carveout Drugs	$12.77	$12.02	$11.58	$12.73	$11.75	$12.21	$12.72	$12.97	$11.84	$13.26	$12.94	$12.81	$12.47
Rx PMPM	1.04	0.99	0.99	1.08	0.95	0.98	1.02	0.99	0.88	0.97	0.91	0.87	0.97
Standard	2.16	2.04	1.97	2.40	1.98	2.11	2.20	2.11	1.88	2.12	1.93	1.88	2.07
Plus	0.89	0.86	0.86	0.99	0.86	0.87	0.92	0.88	0.76	0.86	0.79	0.75	0.86
Medicare Wrap	1.04	1.00	1.00	0.94	0.86	0.89	0.88	0.87	0.82	0.87	0.84	0.83	0.90
FFS Drugs	0.87	0.83	0.84	0.92	0.80	0.82	0.87	0.83	0.74	0.82	0.76	0.73	0.82
Mental Health Carveout Drugs	0.17	0.16	0.16	0.16	0.15	0.15	0.16	0.16	0.14	0.15	0.15	0.15	0.15
Utilization Percentages													
Generic %	88.5%	88.4%	88.4%	88.1%	88.1%	88.1%	87.9%	87.8%	87.9%	87.8%	87.8%	87.7%	88.0%
FFS Drugs	91.3%	91.5%	91.4%	91.2%	91.5%	91.5%	91.6%	91.6%	91.7%	91.5%	91.6%	91.5%	91.5%
Mental Health Carveout Drugs	86.2%	86.3%	86.2%	86.0%	85.7%	85.8%	85.4%	85.4%	85.4%	85.4%	85.4%	85.3%	85.7%
PDL %	94.1%	93.9%	93.7%	92.4%	92.5%	92.2%	92.3%	91.1%	91.4%	91.2%	91.6%	91.8%	92.3%

PMPM calculated as sum of physical health and mental health carve-outs
Data from DSSURS and DMAP FCHP first of month reports
Dates are service dates
All eligibility groups included except for CAWEM, QS, QB
Drug Cost = Amt Paid +Copay + Other Insurance Paid

Last Updated: October 20, 2013

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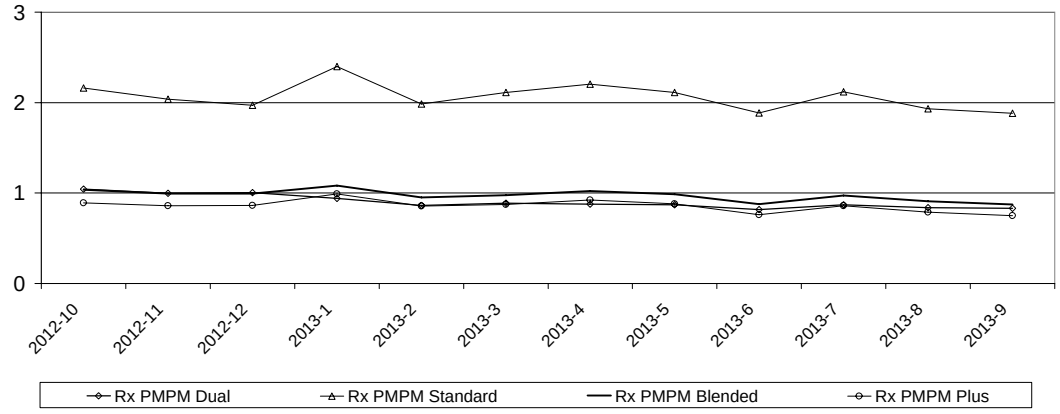
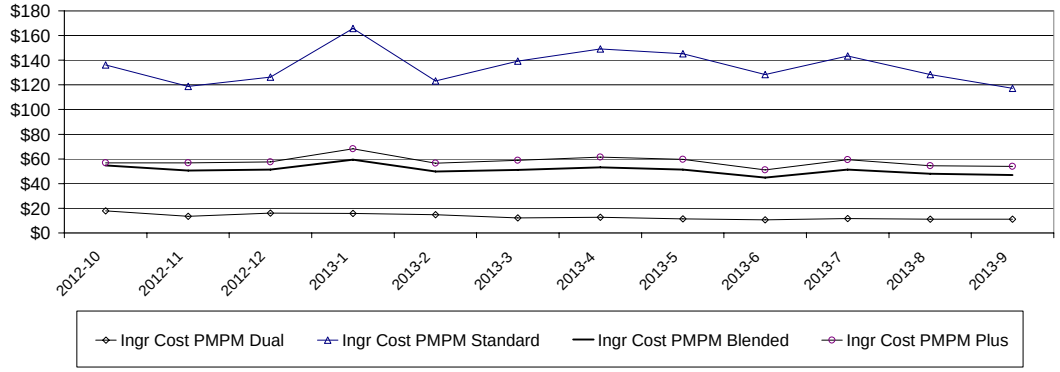
Pharmacy Utilization Summary Report: October 2012 - September 2013

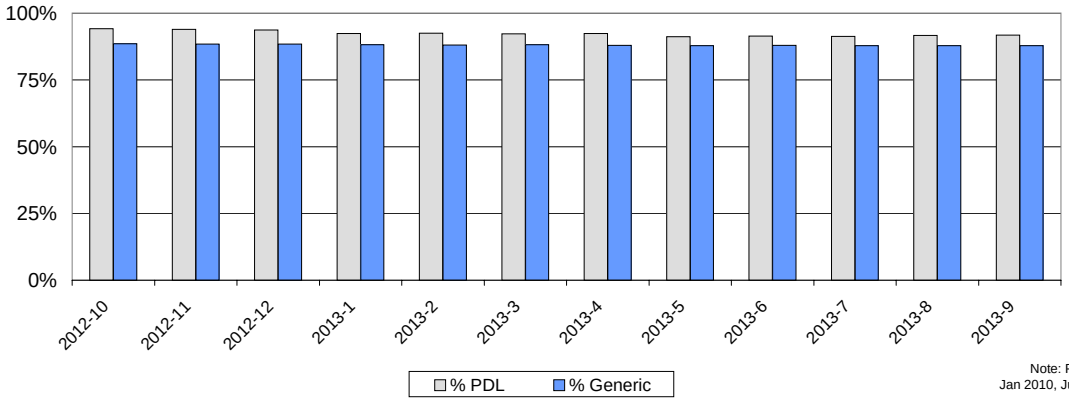
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



Note: PDL updated
Jan 2010, Jul 2010, Jan 2011

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OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - Third Quarter 2013

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Brand Name**	**2013**	**2012**	**%**	**2013**	**2012**	**%**	**2013**	**2012**	**%**
1	7	ABILIFY	$3.96	$3.66	8.2%	0.52	0.55	-4.2%	$758	$671	13.0%
2	11	CYMBALTA	$1.92	$1.69	13.3%	0.68	0.70	-3.4%	$282	$240	17.4%
3	10	METHYLPHENIDATE ER	$1.07	$1.33	-19.3%	0.61	0.77	-21.4%	$176	$172	2.6%
4	71	REMODULIN	$0.78	$1.69	-54.0%	0.00	0.01	-56.0%	$26,116	$24,915	4.8%
5	58	LANTUS	$0.69	$0.70	-2.1%	0.26	0.31	-16.9%	$264	$224	17.9%
6	15	PROAIR HFA	$0.65	$0.73	-11.7%	1.12	1.33	-16.2%	$58	$55	5.4%
7	7	SEROQUEL XR	$0.64	$0.63	1.9%	0.12	0.13	-7.2%	$515	$469	9.8%
8	42	HUMIRA	$0.64	$0.65	-1.9%	0.02	0.03	-16.3%	$2,562	$2,182	17.4%
9	11	INTUNIV	$0.63	$0.45	41.8%	0.27	0.22	21.3%	$235.29	$201.34	16.9%
10	99	PROCYSBI	$0.55			0.00			$22,758.20		
11	99	PULMOZYME	$0.54	$0.56	-2.1%	0.02	0.02	-12.2%	$2,750.61	$2,465.58	11.6%
12	11	STRATTERA	$0.53	$0.51	3.8%	0.21	0.23	-8.8%	$251.17	$220.71	13.8%
13	15	ADVAIR DISKUS	$0.51	$0.43	17.1%	0.18	0.17	6.9%	$287	$262	9.6%
14	7	INVEGA SUSTENNA	$0.47	$0.31	53.9%	0.04	0.03	41.0%	$1,307	$1,197	9.2%
15	42	ENBREL	$0.44	$0.41	8.8%	0.02	0.02	-7.3%	$2,316.59	$1,974.94	17.3%
16	51	FLOVENT HFA	$0.44	$0.46	-4.6%	0.25	0.27	-8.5%	$174.80	$167.41	4.4%
17	48	VIMPAT	$0.42	$0.21	99.5%	0.06	0.04	66.6%	$669.70	$559.41	19.7%
18	12	VYVANSE	$0.41	$0.39	2.8%	0.21	0.24	-9.5%	$189.82	$167.06	13.6%
19	33	ATRIPLA	$0.40	$0.75	-47.0%	0.02	0.04	-48.0%	$1,730.97	$1,694.76	2.1%
20	58	HUMALOG	$0.39	$0.34	15.2%	0.14	0.14	0.2%	$286.17	$249.11	14.9%
21	33	TRUVADA	$0.36	$0.72	-49.3%	0.03	0.07	-48.8%	$1,081.50	$1,090.27	-0.8%
22	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.36	$0.48	-24.2%	0.23	0.28	-15.3%	$155.62	$173.63	-10.4%
23	40	HYDROCODONE-ACETAMINOPHEN	$0.35	$0.42	-15.7%	2.11	2.85	-25.9%	$16.79	$14.76	13.7%
24	40	OXYCONTIN	$0.35	$0.60	-41.4%	0.07	0.12	-46.2%	$522.01	$479.20	8.9%
25	15	SPIRIVA	$0.35	$0.36	-3.2%	0.13	0.14	-8.9%	$272.70	$256.48	6.3%
26	77	LOVENOX	$0.35	$0.31	11.3%	0.02	0.03	-21.0%	$1,524.00	$1,082.71	40.8%
27	48	SABRIL	$0.34	$0.11	200.7%	0.00	0.00	179.7%	$7,324.48	$6,784.73	8.0%
28	7	LATUDA	$0.34	$0.21	64.7%	0.05	0.04	40.4%	$631.21	$538.39	17.2%
29	23	TOBI	$0.33	$0.40	-15.6%	0.01	0.01	-1.5%	$4,338.45	$5,110.74	-15.1%
30	48	DIVALPROEX SODIUM ER	$0.29	$0.05	505.2%	0.16	0.17	-4.2%	$182.62	$28.90	531.9%
31	7	INVEGA	$0.29	$0.25	15.1%	0.04	0.04	4.6%	$714.91	$649.67	10.0%
32	69	CREON	$0.29	$0.26	11.5%	0.03	0.03	3.4%	$1,027.93	$955.36	7.6%
33	58	NOVOLOG	$0.28	$0.29	-1.1%	0.11	0.13	-15.5%	$259.47	$221.34	17.2%
34	7	ZIPRASIDONE HCL	$0.25	$0.12	108.4%	0.15	0.06	170.5%	$164.66	$213.71	-23.0%
35	23	TOBI PODHALER	$0.25			0.00			$6,731.15		
36	30	XELODA	$0.22	$0.35	-37.3%	0.01	0.01	-42.4%	$2,637.31	$2,425.73	8.7%
37	1	PREVACID	$0.22	$0.17	31.6%	0.07	0.06	11.5%	$305.88	$259.32	18.0%
38	40	OXYCODONE HCL	$0.22	$0.25	-11.7%	0.89	1.09	-18.1%	$24.66	$22.86	7.9%
39	15	COMBIVENT RESPIMAT	$0.22	$0.01	1712.4%	0.08	0.00	1623.6%	$263.20	$250.03	5.3%
40	48	LYRICA	$0.22	$0.19	13.9%	0.08	0.09	-9.4%	$283.99	$226.09	25.6%
		Aggregate	$50.71	$51.23	-1.0%	92.45	96.35	-4.0%	$71	$65	9.4%
		75th Percentile			44.2%			30.3%			18.5%
		50th Percentile (Median)			8.3%			2.5%			3.9%

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OHP FFS Average Cost PMPM Top 30 Drug Class – Third Quarter 2013

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Class Description**	**2013**	**2012**	**%**	**2013**	**2012**	**%**	**2013**	**2012**	**%**
1	7	Ataractics, Tranquilizers	$7.40	$7.26	2.0%	4.9	5.9	-18.3%	$152	$122	24.9%
2	11	Psychostimulants, Antidepressants	$4.86	$4.88	-0.6%	8.9	9.0	-0.4%	$54	$54	-0.2%
3	48	Anticonvulsants	$3.49	$2.55	36.7%	4.0	5.3	-24.3%	$71	$45	59.1%
4	99	Miscellaneous	$3.22	$2.61	23.5%	1.4	1.5	-1.8%	$199	$180	10.2%
5	15	Bronchial Dilators	$2.53	$3.04	-16.7%	2.7	3.3	-15.9%	$92	$94	-2.4%
6	58	Diabetic Therapy	$2.45	$2.44	0.2%	1.8	2.1	-12.8%	$136	$119	14.9%
7	33	Antivirals	$2.41	$3.60	-33.0%	0.4	0.6	-27.0%	$540	$589	-8.3%
8	10	CNS Stimulants	$1.78	$2.12	-15.9%	1.3	1.7	-19.3%	$132	$127	4.1%
9	40	Narcotic Analgesics	$1.51	$2.10	-28.2%	5.1	6.8	-25.7%	$30	$31	-3.6%
10	42	Antiarthritics	$1.41	$1.43	-1.3%	1.8	2.1	-16.0%	$77	$67	16.0%
11	71	Other Hypotensives	$1.35	$2.28	-40.7%	2.3	2.8	-15.6%	$54	$82	-34.3%
12	51	Gluco Corticoids	$1.18	$1.15	2.4%	1.5	1.7	-13.0%	$77	$66	16.4%
13	30	Antineoplastic	$1.15	$1.22	-5.9%	0.2	0.4	-34.9%	$320	$314	1.9%
14	12	Amphetamine Preps	$1.12	$1.26	-11.7%	0.8	0.9	-11.6%	$136	$136	-0.1%
15	63	Oral Contraceptives	$1.10	$1.09	1.5%	2.2	2.3	-3.6%	$49	$47	4.7%
16	64	Other Hormones	$0.96	$0.80	20.6%	0.1	0.1	-12.6%	$931	$659	41.3%
17	1	Antacids	$0.88	$1.01	-12.3%	2.8	3.4	-16.4%	$31	$30	5.0%
18	41	Non-narcotic Analgesics	$0.81	$0.77	5.5%	6.4	5.1	24.5%	$12	$15	-16.5%
19	6	Laxatives	$0.78	$0.69	13.9%	6.4	5.4	19.1%	$12	$13	-4.6%
20	27	Other Antibiotics	$0.74	$0.65	14.4%	0.7	0.8	-3.6%	$95	$78	21.4%
21	87	Electrolytes and Misc Nutr	$0.68	$0.57	18.7%	3.0	2.6	15.2%	$22	$22	-0.8%
22	23	Streptomycins	$0.59	$0.43	37.0%	0.0	0.0	15.2%	$1,043	$1,135	-8.1%
23	77	Anticoagulants	$0.59	$0.53	11.5%	0.4	0.4	-4.9%	$142	$126	13.0%
24	65	Lipotropics	$0.51	$0.58	-11.3%	1.9	2.0	-4.0%	$27	$30	-7.7%
25	80	Fat Soluble Vitamins	$0.47	$0.37	25.7%	4.8	3.7	27.9%	$10	$10	-1.7%
26	69	Enzymes	$0.40	$0.41	-1.1%	0.0	0.0	0.9%	$877	$872	0.5%
27	82	Multivitamins	$0.39	$0.33	17.0%	3.7	3.3	13.5%	$10	$10	2.5%
28	14	Antihistamines	$0.32	$0.31	1.7%	2.7	2.7	-3.3%	$12	$11	5.8%
29	90	Biologicals	$0.30	$0.07	320.5%	0.2	0.0	450.4%	$238	$174	36.5%
30	88	Hematinics with/without Iron	$0.29	$0.34	-15.9%	1.7	1.4	20.5%	$14	$24	-41.3%
		Aggregate	$50.71	$51.23	-1.0%	92.45	96.35	-4.0%	$71	$65	9.4%
		75th Percentile			28.9%			15.2%			18.2%
		50th Percentile (Median)			5.6%			-3.7%			4.7%

Last updated: October 20, 2013

ProDUR Report for August 2013- October 2013

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	45,189	8,704	42	36,439	66.00%
PG (Pregnancy/Drug Interaction)	2,150	1,401	5	735	3.10%
ID (Ingredient Duplication)	11,710	3,102	2	8,597	17.00%
TD (Therapeutic Duplication)	4,702	1,516	2	3,182	6.80%

ProDUR Report for August 2013- October 2013

Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden	% Change from March/April to Aug-Oct
ER	Remeron (Mirtazapine)-March/April	497	97	400	3,535	14.1%	19.5%	
	Remeron (Mirtazapine)-Aug-Oct	**576**	**81**	**495**	**4,926**	11.7%	14.1%	-27.9%
	Hydrocodone Bit/APAP-March/April	210	33	177	3,951	5.3%	15.7%	
	Hydrocodone Bit/APAP-Aug-Oct	**215**	**62**	**153**	**4,913**	4.4%	28.8%	83.5%
	Oxycodone HCl-March/April	122	50	72	1,811	6.7%	41.0%	
	Oxycodone HCl-Aug-Oct	**168**	**67**	**100**	**2,774**	6.1%	39.9%	-2.7%
	Lorazepam-March/April	1,018	243	775	12,973	7.8%	23.9%	
	Lorazepam-Aug-Oct	**1,260**	**268**	**992**	**15,006**	8.4%	21.3%	-10.9%
	Alprazolam-March/April	806	150	656	9,637	8.4%	18.6%	
	Alprazolam-Aug-Oct	**916**	**170**	**746**	**11,651**	7.9%	18.6%	-0.3%
	Diazepam-March/April	476	78	398	5,968	8.0%	16.4%	
	Diazepam-Aug-Oct	**545**	**114**	**431**	**7,618**	7.2%	20.9%	27.6%
	Buspar (Buspirone)-March/April	459	80	379	4,800	9.6%	17.4%	
	Buspar (Buspirone)-Aug-Oct	**679**	**125**	**554**	**6,786**	10.0%	18.4%	5.6%
	Lamictal (Lamotrigine)-March/April	1,388	287	1,101	10,887	12.7%	20.7%	
	Lamictal (Lamotrigine)-Aug-Oct	**1,840**	**385**	**1,455**	**15,761**	11.7%	20.9%	1.2%
	Depakote (Divalproex Sodium)-March/April	828	203	624	6,692	12.4%	24.5%	
	Depakote (Divalproex Sodium)-Aug-Oct	**1,119**	**258**	**861**	**9,091**	12.3%	23.1%	-6.0%
	Clonazepam-March/April	156	44	112	1,666	9.4%	28.2%	
	Clonazepam-Aug-Oct	**178**	**58**	**120**	**1,562**	11.4%	32.6%	15.5%
	Gabapentin-March/April	218	65	153	1,626	13.4%	29.8%	
	Gabapentin-Aug-Oct	**231**	**54**	**177**	**2,038**	11.3%	23.4%	-21.6%
	Abilify (Aripiprazole)-March/April	1,122	215	906	8,256	13.6%	19.2%	
	Abilify (Aripiprazole)-Aug-Oct	**1,521**	**264**	**1,257**	**11,232**	13.5%	17.4%	-9.4%
	Seroquel (Quetiapine)-March/April	1,412	303	1,107	9,280	15.2%	21.5%	
	Seroquel (Quetiapine)-Aug-Oct	**1,721**	**371**	**1,350**	**12,213**	14.1%	21.6%	0.5%
	Risperdal (Risperidone)-March/April	1,241	283	958	8,997	13.8%	22.8%	
	Risperdal (Risperidone)-Aug-Oct	**1,689**	**320**	**1,369**	**12,009**	14.1%	18.9%	-16.9%
	Zyprexa (Olanzapine)-March/April	675	170	505	5,252	12.9%	25.2%	
	Zyprexa (Olanzapine)-Aug-Oct	**938**	**205**	**733**	**7,365**	12.7%	21.9%	-13.2%
	Geodon (Ziprasidone)-March/April	342	66	276	2,628	13.0%	19.3%	
	Geodon (Ziprasidone)-Aug-Oct	**440**	**94**	**346**	**3,499**	12.6%	21.4%	10.7%
	Albuterol-March/April	237	38	199	3,457	6.9%	16.0%	
	Albuterol-Aug-Oct	**304**	**54**	**250**	**4,370**	7.0%	17.8%	10.8%
	Lithium Carbonate-March/April	484	95	389	3,663	13.2%	19.6%	
	Lithium Carbonate-Aug-Oct	**710**	**148**	**562**	**5,063**	14.0%	20.8%	6.2%
	Wellbutrin (Bupropion)-March/April	1,317	164	1,153	12,654	10.4%	12.5%	
	Wellbutrin (Bupropion)-Aug-Oct	**1,651**	**260**	**1,391**	**17,055**	9.7%	15.7%	26.5%
	Prilosec (Omeprazole)-March/April	273	49	224	3,068	8.9%	17.9%	
	Prilosec (Omeprazole)-Aug-Oct	**298**	**72**	**226**	**3,362**	8.9%	24.2%	34.6%
	Zoloft (Sertraline)-March/April	1,768	302	1,466	15,853	11.2%	17.1%	
	Zoloft (Sertraline)-Aug-Oct	**2,289**	**392**	**1,897**	**21,456**	10.7%	17.1%	0.3%
	Celexa (Citalopram)-March/April	1,399	192	1,206	14,486	9.7%	13.7%	
	Celexa (Citalopram)-Aug-Oct	**1,693**	**254**	**1,439**	**19,472**	8.7%	15.0%	9.3%
	Prozac (Fluoxetine)-March/April	1,408	203	1,205	13,739	10.2%	14.4%	
	Prozac (Fluoxetine)-Aug-Oct	**1,882**	**276**	**1,606**	**18,975**	9.9%	14.7%	1.7%
	Lexapro (Escitaloprim)-March/April	698	98	600	6,854	10.2%	14.0%	
	Lexapro (Escitaloprim)-Aug-Oct	**898**	**132**	**766**	**8,799**	10.2%	14.7%	4.7%
	Paxil (Paroxetine)-March/April	452	47	405	5,181	8.7%	10.4%	
	Paxil (Paroxetine)-Aug-Oct	**574**	**74**	**500**	**6,648**	8.6%	12.9%	24.0%
	Trazodone-March/April	2,102	329	1,772	17,714	11.9%	15.7%	
	Trazodone-Aug-Oct	**2,699**	**452**	**2,247**	**23,251**	11.6%	16.7%	7.0%
	Cymbalta (Duloxetine)-March/April	1,075	135	940	10,058	10.7%	12.6%	
	Cymbalta (Duloxetine)-Aug-Oct	**1,308**	**169**	**1,139**	**13,542**	9.7%	12.9%	2.9%
	Effexor (Venlafaxine)-March/April	623	91	532	7,288	8.5%	14.6%	
	Effexor (Venlafaxine)-Aug-Oct	**828**	**114**	**714**	**10,332**	8.0%	13.8%	-5.7%
	Amitriptyline-March/April	866	123	743	8,801	9.8%	14.2%	
	Amitriptyline-Aug-Oct	**1,078**	**177**	**901**	**11,617**	9.3%	16.4%	15.6%
	Straterra (Atomoxetine)-March/April	357	45	312	3,652	9.8%	12.6%	
	Straterra (Atomoxetine)-Aug-Oct	**452**	**54**	**398**	**4,744**	9.5%	11.9%	-5.2%

ProDUR Report for August 2013- October 2013

Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)-March/April	2	4	23	2	26	0
	Hydrocodone Bit/APAP-March/April	1	1	25	0	13	0
	Oxycodone HCl-March/April	2	1	23	1	20	0
	Lorazepam-March/April	4	10	83	2	79	0
	Alprazolam-March/April	9	9	55	1	36	0
	Diazepam-March/April	1	2	49	1	25	0
	Buspar (Buspirone)-March/April	4	4	37	0	29	0
	Lamictal (Lamotrigine)-March/April	5	12	125	3	87	0
	Depakote (Divalproex Sodium)-March/April	6	5	71	1	69	0
	Clonazepam-March/April	1	1	18	0	21	0
	Gabapentin-March/April	0	2	21	3	6	0
	Abilify (Aripiprazole)-March/April	14	4	72	5	79	0
	Seroquel (Quetiapine)-March/April	9	8	108	6	83	0
	Risperdal (Risperidone)-March/April	4	9	95	2	92	0
	Zyprexa (Olanzapine)-March/April	5	3	45	1	67	1
	Geodon (Ziprasidone)-March/April	1	3	17	0	32	0
	Albuterol-March/April	1	3	10	0	19	0
	Lithium Carbonate-March/April	3	4	56	0	34	0
	Wellbutrin (Bupropion)-March/April	5	20	52	1	77	0
	Prilosec (Omeprazole)-March/April	0	1	20	1	23	0
	Zoloft (Sertraline)-March/April	8	14	158	3	78	0
	Celexa (Citalopram)-March/April	6	12	50	8	80	0
	Prozac (Fluoxetine)-March/April	12	16	89	3	63	0
	Lexapro (Escitaloprim)-March/April	3	8	33	1	43	0
	Paxil (Paroxetine)-March/April	3	2	20	1	21	0
	Trazodone-March/April	10	19	129	7	134	0
	Cymbalta (Duloxetine)-March/April	4	7	46	4	45	0
	Effexor (Venlafaxine)-March/April	5	4	29	0	24	0
	Amitriptyline-March/April	4	14	53	2	40	0
	Straterra (Atomoxetine)-March/April	5	2	13	1	21	0
	TOTALS	**137**	**204**	**1625**	**60**	**1466**	**1**

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Retro-DUR Intervention History by Quarter - FFY 2012-2013 — Letters Sent

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	**Prescription Change Form Request**	Antidepressants	Atypical antipsychotics
Quarter 1 Oct-Dec										
Unique Patients	0	0	0	0	0	33	92	26		
Unique Patients Sent Interventions	0	0	0	0	0	0	92	26		
% Sent	-	-	-	-	-	0%	100%	100%		
Quarter 2 Jan-Mar										
Unique Patients	0	0	0	0	30	43	88	28		
Unique Patients Sent Interventions	0	0	0	0	15	0	88	28		
% Sent	-	-	-	-	50%	0%	100%	100%		
Quarter 3 Apr-Jun										
Unique Patients	0	0	0	0	76	96	49	16		
Unique Patients Sent Interventions	0	0	0	0	44	0	49	16		
% Sent	-	-	-	-	58%	0%	100%	100%		
Quarter 4 Jul-Sep										
Unique Patients	1	0	0	0	27	132	0	0		
Unique Patients Sent Interventions	0	0	0	0	23	0	0	0		
% Sent	0%	-	-	-	85%	0%	-	-		
Year to date summary										
Unique Patients	1	0	0	0	133	304	229	70		
Unique Patients Sent Interventions	0	0	0	0	82	0	229	70		
% Sent	0%	-	-	-	62%	0%	100%	100%		
ROI per intervention	$51	NA	NA	NA	NA	NA	$49	$220		
Estimated program savings	$0	NA	NA	NA	NA	NA	$11,221	$15,400		

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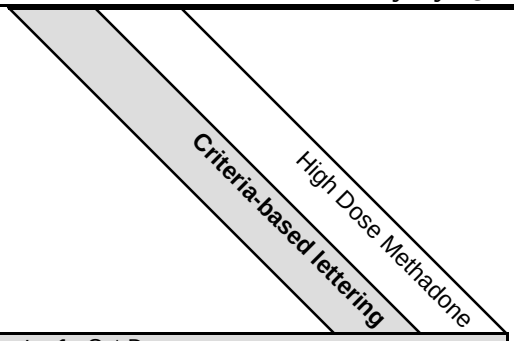
Retro-DUR Intervention History by Quarter - FFY 2012-2013 Le



Quarter 1 Oct-Dec	
All Patients on Drug of Interest	235
Patients Hitting Criteria in Qtr	30
Patients Hitting Criteria / 100 Users	13
Unique Patients	11
Unique Patients Sent Interventions	5
% Sent	45%
Quarter 2 Jan-Mar	
All Patients on Drug of Interest	167
Patients Hitting Criteria in Qtr	25
Patients Hitting Criteria / 100 Users	15
Unique Patients	2
Unique Patients Sent Interventions	2
% Sent	100%
Quarter 3 Apr-Jun	**Discontinued**
All Patients on Drug of Interest	149
Patients Hitting Criteria in Qtr	23
Patients Hitting Criteria / 100 Users	15
Unique Patients	0
Unique Patients Sent Interventions	0
% Sent	-
Quarter 4 Jul-Sep	**Discontinued**
All Patients on Drug of Interest	138
Patients Hitting Criteria in Qtr	22
Patients Hitting Criteria / 100 Users	16
Unique Patients	0
Unique Patients Sent Interventions	0
% Sent	-
Year to date summary	
Unique Patients	13
Unique Patients Sent Interventions	7
% Sent	54%
ROI per intervention	NA
Estimated program savings	NA

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Retro-DUR Intervention History by Quarter - FFY 2012-2013 Responses Received

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	**Criteria-based lettering**	High Dose Methadone	
Quarter 1 Oct-Dec										
Unique Prescribers Sent Interventions	0	0	0	0	0	0	0	0	0	7
Responses Received	0	0	0	0	0	0	0	0	0	2
Response Rate	-	-	-	-	-	-	-	-	-	40%
% Agree with message	-	-	-	-	-	-	-	-	-	-
% Consider in future prescribing	-	-	-	-	-	-	-	-	-	-
Quarter 2 Jan-Mar										
Unique Prescribers Sent Interventions	0	0	0	0	0	0	14	0	0	2
Responses Received	0	0	0	0	0	0	0	0	0	1
Response Rate	-	-	-	-	-	-	-	-	-	50%
% Agree with message	-	-	-	-	-	-	-	-	-	100%
% Consider in future prescribing	-	-	-	-	-	-	-	-	-	-
Quarter 3 Apr-Jun										
Unique Prescribers Sent Interventions	0	0	0	0	0	0	8	0	0	0
Responses Received	0	0	0	0	0	0	0	0	0	0
Response Rate	-	-	-	-	-	-	-	-	-	-
% Agree with message	-	-	-	-	-	-	-	-	-	-
% Consider in future prescribing	-	-	-	-	-	-	-	-	-	-
Quarter 4 Jul-Sep										
Unique Prescribers Sent Interventions	0	0	0	0	0	0	0	0	0	0
Responses Received	0	0	0	0	0	0	0	0	0	0
Response Rate	-	-	-	-	-	-	-	-	-	-
% Agree with message	-	-	-	-	-	-	-	-	-	-
% Consider in future prescribing	-	-	-	-	-	-	-	-	-	-
Year to date summary										
Unique Prescribers Sent Interventions	0	0	0	0	0	0	22	0	0	9
Responses Received	0	0	0	0	0	0	0	0	0	3
Response Rate	-	-	-	-	-	-	-	-	-	43%
% Agree with message	-	-	-	-	-	-	-	-	-	33%
% Consider in future prescribing	-	-	-	-	-	-	-	-	-	-

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Managing Metabolic Side Effects in Children Receiving Antipsychotics

By Ted Williams, Pharm. D. OSU College of Pharmacy Drug Use Research and Management

Awareness of mental health disorders in children has increased in recent years, with an estimated 15-25% of children in the United States having a diagnosable mental health disorder.[1] A study reviewing data from 2001-2002 showed 13.5% of all child welfare patients were receiving psychotropics. Studies indicate that providers in rural areas are more likely to prescribe psychotropics that those in urban areas.[2,3,4] Although the use of antipsychotics in children is controversial, there is no doubt it is common practice. In light of the prevalence of antipsychotic use in children, an understanding of appropriate use and adequate monitoring practices are essential for all prescribers.

Effectiveness of Antipsychotics in Children

There is a growing use of antipsychotics for non-traditional and poorly supported indications.[5,6] A 2012 Agency for Healthcare Research and Quality (AHRQ) report evaluated the use of antipsychotics in children.[7] Ninety percent of all studies reviewed had significant risks of bias due to methodological flaws including inadequate blinding and incomplete outcome data. There is limited pediatric evidence supporting the short term use of antipsychotics in Pervasive Developmental Disorder, ADHD with Disruptive Behavior, Bipolar Disorder, and Schizophrenia. Long term efficacy and safety data for the use of antipsychotics for any pediatric indication are severely limited. There is limited head to head comparison of antipsychotics making comparisons difficult.[6] In the Treatment of Early-Onset Schizophrenia Spectrum study (TEOSS), only 14 of 54 patients completed the 44 week study due to adverse side effects or lack of benefit.[8] A comparative effectiveness review found no difference between second generation antipsychotics (SGAs) or between first generation antipsychotics (FGA) and SGAs, with the exception of Clinical Global Impression (CGI) scores in the treatment of schizophrenia in which SGAs (clozapine, olanzapine, risperidone) were found to be superior to haloperidol (FGA).[6] Evidence supporting the anticipated benefits of injectable antipsychotics for relapse prevention is mixed. Randomized control trials do not show superior benefit, where more naturalistic studies have shown benefits.[9,10] Given the limited data available, antipsychotic agent and formulation selections remain largely up to clinician expertise and patient-specific factors. Aripiprazole and risperidone are the only SGAs which have FDA approved indications for children under 10yrs old (irritability associated with autistic disorder). In all, only five SGAs have approved indications in children under 18 years old (olanzapine, quetiapine, risperidone for bipolar I and aripiprazole, olanzapine, paliperidone, quetiapine and risperidone for schizophrenia).

There is a wide range of costs for antipsychotic agents and formulations. Current Centers for Medicare and Medicaid Services Survey of Retail Prices indicates monthly antipsychotic prescription costs range from $13-$779 per person.[11] Although cost should never supersede clinical benefits, the cost differential should be considered when agents are not distinguishable in effectiveness and adverse effect profiles.

Metabolic Monitoring of Antipsychotics in Children

The metabolic risks of antipsychotic medications are well documented.[12–14] SGAs have an FDA warning about metabolic abnormalities but FGAs also have metabolic effects.[15,16] SGAs described as "weight neutral" are neutral when compared to a FGA (typically lower dose haloperidol).[17,18] Both SGAs and FGAs have been demonstrated to have some amount of weight gain upon initiation of therapy.[3,19] Children may be particularly susceptible to the metabolic effects of antipsychotics.[20] Despite FDA recommendations, consensus guidelines, and primary literature highlighting the importance of monitoring for metabolic abnormalities, recent studies have shown that glucose and lipid monitoring rates continue to be low in adults and children.[21,22] Recommended schedules for monitoring of glucose and lipids have been proposed by multiple groups including the American Diabetes Association (ADA), American Psychiatric Association (APA) and American Association of Clinical Endocrinologists (AACE).[23,24] The ADA recommends monitoring of blood glucose, blood pressure and waist circumference at baseline, 12 weeks, and annually thereafter. BMI monitoring is recommended at baseline and every four weeks for 12 weeks and quarterly for the first year. Lipids checks are recommended at baseline, 12 weeks and every 5 years. More frequent monitoring may be indicated based on patient-specific factors. Patient specific factors include a personal or family history of diabetes, metabolic syndrome, or cardiovascular disease.

Many children resist blood draws and compliance with fasting does not always occur. Recent guidelines endorse the use of A1C for monitoring for metabolic syndrome.[25] Non-fasting LDL cholesterol can be evaluated using a direct LDL test, though the results may somewhat lower (11.5 mg/dL).[26]

Metabolic Syndrome Detection and Management

There is a lack of long term clinical data to define metrics and risk thresholds predicting development of diabetes and cardiovascular disease on which to base diagnostic criteria for metabolic syndrome in children.[27] In 2007, the International Diabetes Federation (IDF) developed consensus guidelines for the diagnosis of metabolic syndrome in children.[27] These guidelines synthesized recommendations from the ADA, the World Health Organization, and National Cholesterol Education Program. The IDF guidelines use waist circumference plus two other risk factors as diagnostic criteria. Waist circumference has been show to predict metabolic syndrome with similar accuracy to body mass index (BMI) when gender, age and ethnic group have been considered.[27] The IDF Guidelines define three age groups: 6-9 years, 10-15 years, and 16 and older. The IDF determined diagnosis of metabolic syndrome in children under 10 years was determined unreliable. Monitoring of children under 10 years with waist circumferences greater that the 90th percentile may be warranted in patients with a family history of diabetes or cardiovascular disease.

Body Composition & Metabolic Changes Over 12 Weeks in Children Receiving Antipsychotics[19]

		Mean	(95% CI)	p Value
Weight (kg)	Aripiprazole	4.44	(3.71 to 5.18)	<.001
	Olanzapine	8.54	(7.38 to 9.69)	<.001
	Quetiapine	6.06	(4.90 to 7.21)	<.001
	Risperidone	5.34	(4.81 to 5.87)	<.001
	Untreated	0.19	(−1.04 to 1.43)	0.77
Waist (cm)	Aripiprazole	5.4	(2.87 to 7.93)	<.001
	Olanzapine	8.55	(7.43 to 9.67)	<.001
	Quetiapine	5.27	(4.07 to 6.47)	<.001
	Risperidone	5.1	(4.49 to 5.71)	<.001
	Untreated	0.7	(−0.87 to 2.27)	0.4
LDL cholesterol (mg/dL)	Aripiprazole	7.38	(0.77 to 13.99)	0.05
	Olanzapine	11.54	(3.97 to 19.11)	0.004
	Quetiapine	3.88	(−3.37 to 11.13)	0.3
	Risperidone	0.21	(−4.14 to 4.56)	0.92
	Untreated	2.99	(−5.18 to 11.16)	0.49

Diagnostic criteria for children over 16 years are identical to criteria in adults. Not all patients develop all abnormalities associated with metabolic syndrome and the alterations vary by agent. Therefore, it is important to monitor all metabolic parameters in all children.

For some patients, changing antipsychotic medications may be an option to manage metabolic abnormalities. The metabolic effect profiles vary from one antipsychotic to another.[20] Weight is not a reliable surrogate marker for glucose and lipid irregularities as weight, glucose and lipid changes are not always parallel, i.e. agents causing more weight gain may cause fewer and lower lipid abnormalities. For patients with a sustained positive response or clinically fragile patients, altering psychotropic therapy may not be a desirable option.

The effects of antipsychotics on weight gain have prompted studies examining agents to mitigate or eliminate weight gain.[28] Two studies suggest metformin may be effective in preventing new weight gain in antipsychotic-naïve patients as well as patients who have already gained weight due to antipsychotic therapy.[29,30] A recent meta-analysis found only metformin, d-fenfluramine, and topiramate to have benefits superior to placebo at reducing weight gain.[31] In the same meta-analysis dextroamphetamine, amantadine, orlistat, famotidine and rosiglitazone all failed to show significant advantages compared to placebo. A naturalistic study of children receiving antipsychotics for behavior control found no benefit in managing antipsychotic-induced side effects including weight gain with the addition of methylphenidate.[32] These results challenge what would seem to be the natural conclusion that stimulants would reduce the weight gain associated with antipsychotics.

Quick Reference Guides

The supplemental materials for this newsletter contain four quick-reference guides summarizing: evidence-informed indications for antipsychotic use in children, national average prescription costs, antipsychotic-induced metabolic effects in children, and the IDF criteria for metabolic syndrome in children. These materials are available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/osdr_articles/volume3/osdr_v3_i3supplements.pdf.

Conclusion

The use of antipsychotics in children requires careful monitoring and thoughtful evaluation of the risk to benefit ratio. There is a general lack of evidence of the safety and effectiveness of long-term use of antipsychotics in children. The treatment of children with antipsychotics therefore relies heavily on provider expertise. When antipsychotics are prescribed, careful monitoring for metabolic abnormalities (body composition, lipids, glucose, blood pressure) is the standard of care.

Peer Reviewed By: Ajit Jetmalani, MD, Director, Division of Child and Adolescent Psychiatry and Psychiatry Education at OHSU and Cydreese Aebi, PhD, RPh, BCPP, Clinical Pharmacy Coordinator at Oregon State Hospital.

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October 2013 Volume 3, Issue 4

Updates and Comparisons of Type 2 Diabetes Treatment Guidelines

By Kala Berkey and Michelle Pfeifer PharmD.Candidates 2014, Megan Herink, Pharm.D.and Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

Due to the increasing prevalence of Type 2 Diabetes Mellitus (T2DM) and recent therapeutic advancements, the treatment of diabetes and its complications are constantly evolving. In response to these changes, treatment guidelines are required to be frequently updated. In 2013, the American Association of Clinical Endocrinologists (AACE) replaced the 2009 algorithm for glycemic control with a comprehensive diabetes management algorithm. This included all elements of type 2 diabetes (hyperglycemia, obesity, prediabetes, hypertension, and dyslipidemia), with limited text, followed by the release of a detailed consensus statement. In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released a joint position statements entitled, "Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach," which described a basic algorithm for the treatment of hyperglycemia. In 2013, the ADA/EASD published its annual guideline update entitled, "Standard of Medical Care in Diabetes". This review will compare and contrast the ADA and AACE's approach to comprehensively treat T2DM and will also highlight the recent revisions for the 2013 ADA position statement.[1-3]

Glycemic Control Update

The current management of T2DM relies on patients working with clinicians to determine an appropriate hemoglobin A1c goal. Optimal glycemic goals are largely based on expert opinion, thus creating varying glycemic goals between professional organizations.[4] The AACE recommends an A1c goal of ≤6.5%, while the ADA recommends <7% for patients with no concurrent illness (cardiovascular disease [CVD], low hypoglycemic risk, long life expectancy, and short duration of diabetes).[2,3] Studies have shown more intensive strategies (A1c goals of ≤6% vs. standard strategies (A1c goal of 7-7.9%%) improve DM nephropathy progression, but have no benefit on cardiovascular outcomes, and instead have shown to increase mortality.[5-7] A slightly higher A1c target, such as 7-8%, is therefore recommended for patients with concurrent illnesses or at high risk of hypoglycemic risk by both the AACE and ADA.[2,3] In addition to fasting and 2-hour plasma glucose, the ADA included an A1c of 5.7-6.4% as a category for prediabetes, while AACE does not have an A1c as part of the diagnostic criteria for prediabetes. Its criteria include impaired glucose tolerance, impaired fasting glucose, or metabolic syndrome.

Treatment guidelines now emphasize a patient-centered approach to diabetes management.[1,3] The AACE recommendations for treatment are based on presenting A1c and do not take into account the acquisition cost of therapy.[3] They note that cost of drug is only a small factor in the overall care of a diabetic patient. However, cost should likely be a consideration as it may affect adherence and patient access to the appropriate level of care. The ADA contrasts the AACE by acknowledging that costs are a critical issue driving the selection of medication.[1]

The preferred first line therapy is metformin, along with lifestyle modifications per the ADA and AACE.[1-3] The AACE algorithm provides directed guidance on second and third line treatment options based upon expert consensus.[3] In contrast, the ADA algorithm does not recommend one therapeutic option over another for second line therapy due to lack of comparative effectiveness evidence. Treatment choice should be based on efficacy, hypoglycemic risk, weight changes, underlying comorbidity, side effects, and cost.[1] AACE recommends dual therapy if baseline A1c is ≥7.5%, while initiation of dual therapy is recommended only when baseline A1c is ≥9% per ADA.[3] Both guidelines recommend considering initial treatment with insulin in patients presenting with severe symptomatic hyperglycemia.[1,3] If the glucose level is not markedly elevated, some patients may also benefit from basal intensification with a dipeptidyl peptidase-4 inhibitor or a glucagon-like peptide-1 agonist, as this approach does not likely cause weight gain or hypoglycemia.

Hypertension Update

Managing high blood pressure (BP) in patients with diabetes is imperative in lowering cardiovascular risk and complications. According to the American Heart Association, heart disease and stroke are the number one causes of death and disability among people with T2DM.[8] However, recent evidence has challenged BP targets of <130/80 mmHg previously established for patients with T2DM.[9-11] The ADA/EASD 2013 position statement revised the target systolic blood pressure (SBP) from below 130mmHg to below 140mmHg.[2] The new target SBP goal is based on recent evidence in demonstrating a small reduction in the risk of stroke with intensive BP goal, but no evidence for decreased mortality or myocardial infarction.[9-11] There was also an increased risk of hypotension and other adverse events with the lower goal compared to the less stringent target. The ADA suggests it is reasonable to target a lower BP goals (<130/80 mmHg) in younger patients and 110-129/65-79 mmHg in pregnant women with chronic hypertension and diabetes.[2] The ADA also suggests that if a person can easily achieve a lower goal, it is likely appropriate and beneficial. A detailed review of trials involving blood pressure targets in patients with diabetes can be found in the June 2012 edition of *The Oregon State Drug Review*.[12]

In contrast, the AACE 2013 consensus statement upholds the goal of <130/80 mmHg.[3] This recommendation is based on the significant reduction in fatal and non-fatal stroke (ARR 1.1%; 95% CI 0.003-0.019; p=0.01), and macroalbuminuria (ARR 2.1%; 95% CI 0.005-0.037; p=0.009) shown in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial.[9] A specific blood pressure goal in pregnancy has not been established by the AACE. [3]

Both the ADA and AACE continue to endorse the use of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) as initial therapy for blood pressure control and stress the importance of lifestyle modifications, in addition to pharmacologic therapy.[2,3] The AACE recommends starting dual therapy (ACEi or ARB with thiazide, calcium channel blocker, or beta blocker) when initial blood pressure is >150/100 mmHg.[3] The ADA recognizes multiple-drug therapy is usually necessary to achieve blood pressure goals, but does not give a specific measurement.[2]

Dyslipidemia Update

Patients with T2DM have a significantly increased risk of CVD compared to those without. Both organizations give a target LDL-C goal of <100 mg/dL in low-moderate risk patients (DM without other CVD risk factors).[2,3] The AACE target LDL-C goal is <70 mg/dL in high risk patients (overt CVD or 1 or more CVD risk factors; family history of CHD, hypertension or on antihypertensive medication, low HDL-C, smoking).[3] The ADA's stance on lipid lowering differs, they are now emphasizing the importance of statin therapy over particular LDL goals in high-risk patients. The ADA 2013 position statement recommends statin therapy regardless of baseline lipid level in patients with overt CVD or for those without CVD who are >40 years old and have ≥1 CVD risk factors (high-risk). Statin therapy is also recommended in lower-risk patients if LDL remains above 100 mg/dl. Per the ADA, the suggested LDL goal of <70 mg/dL is optional in patients with overt CVD. In patients who cannot achieve LDL goals on maximum tolerated statin therapy, the ADA recommends an alternative goal of 30-40% reduction in LDL levels from baseline.[2]

The organizations differ in their stance on combination therapy. The AACE recommends combination therapy with ezetimibe, colesevelam, and/or niacin in patients who have not reached their LDL goal despite optimal statin therapy. It recommends adding omega-3-acid ethyl esters, and/or niacin to

lower non-HDL cholesterol or triglycerides.[3] Combination therapy with fenofibrate or niacin is not recommended by the ADA because these therapies have failed to provide any additional cardiovascular benefit above statin therapy alone, as demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial and the Atherothrombosis Intervention in Metabolic syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial.[13-14] This is a new recommendation since the 2012 update.[15]

Weight Management Strategies

A new addition to the AACE algorithm is a section specifically focusing on the overweight/obese population, targeting weight loss strategies.[3] The focus is on a complications-centric model, as opposed to a BMI-centric model, incorporating lifestyle, medical, and surgical options. Weight loss can have a positive impact on blood glucose, lipids, and BP.[3] The AACE recommendation is a culmination of evidence from the Look Action for Health in Diabetes (Look AHEAD) and the newer weight loss pharmacotherapy clinical trials.[16-19] Although the Look AHEAD trial was terminated early due to lack of observed cardiovascular benefit, results did show that significant weight loss is associated with a significant reduction in blood pressure (-6.8/3.0 mmHg; p<0.001).[16-17] These patients were enrolled in a program of decreased caloric intake and increased physical activity.[16]

The AACE algorithm recommends phentermine, orlistat, lorcaserin, and phentermine/topiramate ER as treatment options, always as adjunct to lifestyle modification, for weight reduction.[3] In clinical trials, these drugs have shown efficacy in reducing weight compared to placebo.[18-20] However, the impact of weight loss drugs on obesity remains controversial due to lack of evidence in reducing long term macro- and microvascular complications. The newer weight loss medications, lorcaserin and phentermine/topiramate ER, were evaluated and reviewed in detail in the December 2012 edition of, *The Oregon State Drug Review.*[21] Much uncertainty remains regarding the long-term efficacy and safety of these drugs.

Other ADA Updates

In addition, many other changes resulting from new evidence were made to the ADA recommendations. The immunization section has been updated to include the new Centers for Disease Control and Prevention (CDC) recommendations for hepatitis B vaccination in patients with diabetes. This includes administering hepatitis B vaccination to unvaccinated adults with diabetes from ages 19 through 59 years, and to consider hepatitis B vaccination in all ≥60 year old patients with diabetes.[2] The CDC recommendation is a result of 29 outbreaks of hepatitis B virus that occurred in long-term care facilities and hospitals.[22]

Lastly, the recommendations for retinopathy treatment now include anti-vascular endothelial growth factor (VEGF) therapy as a treatment option for diabetic macular edema in addition to laser photocoagulation therapy. Anti-VEGF therapy has been shown to improve vision and reduce the need for laser photocoagulation in patients.[2]

Conclusion

There are many practice guidelines and algorithms available for the treatment of diabetes mellitus. However, many of these are conflicting and vary in quality. Guidelines and algorithm updates and changes have a significant impact on clinical practice and it is therefore imperative that they be scrutinized for quality and consistency. The ADA and AACE guidelines were both appraised for quality using the AGREE II instrument. [23] The AACE guidelines scored very low in the "rigor and development" domain, which accounts for methodological quality. Rather, the recommendations were highly opinion based and thus should be interpreted with caution. In contrast, the ADA guidelines scored much better in the domain reflecting methodological quality. Both guideline development groups were comprised of members with direct ties or support to industry. Ultimately, the main goal should be to individualize care by aiming for A1c, blood pressure, and lipid goals that are safe and well tolerated so that complications related to diabetes can be minimized.

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Abbreviated New Drug Evaluation:

Month/Year of Review: November 2013
Generic Name: Naltrexone
Dossier Received: Pending
PDL CLASS: Opioid Dependence Treatment

End date of literature search: August, 31, 2013
Brand Name (Manufacturer): Vivitrol® (Alkermes, Inc.)

FDA Approved Indications: Naltrexone injection is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with naltrexone. It is also indicated for the prevention of relapse to opioid dependence following opioid detoxification. It should be part of a comprehensive management program that includes psychosocial support.[1]

Research Questions:

- What is the evidence for the effectiveness of naltrexone injection in the treatment of alcohol and opioid dependence? What is the evidence for the safety of naltrexone injection for the treatment of alcohol and opioid dependence?
- Are there subpopulations that will benefit from naltrexone injection in terms of effectiveness or harms for the treatment of alcohol and opioid dependence?

Conclusions:

- For the treatment of opioid dependence, there is moderate level evidence that when compared to placebo, naltrexone extended-release injectable suspension is associated with reduced opioid use after detoxification and reduces confirmed total abstinence in 35.7% vs. 22.6% (p = 0.0224, NNT 8) of patients when studied for 24 weeks, in combination with drug counseling.
- For the treatment of alcohol dependence, there is moderate level of evidence that when compared to placebo, naltrexone extended-release injectable suspension reduces the rate of self-reported heavy drinking days and return to any drinking (RR 0.92, 95% CI 0.84-1.00).[3,4]
- There is moderate level of evidence that when compared to placebo, injectable naltrexone results in more discontinuations due to side effects (RR 1.57, 95% CI 0.92 to 2.69).[5]
- Extended release naltrexone is a viable option when medication adherence is a significant concern.

Recommendations

- Evaluate comparative costs of injectable extended release naltrexone in executive session and consider prior authorization to ensure use in appropriate patients (appendix B).

Background/Current landscape

Naltrexone is a highly effective opioid antagonist that binds to mu-receptors. It has a higher affinity for mu receptors than has heroin, morphine, or methadone. It displaces those drugs from receptors and blocks their effects. As a result, it can precipitate withdrawal in patients who have not been abstinent from short-acting opioids for at least 7 days and have not been abstinent from long-acting ones, such as methadone, for at least 10 days.[6] Naltrexone displaces buprenorphine to a lesser degree, but when used in higher doses, it overrides buprenorphine's activity as well. Naltrexone has no narcotic effects, there are no withdrawal symptoms when discontinued, nor does naltrexone have abuse potential. Naltrexone in all forms carries a black-box warning for hepatotoxicity and warnings for use in patients with elevated hepatic enzymes and acute hepatitis. The FDA approved naltrexone in tablet form for opioid maintenance treatment in 1984 based on its pharmacological effects without requiring evidence showing efficacy in the clinical trials. Despite its potential advantages, it has little impact on the treatment of opioid dependence in the United States due to poor patient compliance.[6] DynaMed concludes that oral naltrexone has insufficient evidence in the treatment of opioid dependence and a Cochrane review found no significant differences between oral naltrexone and placebo in retention and abstinence (RR 1.43, 95% CI 0.72-2.82). In 2010 an extended release once monthly intramuscular injection of naltrexone under the trade name Vivitrol® was approved by FDA to improve treatment adherence. Extended release naltrexone was originally approved in 2006 for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. It is administered by intramuscular (IM) injection once per month. Naltrexone extended release injection must be administered by a healthcare professional and therefore is currently covered under the medical benefit. There is limited head to head evidence evaluating extended-release naltrexone injection. A sustained release naltrexone implant has been shown to result in more patients with opioid dependency to remain in treatment without relapse than oral naltrexone (52.9% vs. 15.7%; p<0.001, NNT 3).[7] However, this is currently not approved in the US. There was are recent feasibility pilot study investigated the using XR-NTX for the treatment previously opioid-dependent parolees and probationers (N = 61), results showed that those who completed treatment (N = 21) had significantly fewer opioid-positive urines (4% vs. 44%; p = 0.003) and were less likely to have been incarcerated than those who had not completed treatment (15% vs. 50%; p = 0.011).[8]

Clinical Efficacy and Safety

Alcohol Dependence

Systematic Reviews:

A 2010 systematic review from the Cochrane Collaboration evaluated the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.[5] All double-blind RCTs comparing naltrexone or nalmefene with placebo or active control were included. Primary outcomes included: return to heavy drinking, return to any drinking, and drinking days. A literature search through January 2010 identified 50 studies (n=7793) to be included in the evidence synthesis; 47 of which were included in the meta-analysis. Only 4 of the RCTs evaluated the injectable ER formulation of naltrexone. These trials showed that injectable naltrexone appears effective, but not all outcomes were statistically significant. Injectable naltrexone was administered at four-week intervals at doses between 150 mg and 400 mg.

Analysis of injectable naltrexone showed reduced risk of any drinking after detoxification to 92% of the placebo group (RR 0.92, 95% CI 0.84-1.0), the percentage of drinking days by about 9% (mean difference [MD] -8.54, 95% CI -15.77 to -1.31), and the percentage of heavy drinking days by about 3% (MD -3.05, 95% CI -8.46 o 2.35). Injectable naltrexone caused significantly more daytime sleepiness, decreased appetite, dizziness, fatigue, and vomiting than placebo. Early withdrawals due to side effects were more frequent in the injectable naltrexone group the the placebo group (RR 1.57, 95% CI 0.92 to 2.69).

Authors concluded that the treatment effects of injectable naltrexone are comparable in magnitude to oral naltrexone. However, statistical significance was missed. Other than a more pronounced sedative effect, the tolerability appears comparable to oral naltrexone.

Clinical Trials:

Naltrexone extended-release injectable suspension was assessed in a 24-week placebo-controlled, multicenter, double-blind, randomized study enrolling 624 outpatients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for alcohol dependence.[3] Injections of placebo (209 patients), naltrexone 190 mg extended-release (210 patients), or naltrexone 380 mg extended-release (205 patients) were administered IM every 4 weeks. Oral naltrexone was not administered prior to the initial or subsequent injections. Low-intensity psychosocial support was provided to all subjects. A total of 6 injections were administered to 401 patients (64%), while 463 patients (74%) received 4 injections. The primary study end point was the rate of heavy drinking days in the intent-to-treat population. Patients treated with naltrexone 380 mg extended-release injection had a greater reduction in days of heavy drinking (defined as self-report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients) compared with those treated with placebo. Heavy drinking days were reduced 25% in the naltrexone 380 mg group (P = 0.03) and 17% in the naltrexone 190 mg group (P = 0.07) compared with placebo. Greater reductions in heavy drinking days were observed in those abstinent at study entry and in men. During the study, complete abstinence was maintained in 7% of patients in the 380 mg group, 6% in the 190 mg group, and 5% in the placebo group. The results suggested even though there was clinically significant reduction in self reported heavy drinking days in treatment groups, it did not result statistically significant difference in abstinence between groups, which is the optimal treatment goal. The subgroup analysis on 53 patients who abstained completely from drinking during the week prior to the first dose of medication and were treated with naltrexone 380 mg extended-release injection had greater reductions in the number of drinking days and the number of heavy drinking days compared with those treated with placebo. In this subgroup, patients treated with naltrexone were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment (41% vs. 35% in the 190 mg group and 17% in the placebo group; differences not statistically significant).[3]

Naltrexone extended-release injectable suspension was also assessed in a 3-month randomized, double-blind, placebo-controlled study enrolling 315 alcohol-dependent subjects.[4] Patients received naltrexone (158 patients) or placebo (157 patients) monthly for 3 months. The naltrexone dose was 300 mg (two 150 mg injections) for the first dose and 150 mg for the subsequent doses. All patients also received 5 sessions of manual-guided motivational enhancement therapy. The time to first drinking day, percentage of patients with no heavy drinking throughout the study, and gamma-glutamyl transpeptidase levels all favored the naltrexone, but were not statistically significant. The median time to first heavy drinking day was 11 days in the naltrexone group compared with 6 days in the placebo group (P = 0.05). The mean number of heavy drinking days was 22.4 in the naltrexone group compared with 25.3 in the placebo group (P = 0.29). The median time to first drinking day was 5 days in the naltrexone group compared with 3 days in the placebo group (P = 0.003). During the 12-week study, 23% of the naltrexone depot group reported no heavy drinking, compared with 16% of placebo (p = 0.12)[4]

The commonly reported adverse reactions during clinical trials for the treatment of alcohol dependence with naltrexone 380 mg extended-release injectable suspension compared with placebo included nausea (33% vs. 11%), vomiting (14% vs. 6%), diarrhea (13% vs. 10%), abdominal pain (11% vs. 8%), injection-site reactions (69% vs. 50%; tenderness, induration, pain, swelling), asthenia (23% vs. 12%), headache (25% vs. 18%), dizziness (13% vs. 4%), and decreased appetite (14% vs. 3%). The most common adverse reactions prompting discontinuation of therapy were injection-site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). Nausea is most common after the first injection. It is generally mild and subsides within a few days post injection. Nausea is less likely to occur following subsequent injections.[1]

Opioid Dependence

Systematic Reviews:

A 2008 Cochrane systematic review of sustained-release depot naltrexone for opioid dependence published in 2008 concluded that evidence was insufficient to evaluate its effectiveness.[9] However, this was before the following clinical trials were completed and was evaluating a slightly different formulation.

Clinical Trials:

The efficacy of naltrexone extended-release injectable suspension in the treatment of opioid dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification.[2] A total of 250 eligible patients were randomized to receive naltrexone 380 mg (n = 126) or placebo (n = 124), both in combination with drug counseling. The primary endpoint was confirmed abstinence, calculated by each patient's rate of opioid-free weeks. All missing urine drug test results were imputed as positive for opioid use. Results demonstrated opioid-free weeks from week 5 to 24 weeks were significantly different between treatment groups (P = 0.0002), with a median of 90% opioid-free urines in the extended-release naltrexone group and 35% in the placebo group. In addition, significantly more naltrexone -treated patients achieved complete abstinence from Week 5 to Week 24 vs. placebo-treated patients (36% vs. 23%, respectively; P = 0.0224).[2] Overall, 51% of the naltrexone -treated patients and 65% of the placebo-treated patients did not complete the 24 weeks of treatment and 13% of naltrexone-treated patients compared to 36% of placebo-treated patients dropped out of the study before week 5.

Patients who completed this initial 6-month study were offered to enroll in a 1-year open-label extension study which provided injectable naltrexone for up to 13 additional doses.[10] Overall, 50.9% of patients remained abstinent from opioids at all scheduled monthly assessments during the open-label phase (49.3% of those continuing with naltrexone vs. 53.2% of those who switched from placebo).

There was another multicenter, randomized, double-blind, placebo-controlled, parallel, 8 –week clinical trial that evaluated the safety and efficacy of long acting injectable naltrexone (Depotrex®) in the treatment of opioid dependence.[11] However, this formulation is not available in the US. It is not included in the review.

In the clinical trial of opioid-dependent patients, 2% of patients treated with injectable naltrexone and 2% of patients treated with placebo discontinued treatment due to an adverse event (AE).[1] The treatment-emergent AEs, regardless of causality, occurring in ≥ 2% of patients for which the incidence was greater in the injectable naltrexone group vs. placebo, were: alanine aminotransferase (ALT) increased (13%), aspartate aminotransferase (AST) increased (10%), gamma-glutamyltransferase (GGT) increased (7%), nasopharyngitis (7%), influenza (5%), insomnia (6%), hypertension (5%), injection site pain (5%), toothache (4%), and headache (3%).[1]

Evidence Table:

Relevant Endpoints:

1) Return to drinking
2) Complete abstinence
3) Discontinuations due to Adverse events

Study Endpoints:

1) Confirmed abstinence or self-reported drinking days
2) Opioid craving score, percent of drinking/no drinking days
3) Relapses
4) Discontinuation rate

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
Garbutt J[2] et al.– alcohol dependence 2005 DB, PC, RCT; MC	N1: 380mg naltrexone N2: 190 mg naltrexone P: placebo	Mean age (N1/N2/P): 45.0/44.6/44.7 Male (N1/N2/P): 67%/68%/66% Caucasian (N1/N2/P): 83.9%/80.5%86.1% % Heavy drinking in 30 days before randomization (N1/N2/P): 25.9/26.4/24.8 Inclusion criteria: ≥18 years of age, had minimum of 2 episodes of heavy drinking per week during 30 days before screening. Exclusion criteria: Evidence o liver failure; ALT or AST > 3x normal limits; dependence within the past year on benzodiazepines, opiates, or cocaine; > 7 days of inpatient tx for substance abuse in the month before screening.	N1: 205 N2: 210 P: 209	24 weeks	Primary endpoint Reduction of Rate of heavy drinking days compared to placebo: N1: 25% (p = 0.03) N2: 17% (p = 0.07) Secondary endpoint Drinking risk reduction compared to placebo: N1: 10% (p = 0.23; NS) N2: 5% (p = 0.58; NS) Reduction of non abstinent days compared to placebo: N1: 4% (p = 0.58; NS) N2: 2% (p = 0.80; NS)	N1: ARR25% NNT 4 N2: ARR17% NNT 6 NA NA	Tx related events (N1/N2/P) N1:5.4% N2:4.8% P:7.2% p value not reported Discontinuation due to AE:: N1:29 (14.1%) N2: 14 (6.7%) P; 14 (6.7%) p = 0.01, N1 vs. N2 and P)	NA ARR 7.4% NNH 13.5	Fair Internal Validity Review of Bias: Selection: Low bias; the randomization and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors Attrition: High attrition at 39.5%, 40% and 38.9% for naltrexone 380mg, 190mg and placebo respectively. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian in range of 80.5 -86.1% among groups. Male consisted 2/3 of the all study groups and differed characteristics from female participant such as concurrent drug use, baseline LFTs. Setting: The study included patients from both public and private treatment settings, and specialty and non-specialty practices. Outcomes: The primary efficacy was based on pt's self report. Although pt was subject to breath alcohol levels, but it is unclear the frequency of the test and who was conducting the test. In addition, it was a short term study investigating potential long term addiction with multiple relapses. Because the study included wide range of patients in different setting, it is unclear which subgroup would potentially benefit the most from the treatment.

Kranzler[4] et. al **– alcohol dependence** 2004 DB, PC, RCT; MC	ND: naltrexone depot 150mg monthly with 300mg loading dose P: placebo	Mean age (ND/P): 44.1/43.6 Female (ND/P): 32.9%/36.9% Caucasian (ND/P): 82.9%/81.5% Alcohol dependence scale, mean (SD): ND: 19.3 (7.7)* P: 17.5 (7.2)* *p < 0.05 Pretreatment heavy-drinking days in 30 days, mean (SD): ND: 20.3 (7.8) P: 21.5 (7.0)	ND = 158 P = 157	12 weeks	Primary endpoint Cumulative #of heavy-drinking days during the treatment period, mean (95% CI): ND: 22.4 (18.3 -26.4) P: 25.3 (21.3 – 29.4) P value = 0.29 (NS) Selected Secondary endpoint Cumulative abstinent days, mean (95% CI) during study period: ND: 52.8 (48.5 – 57.2) P: 45.6 (41.1 – 50.0) P value = 0.018 Time to 1st heavy drinking day, median (95% CI): ND: 11 (8-17) P: 6 (4-10) P Value = 0.05 (NS)	NA NA N/A	Discontinuations due to AE ND: 4 (2.5%) P: 2 (1.3) p-values not provided	NA	Fair Internal Validity Review of Bias: Selection: Low bias; the randomizatio and allocation concealment was clear. Performance: Potential bias; blinding of patients was described; however it was unclear the binding of the study monitors Attrition: Attrition rates for treatmen and placebo groups at 19.6% and 28.7% respectively, which were lower than other RCT. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian and female pts. The concurrent use of other medications was unknown. Participants were subjects who responded to media advertisement or referred by community clinicians who were treatment-seeking individuals, which potentially limit generalizability. Setting: The study was conducted in 30 treatment centers. Pts were provided with 5 sessions of motivational enhancement therapy (MET). Outcomes: The primary efficacy was based on pt's self report. No secondary method to ensure the accuracy of the self-reporting results. The primary goal of abstinence can't be fully demonstrated in a short term study. The study was not a direct comparison to oral naltrexone.

Krupitsky[2] et. al – opioid dependence, 2011 DB, PC, RCT; MC	ND: naltrexone extended release 380mg monthly P: placebo	Mean age (ND/P): 29.4/29.7 Male (ND/P): 90%/86% Caucasian (ND/P): 98%/100% Duration of opioid dependence (yrs) (ND/P): 9.1/10.0 Opioid craving scale (ND/P): 18/22	N: 250 ND: 126 P: 124	24 weeks	**Primary endpoints** Confirmed abstinence during week 5-24: 1. Proportion of wks of confirmed abstinence : ND: 90% P: 35% p =0.0002 2. % of pts with total confirmed abstinence: ND: 45 (35.7%) P: 25 (22.8%) RR 1.58, 95% CI1.06 – 2.36); p = 0.0224 **Secondary endpoints** Proportion of self-reported opioid-free days over 24 wks:: ND: 99.2% P:60.4% p = 0.004	N/A ARR12.9% NNT 8 ARR 38.8% NNT3	Discontinuation due to AE: ND: 2 (1.6%) P: 2 (1.6%)	**NS**	Fair Internal Validity Review of Bias: Selection: Low bias; the randomization and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors Attrition: High attrition at 46.8% and 62.1% for treatment group and placebo group respective. ITT analysis External Validity Review of Bias: Patient characteristics: predominantly young white males. Setting: The study was conducted in Russia where opioid agonist therapy is unavailable. The high retention rate in placebo group may influenced by lack of accessibility to opioid agonist. Generalizability of its use in the U.S needs further research. Outcomes: The primary goal of abstinence can't be fully demonstrated in a short term study. The study was not a direct comparison to oral naltrexone.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix A: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has little or no opioid agonist activity. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism. Naltrexone inj. ® is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): Black Box warning on hepatotoxicity. It can cause hepatic injury in excessive doses. It is contraindicated if acute hepatitis or hepatic failure. In addition, naltrexone is contraindicated in patients receiving opioid analgesics; patients with current physiologic opioid dependence; patients in acute opioid withdrawal; any individual who has failed the naloxone challenge test or has a positive urine screen for opioids; or patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluents.

Tolerability: Serious adverse reactions that may be associated with naltrexone injection in clinical use include: severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose and depression and suicidality. The adverse events seen most frequently in association with naltrexone injection therapy for alcohol dependence (ie, those occurring in ≥ 5% and at least twice as frequently with naltrexone injection than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.The adverse events seen most frequently in association with naltrexone injection therapy in opioid dependent patients (ie, those occurring in ≥ 2% and at least twice as frequently with NALTREXONE INJ. than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

Pregnancy/Lactation rating: C. There are no adequate and well-controlled studies of naltrexone injection in pregnant women. naltrexone injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Reproduction and developmental studies have not been conducted for naltrexone injection. Studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits

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

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for perampanel [generic]	None	None	None	None	Nalfon®, naloxone, nalbuphine
LA/SA for Fycompa™[brand]	None	None	None	None	Vivactil®, Vivarin®, Vivotif®

ADVERSE REACTIONS[1]

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
Disorders	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea[a)]	21	10	3	12	27	13	27	13	57	13
	Abdominal pain[b)]	17	8	4	16	23	11	23	11	50	11
	Dry Mouth	9	4	6	24	10	5	8	4	24	5
Infections & Infestations	Pharyngitis[c)]	23	11	0	0	22	11	35	17	57	13
Psychiatric Disorders	Insomnia, sleep disorder	25	12	2	8	29	14	27	13	58	13
	Anxiety[d)]	17	8	2	8	24	12	16	8	42	10
	Depression	9	4	0	0	17	8	7	3	24	5
General Disorders & Administration Site Conditions	Any ISR	106	50	22	88	142	69	121	58	285	65
	Injection site tenderness	83	39	18	72	92	45	89	42	199	45
	Injection site induration	18	8	7	28	71	35	52	25	130	30
	Injection site pain	16	7	0	0	34	17	22	10	56	13
	Other ISR (primarily nodules, swelling)	8	4	8	32	30	15	16	8	54	12
	Injection site pruritus	0	0	0	0	21	10	13	6	34	8
	Injection site ecchymosis	11	5	0	0	14	7	9	4	23	5
	Asthenic conditions[e)]	26	12	3	12	47	23	40	19	90	20
Musculoskeletal & Connective Tissue Disorders	Arthralgia, arthritis, joint stiffness	11	5	1	4	24	12	12	6	37	9
	Back pain, back stiffness	10	5	1	4	12	6	14	7	27	6
	Muscle cramps[f)]	3	1	0	0	16	8	5	2	21	5
Skin & Subcutaneous Tissue Disorders	Rash[g)]	8	4	3	12	12	6	10	5	25	6
Nervous System Disorders	Headache[h)]	39	18	9	36	51	25	34	16	94	21

Table 2: Treatment-emergent Clinical Adverse Events (Events in ≥2% of patients with opioid dependence treated with VIVITROL and occurring more frequently in the VIVITROL group than in the placebo group)

Body System	Adverse Event / Preferred Term	Placebo N=124		VIVITROL 380 mg N=126	
		n	%	n	%
Investigations	Alanine aminotransferase increased	7	6	16	13
	Aspartate aminotransferase increased	3	2	13	10
	Gamma-glutamyltransferase increased	4	3	9	7
Infections and Infestations	Nasopharyngitis	3	2	9	7
	Influenza	5	4	6	5
Psychiatric Disorders	Insomnia	1	1	8	6
Vascular Disorders	Hypertension	4	3	6	5
General Disorders and Administration Site Conditions	Injection site pain	1	1	6	5
Gastrointestinal Disorders	Toothache	2	2	5	4
Nervous System Disorders	Headache	3	2	4	3

DOSE & AVAILABILITY:[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
380mg	Injection	IM	Every 4 weeks or once a month	Mild impairment; no adjustment; moderate to severe impairment: not defined, caution advised.	Mild impairment; no adjustment; moderate to severe impairment: not defined, caution advised. Acute hepatitis/hepatic failure: contraindicated	NA	Same as adult dose.	Must be opioid free for 7-10 days; consider naltrexone challenge test if risk of withdrawal suspected. Must be administered by healthcare professional.

PHARMACOKINETICS:[1]

Parameter	Result
Oral Bioavailability	NA
Tmax	After IM injection, the naltrexone plasma concentration time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2-3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.
Protein Binding	Approximately 21%
Elimination	Primarily via urine, with minimal excretion of unchanged naltrexone.
Half-Life	About 5-10 days.
Metabolism	The cytochrome P450 system is not involved in naltrexone metabolism. Production of the primary metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes.

ALLERGIES/INTERACTIONS:[1]

Drug-Drug: Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of Naltrexone inj. ®. An in vitro CYP inhibition study demonstrated that naltrexone is not an inhibitor of major CYP enzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4). An in vitro CYP induction study demonstrated that naltrexone is not an inducer of CYP3A4 and CYP1A2. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations, and opioid analgesics.

Appendix B: Suggested PA Criteria

Naltrexone Extended Release Inj. (Vivitrol)

Goal(s):

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

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

Covered Alternatives: NA.

Approval Criteria - Initial		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the member have a diagnosis of alcohol dependence?	**Yes:** Go to #3.	**No:** go to #4
3. Is the member part of a comprehensive treatment program for alcohol dependence that includes a psychosocial support system?	**Yes:** Go to #4	**No:** Deny for criteria not met.
a) Has the patient had an intolerance to, or treatment failure of at least one oral medication or requires injectable therapy?	**Yes:** Approve for 3 months.	**No:** Deny and recommend untried agent(s).
4. Does the member have a diagnosis of opioid dependence?	**Yes:** go to #5	**No:** Deny for investigational use.
a) Has the patient had an interolance to, or treatment failure of at least one oral medication or requires injectable therapy?	**Yes:** approve for 3 months.	**No:** Deny and recommend untried agent(s).
Approval Criteria – Renewal		
• For the treatment of opioid dependence: Has the member maintained abstinence with the use of Vivitrol based on negative urine toxicology screens? • For the treatment of alcohol dependence: Is there any documented response from the use of Vivitrol such as abstinence and there continues to be a medical need for the medication?	**Yes:** Approve for 12 months.	**No:** Deny for lack of treatment response.

Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
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High Cost Marginal Benefit Subcommittee

Thursday, November 7, 2013 1:30 -5:00 PM
Barbara Roberts Human Services Building
500 Summer St, NE, Room 137 C – D
Salem, OR 97301

MEETING MINUTES

NOTE: Any agenda items discussed by the Subcommittee will not result in changes to coverage, PDL composition, or utilization control recommendations to the OHA until recommendations are submitted by the P&T Committee. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, HCMB Committee and staff.

Staff Present: Megan Herink PharmD, BCPS; Roger Citron, RPh; Trevor Douglass, DC, MPH; Rich Clark, MD, MPH; Shannon Jasper

Staff Present by Phone: David Pass, MD; William Origer, MD; Stacy Ramirez, PharmD; Irene Croswell, RPh.

Audience: Bruce Howard (Acorda); Dr. Faith Yao (Acorda)

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:45 pm.

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

c. The election of Chair and Vice Chair
ACTION: Stacy Ramirez, PharmD elected Chair, all in favor, approved
Tracy Klein elected Vice Chair, all in favor, approved

d. Review of Draft procedures.
Mr. Citron introduced the agenda and explained the draft for the Policy of Committee on page 2 of the packet. The expectations for a quorum is at least 3 (three) P & T Committee members, 1 (one) member from HERC, and 1 (one) expert in Biostatistics.

e. Dr. Trevor Douglass stated rebatable drugs with a path for covereage for appropriate use will be recommended for the HCMB list.

II. HCMB Discussion

a. Ampyra® (dalfampridine)
Dr. Megan Herink presented the same information and insert from an earlier P & T meeting. The studies showed lack of long term data and studies. Dr. Origer

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the P & T Committee.*

commented that it is the only drug in this class and they are unable to compare outcomes.

Testimony: Dr. Faith Yao from Acorda spoke in regards to the studies that Megan had presented. Phase II study did not meet primary objective, the post analysis at suggestion of the FDA wanted a new way to look at the outcome. Phase III study requested by the FDA had an increased responder rate in efficacy per new critera. As of 6/18 the FDA approved to remove REMS program and completed a communication plan. FDA required endurance testing, and endurance was not tested.

b. Kuvan® (saproterin)

Dr. Megan Herink presented the same information and insert from an earlier P & T meeting. There was a discussion regarding the two trials. The results were a limited outcome and it does not replace the current benefit of good diet.

Testimony: No public comment given.

III. Executive Session

Ampyra®: Insignificant improvement, does 1 second make a difference for clients. Not enough testing has been completed.

- Reviewed PA criteria.
- Dr. Herink will bring back to the P&T committee meeting in November.
- Recommendation to HERC and P&T committee to add to HCMB list.

ACTION: All in favor.

Kuvan®: Edit to be made on PA criteria line item 4.

- Dr. Herink will bring back to the P&T committee meeting in November.
- Recommendation to HERC and P&T committee to add to HCMB list.

ACTION: All in favor.

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the P & T Committee.*

Mipomersen (Kynamro®) and Lomitapide (Juxtapid®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen 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. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs (see Clinical Notes below)?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Has the patient failed or are they not appropriate for LDL-C apheresis ~~OR Is LDL-C apheresis not available to them?~~	**Yes:** Approve for 6 months.	**No:** Pass to RPH; Deny (medical appropriateness)

Clinical Notes:

Mipomersen and lomitapide are approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. Both are proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of mipomersen and lomitapide in patients with lower CHD risk.[1, 2]

Few patients with homozygous FH achieve adequate LDL-C lowering even with 4-drug therapy. Maximum lipid lowering therapy is defined as reaching the highest tolerated statin dose or maximum FDA recommended high potency statin dose defined as follows:

Atorvastatin 80mg daily[3]
Rosuvastatin 40mg daily[3]
Simvastatin 40mg daily[3]
Pitavastatin 4 mg daily[3]

PLUS

Combination therapy with ezetimibe 10 mg per day, colesevelam, and/or niacin. Niacin and bile acid sequestrants should both be used unless they do not produce significant LDL-C lowering (< 5%) and/or if significant side-effects are occurring.[4, 5]

OR

If statins are contraindicated or not tolerated then, combination therapy with ezetimibe 10mg per day, colesevelam and/or niacin is recommended.[4, 5] Statin intolerance includes but is not limited to: evidence of new-onset muscle pain, significant gastrointestinal disturbance or alterations of liver function tests.[4, 5]

1. FDA Summary Review. Reference ID 3252189. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.

2. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.

3. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2012;97(9):2969–2989. doi:10.1210/jc.2011-3213.

4. NICE. Identification and management of familial hypercholesterolaemia. 2008. Available at: http://www.nice.org.uk/nicemedia/live/12048/41697/41697.pdf. Accessed April 1, 2013.

5. Ito MK, McGowan MP, Moriarty PM. Management of Familial Hypercholesterolemias in adult patients: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3):S38–S45. doi:10.1016/j.jacl.2011.04.001.

P&T Action: *9/26/2013 (KK); 7/25/2013(MH); 5/30/2013 (KK/MH)*
Revision(s):
Initiated:

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Oregon Health Authority

OHP Benzodiazepine Drug Use Evaluation

The reported prevalence rate of benzodiazepine (BZO) use varies from 2-17% depending on the definition of "benzodiazepine" and the observation period.[1] And, despite a recognition that long-term use is not supported by any prescribing guidelines, the utilization has remained fairly stable in the United States[2] and even in The Netherlands where interventions have sought to lower it.[3] The goal of this drug use review is to describe BZO utilization in the Oregon Health Plan (OHP) population and propose policy changes to address any inappropriate prescribing identified.

BACKGROUND

Oral BZOs are Food and Drug Administration (FDA) primarily indicated for short-term treatment of anxiety, panic, and ethanol withdrawal syndrome. Off-label uses include short-term treatment of insomnia and as an adjunct to bipolar treatment and schizophrenia, among others (Table 1). Long-term treatment is limited to epilepsy.

Table 1: Benzodiazepine Indications[4]

Drug	Action	FDA Indication (oral) ; recommended dose	Off-label Indication; recommended dose
alprazolam (Xanax™)	Short / Intermediate Acting	Anxiety; 0.25-0.5mg TID; 4 mg Panic Disorder; 0.5mg - 1mg QD-TID; 6mg	ETOH withdrawal 0.5-1 mg BID x 7-10 days Depression
chlordiazepoxide (Librium™)	Long-acting	Anxiety; 5-25mg TID-QID; 4 mg ETOH withdrawal; 50-100mg q2-4h; 300mg	
clonazepam (Klonopin™)	Short / Intermediate Acting	Panic Disorder; 0.25 - 1mg BID; 4mg Seizure; 0.5mg - 1 mg TID; 20mg	Schizophrenia adjunct (acute catatonic reactions & akathisia) Bipolar disorder adjunct (short-term acute mania/mixed episode) RLS/Tics/Sleep Walking
clordiazepate (Tranxene™)	Long-acting	Anxiety; 15-30mg per day ETOH withdrawal; 30mg TID x 4 days Partial Seizures; 7.5mg TID; 90mg	Epilepsy
diazepam (Valium™)	Long-acting	Anxiety; 2-10mg BID-QID; ETOH withdrawal; 5-10mg TID-QID Seizure; 2-4mg BID-QID; Skeletal Muscle Spasm; 2-10mg TID-QID;	Benzodiazepine withdrawal
lorazepam (Ativan™)	Short / Intermediate Acting	Anxiety; 1-3mg BID-TID; 10 mg Insomnia due to anxiety/stress; 2-4 mg QHS	Psychotic agitation ETOH withdrawal 1-2mg Q6H x12 doses
oxazepam (Serax™)	Short / Intermediate Acting	Anxiety;10-30mg TID-QID ETOH withdrawal 15-30mg TID-QID	Insomnia; 15mg QHS

The evidence for selected indications is summarized below.

Ethanol withdrawal syndrome is short-term, lasting hours to days. Long-acting BZOs are recommended by the American Society of Addiction Medicine to control agitation, prevent withdrawal seizures and aid in a smoother withdrawal with fewer rebound symptoms.[5]

Intravenous, rectal, and buccally administerd BZOs are primarily used for status epilepticus or prolonged or repeated seizures. Oral clonazepam may be used chronically third or fourth line in some epilepsy syndromes and clordiazepate is FDA indicated for partial seizures.[6]

First line treatment for generalized anxiety disorder and panic is cognitive behavioral therapy (CBT). National Institute of Health and Clinical Excellence treatment guidelines[7] recommend selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) first for patients electing to use drug therapy. BZO therapy is not recommended for patients that are at risk for substance abuse. BZO therapy is recommended for short-term crisis management only.[7] Evidence is lacking to guide refractory anxiety treatment. Clinical Evidence reports moderate level evidence from two systematic reviews (search date 1996, 17 RCTs; and search date 2002, 37 RCTs) that BZOs are effective at relieving symptoms of generalized anxiety in the short-term (<9 weeks) when compared to placebo.[8] However, there are trade-offs including increased risk of dependence, sedation, and accidents. [8] There is insufficient evidence for treatment beyond 8 weeks. Clinical Evidence reports similar findings for BZO use for panic treatment.[9] However, the American Psychiatric Association (APA) gives CBT, SSRIs, SNRIs, tricyclic antidepressants (TCA) and BZOs (in the absence of a co-occurring depression or substance use disorders) equal footing for the initial treatment of panic but recommend SSRIs and SNRIs preferentially based upon adverse effect profile.[10] BZOs are recommended as monotherapy or adjunctive therapy for patients needing rapid symptom control. [10]

The APA suggests short-term treatment with a BZO may be helpful to control acute mania or mixed episodes in patients with bipolar disorder (APA Grade II) . No evidence is cited to support this recommendation and it is not included in the 2005 update of the guidelines. [11] The Texas Medication Algorithm Project also recommends benzodiazepines as an adjunct in mania or mixed episodes for short-term management of anxiety or insomnia.[12] The Scottish guidelines for bipolar affective disorder recommend short-term use of benzodiazepines (specifically lorazepam and clonazepam) in acutely agitated patients needing sedation based upon three randomized controlled trials (RCT).[13] The Veteran's Affairs/Department of Defense bipolar disease treatment guidelines recommend extreme caution be used when prescribing short-acting BZOs, short-term for agitation associated with manic episodes. [14]

There is insufficient evidence to recommend use of benzodiazepines for primary treatment of schizophrenia[15] as well as insufficient evidence for treatment of catatonia in patients with schizophrenia.[16] The evidence is low from two very small RCTs (n=27) demonstrating a reduction in akathisia symptoms for patients receiving clonazepam compared to placebo (RR 0.09 95% CI 0.01-0.6).[17]

Despite the lack of evidence for long-term use of benzodiazepines, a retrospective study of benzodiazepine use during calendar year 1999 by New Hampshire Medicaid patients with severe mental illness found that more than 50% of patients used a benzodiazepine for four months or more and patients with co-morbid substance abuse used benzodiazepines at an even higher rate (>65%).[1] The authors concluded that more careful monitoring of this population was needed but still recommended against restrictive prescription policies. [1]

The adverse effects of BZO use include sedation, dependence, impaired psychomotor performance, impaired memory and cognitive decline.[18] These effects increase the likelihood of falls and injuries. While there is evidence that benzodiazepine use, especially in the elderly, is associated with increased risk of hip fracture,[19] the implementation of benzodiazepine restrictions and subsequent lower benzodiazepine utilization rates did not reduce the rate of hip fractures[20] and may have disproportionally hindered access to appropriate benzodiazepine use by racial minorities.[21] The risk of dependence increases with doses ≥3mg per day of diazepam equivalents, use of high potency short half-life BZOs (i.e. alprazolam, clonazepam or lorazepam), daily dosing for more than 4 months, increased age or a history of substance or ethanol abuse.[1] The New York State Office of Mental Health Scientific Advisory Committee[22] developed the following drug use indicators for questionable use of BZOs for use in the New York Medicaid program:

1) Patient use > 90 days (aka long-term use)
2) BZO use by patient with known history of substance abuse
3) ≥3 mg per day of diazepam equivalent of long-acting benzodiazepines in patients >64 years old
4) Patient on ≥2 BZOs concurrently
5) Multiple prescribers for controlled substances (including benzodiazepines)

METHODS

Patients with a fee-for-service (FFS) or encounter drug claim for a BZO and not classified as a Class 47 (Sedative-Hypnotic) by First Databank (see Appendix A) during calendar year 2012 were included. Class 47 is subject to quantity and duplication limits in most of the OHP population.[23] Patients with Medicare as defined by benefit packages BMM or BMD were excluded. Patients with < 75% of days of eligibility during 2012 were excluded as were patients with seizure disorders as defined by a claim with ICD9 = 345xx at any time during the study period or an antiepileptic drug in 2012 (see Appendix B). Patients with total BZO use ≤ 5 days were excluded with the assumption these were likely pre-procedure or emergent use only.

Patients were further classified as Long-Term if they had a treatment span of one or more BZO for ≥ 90 days with a gap not to exceed 14 days. All others were classified as Short-Term. A sub-group of "New Starts" was also identified for both groups that had no BZO claim 100 days prior to the index BZO claim.

The first BZO claim for a patient in 2012 was designated the "index BZO claim." The study period was 12 months prior to the index BZO claim and 6 months after. Medical claims were surveyed the year prior to the "index BZO claim" for selected diagnoses of interest (Appendix C). The number of patients with

a hospitalization or emergency department (ED) visits for all causes and with "poisoning" diagnosis codes (965xx-970xx, 977xx, E850xx-E858xx, E950xx) in the 6 months after the index event were quantified.

RESULTS

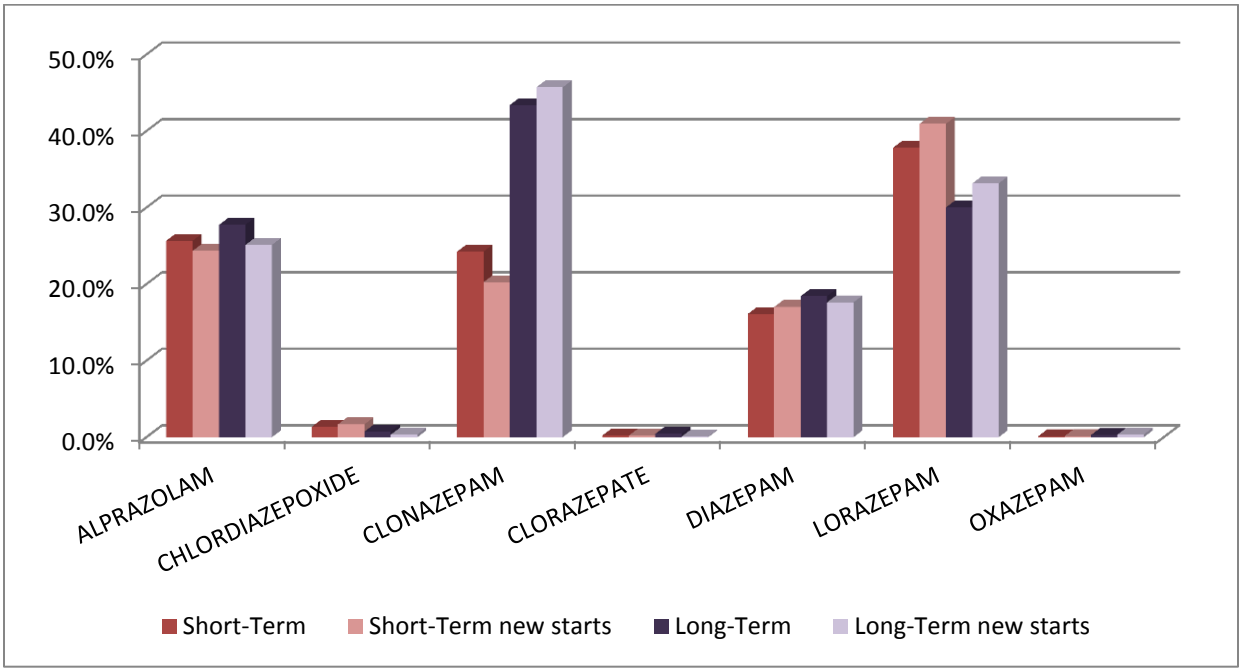
There were 20,131 patients with BZO therapy for longer than 5 days and without an epilepsy diagnosis. This was an overall prevalence rate of 4% (See Appendix D). Short-term users comprised 62.5% (n=12,572) and Long-Term users comprised 37.5% (n=7,559). More than 63% (7,952) of Short-Term users were New Starts whereas only 15% (n-1,146) of Long-Term users were New Starts. Long-Term users were somewhat older with a mean age of 44 years versus 39 years for Short-Term users. Over 90% of all users were non-elderly adults and most are white females.

TABLE 2 - DEMOGRAPHICS

	Short-Term		Short-Term New Starts		Long-Term		Long-Term New Starts	
n=	**12,572**	**100%**	**7,952**	**63.3%**	**7,559**	**100%**	**1,146**	**15.2%**
Age								
Mean (Min - Max)	39 (1-91)		37 (1-82)		44 (0-88)		40 (3-67)	
< 13	236	1.9%	204	2.6%	47	0.6%	17	1.5%
13-18	630	5.0%	523	6.6%	134	1.8%	50	4.4%
19-64	11,661	92.8%	7,199	90.5%	7,344	97.2%	1,073	93.6%
> 64	45	0.4%	26	0.3%	34	0.4%	6	0.5%
Sex								
M	3,397	27.0%	2,174	27.3%	2,336	30.9%	373	32.5%
F	9,175	73.0%	5,778	72.7%	5,223	69.1%	773	67.5%
Ethnicity								
Caucasian	10,613	84.4%	6,638	83.5%	6,663	88.1%	968	84.5%
Non-Caucasian	1,959	15.6%	1,314	16.5%	896	11.9%	178	15.5%

Figure 1 displays the utilization rates of each BZO by group and subgroup. More than one drug can be used by a single patient, thus the totals are > 100%. Four drugs are highly utilized; alprazolam, clonazepam, diazepam and lorazepam. Alprazolam (24-28% of patients) and diazepam (16 -18% of patients) were used at about the same rate by all groups. Clonazepam is more highly utilized by Long-Term patients (43-46%) versus Short-Term patients (20-24%). Conversely, lorazepam is used less by Long-Term patients (30-33%) versus Short-Term patients (38-41%).

FIGURE 1 – PERCENT OF PATIENTS USING INDIVIDUAL BZO (TOTALS >100% AS PATIENTS MAY USE MORE THAN 1 BZO)



BZO therapy is further described in Table 3. The mean therapy length for Short-Term users was 24-29 days. Long-Term user mean therapy length was 256 days and Long-Term new starts averaged 183 days. There was little evidence of duplicate BZOs among Short-Term Users, where as there is indication of limited duplicate BZO use in the Long-Term group as noted by the count of unique drug per patient greater than 1. This method does not restrict to concurrency and is a blunt indicator of duplication.

TABLE 3 – BZO THERAPY DESCRIPTION

	Short-Term		Short-term new starts		Long-Term		Long-Term new starts	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
BZO Therapy Length (Days)	29.2	6-89	24.4	6-89	255.7	90-395	183.1	90-391
Count of Unique BZO Drugs per Patient	1.06	1-3	1.05	1-3	1.21	1-5	1.22	1-4

Selected diagnoses in the year prior to the index BZO claim are presented in Figure 2. Fibromyalgia or chronic back pain was the most highly associated diagnosis at 59-62% of Long-Term users and 53-55% of Short-Term users. All forms of anxiety are associated with 47-52% of all users. Substance abuse is highly associated with both groups but higher in the Long-Term users (48-50%) versus Short-Term users (41-43%). Long-Term BZO use is slightly more associated with severe mental health diagnoses (Bipolar Disease, Depression and Schizophrenia). Attention Deficit Hyperactivity Disorder is associated with 6-

7% of all BZO users. There is low association (≤ 2%) with the diagnoses of Insomnia and Restless Leg Syndrome or Tics.

FIGURE 2 –

PERCENT BZO PATIENTS WITH SELECTED DIAGNOSES (TOTALS >100% AS PATIENTS MAY HAVE >1 DIAGNOSIS)

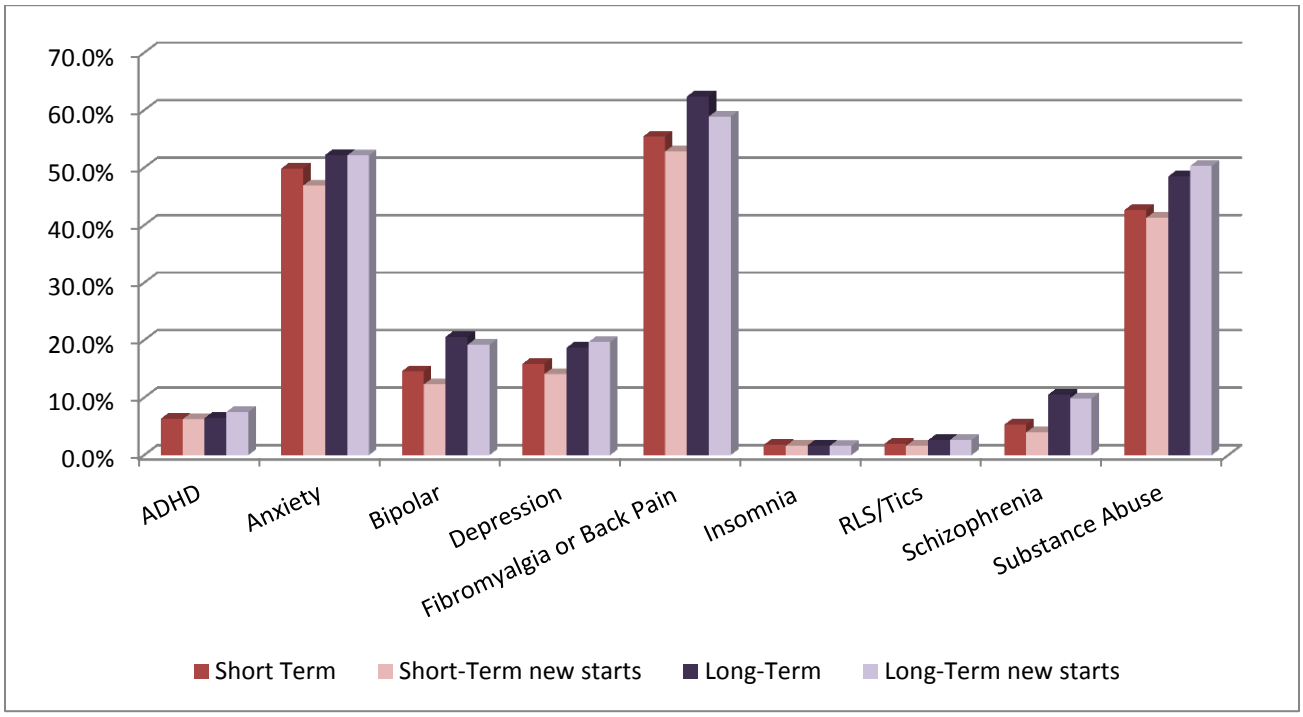


Table 4 displays the number of patients with hospital or ED visits within 6 months of the index BZO claim. Between 39% and 46% of patients visited an ED and 9-9.5% were admitted to hospital. The highest ED rates were for the sub-group of Long-Term New Starts. The rates of hospitalizations and ED visits were low (1.3-2.4%) when limited to poisonings but again the Long-Term New Starts were close to double that of the other groups at 2.4%.

TABLE 4 – HOSPITALIZATIONS AND EMERGENCY DEPARTMENT VISITS WITHIN 6 MONTHS AFTER INDEX BZO CLAIM

	Short Term		Short Term New Starts		Long Term		Long-Term New Starts	
n=	12,572		7,952		7,559		1,146	
All cause hospitalizations / ED visits	5248	41.7%	3355	42.2%	3056	40.4%	544	47.5%
Hospitalizations	1177	9.4%	733	9.2%	682	9.0%	109	9.5%
ED visits	5031	40.0%	3216	40.4%	2928	38.7%	523	45.6%
Hospitalizations / ED visits for Poisoning, Accidental poisoning, Suicide by poisoning	179	1.4%	101	1.3%	114	1.5%	27	2.4%
Poisoning hospitalizations	79	0.6%	44	0.6%	50	0.7%	11	1.0%
Poisoning ED visits	130	1.0%	79	1.0%	89	1.2%	23	2.0%

DISCUSSION

This drug use evaluation found 37.5% of patients on a BZO used it longer than 90 days despite little evidence to support use longer than 8 weeks. The mean length of long-term use was 256 days (8.5 months). The most commonly used long-term BZOs were all highly potent, short acting drugs. In addition, there was a high rate of patients on BZOs with a substance abuse history. It is difficult to determine if the substance abuse diagnosis is a result of long-term BZO therapy or occurred prior to it. However, for patients newly started on BZO therapy and who used it more than 90 days it is more common the substance abuse was present upon initiation of BZO and the association was with 50% of patients. These three indicators (use for $\geq$ 90 days, short acting potent drugs and co-morbid substance abuse history) independently increase the risk of dependence for these patients.[1]

It is difficult to interpret the diagnoses from administrative claims data. The high association of BZO use with chronic pain syndromes suggests these are highly complex patients with difficult psychosocial situations. This is further suggested by the high rate of ED use (39-46%) in the entire study population and which is highest in the Long-Term New Starts.

This study has the typical limits of an observational, retrospective study that uses administrative claims. The primary limitation was that administrative data may be missing or may "under code" mental health and substance abuse diagnoses. This only strengthens the conclusion that BZOs are inappropriately prescribed at a high rate for patients with substance abuse.

Long-term use of BZOs is a long standing area of concern in Medicaid programs as well as other health systems. Lader suggests this problem has existed since the first BZOs were approved 50 years ago and persist largely because of the difficulty in preventing long-term dependence from developing from short-term use.[18] There have been many attempts to reduce the use of BZOs long-term ranging from patient education[24] to triplicate forms [20] and prescription drug monitoring programs. [25] Educational interventions typically have short-lasting effects and are difficult to deploy. [24] Regulatory approaches have successfully reduced the rate of BZO use, both inappropriate and inappropriate and, at least in the case of New York, did not reduce the rate of hip fracture.[20]

RECOMMENDATION

In an effort to prevent inappropriate long-term use, it is recommended to focus a prior authorization intervention on newly started patients (no history within last 100 days) with prescriptions beyond an initial 4 weeks. Approval would be granted in any of the three situations:

1. Diagnosis of malignant neoplasm or other end of life diagnosis
2. Diagnosis of epilepsy
3. OHP Covered Indication and all of the following
    - Evidence to support long-term BZO use for the supplied indication(s)
    - No history of substance abuse
    - No concurrent sedative/hypnotic or opioid
    - Dose < 3mg diazepam equivalents

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APPENDIX A

BZO defined as:

HICL Sequence Number	Route	Generic Drug Name
1617	PO	ALPRAZOLAM
34747	PO	ALPRAZOLAM/DIETARY SUPPL NO.17
1656	PO	AMITRIP HCL/CHLORDIAZEPOXIDE
1611	PO	CHLORDIAZEPOXIDE
1610	PO	CHLORDIAZEPOXIDE HCL
2037	PO	CHLORDIAZEPOXIDE/CLIDINIUM BR
1894	PO	CLONAZEPAM
1612	PO	CLORAZEPATE DIPOTASSIUM
1615	PO	DIAZEPAM
4846	PO	LORAZEPAM
1616	PO	OXAZEPAM

APPENDIX B

Drug claim with NDC in Standard Therapeutic Class = 48 AND HSN in list below:

Therapeutic Class Standard Code	HICL Sequence Number	Generic Drug Name
48	11060	TOPIRAMATE
48	11679	FOSPHENYTOIN SODIUM
48	11735	OXCARBAZEPINE
48	15773	TIAGABINE HCL
48	1615	DIAZEPAM
48	1877	PHENYTOIN SODIUM EXTENDED
48	1878	PHENYTOIN SODIUM
48	1879	PHENYTOIN
48	1880	ETHOTOIN
48	1882	VALPROATE SODIUM
48	1883	VALPROIC ACID
48	1886	PRIMIDONE
48	1887	TRIMETHADIONE
48	1888	PARAMETHADIONE
48	1890	METHSUXIMIDE
48	1891	ETHOSUXIMIDE
48	1892	PHENACEMIDE
48	1893	CARBAMAZEPINE
48	1895	MEPHOBARBITAL
48	20952	LEVETIRACETAM
48	21140	ZONISAMIDE
48	26470	PREGABALIN
48	34982	RUFINAMIDE
48	35872	LACOSAMIDE
48	37667	EZOGABINE
48	38373	LEVETIRACETAM IN NACL (ISO-OS)
48	6536	CLOBAZAM
48	7377	VIGABATRIN
48	8186	FELBAMATE

APPENDIX C

Diagnosis
ADHD (314xx)
Bipolar (2961x, 2964x – 2969x)
Cancer (140xx – 209xx)
Depression (2962x-2963x)
Anxiety (3000x)
Insomnia (30741-2, 32701-2, 29182, 29285)
Fibromyalgia or Back Pain (7290x-2x, 72931-9, 7294x-7299x, 721-724[except 723.3], 739, 839.2, 847)
RLS/Tics (33394, 3333x)
Substance Abuse (304xx-305xx)

APPENDIX D

Exclusions

	Count	Patients Left
BZO claim in 2012	52,375	
Duals	-15,242	37,133
Seizure diagnosis	-5,103	32,030
Less than 75 percent eligibility	-5,796	26,234
Treatment length less than 5 days	-6,103	**20,131**
Study Group (treatment length >= 90 days)		7,559
Control Group (treatment length >5 days and < 90 days)		12,572

Patients not in Medicare AND >75% Eligible months of 2012	537,193
Prevalence rate	5%
Prevalence rate >5 days	4%

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: Newer Diabetes Medications

Month/Year of Review: September 3013
Last Review: June 2009 (pramlintide, exenatide, sitagliptin)
March 2011 (pramlintide, sitagliptin, saxagliptin, exenatide, liraglutide)

End date of literature search: July 2013
Source: Health Resources Commission
OSU DURM

Current PDL Status:

Preferred

Drug Class	Drug
Incretin Enhancers	**sitagliptin**
Biguanide	**metformin**
Sulfonylurea (second generation)	**glimepiride, glipizide, glyburide**
Thiazolidinedione (TZD)	**Pioglitazone**
Insulin	**various preparations**

Non-preferred

Drug Class	Drug
Alpha-glucosidase inhibitors	**acarbose, miglitol**
Amylin analog	**pramlintide**
Dipeptidyl peptidase-4 (DPP-4) inhibitor or incretin enhancer	**linagliptin, saxagliptin**
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic	**exenatide, exenatide ER, liraglutide**
Insulin	**various preparations**
Meglitinide	**nateglinide, repaglinide**
Sulfonylureas (first generation)	**chlorpropamide,**

	tolazamide, tolbutamide
Thiazolidinedione (TZD)	**rosiglitazone**
Others - bile acid sequestrant	**colesevelam**
Others – dopamine agonist	**bromocriptine**

Research Questions:

- Are canagliflozin and/or alogliptin more effective than preferred PDL treatments for patients with type 2 diabetes mellitus (DM)?
- Are canagliflozin and/or alogliptin a safer alternative to preferred PDL treatments for patients with type 2 DM?
- Are there indications or subpopulations where canagliflozin and/or alogliptin may be more effective or safer than other available agents?
- Are there new guidelines and/or evidence that suggest that sulfonylureas should not be a preferred second-line option after metformin?

Conclusions:

- There is moderate evidence that canagliflozin is more effective than placebo in lowering glycated hemoglobin (A1C) (-0.77% to -1.06%) in type 2 DM patients. Canagliflozin treatment is associated with genital mycotic infections and hypotension. There is a concern of potential increased risk of cardiac events and fractures that needs further study.
- There is moderate evidence that alogliptin lowered A1C in type 2 DM patients by 0.4%-0.9% compared to placebo. Alogliptin is generally well tolerated but there are outstanding concerns over risk of acute pancreatitis, hepatotoxicity, hypersensitivity reactions and cardiovascular risk that need to be further delineated.
- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk.

Recommendations:

- Make canagliflozin non-preferred and prior authorize canagliflozin as a third –line treatment option for patients unable to tolerate or have contraindications to metformin, sulfonylurea therapy, and other third line treatments.
- Make alogliptin non-preferred and prior authorize alogliptin as a third –line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.
- Make the new combination products alogliptin/pioglitazone (Oseni®) and alogliptin/metformin (Kazano®) non-preferred.

Reason for Review:

Newer drugs for the treatment of diabetes mellitus was reviewed by the Oregon Health Resources Commission (HRC) in June 2009[1]. Since this review additional new agents for the treatment of diabetes have been approved. In addition, National guidelines have been revised and there is a shift toward a more patient centered approach to treatment management. This review will analyze the comparative effectiveness of the newer medications for diabetes and incorporate important updates and revisions as they are related to this class since the last review. New evidence-based guidelines have been released and new systematic reviews were also updated and will be included.

Previous HRC Conclusions/June 2009:

- Evidence was insufficient to determine long term effectiveness of pramlintide when added to prandial insulin compared to conventional insulin therapy, with or without concurrent oral agents, in patients with type 2 DM.
- Evidence was insufficient to determine long term effectiveness of sitagliptin.
- No studies met inclusion criteria for exenatide.

Background:

Type 2 diabetes is a prevalent disease which affects an estimated 25.6 million people in the United States.[2] Despite a variety of treatments a significant number of patients fail to meet A1C goals and within three years of being diagnosed 50% of patients require combination therapy to control rising glucose levels. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have diabetes by 2050.[4] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with type 2 diabetes and add pharmacotherapy for persistent elevated glucose levels. Guidelines recommend a goal A1C of ≤6.5% to ≤ 7% but in all cases should be tailored according to patient specific factors, such as concomitant comorbidities.[5,6] A number of therapeutic options are available for management of glycemic variances associated with diabetes yet no agent has demonstrated clear superiority.[7] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 analogues, insulins, meglitinides, sulfonylureas, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. A1C is often used as a surrogate outcome to assess comparative efficacy of different AHA therapies, as hyperglycemia has been shown to correlate with microvascular complications and potentially macrovascular outcomes.[6] Available data is limited to short-term studies, which prevents the assessment of the durability of available AHAs to control glucose levels long-term and to compare the effectiveness of AHAs on outcomes such as microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of cardiovascular disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.[6] UKPDS data has also indicated a reduced incidence of microvascular risk with sulfonylurea and insulin therapy. TZDS, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular disease events but additional data is needed.[6] The long-term effect of many of the AHAs on complications of diabetes is unknown.

Methods:

A Medline literature search ending in July 2013 for new systematic reviews and randomized controlled trials (RCTs) for diabetic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: five clinical treatment guidelines[5,6,], four systematic reviews[8-11] and ten RCTs [19-22,25-30].

Systematic Reviews:

CADTH- Second-Line Pharmacotherapy for Type 2 Diabetes – Update[8]

A CADTH Optimal Use Report, including a systematic review and network meta-analysis (NMA), was done in July of 2013 to update their previous recommendation for AHA therapies in patients not at A1C goals despite optimal metformin use. Previous analysis and recommendations from a similar 2010 report suggest that there were no apparent differences in efficacy of AHA agents and sulfonylureas were recommended for those requiring a second-line treatment beyond metformin monotherapy. The recent update analyzed 56 trials using the GRADE evaluation method. Eight AHA classes were included: sulfonylureas, DPP-4 inhibitors, TZDs, GLP-1 analogues, basal insulin, alpha-glucosidase inhibitors, meglitinides, and biphasic insulin. Outcomes that were tracked were mortality, diabetes-related complications, A1C, body weight, hypoglycemia and severe adverse events (SAE). Changes from baseline A1C for all included AHA classes were found to be -0.64 (95% Crl: -0.91 to -0.38) to -1.06 (95% Crl: -1.32 to -0.80), with all classes significantly lowering A1C compared to metformin monotherapy. Significantly greater changes in baseline body weight (1.7 to 3.1 kg), compared to metformin monotherapy, were found for sulfonylureas, insulin (basal and biphasic), TZDs, and meglitinides. Weight neutral classes were DPP-4 inhibitors and alpha-glucosidase inhibitors. AHA agents found to cause significant weight loss compared to metformin were GLP-1 analogues. Hypoglycemia rates were significantly higher for sulfonylureas (OR 7.5), insulins (OR 4.1 to 7.0) and meglitinides (OR 8.3). Incidence of severe hypoglycemia was low for all classes (0.1% to 1.6% of total population). Severe adverse events occurred in patients at a rate of 0.7% to 9.1%, with the exception of two long-term extension trials in which SAE rates were as high as 21%. There was insufficient evidence to determine clinically important differences between the classes of AHA agents in regards to long-term complications.

CADTH- Third-Line Pharmacotherapy for Type 2 Diabetes – Update[9]

A second CADTH Optimal Use Report was done in July of 2013 to update previous recommendations for third-line treatment options for patients with diabetes. This report updates the August 2010 version, specifically including an analysis of GLP-1 analogues that were not approved at the time of previous report. The systematic review evaluated the comparative efficacy and safety of third-line AHA treatment in patients that were not reaching A1C goals on metformin and sulfonylurea therapy. This review included 41 trials of the following classes of AHA agents: alpha-glucosidase inhibitors, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, basal insulin, bolus insulin, and biphasic insulin. Changes from baseline A1C were statistically significantly lower, -0.72% to -1.15%, for all classes studied except alpha-glucosidase inhibitors and meglitinides. Basal and biphasic insulin produced the greatest A1C lowering. Similar to the review of second-line agents, basal insulin, biphasic insulin, rapid acting insulin, and TZDs all produced significant increases in weight, 1.9-5.0 kg, when compared to metformin and a sulfonylurea alone. For this same comparison, DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral and GLP-1 analogues were shown to produce significant decreases in weight (-1.6 kg, 95% Crl, -2.8 to -0.4). Data revealed uncertain results regarding meglitinides effect on weight, with a trend toward increased body weight. The risk of hypoglycemia was found to be increased for TZDs, DPP-4 inhibitors, basal insulin and GLP-1 analogues when compared to placebo when given in combination with metformin and a sulfonylurea. Active treatment comparisons showed hypoglycemia risk was highest with the insulin preparations, with basal insulin having significantly less risk of hypoglycemia compared to biphasic and bolus regimens. Severe hypoglycemia was rare, making comparisons difficult. There was insufficient data to compare the effect of the AHA classes on the occurrence of the long-term complications of diabetes.

Cochrane- Sulphonylurea Monotherapy for Patients with Type 2 Diabetes Mellitus (Review)[10]

A systematic review of 72 trials was analyzed to compare sulfonylureas, first and second generation, with other AHAs in the treatment of type 2 diabetes. The primary outcome was all-cause mortality and cardiovascular mortality. Study durations ranged from 24 weeks to over 10 years. All studies were associated with bias and individual comparisons were comprised of a small number of participants. First-generations sulfonylureas were associated with an increased risk of cardiovascular mortality compared to placebo (RR 2.63, 95% CI 1.32 to 5.22, p=0.006). Comparison of first-generation sulfonylureas to insulin showed no significant differences in all-cause mortality rates. When compared to insulin, first-generation sulfonylureas were not shown to increase cardiovascular mortality and were favored over alpha-glucosidase inhibitors for adverse events. Second-generation sulfonylureas were shown to not be significantly different from metformin, TZDs, insulin, meglitinides, or incretin-based therapies for the outcome of all-cause mortality. Cardiovascular mortality was not found to be different between second-generation sulfonylureas and metformin, insulin, TZDs and meglitinides. Based on data from three trials, second-generation sulfonylureas were favored over metformin for the composite outcome of non-fatal macrovascular events (RR 0.67, 95% CI 0.48 to 0.93, p=0.02). Second-generation sulfonylureas weren't found to be significantly different in adverse events compared to placebo, metformin, TZDs, alpha-glucosidase inhibitors, or meglitinides. Second generation sulfonylureas were less likely than alpha-glucosidase inhibitors to be associated with drop-outs due to adverse events. Metformin and TZDs were favored over second-generation sulfonylureas for severe hypoglycemia (RR 6.11, 95% CI 1.57 to 23.79, p=0.009). No difference was found between meglitinides and second-generation sulfonylureas in for severe hypoglycemia. Data on third-generation sulfonylureas was lacking for all-cause mortality, cardiovascular mortality and other macrovascular and microvascular outcomes. None of the outcomes met the criteria for firm RRR in a trial sequential analysis and therefore the authors concluded that additional studies are needed in order to support recommending sulfonylurea monotherapy.

Cardiovascular Safety of Sulfonylureas: A Meta-analysis of Randomized Controlled Trials[11]

The cardiovascular safety of sulfonylureas was examined in a meta-analysis by Monami, et al. This analysis included randomized trials that compared sulfonylureas to active treatment or placebo in patients with type 2 diabetes. One hundred fifteen trials were included, lasting at least 6 months in duration, with a mean duration of 70 weeks. Patients had a mean age of 56.6 years, mean duration of diabetes of 6.3 years and mean A1C of 8.4%. Types of sulfonylureas included were three second generation agents available in the United States (US) (glimepiride, glyburide, and glipizide), four first generation agents available in the US (chlorpropamide, tolazamide, tolbutamide and acetohexamide), two second generation agents not available in the US (glibenclamide, gliquidone) and one mixed generation agent not available in the US (gliclazide). The quality of the trials were accessed using Jadad parameters but no minimum score was required. The principle outcome was the incidence of major cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI) and stroke, and acute coronary syndrome and/or heart failure reported as serious adverse events of sulfonylureas compared to placebo or active treatment. Secondary outcomes were fatal and non-fatal MI and stroke, all-cause and cardiovascular mortality and severe hypoglycemia.

Sulfonylureas were not found to have a significant difference in the occurrence of MACE compared to active treatment and placebo (MH-OR: 1.08 [0.86 to 1.36], p=0.52). However, sulfonylureas were found to have a significantly higher incidence of MACE compared to DPP-4 inhibitors in a subgroup analysis. The incidence of MI was not found to be different between sulfonylureas and active treatment and placebo. The analysis of 16 trials found the risk of stroke to be significantly higher with sulfonylureas (MH-OR: 1.28 [1.03 to 1.60], p=0.026). The risk of stroke was found to be significant when compared to DPP-4 inhibitors and with glimepiride (MH-OR: 4.22 [1.65 to 10.79], p=0.003). In the analysis of 88 trials, sulfonylureas were found to increase all-cause mortality significantly compared to other treatments and placebo (MH-OR: 1.22 [1.01 to 1.49], p=0.047). Cardiovascular mortality rates were not found to be significantly different between sulfonylureas and other treatments. Sulfonylureas were found to have a higher incidence of hypoglycemia when compared to metformin and placebo. The authors concluded that in general sulfonylurea treatment is not associated with a significant increase in cardiovascular risk. Limitations to this meta-analysis are the following; the inclusion of sulfonylureas not applicable to the most commonly used treatments in the US, the lack of reporting of cardiovascular events and sample size limitations.

Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitor: Meta-Analysis and Systematic Review[12]

In a recent meta-analysis and systematic review Aroda, et al, summarized the overall evidence related to incretin therapies in patients with type 2 diabetes. Exenatide, exenatide weekly, liraglutide, alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin (not available in the US) were included in the analysis. Eighty studies were included for evaluation, lasting from 12-52 weeks with the change from baseline A1C being the primary outcome. Seventy-six percent of the included studies were comparisons of combined treatments. GLP-1 were found to result in mean A1C changes of -1.1% to -1.6%. DPP-4 inhibitors were associated with decreases of -0.6% to -1.1% in A1C. Specifically, reductions from baseline in A1C were the following; alogliptin -0.70% (95% CI -0.90 to -0.50); linagliptin -0.60% (95% CI -0.80 to -0.40); saxagliptin -0.71% (95% CI -0.89 to -0.54); sitagliptin -0.70% (95% CI -0.78 to -0.63) and vildagliptin -0.98% (95% CI -1.46 to -0.52). GLP-1 analogues were associated with significant weight loss and DPP-4 inhibitors trended toward weight loss.

Oral Diabetes Medications for Adults with Type 2 Diabetes. An Update[13]

An AHRQ review was updated in March 2011 to include the benefit and harms of AHAs in patients with type 2 diabetes. The following treatments were included: metformin, second generation sulfonylureas, thiazolidinediones, meglitinides, DPP-4 inhibitors and GLP-1 agonists. Randomized controlled trials lasting 3 months or longer and enrolling at least 40 subjects were included. Studies were evaluated according to the Jadad criteria for quality and given an overall grade for the strength of evidence. The analysis found that there was a high strength of evidence that most AHA agents reduced A1C to a similar extent, approximately one percent compared to baseline values. The DPP-4 inhibitors were the only exception, which did not lower A1C as much as metformin (moderate strength of evidence). Most combination therapies were shown to decrease A1C by and additional one percent. There was high strength of evidence that metformin had beneficial effects on body weight and lipids compared to other AHAs. There was high strength of evidence that sulfonylureas were associated with a higher risk of mild-to-moderate hypoglycemia as monotherapy and when used in combination with other AHAs. There was limited data on long-term clinical outcomes for many of the AHAs.

New Guidelines:

ADA/EASD Guideline – Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[6]

The ADA/EASD recently updated their 2008 guideline recommendations in 2012. Recommendations were based on evidence and expert opinion. Due to the complex nature of treating patients with type 2 diabetes the guideline replaced their previous algorithm of recommendations with a more patient-centered approach, which takes into consideration patient preferences and tolerances. The guideline also recommends that a variety of factors should be taken into account when considering if the patient is a candidate for more stringent or less stringent glucose control. Metformin is suggested as the most commonly recommended first-line choice. If metformin is not an option then sulfonylureas/glinides, pioglitazone or DPP-4 inhibitors are considered good options. GLP-1 analogues may be an appropriate first-line choice for those with specific weight loss concerns. AHAs not already mentioned may be appropriate for specific patients but are less commonly recommended initially to due adverse effects and modest lowering of A1C. For patients requiring a dual glucose lowering treatment, the guidelines recommend a second oral AHA, a GLP-1 analogue or basal insulin. If triple therapy is required, insulin was found to provide the most A1C lowering.

NICE Guideline – Type 2 Diabetes: Newer Agents[14]

A short clinical guideline was produced in May of 2009 to update current NICE guidelines on recommendations for therapy for elevated glucoses in patients with type 2 diabetes. An evidence based, clinical pathway outlines preferences for 1st, 2nd and 3rd line therapies with exceptions for each based on specific patient characteristics. In general metformin is considered the first-line therapy, sulfonylureas as the preferred second-line treatment option and insulin is recommended third line. DPP-4 inhibitors (only sitagliptin approved at the time of the guideline) are to be considered second-line in patients with a high risk of hypoglycemia (or the consequences), or for those whom a sulfonylurea or metformin is not tolerated or contraindicated. For those unable to use insulin, DPP-4 inhibitors are also recommended as a third-line treatment. TZDS are recommended as second-line agents in patients who are at elevated risk of hypoglycemia (or the consequences) or if they are not candidates for metformin or sulfonylurea therapy. TZDs are to be considered third-line in patients unable to use insulin. GLP-1 analogues (only exenatide approved at the time of guideline) are recommended as third-line agents if patient weight is of particular concern. Long-acting insulins (insulin detemir and insulin glargine) were recommended, in lieu of preferred first line NPH, if patient requires a caregiver for injections and use of a long-acting insulin would decrease injections to once-daily, decrease hypoglycemia, or patient would require multiple doses of NPH in addition to oral AHAs.

* This guideline was also updated in 2010 to include the suspension of marketing of rosiglitazone by the European Medicines Agency due to the risks of treatment exceeding benefit and again in 2011 to due to new recommendations on the risk of bladder cancer with pioglitazone.

AACE Guidelines – American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013 Consensus Statement[5]

AACE recently updated guidelines for comprehensive diabetes management and hyperglycemia treatment algorithm in 2013. Recommendations for pharmacotherapy are similar to the previous 2009 algorithm and use A1C to guide treatment selection.[5,14] Monotherapy is recommended for those patients with A1C <7.5%, with metformin being the agent of choice for initial therapy. Alternatives to metformin are GLP-1 analogues, DPP-4 inhibitors and alpha-glucosidase inhibitors. Other agents that are options but should be used with caution are TZDs, sulfonyulureas/glinides and SGLT2s. Dual therapy is recommended for patients with an A1C $\geq$7.5% or for those unable to obtain their goal A1C on monotherapy. Metformin in combination with a second agent is preferred or any combination with complimentary mechanisms of action. GLP-1 analogues and DPP-4 inhibitors are recommended as the preferred dual pharmacotherapy options (with metformin), followed by TZDs, SGLT2s and basal insulin, all which should be used with caution. Additional potential combination therapy includes (in order of preference): colesevelam, bromocriptine, alpha-glucosidase inhibitors and sulfonylureas/glinides. For patients with an A1C >8%, a third AHA may be considered. GLP-1 analogues are preferred, followed by TZDs, SGLT2s, basal insulin, DPP-4 inhibitors, colsevelam, bromocriptine, alpha-glucosidase inhibitors and sulfonylureas/glinides. For patients with an A1C >9.0% insulin is recommended.

IDF Guidelines- Global Guideline for Type 2 Diabetes[16]

In 2012 the International Diabetes Federation (IDF) updated its 2005 guidelines for the treatment and management of diabetes. Recommendations were made based on available evidence and expert opinion. Metformin was recommended as initial therapy. For second-line therapy sulfonylureas are recommended with other options including alpha-glucosidase inhibitor, DPP-4 inhibitors, TZD or meglitinides. Insulin (basal or pre-mix) or a third oral agent is recommended third-line. Other third-line options are alpha-glucosidase inhibitors, DPP-4 inhibitors, TZD or a GLP-1 analogue. Insulin is recommended as the only fourth-line agent.

ACP Guideline – Oral Pharmacological Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians[17]

This 2012 Guideline provides recommendations for AHAs based on comparative efficacy and safety for the outcomes of A1C, lipids, weight, all-cause mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, neuropathy, hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, server allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision and gastrointestinal side effects.

Additional data on safety and effectiveness of subgroups was also studied. Trial quality was rated via Jadad and the overall evidence was graded using the GRADE system. Metformin is recommended first-line for most patients based on high quality evidence but no specific second-line therapy is suggested.

One hundred and four trials were used for the A1C comparison of medications used for the treatment of type 2 diabetes. Comparison of monotherapy treatments showed similar A1C lowering across the groups, average of 1%, with the exception of metformin compared to DPP-4 inhibitors. Metformin was shown to decrease A1C to a greater extent than DPP-4 inhibitors by a mean difference of -0.37% (moderate quality of evidence). Combination therapy was shown to be more effective than monotherapy with the metformin and sulfonylurea combination producing the largest mean decrease (-1.0%), metformin and DPP-4 inhibitors with a -0.69 men decrease and metformin with a TZD with a -0.66 mean decrease. There was insufficient evidence provided on GLP-1 analogue combination therapy (moderate to high quality evidence). Moderate to high quality evidence demonstrated that metformin therapy resulted in more weight loss compared to TZDs, sulfonylureas and DPP-4 inhibitors. Metformin was also had the most favorable effect on low density lipoprotein (LDL) compared to TZDs, sulfonylureas and DPP-4 inhibitors (moderate-high quality of evidence). TZDs had them most effect on increasing high density lipoprotein (HDL) compared to metformin and sulfonylureas. Metformin was favored with moderate quality of evidence over sulfonylureas and for decreasing triglyceride (TG) levels. For many of the long-term outcomes only low-quality or insufficient evidence was available for analysis. Nephropathy rates (based on albumin levels) were the only long-term outcomes with moderate quality of evidence, in which pioglitazone was shown to decrease urinary albumin ratio to a greater extent than metformin.

Severe hypoglycemia rates were similar across treatment groups. Sulfonylureas were shown to increase mild and moderate hypoglycemia rates compared to metformin, TZDS, DPP-4 inhibitors, GLP-1 analogues and meglitinides based on low to high quality evidence. Combination therapy with metformin and a sulfonylureas also was shown to increase hypoglycemia compared to combinations containing TZDs. Moderate quality of evidence from observational studies favored metformin over sulfonylureas and sulfonylureas over TZDs for risk of congestive heart failure (CHF). Combination therapy of TZD and sulfonylureas doubled the risk of CHF compared to metformin and sulfonylurea combination therapy. There was high quality of evidence that sulfonylureas were associated with less fracture risk than TZDs.

New Safety Alerts:

Pioglitazone and Bladder Cancer- FDA Safety Review[18]

In August of 2011 the FDA issued label changes to be made to pioglitazone prescribing information detailing the findings of a potential increased risk of bladder cancer when the drug is used beyond one year. The FDA made these recommendations based on a five year interim analysis of a 10 year epidemiological study which found no increased risk in bladder cancer overall but there was an increased risk in those whom had been taking pioglitazone for the longest time and at the highest doses. The FDA recommends against using pioglitazone in those with active bladder cancer and cautions against its use in those with a history of bladder cancer.

Incretin Mimetic Drugs and Pancreatitis/Pre-cancerous Findings in the Pancreas[19]

In March of 2013 the FDA announced that it is investigating the findings of a potential risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia) in patients with type 2 diabetes taking incretin mimetic type drugs (exenatide, liraglutide, sitagliptin, saxagliptin, alogliptin, and linagliptin). Current labeling includes warnings of acute pancreatitis with these agents. There is no conclusive link of pancreatic cancer and incretin mimetics. The FDA is involved in ongoing evaluations to gain additional information.

New Primary Literature:

New Drug Evaluation- Canagliflozin (Invokana ®)[20]

FDA Indications:
Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor, which is a new class of AHAs. SGLT2 inhibitors work by preventing reabsorption of glucose by the kidney and increaseing urinary glucose excretion. This results in mild osmotic diuresis and net calorie loss. Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Canagliflozin is not to be used for the treatment of type 1 diabetes or diabetic ketoacidosis.[18]

Clinical Efficacy Data (see evidence table below):
Canagliflozin was studied in over 10,000 patients in multiple trials as monotherapy and in combination with other agents (metformin, sulfonylurea, metformin and sulfonylurea, metformin and TZD and insulin). Active treatment comparisons were between canagliflozin and sitagliptin and canagliflozin and glimepiride. At this time only four trials have been published and available to be critically evaluated. In all studies the primary endpoint was the change in baseline A1c at specified durations. Important secondary endpoints were percent of subjects obtaining an A1c <7.0%, fasting plasma glucose levels, and percent change in body weight.

CANATA-M was a poor to fair quality, phase III trial comparing canagliflozin 100mg and 300mg daily to placebo in 584 patients for 26 weeks.[21] Patients in the main study had a mean HbA1c of 8.0% and a mean duration of diabetes of 4.3 years. A substudy of patients with elevated glucose concentrations was also conducted and included patients with a mean HbA1c of 10.6% and duration of diabetes of 4.9 years. The primary endpoint was the change in baseline HbA1c at week 26. An important secondary endpoint was the percent of patients achieving HbA1c <7%. Canagliflozin 100mg and canagliflozin 300mg both reduced HbA1c to a greater extent than placebo, -0.77, -1.03 and 0.14%, respectively ($p<0.001$ for both comparisons). There were also a greater percentage of patients that obtained a HbA1c <7% compared to placebo, with a NNT of 2-4. Patients in the high glycemic substudy also experienced greater HbA1c lowering compared to placebo. The lack of blinding details as it relates to patients, caregivers and outcomes assessors limits the ability to determine the likelihood of bias represented in the results. Description of randomization methodology was also lacking.

A 52 week, head to head comparison of canagliflozin 300 mg and sitagliptin 100 mg, on background metformin and sulfonylurea therapy, was studied in the CANTATA-D2 trial.[22] This was a fair quality, phase III, DB, RCT of 755 patients with type 2 diabetes whom were previously inadequately controlled on metformin and sulfonylurea therapy. Included patients had a mean duration of diabetes of 9.2 years with a mean A1C of 8.1%. The primary endpoint was change in baseline A1C at week 52. Canagliflozin was shown to be noninferior and superior to sitagliptin with A1C changes of -1.03% and -0.66%, respectively. Improvements in FPG, body weight and systolic blood pressure were significantly greater with canagliflozin compared to sitagliptin. When A1C changes were analyzed according to baseline A1C subgroups, the greatest difference was shown in those with the highest baseline A1cs ($\geq$9.0%). The overall discontinuation rate was high (38.5%) and occurring in 44% of the sitagliptin group and 33% in the canagliflozin group. Last observation carried forward imputation was used to provide results for missing data. This method may introduce assessment bias especially in circumstances such as in this study where there was a higher percentage of drop out in the active comparator group (sitagliptin) which assumes no change, potentially overestimating the true treatment effect of canagliflozin.

In a small fair quality, phase III, PC, RCT canagliflozin 100mg and 300mg was studied for 26 weeks in patients with type 2 diabetes and chronic kidney disease (eGFR ≥30 and <50 ml/min /1.73 m^2).[23] Patients were a mean age of 69 years old with a baseline A1C of 8.0% and eGFR of 39 ml/min/1.73m^2. Canagliflozin 100mg and 300mg decreased A1C to a greater extent than placebo, -0.33%, -0.44% and -0.03%, respectively ($p<0.05$). Reduction in FPG were also greater for canagliflozin but not significantly so.

Recently, a trial was published on the use of canagliflozin, 100mg and 300mg daily, compared to glimepiride, 6-8 mg daily, in patients (n=1452) uncontrolled on metformin (CANTATA-SU).[24] This was a fair quality, phase III, DB, randomized, non-inferiority trial lasting 52 weeks. The mean patient age was 57 years with a mean baseline A1C of 7.8%. As with the other studies, the primary endpoint was the change from baseline in A1C. Canagliflozin 100 mg and 300mg were shown to be non-inferior to glimepiride and canagliflozin 300 mg was shown to be superior to glimepiride. A1C changes were -0.82%, - 0.93%, -0.81% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively. The percent of patients obtaining an A1C <7% was similar between groups. Both canagliflozin groups were associated with significant decreases in body weight compared to the glimepiride group.

FDA approval summary documents for canagliflozin noted that the efficacy of canagliflozin is attenuated as renal function declines.[24] FDA statements include the need for future research related to the risk of cardiovascular events and fracture risk, which were shown to be increased in canagliflozin groups but correlation to canagliflozin treatment is not definitive and studies are ongoing.[25]

Clinical Safety[20]:

The most common adverse effects associated with canagliflozin were fatigue, female genital mycotic infections, urinary tract infections, increased urination and male genital mycotic infections. Hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration as a result of osmotic diuresis with potential decreases in intravascular volume have also been associated with canagliflozin treatment. Patients at increased risk of osmotic diuresis were those over 75 years of age, use of loop diuretics and moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2). Dose-related increases in serum creatinine were also noted. Slightly higher rates of hypoglycemia were experienced in canagliflozin groups compared to placebo and were more common when canagliflozin was combined with insulin or sulfonylureas.

Lab abnormalities were seen in patients randomized to canagliflozin, including hemoglobin elevations and dose-related increases in potassium, magnesium and phosphate. Changes in LDL levels of 4.4 mg/dL (4.5%) in the canagliflozin 100mg group and 8.2 mg/dL (8.0%) in the 300mg group were demonstrated.

Conclusion: Canagliflozin is has been shown to be modestly effective in lowering A1C as monotherapy and in combination with other AHA agents, with A1C lowering from -0.63% to -1.06%. Canagliflozin is unlikely to cause hypoglycemia as monotherapy and has demonstrated positive effects on FPG, BP, HDL and body weight while negatively impacting LDL levels. The use of canagliflozin in patients with chronic renal failure has been shown to be effective, but efficacy is attenuated with declining renal function. There is insufficient evidence to determine the impact of canagliflozin therapy on cardiovascular risk and fractures.

New Drug Evaluation- Alogliptin (Nesina ®), Alogliptin + Pioglitazone (Oseni ®) and Alogliptin + Metformin (Kazano®)

FDA Indications:

Alogliptin is a DPP-4 inhibitor available as a single agent and in combination with pioglitazone (Oseni) and metformin (Kazano).[26,27,28] Alogliptin and its combination products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM. Alogliptin should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis. Alogliptin differs from currently offered agents by being more selective and potent at inhibiting the DPP-4 enzyme but the clinical relevance of this is unknown.

Clinical Efficacy Data (see evidence table below):

Alogliptin 12.5 mg and 25 mg have been extensively studied in many trials. Due to lack of details on randomization, treatment allocation, blinding and high attrition rates not all studies were able to be adequately evaluated for internal and external validity and are therefore not included in the evidence table. Alogliptin studies were of similar design, enrolling patients 18-80 years with A1C of 7-10% (except for alogliptin and insulin trial, which patients had an A1C $\geq$8%) for 26 weeks with a 4-week run-in period.[29-34] The primary endpoint was the change in A1C from baseline at week 26 or 52. Key secondary endpoints were: changes in fasting plasma glucose, number of patients obtaining an A1C <7.0% and changes in baseline body weight.

Nauke, et al studied aloglitptin 12.5 mg and 25mg with metformin compared to placebo in patients with a baseline A1C of 8% and mean age of 55 years.[29] Change in A1C was -0.6% for both alogliptin groups compared to a placebo decrease of -0.1%, p<0.001 for both groups. Results were similar when alogliptin was studied with pioglitazone in a study by Prately, et al.[30] Patients were allowed to continue background metformin and/or sulfonylurea. Decreases in baseline A1C for alogliptin 12.5 mg and alogliptin 25 mg were -0.66% and 0.8%, respectively, compared to a placebo A1C increase of 0.19%. Smaller but still significant A1C changes were shown in a trial by Pratley, et al that compared alogliptin 12.5 mg and 25 mg to placebo with background glyburide therapy.[31] Decrease from baseline A1C were -0.38% for alogliptin 12.5 mg and -0.52% for alogliptin 25 mg compared to placebo 0.01% (p<0.001 for both groups). A poor-fair study by Rosenstock, et al found A1C decreases for alogliptin significantly more than placebo when patients were on background insulin therapy with or without metformin.[32] Changes from baseline A1C were -0.13%,-0.63%, -0.71% for placebo, alogliptin 12.5 mg and alogliptin 25 mg, respectively. Defronzo, et al compared alogliptin 12.5 mg and 25 mg to placebo and pioglitazone 15, 30 and 45 mg, as well as the combination of alogliptin 12.5 mg and all pioglitazone doses and alogliptin 25 mg and all pioglitazone doses.[33] Decreases in A1C were greater for alogliptin and pioglitazone combination therapy compared to pioglitazone alone ($p \leq 0.001$ for all groups). Changes from baseline A1C were similar for alogliptin 12.5 mg and pioglitazone 15 mg (-0.7%) and for alogliptin 25 mg and pioglitazone 30mg (-0.9%). The combination of alogliptin and pioglitazone was superior to pioglitazone alone with decreases in A1C ranging from -1.25% to -1.6%. Changes in fasting plasma glucose and percent of subjects obtaining an A1C <7% were significantly more for alogliptin 25mg compared to placebo in all studies. A study of alogliptin 25mg, metformin (≥1500 mg) and pioglitazone 30mg (A/M/P) was compared to pioglitazone 45mg and metformin (≥1500mg) (P/M).[34] At week 52 least squares mean change from baseline in A1C were significantly greater for the A/M/P compared to P/M, -0.70% and -0.29% (p<0.001), respectively. Significantly more patients were able to achieve an A1C of ≤7%, with a NNT of 8.

Evaluation of efficacy data for alogliptin was limited by high drop out rates that were highest in the study using alogliptin and insulin together (47%) and ranged from 11-40% in other studies. In the alogliptin and insulin trial, high attrition rates can be attributed to a large number of patients requiring hyperglycemic rescue, which was determined by A1C at 12 weeks compared to FPG. An additional concern with data analysis in light of data imputation due to drop outs is the sustained efficacy of alogliptin out to 52 weeks. True efficacy is difficult to determine due to high drop out rates and differing rates of attrition between alogliptin and placebo groups which introduce selection and attrition bias.

Clinical Safety:

The adverse effects that alogliptin therapy is most commonly associated with are; nasopharyngitis, headache, upper respiratory infection and urinary tract infections. Studies showed that alogliptin was weight neutral and hypoglycemia rates were similar to placebo. Discontinuations due to adverse effects were low (2% to 5%). Studies of alogliptin were found to be associated with a higher incidence of serious cardiovascular events compared to placebo. This increase may be due to study design and implementation, however, the association can not be ruled out and is being further evaluated. Additional FDA post marketing study requirements are a cardiovascular outcomes trial (EXAMINE study), an enhanced pharmacovigilance program to monitor for liver abnormalities, serious cases of pancreatitis and severe hypersensitivity reactions as well as three pediatric studies.[35] Combination products, Oseni and Kazano, carry black box warnings due to congestive heart failure risk with pioglitazone and lactic acidosis risk with metformin.[27,28]

Conclusion

Alogliptin is a moderately effective agent to treat glucose abnormalities in patients with type 2 DM as monotherapy and as a combination product. Placebo adjusted mean FPG changes from baseline ranged from -4 to -28 and mean A1C reductions were 0.4%-0.6% for alogliptin monotherapy compared to placebo, with the 25mg alogliptin dose being only slightly more effective than the 12.5 mg dose.[34] Alogliptin does not appear to have any advantages over currently available DPP-4 inhibitors and is associated with similar adverse reactions (infections, skin reactions, hepatoxicity, hypersensitivity reactions, pancreatitis and renal safety issues).[26,35] Alogliptin has been shown to be weight neutral with a low risk of hypoglycemia. Additional studies are needed to determine safety and efficacy of chronic use as randomized trial durations were limited to 52 weeks.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1.) Microvascular Outcomes
2.) Macrovascular Outcomes
3.) Hypoglycemic Episodes
4.) Adverse Effects leading to discontinuation

Primary Study Endpoints:

1.) Changes in HbA1c
2.) Changes in weight

Evidence Table

CANTATA-M[21]

Stenlöf, et al Phase III, RCT, DB, PC 17 Countries	1. Canagliflozin 100mg QD (C100) 2. Canagliflozin 300mg QD (C300) 3. Placebo QD (P)	Mean Age (main study): 55 Mean Age (substudy): 49 Female: 55% Main study baseline A1C: 8.0% Substudy baseline A1C: 10.6% **Inclusion**: Patients 18-80 years with type 2 DM with the either of the following: not on a AHA with A1C of ≥7.(and ≤10.0% or on AHA monotherapy (except PPARγ) or metformin plus sulfonylurea combination therapy with A1C of ≥6.5 and ≤9.5% at screening and A1C ≥7 and ≤10.0% and FPG of <150 mmol/L at week -2. Substudy: A1C of >10.0 and ≤12.0% at screening or week -1 and FPG ≤19.4 mmol/l at week -1. **Exclusion**: FPG >15 mmol/l during pre-treatment phase (or >19.4 mmol/l for the substudy), type 1 DM, hereditary glucose-galactose malabsorption, primary renal glucosuria or CV disease, tx with other SGLT2	Main Study: 1. 195 2. 197 3. 192 Sub-study: 1. 47 2. 44	26 weeks	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.77% C300: -1.03% P: 0.14% LS Mean Change C100: -0.91% (95% CI -1.1 to -0.7, p<0.001) LS Mean Change C300: -1.16% (95% CI -1.3 to -1.0, p<0.001) <u>Fasting Plasma Glucose:</u> C100: -1.5 mmol/l (27 mg/dl) C300: -1.9 mmol/l (34 mg/dl) P: 0.5 mmol/l (9 mg/dl) LS Mean Change C100: -2.0 mmol/l (95% CI -2.3 to -1.6, P<0.001) LS Mean Change C300: -2.4 mmol/l (95% CI -2.8 to -2.0, p <0.001) <u>Subjects reaching A1C <7.0%:</u> C100: 44.5% C300: 62.4% P: 20.6% P<0.001 for both doses <u>Changes in Baseline body weight:</u> C100: -2.5 kg (2.8%) C300: -3.4kg (3.9% P: -0.5 kg (-0.6%) LS Mean Change C100: -2.2% (95% CI -2.9 to -1.6, p<0.001)	NA NA C100 ARR: 24 NNT: 4 C300 ARR: 42 NNT: 2 NA	<u>Urinary tract infection:</u> C100: 14 (7.2%) C300: 10 (5.1%) P: 8 (4.2%) <u>Males genital mycotic infection:</u> C100: 2 (2.5%) C300: (5.6%) P: 0 <u>Female genital mycotic infection:</u> C100: 10 (8.8%) C300: 8 (7.4%) P: 4 (3.8%) <u>Hypoglycemia:</u> C300: 3.6% C100: 3.0% P: 2.6% <u>Withdrawal due to Adverse Events:</u> C100: 6 (3.1%) C300: 4 (2.0%) P: 2 (1.0%)	NA NA NA NA	**Quality Rating: Poor-Fair** **Internal Validity: RofB** Selection: not described Performance: double-blind treatment design was stated but no details on blinding were provided Detection: details were not provided Attrition: mITT analysis was used with LOCF fo missing data. Overall 13.1% discontinued treatment prior to 26 weeks **External Validity** Recruitment: recruited from 17 countries Patient Characteristics: almost half of patients had prior exposure to glucose lower therapy, but HbA1c lowering was similar regardless of prior treatment. Patients with mild to moderate renal impairment were included. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

CANTATA-D2[22]									
Schern-thaner, et al Phase III, RCT, DB, active control, non-inferiority trial 17 countries	1. Canagliflozin 300 mg (C300) 2. Sitagliptin 100 mg (S100) * Both groups on background metformin and sulfonylurea	Age: 56 years Female: 43.5% Main study baseline A1C: 8 % Male: 56% <u>Inclusion:</u> Subjects 18 years and older, type 2 diabetes diagnosis, on stable doses or adjustment period of metformin (1500-2000mg dose) and sulfonylurea (at least half of maximum labeled dose) therapy and A1C ≥7.0% and ≤ 10.5%. <u>Exclusion</u>: Prior AHA therapy other than metformin and sulfonylurea up to 12 weeks prior to study enrollment, type 1 diabetes, uncontrolled hypertension, cardiovascular disease and eGFR <55 mL/min/1.73m^2.	1. 378 2. 378	52 weeks with 2 week prior single-blind placebo run-in	<u>Change from Baseline in A1C at 52 weeks :</u> C300: -1.03% S100: -0.66% LS means: -0.37 (95% CI -0.50 to -0.25) noninferiority and superiority was achieved <u>Fasting Plasma Glucose:</u> C300: -1.7 mmol/l (29 mg/dl) S100: -0.3 mmol/l (2.2 mg/dl) LS Mean Change: -1.3 mmol/l P<0.001 LS Mean Change C300: -2.4 mmol/l (95% CI -2.8 to -2.0, p <0.001) <u>Subjects reaching A1C <7.0%:</u> C300: 47.6% S100: 35.3% <u>Changes in Baseline body weight:</u> C300: -2.3 kg (-2.5%) S100: 0.1 kg (0.3%) LS Mean Change: -2.8%, p<0.001	NA NA NA	<u>Urinary tract infection:</u> C100: 15 (4.0%) S100: 10 (5.6%) <u>Males genital mycotic infection:</u> C300: 19 (9.2%) S100: 1 (0.5%) <u>Female genital mycotic infection:</u> C300: 26 (15.3%) S100: 7 (4.3%) <u>Severe Hypoglycemia:</u> C300: 4.0% S100: 3.4% <u>Withdrawal due to Adverse Events:</u> C300: 20 (5.3%) S100: 11 (2.9%)	NA NA NA NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. High and different levels of attrition may have affected the ability to maintain randomization. Performance: Study was double-blind with study personnel remaining blinded to treatment allocation. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Potential for bias due to only 39% of patients completed 52 week study, most withdrawals due to rescue therapy. **External Validity:** Recruitment: 140 centers in 17 countries. Patient Characteristics: Patients with almost 10 years of diabetes and moderate A1cs were included. Not studied in newly diagnosed and those with cardiovascular disease. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
Canagliflozin and Chronic Kidney Disease[23]									
Yale, et al Phase III, DB,	1. Canagliflozin 100mg (C100)	Age: 69 yrs Female: 36-46% Baseline A1C: 8.0% Baseline eGFR: 39	1. 90	26 weeks with 2 week single-blind placebo run-in	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.33% C300: - 0.44%	NA	<u>Urinary tract infection:</u> C100: 5 (5.6%) C300: 7 (7.9%)	NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via

PC	2. Canagliflozin 300mg (C300) 3. Placebo (P)	ml/min/1.73 m^2 Mean duration of DM: 16.3 years Inclusion: Type 2 diabetes, stage 2 chronic kidney disease (eGFR ≥30 and <50 ml/min/1.73 m^2, ≥25 years old, A1C ≥7.0 and ≤10.5%, not on AHA therapy or on stable regimen for ≥8 weeks Exclusion: FPG >15.0 mmol/l, type 1 diabetes, renal disease requiring treatment, and cardiovascular diseases or disorders.	2. 89 3. 90		P: -0.03% LS Mean Change C100: -0.30% (95% CI -0.5 to -0.1, p<0.05) LS Mean Change C300: -0.40% (95% CI -0.6 to -0.2, p<0.001) Fasting Plasma Glucose: C100: -0.83 mmol/l (15 mg/dl) C300: -0.65 mmol/l (12 mg/dl) P: -0.03 mmol/l (0.5 mg/dl) LS Mean Change C100: -0.85 mmol/l (95%CI -1.6 to -0.1) p-value not calculated since C300 not SS LS Mean Change C300: -0.67 mmol/l (95% CI -1.4 to -0.1, not SS) Subjects reaching A1C <7.0%: C100: 27.3% C300: 32.6% P: 17.2% Changes in Baseline body weight: C100: -1.2 kg (1.2%) C300: -1.4kg (1.5%) P: -0.3 kg (-0.3%) LS Mean Change C100: -	 NA NA	P: 5 (5.6%) Males genital mycotic infection: C100: 1 (1.7%) C300: 1 (2.1%) P: 0 Female genital mycotic infection: C100: 1 (1.3%) C300: 1 (2.4%) P: 0 Severe Hypoglycemia: C300: 4 (4.7%) C100: 1 (1.2%) P: 1 (1.1%) Withdrawal due to Adverse Events: C100: 4 (4.4%) C300: 2 (2.2%) P: 5 (5.6%)	 NA NA NA	interactive voice-response system. Performance: double-blind treatment design was stated but no details on blinding were provided. Detection: details were not provided Attrition: mITT analysis was used with LOCF for missing data. Overall 12.9% discontinued treatment prior to 26 weeks **External Validity:** Recruitment: from 89 centers in 19 countries. Patient Characteristics: Most patients (98%) were on background AHA therapy, 74% of these were on insulin. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.

					1.6% (95% CI -2.3 to -0.8) LS Mean Change C300: -1.8% (95% CI -2.6 to -1.0)				
CANTATA-SU[24]									
Cefalu, et al Phase III, DB, non-inferiority, RCT 157 centers and 19 countries	1. Canagliflozin 100mg (C100) 2. Canagliflozin 300mg (C300) 3. Glimepiride 6-8mg (G) * All patients on background metformin	Age: 57 yrs Male: 52% Baseline A1C: 7.8% Mean duration of DM: 6.6 years <u>Inclusion:</u> Type 2 diabetes, 18-80 years old, A1C ≥7.0 and ≤9.5%, and stable metformin dose for at least 10 weeks. <u>Exclusion:</u> History of severe hypoglycemia requiring treatment, FPG ≥15 mmol/L, (eGFR <55 ml/min/1.73 m^2, SrCr ≥124 µmol/L for men or SrCr ≥115 µmol/L for women or TZD in prior 16 weeks.	1. 483 2. 485 3. 482	52 weeks with 2-week placebo run-in period	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.82% C300: - 0.93% G: -0.81% LS Mean Change C100: -0.01% (95% CI -0.11 to -0.09) C100 non-inferior to glimepiride LS Mean Change C300: -0.12% (95% CI -0.22 to -0.02) C300 superior to glimepiride (no p-value given) <u>LS Mean Change in Fasting Plasma Glucose:</u> C100: -1.35 mmol/l (24 mg/dl) C300: -1.52 mmol/l (27 mg/dl) G: -1.02 mmol/l (18 mg/dl) <u>Subjects reaching A1C <7.0%:</u> C100: 54% C300: 60% G: 56% p-value not given <u>Changes in Baseline body weight:</u>	NA NA NA	<u>Urinary tract infection:</u> C100: 31 (6%) C300: 31 (6%) G: 25 (5%) <u>Males genital mycotic infection:</u> C100: 17 (7%) C300: 20 (8%) G: 3 (1%) <u>Female genital mycotic infection:</u> C100: 26 (11%) C300: 34 (14%) G: 5 (2%) <u>Severe Hypoglycemia:</u> C300: 3 (<1%) C100: 2 (<1%) G: 15 (3%) <u>Withdrawal due to Adverse Events:</u> C100: 25 (5%) C300: 32 (7%) G: 28 (6%)	NA NA NA NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Study was double-blind. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Overall attrition was 18-22% with similar rates between the groups. **External Validity:** Recruitment: 157 centers in 17 countries. Patient Characteristics: Patients had an approximate 7 year history of diabetes who were predominately white. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

					C100: -3.7 kg (4.2%) C300: -4.0kg (4.7%) G: 0.7 kg (1%) P<0.0001 for both doses				
ALOGLIPTIN PLUS METFORMIN[29]									
Nauk, et al Phase III, PC, DB, RCT	1. Alogliptin 12.5mg (A12.5 2. Alogliptin 25mg (A25) 3. Placebo * All on background metformin (>1500mg) therapy	Mean Age: 54-56 years Male: 47-54% Baseline A1C: 7.9-8.0% Inclusion: 18-80 years, type 2 diabetes, A1C 7-10%, BMI 23-45 kg/m^2, stable metformin dose. Exclusion: Current AHA treatment other than metformin, abnormal labs, heart disease, glucocorticoid or weight loss drug use.	1. 213 2. 210 3. 104	26 weeks with 4 week single-blind run-in period	<u>Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.6% A25: -0.6% P: -0.1 P<0.001 for both <u>Fasting Plasma Glucose LS mean change:</u> A12.5: -19 mg/dl A25: -17 mg/dl P: 0.0 mg/dl P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 110 (52%) A25: 92 (44%) P: 19 (18%) P<0.001 <u>LS Mean differences in Baseline body weight compared to placebo:</u> A12.5: -0.0 kg (95% CI -0.7 to 0.7) A25: -0.3 kg (95% CI -0.9 to 0.4)	NA NA A12.5 ARR: 34 NNT: 3 A25 ARR: 26 NNT: 4 NS	<u>Upper Respiratory Infection:</u> A12.5: 68 (32%) A25: 5 (2%) P: 7 (7%) <u>Withdrawal due to Adverse Events:</u> A12.5: 7 (3%) A25: 4 (2%) P: 1 (1%)		**Quality Rating: Poor-fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice-response system. Performance: Double-blind design but no details provided. Detection: Details on outcome assessment not described. Attrition: FAS analysis with LOCF. Attrition rates ranged from 17-31%. **External Validity:** Recruitment: Patients were from 115 sites in 15 countries. Patient Characteristics: Patients were predominately white, a mean duration of diabetes of 6 years and mean metformin dose of ~1850mg. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.
ALOGLIPTIN PLUS PIOGLITAZONE[30]									
Prately, et al	1. Alogliptin 12.5 mg (A12.5)	Mean Age: 55 yrs. Mean baseline A1C 8.0%	1. 2. 9081	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.66%		<u>Hypoglycemia:</u> A12.5: 5.1% A25: 7.0% P: 5.2%		**Quality Rating: Fair** **Internal Validity: RofB** Selection: Randomization was done via

Phase III, RCT, DB, PC 125 sites	2. Alogliptin 25 mg (A25) 3. Placebo (P) * All on background pioglitazone ± metformin and/or sulfonylurea	Inclusion: type 2 DM, BMI 23-45 kg/m2, A1C 7-10%, ≥ 3 mo. of stable dose TZD with or without metformin or sulfonylurea Exclusion Criteria: Heart disease, abnormal lab values, uncontrolled HTN, and use of other AHAs.			A25: -0.80% P: 0.19% P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 87 (44.2%) A25: 98 (49.2%) P: 18 (18.2%) p=≤ 0.016 for both <u>LS Mean Changes in Baseline body weight from placebo:</u> A12.5: 0.42 kg A25: 0.05 kg P: not given		<u>Upper Respiratory Infection:</u> A12.5: 11 (5.6) A25: 10 (5.0) P: 5 (5.2) <u>Withdrawal due to Adverse Events:</u> A12.5: 6 (3.0%) A25: 6 (3.0%) P: 3 (3.1%)		automated, interactive voice response system. Baseline characteristics were well matched. Performance: Double-blind design but no details were provided. Detection: Blinding of outcomes assessors was not described. Attrition: Patient results were included for those with baseline and at least one post-baseline measurement with LOCF for missing data. Overall attrition was 12%. **External Validity:** Recruitment: Patients from 125 sites. Patient Characteristics: Study participants had few comorbidities, predominantly white and middle-aged. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN PLUS GLYBURIDE[31]									
Pratley, et al Phase III, RCT DB, PC 124 centers and 16 countries	1. Alogliptin 12.5 mg (A12.5) 2. Alogliptin 25 mg (A25) 3. Placebo (P) * All on background glyburide (5-10mg or greater)	Age: 57 years Female: 45-50% Mean Baseline A1C 8.1% Inclusion Criteria: 18-80 years old, type 2 DM, A1C 7-10% and sulfonylurea therapy ≥3 months Exclusion Criteria: Use of AHA therapy within 3 months of study, BMI <23 or >45 kg/m^2, abnormal lab values, heart disease, use of weight loss drugs, oral glucocorticoids and bosentan within 3 months.	1. 203 2. 198 3. 99	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.38% A25: -0.52% P: 0.01% P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 60 (29.6%) P: 18 (18.2%) p= 0.057 A25: 69 (34.8%) P: 18 (18.2%) p=0.008 <u>Changes in Baseline body weight:</u> A12.5: 0.60 kg A25: 0.68 kg P: -0.20 kg	NA NS ARR: NNT: NA	<u>Hypoglycemia:</u> A12.5: 32 (15.8%) A25: 19 (19.6%) P: 11 (11.1%) <u>Upper Respiratory Infection:</u> A12.5: 4 (2.0%) A25: 5 (2.5%) P: 6 (6.1%) <u>Withdrawal due to Adverse Events:</u> A12.5: 5 (2.5%) A25: 4 (2.0%) P: 2 (2.0%)		**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patients randomized according to a permuted block schedule other methodology was not described. Baseline characteristics were well matched. Performance: limited to double-blind designation, details not provided. Detection: no details were provided. Attrition: Levels of attrition ranged from 25-37%, patients with baseline and post-baseline measurement(s) were included with LOCF applied to missing data. **External Validity:** Recruitment: Included patients from 16 countries and 124 centers. Patient Characteristics: Patients were predominately white without significant co-morbidities including heart disease and reduced renal function. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

ALOGLIPTIN AND INSULIN[32]									
Rosenstock, et al Phase III, RCT DB, PC 110 sites and 13 countries	1. Alogliptin 12.5 mg (A12.5) 2. Alogliptin 25 mg (A25) 3. Placebo (P) * On background insulin therapy ± metformin	Mean Age:55 years Female: 65-85% Mean A1c: 9.3% Inclusion: Patients 18-80 years, A1C ≥8%, BMI 23-45 kg/m^2 and on insulin with or without metformin. Exclusion: heart disease, retinopathy, diabetic gastroparesis, cancer, use of other AHAs, weight loss drugs or glucocorticoids.	1. 131 2. 129 3. 130	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.63% A25: -0.71% P: -0.13% P<0.001 for both <u>Mean FPG decrease from baseline:</u> A12.5: 0.1 mmol/l (2 mg/dl) A25: -0.6 mmol/l (11 mg/dl) P: 0.3 mmol/l (5.4 mg/dl) <u>Changes in Baseline body weight:</u> A12.5: 0.60 kg A25: 0.7 kg P: 0.6 kg	NA NA NA	<u>Hypoglycemia:</u> A12.5: 26.7% A25: 27.1% P: 24% <u>Any Infection/Infestation</u> A12.5: 43 (33%) A25: 38 (30%) P: 40 (30.1%) <u>Withdrawal due to Adverse Events:</u> A12.5: 1 (0.8%) A25: 6 (4.7%) P: 4 (3.1%)	NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patients randomized with an automated interactive voice response system using a randomization schedule generated before study initiation. Performance: Limited to double-blind designation, details not provided. Detection: no details were provided. Attrition: Analysis was based on FAS. Attrition rates were high; 58% for placebo, 37% for A12.5 and 40% for A25. **External Validity:** Recruitment: Included patients from 13 countries and 110 centers. Patient Characteristics: Patients attended weekly visits to discuss diet and exercise. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN AND PIOGLITAZONE[33]									
DeFronzo, et al Phase III, DB, PC, DD, RCT 20 countries 327 study sites	1. Alogliptin 12.5 mg (A12.) 2. Alogliptin 2 mg (A25) 2. Pioglitazone 15 mg (P15) 3. Alogliptin 12.5 mg + pioglitazone 15mg (A12.5/P) 4. Alogliptin 2 mg + pioglitazone	Mean Age: 54 years Female: 51.1% Baseline mean A1C 8.5% Inclusion: Patients 18-80 years, type 2 DM, AIC 7.5 -11%, failed metformin monotherapy, normal labs, BMI 23-45 kg/m^2 Exclusion: use of glucocorticoids, weight loss drugs, abnormal labs and heart disease	1. 164 2. 163 3. 164 5. 164	26 weeks with 4-week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks for alogliptin monotherapy :</u> A12.5: -0.7% A25: -0.9% P: -0.1% <u>LS Mean Change from Baseline in A1C at 26 weeks for alogliptin/pioglitazone combination therapy :</u> P15/P: -0.7% P15/A12.5: -1.3% P15/A25: -1.25 P30/P: -0.9%	NA	<u>Any hypoglycemia for pooled groups:</u> Pioglitazone groups: 8 (2.1%) A12.5/all pioglitazone doses: 4 (1.0%) A25/all pioglitazone doses: 6 (1.5%) <u>Any Infection/Infestation for pooled groups:</u> Pioglitazone groups: 26.6% A12.5/all pioglitazone doses: 25.1% A25/all pioglitazone	NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patient randomization details not described. Performance: Limited to double-blind designation, details not provided. Detection: No details provided. Attrition: Attrition rates ranged from 11-46%, with the highest rate in the placebo group. Treatment attrition ranged from 11-28%. FAS with LOCF were used for missing data. **External Validity:** Recruitment: Patients were recruited from 20 countries and 327 sites. Patient Characteristics: Patients were predominately white with the mean duration

	15mg (A12.5/P) 5. Pioglitazone 30 mg (P30) 6. Pioglitazone 30 mg + alogliptin 12.5 mg (P30/A12.5) 7. Pioglitazone 30 mg + alogliptin 25 mg (P30/A25) 8. Pioglitazone 45 mg (P45) 9. Pioglitazone 45 mg + alogliptin 12.5 mg (P45/A12.5) 10. . Pioglitazone 45 mg + alogliptin 25 mg (P45/A25) 11. Placebo (P Alogliptin 25mg + pioglitazone 30mg (A25/P)				P30/A12.5: -1.4% P45/P: -1.0 P45/A12.5: -1.5% P45/A25: -1.6% p≤0.001 for pioglitazone vs. combination therapies (all groups) <u>Subjects reaching A1C <7.0%:</u> All pioglitazone doses: 118 (30.5%) A12.5/all pioglitazone doses: 213 (54.6%) A25/all pioglitazone doses: 218 (55.9%) P<0.001 for all groups compared to pioglitazone alone <u>Changes in Baseline body weight for pooled groups:</u> Pioglitazone groups: 1.5 kg A12.5/P groups: 1.8 kg A25/P groups: 1.9 kg P-value: NS	A12.5/P ARR: 24.1% NNT: 4 A25/P ARR: 25.4 NNT: 4	doses: 30.8% <u>Withdrawal due to Adverse Events:</u> Pioglitazone groups: 11 (2.8%) A12.5/all pioglitazone doses: 6 (2.1%) A25/pioglitazone doses: 6 (1.5%)	NA	of diabetes of 6 years. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN VS INCREASED PIOGLITAZONE DOSE[34]									

Bosi, et al Phase III, PG, DB, RCT	1. Alogliptin 25 mg (A/P/M)* 2. Pioglitazone 15 mg (P/M)* * All patients were on metformin (≥1500mg or maximum tolerated dose and pioglitazone 30mg	Mean Age: 55 yrs. Female: 49% Inclusion: Patients 18-80 year type 2 DM, systolic BP <160 mm Hg diastolic BP <100 mm Hg, A1C ≥ 7.0 and ≤ 10.0% on metformin and pioglitazone 2 months prior or A1C 7.5% on metformin and other AHA and later A1C ≥ 7.0 and ≤ 10.0% after switching to metformin and pioglitazone for 16 weeks and BMI 23-45 kg/m^2 Exclusion: Elevated BP, heart disease or any other severe disease.	1. 404 2. 399	52 weeks with 4-week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A/P/M: -0.70% P/M: -0.29% P<0.001 <u>Mean FPG decrease from baseline:</u> A/P/M: -0.8 mmol/l (14.4 mg/dl) P/M: -0.2 mmol/l (3.6 mg/dl) P<0.001 <u>Subjects reaching A1C <7.0%:</u> A/P/M: 33.2% P/M: 21.3% P< 0.001 <u>Changes in Baseline body weight:</u> A/P/M: 1.10 kg P/M: 1.60 kg P=0.071	NA NA ARR: 11.9% NNT: 8 NA	<u>Hypoglycemia:</u> A/P/M: 16 (4.0%) P/M: 6 (1.5%) <u>Upper Respiratory Tract Infection:</u> A/P/M: 29 (7.2%) P/M: 16 (4.0%) <u>Withdrawal due to Adverse Events:</u> A/P/M: 12 (3%) P/M: 16 (4.0%)	NA NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Randomization methods were unclear, no details were provided. Performance: Double-blind design but no details were provided. Detection: Final analysis investigators blinded to interim analysis results but unknown if allocation was concealed. Attrition: Attrition rates in the alogliptin group were 30% and 40% in the pioglitazone group, this includes patients removed from study to due hyperglycemia rescue. A per protocol analysis was used with LOCF for missing data. **External Validity:** Recruitment: Patients were recruited from multiple sites and countries. Patient Characteristics: Patients were predominately white with a 7 year history of diabetes. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis, FAS- full analysis set
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: AHA = antihyperglycemic agent, PPARγ = peroxisome proliferator-activated receptor-γ, FPG = fasting plasma glucose, A1c- hemoglobin A1c

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Appendix 1: Drug Information

NDE: Canagliflozin[18]

Pharmacology: Canagliflozin works by inhibiting the SGLT2, which is responsible for reabsorbing glucose that is filtered by the kidney. Inhibition of SGLT2 causes less glucose reabsorption and lowers the renal threshold for glucose which causes urinary glucose excretion.

Table 1. Pharmacokinetics[18]

Parameter	Canagliflozin
Half-life	10.6-13.1 hours
Metabolism	*O*-glucuronidation
Elimination	33% renal and 52% hepatic
Renal Dose Adjustment	In patients with an eGFR of 45 to <60 mL/min/1.73 m^2 dose should be limited to 100mg daily In patients with a eGRF of 45 mL/min/1.73 m^2 or less canagliflozin is not recommended
Hepatic Dose Adjustment	No adjustment is recommended for patients with Child-Pugh class A-B hepatic impairment Canagliflozin is not recommend for patients with Child-Pugh class C hepatic impairment

Contraindications/Warnings[18]:

- **Contraindications:** Canagliflozin should not be used in patients with a history of severe hypersensitivity to canagliflozin, severe renal impairment or end-stage renal disease (ESRD).
- **Warning:** Hypotension has been associated with canagliflozin treatment. Caution is advised and correction of volume status and hypovolemia in patients with renal impairment, the elderly, and low systolic blood pressure or on diuretics, ARBs, or ACE inhibitors is recommended. It is recommended that renal function be monitored throughout treatment.

Dose[18]

It is recommended that canagliflozin be started at 100mg with the first meal of the day, with the option of increasing the dose to 300mg once daily if tolerated. See table for renal and hepatic dosing.

NDE: Alogliptin[22]

Pharmacology: Alogliptin is a DDP-4 inhibitor which slows the inactivation of incretin hormones by the DPP-4 enzyme. Incretin hormones cause insulin release and subsequent glucose lowering.

Table 1. Pharmacokinetics[22]

Parameter	Alogliptin
Half-life	21 hours
Metabolism	60-70% excreted unchanged in the urine
Elimination	76% renal and 13% hepatic
Renal Dose Adjustment	In moderate renal impairment (CrCl ≥30 to <60 mL/min) 12.5 mg once daily is recommended In severe renal impairment (CrCl ≥15 to <30 mL/min)/ESRD (CrCl <15 mL/min or dialysis) 6.25 mg once daily is recommended
Hepatic Dose Adjustment	No adjustment is recommended for patients with Child-Pugh class A-B hepatic impairment Alogliptin has not been studied in patients with Child-Pugh class C hepatic impairment

Contraindications/Warnings[22]:

- **Contraindications:** Alogliptin should not be used in patients with a history of severe hypersensitivity to alogliptin.
- **Warning:** Cases of acute pancreatitis have been reported and patients with signs of pancreatitis should discontinue therapy. There have been postmarketing reports of serious hypersensitivity reactions and hepatic failure with alogliptin. To minimize hypoglycemia, consider lowering the dose of insulin secretagogues or insulins when combining with alogliptin.

Dose[18]

It is recommended that alogliptin be taken as a 25mg tablet daily. See table for renal and hepatic dosing recommendations.

APPENDIX 2:
Suggested PA Criteria

Incretin Enhancers

Initiative:

- Optimize appropriate prescribing of incretin enhancers.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- Sitagliptin (Januvia®)
- Sitagliptin/metformin (Janumet®)
- Saxagliptin (Onglyza®)
- Saxagliptin/metformin (Kombiglyze XR®
- Linagliptin (Tradjenta®)
- Linagliptin/metformin (Jentadueto®)
- Alogliptin (Nesina®)
- Alogliptin/metformin (Kazano®)
- Alogliptin/pioglitazone (Oseni®)

Covered Alternatives:

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

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.

Approval Criteria		
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Go to #3.	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
3. Is the request for sitagliptin (Januvia®) or sitagliptin/metformin (Janumet®)?	Yes: Approve for up to 12 months.	No: Recommend trial of preferred incretin enhancers (sitagliptin or sitagliptin/metformin).

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

P&T / DUR Action: *9/26/13 (KS), 4/26/12 (KS), 3/17/11 (KS)*
Revision(s):
Initiated: *7/16/12, 1/1/12*

Sodium-Glucose Co-Transporter 2 (SGLT2)

Initiative:

- Optimize appropriate prescribing of SGLT2s.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- Canagliflozin (Invokana®)

Covered Alternatives:

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

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Go to #3	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Approval Criteria		
3. Has the patient tried and failed other third-line treatments for Diabetes or have contraindications to third-line treatments?	Yes: Approve for up to 12 months.	No: Recommend a trial of third-line agents.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

P&T / DUR Action: *9/26/13 (KS)*
Revision(s):
Initiated: *9/26/13*

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Abbreviated Class Review: First Generation Antipsychotic Drugs (First vs. Second Generation)

Month/Year of Review: November 2013 **End date of literature search:** August 31, 2013

Current Status of Voluntary PDL Class: First Generation Antipsychotics have not previously been reviewed

Research Questions:

- What is the comparative efficacy of first and second generation antipsychotics in the treatment of schizophrenia and schizophrenia-related psychoses?
- What is the comparative efficacy of first and second generation antipsychotics in the treatment of bipolar disorder?
- How do first and second generation antipsychotics differ in type and incidence of adverse events?
- Should first generation antipsychotics be added to the PDL?

Conclusions:

- There is robust evidence to support the use of antipsychotics in the management of schizophrenia. While there is evidence to show that individual second generation antipsychotics are superior to individual first generation antipsychotics, several systematic reviews/meta-analyses demonstrate that second generation antipsychotics, as a class, are not collectively superior to first generation antipsychotics.
- There is evidence to support the use of antipsychotics in the treatment of acute mania, however their role in maintenance treatment is much less clear. Head-to-head studies show that second generation antipsychotics are similar in efficacy to haloperidol, albeit there were large variations in study designs and a lack of large trials. More evidence is needed to evaluate any class effect of first or second generation antipsychotics.
- Assessment of safety in a comprehensive meta-analysis shows that rates and types of adverse effects cannot be generalized across the classes of first and second generation antipsychotics. The favorability of each drug varies depending on the adverse effect in question.
- The decision of what antipsychotic to select should be based on individual patient characteristics and the consideration of the unique side effects of each antipsychotic medication.

Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with the NICE guidelines, patients and providers should work together to determine the best drug therapy for the patient, begin therapy at low doses, frequently assess efficacy and safety, avoid loading doses, and give an adequate trial of 4 to 6 weeks. One particular drug or drug group should not necessarily be used preferentially over all others.
- To reduce the copay burden, first generation antipsychotics should be included on the voluntary PDL list to promote the use of cost-effective and individualized treatment options for schizophrenia and bipolar disorder.
- Further review second generation antipsychotics in upcoming meeting for comparative effectiveness and safety.

Reason for Review:
Recent literature has led health care providers to reevaluate the approach to medication management for schizophrenia and bipolar disorder. As the incidence and overall costs of mental health disorders continues to rise, it is critical to understand how to treat these conditions in the most cost-effective manner. Over $10 billion was spent on second generation antipsychotics in 2008, which accounted for almost 5% of all drug costs.[1] Prescribing patterns indicate that second generation antipsychotics are preferred treatment options, presumably due to a perceived increase in efficacy and/or tolerability, but studies are available that refute the claim of general superiority of second generation antipsychotics over first generation antipsychotics. The purpose of this review is to understand the comparative efficacy of first and second generation antipsychotics and to distinguish any class effects in the treatment of schizophrenia or bipolar disorder.

Currently, all antipsychotics are available without restriction and are not subject to prior authorization. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs, such as prior authorization. Thus, the mental health PDL is strictly voluntary. Second generation antipsychotics have been reviewed for clinical efficacy and safety and specific agents have been chosen as clinically preferred. The advantage to this is the elimination of a copay. Studies in Medicaid patients have shown that copays can be associated with significant reductions in use of clinically important medications. Oregon's Medicaid program currently charges no copayment for preferred PDL generics. Reviewing the first generation agents and adding clinically appropriate agents to the PDL would reduce the copay burden to the client, while improving access to these medications.

Background:
Schizophrenia is a complicated illness that occurs in 0.4% to 1.4% of people in the United States.[2] The incidence is similar between men and women and the causes are not well understood. Schizophrenia, among other psychotic disorders, is managed through the use of antipsychotic medications. First generation antipsychotics (FGAs), otherwise known as 'typical antipsychotics,' have been available since the 1950's. Second generation antipsychotics (SGAs), or 'atypical antipsychotics, have been available since the 1980's.[3]

While antipsychotics revolutionized the treatment of schizophrenia, they are also associated with significant adverse effects. The FGAs are high-affinity antagonists of dopamine D2 receptors, which have been shown to be effective against psychotic symptoms, but are also responsible for many of the FGAs adverse effects, including lethargy, sedation, weight gain, and sexual dysfunction. [4] Extrapyramidal symptoms (EPS) and other movement disorders, such as parkinsonism and dystonia, are known to be some of the most debilitating side effects associated with FGAs. Around 20% of patients taking FGAs develop tardive dyskinesia, which involves abnormal involuntary movements that the user is not aware of.

SGAs were developed to reduce relapse rates and adverse events. Compared to FGAs, SGAs have lower affinity for the D2 receptors and act on other receptors, namely serotonin (5-hydroxytryptamine $_{1A, 2A, 2C, 3, 6, \text{and } 7}$) and norepinephrine ($\alpha_1$ and α_2). The first SGA to be introduced to the market was clozapine in 1971, but was voluntarily withdrawn from the market by the manufacturer due to agranulocytosis. Subsequent SGAs later became first-line treatment for many patients due to a lower potential risk of EPS. However, SGAs are less affordable and are associated with metabolic side effects including weight gain, elevated lipid levels, and the development of type 2 diabetes mellitus.[5]

Almost 6 million people in the United States have bipolar disorder, which counts for 2.6% of the US population over age 18.[67] The role of SGAs in bipolar disorder is much less clear. Maintenance treatment usually consists of a mood stabilizer, such as divalproex or lithium, while SGAs are reserved for the treatment of manic episodes. The first SGA approved for bipolar disorder was olanzapine in 2000. Since then, prescribing SGAs for bipolar disorder has become more widely accepted, with one study showing that the percentage of bipolar disorder treatment visits related to SGAs increased from 18% to 49% between January 1998

and December 2009, despite a lack of strong efficacy or safety evidence for this indication.[8] More recent studies are available that evaluate use of SGAs as an add-on maintenance therapy or single maintenance therapy, but this evidence has yet to be incorporated into treatment guidelines.[9]

Recent literature has led health care providers to reevaluate the approach to medication management for schizophrenia and bipolar disorder. As the incidence and overall costs of mental health disorders continues to rise, it is critical to understand how to treat these conditions in the most cost-effective manner. Over $10 billion was spent on SGAs in 2008, which accounted for almost 5% of all drug costs.[1] Prescribing patterns indicate that SGAs are preferred treatment options, presumably due to a perceived increase in efficacy and/or tolerability, but studies are available that refute the claim of general superiority of SGAs over FGAs. The purpose of this review is to understand the comparative efficacy of FGAs and SGAs and to distinguish any class effects in the treatment of schizophrenia or bipolar disorder.

Methods:
A Medline literature search ending August 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing first generation antipsychotics to second generation antipsychotics. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

1. Systematic Reviews/Meta-analyses:

I. Schizophrenia and schizophrenia-related psychoses

a. Change in Symptoms

Three systematic reviews/meta-analyses assessed the relative impact of FGAs and SGAs on symptom scores in people with schizophrenia or related disorders. Symptoms were typically measured using the change in Positive and Negative Syndrome Scale (PANSS); where PANSS scores were not available, the change in Brief Psychiatric Rating Scale (BPRS) was considered a valid tool.

The largest and most recently completed meta-analysis, published June 2013, was a multiple-treatments meta-analysis which allowed for both direct and indirect comparisons of randomized controlled trials comparing 15 different antipsychotics and placebo in the acute treatment of schizophrenia. Two FGA's were assessed in the review: haloperidol and chlorpromazine. The study included 212 published/unpublished randomized controlled trials with 43,049 participants, and each trial was at least single-blinded. This study created an evidence-based hierarchy of effectiveness, measured by the standardized mean difference in PANSS scores, compared to placebo. In this hierarchy, the FGAs haloperidol and chlorpromazine were the 7th and 12th most effective antipsychotics. Clozapine was more effective than all other studied drugs; amisulpride (not available in the United States), olanzapine, and risperidone were superior to the remaining drugs, aside from paliperidone and zotepine (not available in the United States). There was a wide range of effect sizes, ranging from -0.33 to -0.88. The standardized mean differences in PANSS scores, compared to placebo, with 95% confidence intervals are shown in Table 1.[10]

Table 1. Efficacy of Antipsychotic Drugs Compared to Placebo[8]

Overall change in symptoms, SMD (95% CI)	
Clozapine	-0.88 (-1.03, -0.73)
Amisulpride	-0.66 (-0.78, -0.53)
Olanzapine	-0.59 (-0.65, -0.53)
Risperidone	-0.56 (-0.63, -0.50)
Paliperidone	-0.50 (-0.60, -0.39)
Zotepine	-0.49 (-0.66, -0.31)
Haloperidol	-0.45 (-0.51, -0.39)
Quetiapine	-0.44 (-0.52, -0.35)
Aripiprazole	-0.43 (-0.52, -0.34)
Sertindole	-0.39 (-0.52, -0.26)
Ziprasidone	-0.39 (-0.49, -0.30)
Chlorpromazine	-0.38 (-0.54, -0.23)
Asenapine	-0.38 (-0.51, -0.25)
Lurasidone	-0.33 (-0.45, -0.21)
Iloperidone	-0.33 (-0.43, -0.22)

SMD: standardized mean difference, CI: confidence interval

The results of this review align with a meta-analysis completed several years earlier, which included 150 double-blind studies that compared one of nine different SGAs to haloperidol (n=95), chlorpromazine (n=28), perphenazine (n=5), fluphenazine (n=4), flupenthixol (n=3), perazine (n=3), thioridazine (n=2), levomepromazine (n=2), and clopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciacine (1 study each). Consistent with the aforementioned meta-analysis, amisulpride [-0.31 (95% CI -0.44, -0.19)], clozapine [-0.52 (95% CI -0.22, -0.05], olanzapine [-0.28 (95% CI -0.38, -0.18)], and risperidone [-0.13 (95% CI -0.22, -0.05)], were more efficacious than the FGAs. The remaining SGAs (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were not significantly different from the FGAs in their effects on overall symptoms, measured by the PANSS or BPRS. The magnitude of effect sizes was considered small to medium by the study authors.[11]

The notion that there is no clear benefit of one class versus the other is supported by a third systematic review and meta-analysis. This analysis included 114 randomized and nonrandomized controlled trials, or cohort studies with a minimum follow-up of up to 2 years, and compared commercially available FGAs and SGAs. This trial evaluated the comparative efficacy on positive and negative symptoms separately, but used the PANSS as the primary scale for outcome measurement. In the assessment of reduction in positive symptoms, there was evidence to show a benefit of risperidone over haloperidol, although the effect size was minimal and not considered clinically significant by study authors. No other differences were observed between haloperidol and the four other SGAs that were studied (clozapine, olanzapine, quetiapine, or aripiprazole). The evidence for negative symptoms was stronger, as there was moderate-strength evidence that showed olanzapine, risperidone, and aripiprazole had statistical benefit compared to haloperidol, however the difference was not considered clinically significant. There was no difference between haloperidol versus clozapine, quetiapine or ziprasidone for the reduction of negative symptoms, presumably due to a lack of precision in effect estimates.[12]

b. Relapse Rates

The National Institute of Health published a systematic review/meta-analysis, which evaluated the comparative efficacy of FGAs and SGAs for relapse prevention in schizophrenia. This analysis included randomized, head-to-head comparisons of oral SGAs and FGAs, with durations of ≥ 6 months. The primary outcome measure was relapse, which was not defined consistently among the 23 studies included in the analysis. Of the 9 studies that did not define relapse rate, hospitalization (n=4) or 'failure to maintain response' (n=5) was used to define relapse. Overall, this study showed that individual SGAs were not consistently superior to FGAs, however when evaluated as a group, treatment with SGAs resulted in superior relapse prevention. Two studies showed that SGAs sertindole and ziprasidone were superior to FGAs, however when requiring ≥ 3 studies per individual antipsychotic, risperidone, clozapine, or olanzapine were not statistically superior to FGAs in preventing relapse. When analyzed as a class, SGAs were significantly superior to FGAs for the prevention of relapse (29% vs 37.5%, p=0.0007). The authors attribute the discrepancy between individual and class effects to the lack of power to detect a difference in individualized studies. A major limitation of this analysis is the inconsistency in the definition of the primary endpoint, in addition to variation in the study methodologies.[13]

c. Quality of Life

Jones et al. investigated whether improvements in health-related quality of life or savings in the use of other health and social care resources would offset the increased acquisition costs of SGAs over FGAs. Study subjects were aged 18-65, had schizophrenia, and a change in drug treatment was being considered for clinical reasons, most commonly suboptimal efficacy or adverse effects. The primary hypothesis was that use of SGAs would be associated with clinically

significant improvement in quality of life across 1 year compared with the use of FGAs. This was measured using the Quality of Life Scale, an interview-based survey with 21 items rated on a 7-point scale from 0 to 6; a higher score reflected normal functioning. Secondary questions concerned wither SGAs (other than clozapine) were associated with fewer adverse effects, improved patient satisfaction, and lower total health care costs. Patients were randomized to either FGAs (n=118) or SGAs (n=109) (other than clozapine). The treating psychiatrists determined individual treatments. The difference in overall quality of life scale estimate at 52 weeks was -1.7 [standard error 1.4 (-4.5 to 1.1); p=0.24], a difference that favored FGAs, but was not statistically significant. No difference was found in side effects using the antipsychotic non-neurological side-effects rating scale (ANNSERS) in the FGAs versus SGAs [10.8 (SD 7.7) versus 12.5 (SD 8.4); p=0.14]. Study participants did not show a preference for either class of drugs, costs were similar, and there was no difference in symptoms. There was a trend for the mean annual cost to be lower for people using FGAs ($34,750) compared to SGAs ($37,185), and the major cost in both groups was psychiatric hospital inpatient admissions (93.2% for FGAs, 81.5% for SGAs).[14]

d. Safety

The multiple-treatments meta-analysis evaluated several safety outcomes as secondary endpoints. The relative effect sizes of antipsychotic drugs compared to placebo are shown in Table 2.

- **All-cause discontinuation** was evaluated as a measure of efficacy and tolerability. All drugs were significantly better than placebo with the exception of zotepine, an SGA that is not currently available in the United States. Additionally, the drugs that were found to be most efficacious had lower rates of discontinuation, with the exception of haloperidol, which was ranked in the middle in terms of efficacy, and lowest for all-cause discontinuation.[10]
- Ziprasidone, lurasidone, and haloperidol were the only drugs that did not produce significantly more **weight gain** compared to placebo. Chlorpromazine had a significant impact on weight gain, in addition to clozapine, iloperidone, sertindole, quetiapine, risperidone, and paliperidone.[10]
- Clozapine, sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride, and asenapine did not cause significantly more **extrapyramidal side effects** compared to placebo. Haloperidol caused the most extrapyramidal side effects, in addition to zotepine, with odds ratios ranging from 3.01-4.76. Chlorpromazine did not produce more extrapyramidal side effects than most SGAs.[10]
- Paliperidone, risperidone, and haloperidol had a larger effect on **prolactin increase**, compared to all other drugs, with risperidone and paliperidone having a greater effect than haloperidol.[10]
- Iloperidone, ziprasidone, amisulpride and sertidole were associated with significant **QTc prolongation**. Haloperidol appeared to increase the risk of QTc prolongation compared to placebo, however magnitude of the effect appears to be small (odds ratio: 0.11).[10]
- All but four of the studied drugs increased **sedation** compared to placebo (amisulpride, paliperidone, sertindole, and iloperidone showed no difference compared to placebo. Clozapine appears to be the most sedating (odds ratio: 8.82).[10]

Table 2. Effect Sizes of Antipsychotic Drugs Compared to Placebo for Safety Outcomes[10]

	All-cause discontinuation (OR, 95%CI)		Weight gain (SMD, 95%CI)		Extrapyramidal side effects (OR, 95%CI)	
Better	Amisulpride	0.43 (0.32, 0.57)	Haloperidol*	0.09 (0, 0.17)	Clozapine	0.3 (0.12, 0.62)
	Olanzapine	0.46 (0.41, 0.52)	Ziprasidone*	0.10 (-0.02, 0.22)	Sertindole*	0.81 (0.47, 1.3)
	Clozapine	0.46 (0.32, 0.65)	Lurasidone*	0.10 (-0.02, 0.21)	Olanzapine*	1 (0.73, 1.33)
	Paliperidone	0.48 (0.39, 0.58)	Aripiprazole	0.17 (0.05, 0.28)	Quetiapine*	1.01 (0.68, 1.44)
	Risperidone	0.53 (0.46, 0.60)	Amisulpride	0.20 (0.05, 0.35)	Aripiprazole*	1.2 (0.73, 1.85)
	Aripiprazole	0.61 (0.51, 0.72)	Asenapine	0.23 (0.07, 0.39)	Iloperidone*	1.58 (0.55, 3.65)
	Quetiapine	0.61 (0.52, 0.71)	Paliperidone	0.38 (0.27, 0.48)	Amisulpride*	1.6 (0.88, 2.65)
	Chlorpromazine	0.65 (0.5, 0.84)	Risperidone	0.42 (0.33, 0.50)	Ziprasidone	1.61 (1.05, 2.37)
	Zotepine*	0.69 (0.41, 1.07)	Quetiapine	0.43 (0.34, 0.53)	Asenapine*	1.66 (0.85, 2.93)
	Asenapine	0.69 (0.54, 0.86)	Sertindole	0.53 (0.38, 0.68)	Paliperidone	1.81 (1.17, 2.69)
	Iloperidone	0.69 (0.56, 0.84)	Chlorpromazine	0.55 (0.34, 0.76)	Risperidone	2.09 (1.54, 2.78(
	Ziprasidone	0.72 (0.59, 0.86)	Iloperidone	0.62 (0.49, 0.74)	Lurasidone	2.46 (1.55, 3.72)
	Lurasidone	0.77 (0.61, 0.96)	Clozapine	0.65 (0.31, 0.99)	Chlorpromazine	2.65 (1.33, 4.76)
	Sertindole	0.78 (0.61, 0.98)	Zotepine	0.71 (0.47, 0.96)	Zotepine	3.01 (1.38, 5.77)
Worse	Haloperidol	0.8 (0.71, 0.90)	Olanzapine	0.74 (0.67, 0.81)	Haloperidol	4.76 (3.7, 6.04)
	Prolactin Increase (SMD, 95%CI)		**QTc prolongation (OR, 95%CI)**		**Sedation (OR, 95%CI)**	
Better	Aripiprazole*	-0.22 (-0.46, 0.03)	Lurasidone*	-0.10 (-0.21, 0.01)	Amisulpride*	1.42 (0.72, 2.51)
	Quetiapine*	-0.05 (-0.23, 0.13)	Aripiprazole*	0.01 (-0.13, 0.15)	Paliperidone*	1.40 (0.85, 2.19)
	Asenapine*	0.12 (-0.12, 0.37)	Paliperidone*	0.05 (-0.18, 0.26)	Sertindole*	1.53 (0.82, 2.62)
	Olanzapine	0.14 (0, 0.28)	Haloperidol	0.11 (0.03, 0.19)	Iloperidone*	1.71 (0.63, 3.77)
	Chlorpromazine*	0.16 (-0.48, 0.8)	Quetiapine	0.17 (0.06, 0.29)	Aripiprazole	1.84 (1.05, 3.05)
	Iloperidone*	0.21 (-0.09, 0.51)	Olanzapine	0.22 (0.11, 0.31)	Lurasidone	2.45 (1.31, 4.24)
	Ziprasidone	0.25 (0.01, 0.49)	Risperidone	0.25 (0.15, 0.36)	Risperidone	2.45 (1.76, 3.35)
	Lurasidone	0.34 (0.11, 0.57)	Asenapine*	0.30 (-0.04, 0.65)	Haloperidol	2.76 (2.04, 3.66)
	Sertindole	0.45 (0.16, 0.74)	Iloperidone	0.34 (0.22, 0.46)	Asenapine	3.28 (1.37, 6.69)
	Haloperidol	0.7 (0.56, 0.85)	Ziprasidone	0.41 (0.31, 0.51)	Olanzapine	3.34 (2.46, 4.5)
	Risperidone	1.23 (1.06, 1.40)	Amisulpride	0.66 (0.39, 0.91)	Quetiapine	3.76 (2.68, 5.19)
	Paliperidone	1.3 (1.08, 1.51)	Sertindole	0.9 (0.76, 1.02)	Ziprasidone	3.8 (2.58, 5.42)
	Amisulpride	N/A	Clozapine	N/A	Chlorpromazine	7.56 (4.78, 11.53)
	Clozapine	N/A	Chlorpromazine	N/A	Zotepine	8.15 (3.91, 15.33)
Worse	Zotepine	N/A	Zotepine	N/A	Clozapine	8.82 (4.72, 15.06)

*: no statistically significant difference compared to placebo; Highlighted cells: first generation antipsychotics; OR: odds ratio; SMD: standardized mean difference; CI: confidence interval. *Difference is not statistically significant compared to placebo

II. Bipolar Disorder

A comparative effectiveness review was published in 2012, which evaluated antipsychotic treatments for bipolar disorder. Overall, 11 trials were included which evaluated 2,217 adult patients and evaluated 4 main outcomes: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; 5) subgroup analysis.[3]

Chlorpromazine was compared to clozapine in a 27 patient study. There were no differences found between groups for mood (mania) based on the Young Mania Rating Scale (YMRS). Two trials evaluated haloperidol versus aripiprazole in 679 patients. No differences were found on the improvement of core illness symptoms in any of the various scoring systems. One trial found a increased incidence of relapse rate in the haloperidol group [RR 0.53 (0.4 to 0.71)]. Two trials compared haloperidol with olanzapine in 463 subjects. There was no difference in improvement of core illness symptoms or relapse, response, and remission rates. There was an increase on the number of days worked for pay favoring olanzapine [RR 0.50 (0.32 to 0.70)]. Haloperidol had a favorable outcome on the mental summary score and olanzapine had a favorable physical summary score. One trial evaluated haloperidol versus quetiapine in 201 subjects. Core illness symptoms were not studied. There was no difference in remission rates or response rates. Four trials evaluated haloperidol versus risperidone. Several different evaluation tools were used to evaluate the improvement of core illness symptoms (YMRS being the most common); however none of the trials found a significant difference between the two study groups. One trial compared haloperidol to ziprasidone in 350 subjects. Haloperidol was found to be superior for the improvement of core illness symptoms based on YMRS [RR -5.52 (-7.79 to -3.25)] and response rates [RR 1.09 (1.02 to 1.16)].[3]

The incidence of diabetes mellitus, tardive dyskinesia, and metabolic syndrome were evaluated among the agents included in the above studies. There was no difference in the incidence of diabetes mellitus. Haloperidol showed a statistically significant increase in tardive dyskinesia compared to clozapine [RR 34.5 (95% CI 2.07 to 573.55)]. Haloperidol was also found to have a higher incidence of metabolic syndrome in one trial comparing it to clozapine [RR 0.27 (95% CI 0.10 to 0.75)].[3]

2. New Guidelines:

Schizophrenia:
The 2004 National Institute for Health & Clinical Excellence (NICE) guidelines reviewed 9 randomized controlled trials, which included 1,801 subjects with first-episode or early schizophrenia (including recent onset and treatment-naïve patients).[15] Studies were excluded if subjects had very late onset schizophrenia (onset after age 60), or had other psychotic disorders (bipolar disorder, mania, or depressive psychosis). The trials studied 1 FGA, haloperidol, and three SGAs, olanzapine, quetiapine, and risperidone. The critical outcomes that were included were mortality (suicide), global state [based on the Clinical Global Impression scale (CGI)], mental state (total symptoms, depression), social functioning, study discontinuation rates, and adverse events. The guidelines concluded that there were no differences in clinical efficacy. In terms of safety, the reported rates of metabolic and neurological side effects were consistent with those previously reported for each drug.

For the acute exacerbation or recurrence of schizophrenia, the NICE guidelines evaluated 72 RCTs (n=16,556) with the critical outcomes of mortality (suicide), global state (CGI), mental state (total symptoms, depression), social functioning, study discontinuation rates, and adverse events. They found no differences in efficacy between FGAs (benperidol, chlorpromazine, flupenthixol, fluphenazine, haloperidol, levomepromazine, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sulpiride, trifluoperazine, zuclopenthixol) and SGAs (amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, sertindole, zotepine). Reported side effects were similar to those described in previous studies.[15]

For relapse prevention, the NICE guidelines evaluated 17 RCTs, which included 3,535 participants and compared FGAs (benperidol, chlorpromazine, flupenthixol, fluphenazine, haloperidol, levomepromazine, pricyazine, perphenazine, pimozide, prochlorperazine, promazine, sulpiride, trifluoperazine, zuclopenthixol) and SGAs (amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, zotepine). The critical outcomes evaluated were global state (relapse), overall treatment failure, and study discontinuation rates. All the antipsychotics reduced the risk of relapse or overall treatment failure. A slight benefit was found for some SGAs over haloperidol, but the evidence was not strong enough to preferentially select an antipsychotic for relapse prevention. The guidelines pooled 138 studies of antipsychotic medications to evaluate metabolic and neurologic side effects. This pooled data did not provide additional insight into long-term adverse effects or clinically significant differences between antipsychotic drugs.[15]

When deciding on a pharmacological intervention for a patient with newly diagnosed schizophrenia, the NICE guidelines recommend providing information and discussing the benefits and side-effect profile of each drug with the service user and to consider:

- The relative potential of individual antipsychotic drugs to cause extrapyramidal symptoms, metabolic side effects and other side effects.
- The views of the caregiver if the patient agrees.

There are no recommendations of specific therapies that should be started. It is recommended that once a medication is selected it should be given for 4-6 weeks at an optimum dosage, and efficacy and side effects should be closely monitored. Loading doses should not be used and as needed medications should have specific dosing instructions and should not go above a maximum dosing.[15]

Bipolar Disorder:

The bipolar disorder guidelines from The American Psychiatric Association (APA) were originally published in 2002 and are somewhat outdated. For the acute treatment of manic or mixed episodes, the APA recommends the initiation of lithium plus an antipsychotic or valproate plus an antipsychotic. The choice of initial treatment should be guided by illness severity and patient preference where possible, keeping in mind the side effect profiles of the individual agents. For less ill patients they state that monotherapy with lithium, valproate, or an antipsychotic may be used, and olanzapine is specifically mentioned as an option. They recommend SGAs over FGAs because of their benign side effect profile [class I recommendation], and they note the benefits of SGAs over haloperidol and chlorpromazine. They also recommend olanzapine or risperidone because of published trials in the use of bipolar disorder [II]. Clozapine is given a class II recommendation for refractory illness. For maintenance treatment of bipolar disorder they recommend that antipsychotics be discontinued unless they are required for control of persistent psychosis [I] or prophylaxis against recurrence [III]. They state that antipsychotics could be considered for maintenance treatment, however there is a lack of evidence to show that they are comparable to lithium or valproate [III].[9]

A guideline watch was developed in 2005 with updates to the 2002 APA guidelines, which incorporated newer studies that evaluated SGAs as monotherapy, and adjunct to mood stabilizers for the acute treatment of mania.[16] Olanzapine was found to be better than placebo for the acute treatment of mania or mixed episodes in two randomized, double-blind, controlled studies. Haloperidol was compared to olanzapine in a randomized, double-blind study and the two groups were found to be equivalent for acute mania, but olanzapine was found to be superior for patients whose index episode did not include psychotic features. When olanzapine monotherapy was compared to divalproex monotherapy in two trials, one found equivalent efficacy and the other found olanzapine to be superior in efficacy, but with a greater incidence of side effects. Olanzapine plus divalproex or lithium was found to be a superior mood stabilizing regimen compared to divalproex or lithium alone. Risperidone monotherapy was evaluated in 3 randomized, double-blind, placebo-controlled trials and was found to be superior to placebo in all three trials for the acute treatment of mania. Risperidone as an adjunctive agent was also found to be beneficial as a mood stabilizer. Aripiprazole and ziprasidone were found to be more effective than placebo for the acute treatment of patients with manic or mixed episodes. Quetiapine was

compared against lithium and haloperidol in patients with manic episodes in two different trials and found to be equivalent. For depressive episodes, olanzapine alone and in combination with fluoxetine were compared to placebo and found to be superior. Quetiapine was also found to be superior to placebo for depression. For maintenance therapy olanzapine was compared to divalproex. The remission rates were not different, however olanzapine had a shorter remission time. Olanzapine was also found to have similar efficacy to lithium in a 52 week study after a manic or mixed episode. The APA has yet to update the guideline recommendations, but information obtained from these studies will be factored into future guidelines and should be considered when treating bipolar disorders.[16]

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

DOSE & AVAILABILITY

MEDICATIONS	INDICATIONS	STRENGTH	ROUTE	DOSAGE and FREQUENCY:
Chlorpromazine[17] (Thorazine)	Schizophrenia	Injection: 25mg/mL (1 mL, 2 mL) Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	PO IV IM	**Oral:** 30-800mg/day in 1-4 divided doses **IM,IV:** Initial 25mg, maximum 400mg/dose every 4-6 hours until patient controlled
Fluphenazine[18] (Prolixin)	Psychotic disorders and schizophrenia	Elixir, oral: 2.5mg/5 mL Injection, oil, as decanoate: 25 mg/mL Injection, solution: 2.5mg/mL Solution, oral [concentrate]: 5mg/mL Tablet: 1mg, 2.5mg, 5mg, 10mg	PO IM	**Oral:** Initial 2.5-10 mg/day in divided doses **IM:** Initial 1.25mg as a single dose, may need 2.5-10 mg/day in divided doses (3-4 times/day) **Long acting IM:** Initial 12.5-25mg every 2-4 weeks
Haloperidol[19] (Haldol)	Management of schizophrenia	Injection, oil, as decanoate: 50mg/mL (1 mL, 5mL),; 100mg/ml (1 mL, 5 mL) Injection, solution: 5mg/mL (1mL, 10mL) Solution, oral: 2 mg/mL (5 mL, 15 mL, 120 ML) Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	PO IM IV	**Oral:** 0.5-5mg 2-3 times/day; usual maximum 30mg/day **IM (as lactate):** 2-5mg every 4-8 hours as needed **IM (as decanoate):** Initial: 10-20 times the daily oral dose administered at 4-week intervals. Maintenance dose: 10-15 times initial oral dose, used to stabilize psychiatric symptoms
Loxapine[20] (Loxitane)	Psychotic disorders	Capsule: 5mg, 10mg, 25mg, 50mg	PO	**Oral:** Initial 10mg twice daily (up to 50 mg/day), increase dose until psychotic symptoms are controlled; usual maintenance: 60-100 mg/day divided doses 2-4 times/day. Maximum 250mg/day.
Perphenazine[21] (Trilafon)	Treatment of schizophrenia	Tablet: 2mg, 4mg, 8mg, 16mg	PO	**Oral:** Non-hospitalized: Initial 4-8mg 3 times/day; reduce dose as soon as possible to minimum effective dosage (maximum 24mg/day) Hospitalized: 8-16mg 2-4 times/day (maximum 64mg/day)
Prochlorperazine[22] (Compro)	Schizophrenia, psychotic disorders	Injection, solution: 5mg/mL (2mL, 10mL) Suppository, rectal: 25mg Tablet: 5mg, 10mg	PO IM IV	**Oral:** 5-10mg 3-4 times/day, titrate slowly every 2-3 days; doses up to 150mg/day may be required. **IM (as edisylate):** Initial 10-20mg, may repeat every 2-4 hours to gain control; convert to oral as soon as possible.

Thioridazine[23] (Mellaril)	Schizophrenia	Oral: 10mg, 25mg, 50mg, 100mg	PO	**Oral:** 150-800mg/day given in 2-4 divided doses.
Thiothixene[24] (Navane)	Schizophrenia	Capsule: 1mg, 2mg, 5mg, 10mg	PO	**Oral:** Mild-moderate psychosis: 6-60mg/day in 2-3 divided doses Rapid tranquilization: 5-30mg
Trifluoperazine[25] (Stelazine)	Schizophrenia	Tablet: 1mg, 2mg, 5mg, 10mg	PO	**Oral:** Outpatients: 1-2mg twice daily Hospitalized or well supervised: 4-40mg/day in 2 divided doses
Aripiprazole[26] (Abilify)	Schizophrenia, Bipolar I	Injection: 9.75mg/1.3mL vial Solution, oral: 1mg/mL Tablets, orally disintegrating: 10mg, 15mg Tablets: 2mg, 5mg, 10mg, 15mg, 20mg, 30mg	PO IM	Schizophrenia: 10-15mg/day, max 30mg/day Bipolar mania, monotherapy: 15mg/day, max 30mg/day Bipolar mania, adjunct to lithium or valproate, 10-15mg/day, max 30mg/day
Asenapine[27] (Saphris)	Schizophrenia, Bipolar I	Tablets, sublingual: 5mg, 10mg Tablets, sublingual, black cherry flavor: 5mg, 10mg	SL	Schizophrenia, acute: 5mg twice daily, max 10mg twice daily Schizophrenia, maintenance: 5-10mg twice daily, max 10mg twice daily Bipolar, monotherapy: 5-10mg twice daily, max 10mg twice daily Bipolar, adjunct to lithium or valproate: 5-10mg twice daily, max 10mg twice daily
Clozapine[28] (Clozaril)	Schizophrenia	Tablets: 25mg, 100mg	PO	Initial: 12.5mg once or twice daily, increase the total daily dosage in increments of 25-50mg per day, if well tolerated. Target dose: 300-450mg per day, in divided doses. Max daily dose: 900mg
Iloperidone[29] (Fanapt)	Schizophrenia	Tablets: 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg	PO	Initial: 1mg twice daily, then increase by 2mg increments. Target dose: 12-24mg/day.
Lurasidone[30] (Latuda)	Schizophrenia Bipolar I	Tablets: 20mg, 40mg, 60mg, 80mg, 120mg	PO	Schizophrenia: 40-60mg/day Bipolar: 20-120mg/day
Olanzapine[31] (Zyprexa)	Schizophrenia Bipolar I	Zyprexa powder for reconstitution: 10mg Zyprexa Relprevv powder for suspension, extended release: 210mg, 300mg, 405mg Tablet: 2.5mg, 5mg, 7.5mg,	PO IM	Schizophrenia: **Oral:** 5-20mg (doses of 30-50mg/day have been used but not found to improve efficacy) **ER IM injection:** Patient established on oral 10mg/day: initial 210mg every 2 weeks for 4 doses or 405mg every 4 weeks for 2 doses; maintenance 150mg every 2 weeks or 3000mg every 4 weeks. Patients established on oral 15mg/day: initial 300mg every 2 weeks for 4 doses; maintenance 210mg every 2 weeks or 405mg every 4 weeks. Patient

		10mg, 15mg, 20mg Orally disintegrating tablet: 5mg, 10mg, 15mg, 20mg		established on 20mg/day: 300mg every 2 weeks. Bipolar 1: **Oral:** 10-20mg/day. Agitation associated with bipolar disorder or schizophrenia: **Short-acting IM:** 10mg, with maximum total daily dose 30mg
Paliperidone[32] (Invega)	Schizophrenia	Injection, suspension, extended release, as palmitate: 39mg/0.25mL; 78mg/0.5mL; 117mg/0.75mL; 156mg/1mL; 234mg/1.5mL XR tablet: 1.5mg, 3mg, 6mg, 9mg	PO IM	Oral: 3-12mg/day IM: 39-234mg monthly maintenance dose
Quetiapine[33] (Seroquel)	Schizophrenia Bipolar I	Tablet: 25mg, 50mg, 100mg, 200mg, 300mg, 400mg Tablet extended release: 50mg, 150mg, 200mg, 300mg, 400mg	PO	Depression: **Immediate release tablet:** 50-600mg/day **Extended release tablet:** 50-300mg/day Mania: **Immediate release tablet:** 50-800mg/day **Extended release tablet:** 300-800mg/day Schizophrenia: **Immediate release tablet:** 25-800mg/day **Extended release tablet:** 300-800mg/day
Risperidone[34] (Risperdal)	Schizophrenia Biopolar I	Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg Tablet, orally disintegrating: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg Injection, extended release: 12.5mg, 25mg, 37.5mg, 50mg Solution, oral: 1mg/mL (30 mL)	PO IM	Bipolar mania: **oral:** 1-6mg/day Bipolar I: **IM:** 12.5-50mg every 2 weeks Schizophrenia: **Oral:** 2-16mg/day; IM 12.5-50mg every 2 weeks
Ziprasidone[35] (Geodon)	Schizophrenia Bipolar disorder	Capsule: 20mg, 40mg, 60mg, 80mg Solution reconstituted, IM: 20mg	PO IM	Bipolar: **Oral:** 40-80mg/day Schizophrenia: **Oral:** 20-100mg twice daily Acute agitation (schizophrenia) I**M:** 10mg every 2 hours or 20mg every 4 hours (max 40mg). Switch to

				oral as soon as possible.

DOSE ADJUSTMENTS

MEDICATIONS	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Chlorpromazine[17] (Thorazine)	No adjustments provided	Avoid use in severe hepatic dysfunction	Oral: 0.5-1 mg/kg/dose every 4-6 hours; older children may require 200mg/day or higher IM, IV: 0.5-1 mg/kg/dose every 6-8 hours; maximum dose for <5 years (<22.7 kg); 40mg/day; maximum for 5-12 years (22.7-45.5 kg): 75 mg/day	Initial 10-25mg 1 or 2 times/day, increase at 4-7 day intervals by 10-25mg/day.	Not dialyzable
Fluphenazine[18] (Prolixin)	Use with caution	Use with caution	None	Oral: initial 1-2.5mg daily, titrated gradually	Long acting IM dose effects may last up to 6 weeks ** Not dialyzable
Haloperidol[19] (Haldol)	No adjustments provided	No adjustments provided	Age 3-12 (15-40 kg): Initial: 0.5mg/day given in 2-3 divided doses; increase by 0.5mg every 5-7 days; maximum 0.15 mg/kg/day	No psychiatric dosing adjustments mentioned	No supplemental dose required for hemodialysis or peritoneal dialysis
Loxapine[20] (Loxitane)	No adjustments provided	No adjustments provided	None	Reduced dosing may be indicated due to risks of adverse events associated with high-dose therapy.	IM formulation not available in the United States
Perphenazine[21] (Trilafon)	No adjustments provided	No adjustments provided	None	No dosing adjustments provided, but initiate at lower end of dosing range.	Zero to minimal removal in dialysis
Prochlorperazine[22]	No adjustments	No adjustments provided	Oral, rectal: 2.5mg 2-3	Initiate at low dose.	Hepatic drug metabolism, so

(Compro)	provided		times/day; do not give more than 10mg the first day; increase dosage as needed for maximum daily dose of 20mg for 2-5 years and 25mg for 6-12 years. IM: 0.13 mg/kg/dose; convert to oral as soon as possible		systemic exposure may be increased in hepatic dysfunction.
Thioridazine[23] (Mellaril)	No adjustments provided	No adjustments provided	Schizophrenia: Age 2-12 years: Range 0.5-3 mg/kg/day in 2-3 divided doses Age >12 years: Use adult dosing	Maximum daily dose (800mg), gradual increases recommended	Not dialyzable
Thiothixene[24] (Navane)	No adjustments provided	None adjustments provided	< 12 years: Oral: 0.25mg/kg/day in divided doses >12 years: Adult dosing	1-30mg in divided doses	Not dialyzable
Trifluoperazine[25] (Stelazine)	No adjustments provided	No adjustments provided	6-12 years: Hospitalized or well supervised: 1mg-15mg/day	Use low end of dosing scale	Not dialyzable
Aripiprazole[26] (Abilify)	No adjustments recommended	No adjustment recommended	Schizophrenia, adolescents: 2-10mg/day, max 30mg/day Bipolar mania, pediatrics: 2-10mg/day, max 30mg/day	No adjustment recommended	Oral: administered once daily without regard to meals IM injection: Wait at least 2 hours between doses. Max daily dose=30mg.
Asenapine[27] (Saphris)	No adjustment recommended	Not recommended in severe hepatic impairment	None	None	Tablets should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Clozapine[28] (Clozaril)	May be necessary	May be necessary	None	None	None

Iloperidone[29] (Fanapt)	No adjustment recommended	Not recommended in patients with hepatic impairment	None	None	Administer without regard to meals
Lurasidone[30] (Latuda)	Initial: 20mg/day, max 80mg/day	Initial: 20mg/day Moderate impairment: max 80mg/day Severe impairment: Max 40mg/day	None	None	Take with food (at least 350 calories)
Olanzapine[31] (Zyprexa)	No adjustment required	Dosage adjustment may be necessary; no specific recommendations.	Adolescents ≥ 13 years: oral 2.5-20mg/day.	Consider lower starting doses.	Not removed by dialysis
Paliperidone[32] (Invega)	CrCl 50-70 mL/min: Oral: Initial dose 3mg/day and maximum 6mg/day IM:156 mg day one, followed by 117mg 1 week later, followed by 78mg/month CrCl 10-49 mL/min: initial dose 1.5mg/day and maximum of 3mg daily CrCl <10 mL/min: Use not recommended For IM CrCl<50: use not recommended	No adjustment necessary for mild to moderate (Child Pugh class A or B) impairment. Not studied in severe impairment.	Adolescents 12-17 years: Oral: 3mg/day	No adjustments given, however renal function and orthostatic blood pressure should be monitored	No efficacy benefit of higher doses in children
Quetiapine[33] (Seroquel)	No dosage adjustment required	30% lower clearance in hepatic impairment. Dosage adjustment may be required.	Bipolar disorder of children ≥10 years old 25-600mg/day Schizophrenia adolescents ≥13 ears: 25-800 mg/day	40% lower mean oral clearance in adults >65 years older, therefore dosage adjustment may be needed.	None
Risperidone[34] (Risperdal)	CrCl <30 mL/minute: starting dose of	Child-Pugh class C: Starting dose of 0.5mg	Bipolar mania: Age 10-17; oral: initial 0.5mg	Oral: initial 0.5mg twice daily, titrate slowly	None

	0.5mg twice dail; titration should progress slowly. IM: initiate with oral dosing; if tolerated begin 25mg IM every 2 weeks.	twice daily, titration should progress slowly. IM: initiate with oral dosing of 0.5mg twice daily for 1 week then 2mg daily for 1 week.	daily Schizophrenia: adolescents 13-17 years: oral: initial 0.5mg daily	IM: 25mg every 2 weeks, consider 12.5mg	
Ziprasidone[35] (Geodon)	No dosage adjustment needed	No dosage adjustment recommended; however drug undergoes hepatic metabolism	Not studied	No dosage adjustment recommended	Cyclodextrin, an excipient of the IM formulation is cleared renally; use with caution.

DRUG SAFETY

Safety information, which includes Black Box Warnings, contraindications, and warnings are listed in Table 4. Drugs are categorized in the following manner:

- FGAs: chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, prochlorperazine, thioridazine, thiothixene, trifluoperazine
- SGAs: aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

Due to the unique safety profile of clozapine, safety information will be reported separately from the other SGAs, in Table 3:

Table 3. Safety Information for Clozapine[28]

Black box warnings ○ Agranulocytosis ○ Orthostatic hypotension ○ Bradycardia and syncope ○ Seizure ○ Myocarditis and cardiomyopathy ○ Increased mortality in elderly patients with dementia-related psychosis Contraindications ○ Hypersensitivity to clozapine or any of its components ○ History of clozapine-induced agranulocytosis or severe granulocytopenia	Warnings ○ Neuroleptic malignant syndrome ○ Metabolic effects – hyperglycemia, dyslipidemia, weight gain ○ QT prolongation ○ Eosinophilia ○ Fever ○ Pulmonary embolism ○ Anticholinergic toxicity REMS programs ○ Registration required

Author: Brandy Fouts, Pharm.D. Date: September 2013

Table 4. Safety Information for FGAs and SGAs[17-35]

All: all drugs listed in the FGA/SGA classification are associated with this safety concern
Most: all but one drug in the FGA/SGA classification are associated with this safety concern
Some: more than one drug in the FGA/SGA classification are associated with this safety concern
One: only drug in the FGA/SGA classification are associated with this safety concern
None: none of the drugs listed in the FGA/SGA classification are associated with this safety concern.

	FGAs	SGAs	Related drug(s)
Black Box Warnings			
↑ QTc interval	One	None	thioridazine
↑ mortality in elderly patients with dementia-related psychoses	All	All	
Suicidal thoughts and behaviors	None	Some	aripiprazole, lurasidone, and quetiapine
Contraindications			
Blood dyscrasias/bone marrow suppression	Some	None	fluphenazine, perphenazine, thiothixene, trifluoperazine
Circulatory Collapse	One	None	thiothixene
Coma/CMS depression	All	None	
Combination with CYP2D6 inhibitors or drugs that prolong the QTc interval	One	None	thioridazine
Hepatic disease	Some	None	fluphenazine, perphenazine, trifluoperazine
Hypersensitivity to ingredient(s)	All	Most	Not included: olanzapine
Hypertensive or hypotensive heart disease	One	None	thioridazine
Parkinson's disease	One	None	haloperidol
Patients on large doses of hypnotics	One	None	fluphenazine
Pediatric surgery/children <2 years or <9kg	One	None	prochlorperazine
Subcortical brain damage	Some	None	fluphenazine, perphenazine
Warnings			
Altered cardiac conduction/QT prolongation	All	Some	asenapine, iloperidone, paliperidone,

			quetiapine, ziprasidone
Anticholinergic effects	Most	None	thioridazine
Antiemetic effects	None	One	risperidone
Cerebrovascular events	None	Most	Not included: ziprasidone
Cognitive impairment	None	Most	Not included: lurasidone
Discontinuation syndrome	None	One	quetiapine
Dysphasia	None	One	quetiapine
Esophageal dysmotility/aspiration	All	One	ziprasidone
Gastrointestinal narrowing	None	One	paliperidone
Hepatic effects	One	None	Fluphenazine
Hyperprolactinemia	All	Some	paliperidone, quetiapine, risperidone, ziprasidone
Hypersensitivity	None	One	asenapine
Hypertension	None	One	quetiapine
Hypotension	Some	Some	chlorpromazine, fluphenazine, prochlorperazine, quetiapine
Hypotension, orthostatic	Most	All	Not included: prochlorperazine
Leukopenia	Most	All	Not included: prochlorperazine
Metabolic effects – hyperglycemia/diabetes mellitus	None	All	
Metabolic effects – weight gain	None	All	
Metabolic effects - dyslipidemia	None	Some	Asenapine, risperidone, ziprasidone (CHECK!!) do not have this warning
Neuroleptic malignant syndrome	All	All	
Ocular effects	Most	Some	Not included: thioridazine Included: quetiapine
Parkinson's disease (increased sensitivity)	None	One	risperidone

Pregnancy, use in	One	None	trifluoperazine
Priapism	None	Some	iloperidone, ziprasidone
Rash	None	One	ziprasidone
Seizures/Convulsions	None	Most	Not included: lurasidone
Suicide	None	Most	Not included: lurasidone
Suicidality and antidepressants	None	One	aripiprazole
Tardive dyskinesia	All	All	
Temperature regulation	Most	Some	Not included: trifluoperazine Included: quetiapine, risperidone

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Abbreviated Class Update: COPD

Month/Year of Review: November 2013 **End date of literature search: August 2013**
New Drug: fluticasone furoate/vilanterol trifenatate inhaled **Brand Name (Manufacturer): Breo® Ellipta® (GSK)**

Current Status of PDL Class:

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

Current PA Criteria: Prior Authorization (PA) criteria is in place for combination long-acting beta(2)-agonists (LABAs) and inhaled corticosteroid (ICS) inhalers (Appendix 2) to ensure that they are being prescribed for appropriate diagnoses and therapy. requires a PA to ensure appropriate therapy for patients with severe Chronic Obstructive Pulmonary Disease (COPD) with a history of chronic exacerbations or prior exacerbations while being treated with a long-acting bronchodilator.

Research Questions:

- Is there new comparative evidence of a meaningful difference between LABAs, long-acting antimuscarinic agents (LAMAs), and ICSs or combinations thereof in long term clinical outcomes or safety in the treatment of COPD that could justify changes in current PDL management?
- Is there any evidence that fluticasone/vilanterol is more effective or safer than other LABA/ICS combination products in adults with COPD?
- Are there subgroups of patients in which fluticasone/vilanterol is more effective or safer than other available treatments for the treatment of COPD in adults?

Conclusions:

- Published trials use the surrogate marker of change in FEV1 to evaluate the efficacy of fluticasone/vilanterol, while mortality remains most desired clinical outcome. There remains insufficient evidence to determine its effects on mortality and other patient-related outcomes.
- There is moderate quality evidence that once daily fluticasone/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the weighted mean FEV1 (0-4 h post-dose) after 24 weeks of treatment compared to placebo (173 ml, $p<0.001$). Trials have been short-term, and the long-term safety and efficacy of fluticasone/vilanterol is unknown.

- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pneumonia, decrease in bone mineral density, nasopharyngitis, upper respiratory tract infection, oral candidiasis and headache (all seen in ≥5% of patients).
- There is insufficient evidence for differences in subpopulations in which fluticasone/vilanterol is more effective or safer.
- There is moderate quality evidence that fluticasone/vilanterol is non-inferior to fluticasone/salmeterol 250/50 ug after 12 weeks of therapy in change in FEV1 after 12 weeks.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, and limited long term effectiveness or safety evidence of aclidinium bromide compared to tiotropium.
- There is evidence of no difference between tiotropium and LABAs in mortality, quality of life, and overall hospitalizations and insufficient evidence to compare the combination of tiotropium plus LABA with tiotropium alone.
- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and long acting agents. Choice of agent should be based on availability, cost of medication and the patient's response.

Recommendations:

- Due to no evidence demonstrating clinical superiority of fluticasone/vilanterol over current agents, recommend comparing costs in executive session.
- Recommend adding LABA/ICS prior authorization criteria to fluticasone/vilaterol and also limit to use in patients who have COPD.
- Recommend comparing costs of agents for any further additions or eliminations to preferred products.

Previous Conclusions and Recommendations:

- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and inhaled anticholinergics.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, recommend making it non-preferred.
- There is moderate quality evidence that ipratropium bromide/albuterol Respimat inhaler is non-inferior to ipratropium bromide/albuterol MDI on lung function in the treatment of moderate to severe COPD.
- Due to limited long term effectiveness or safety evidence compared to multiple alternatives, recommend making indacaterol a nonpreferred LABA.
- Recommend maintaining roflumilast as a non-preferred agent and include clinical PA criteria necessary for approval to ensure it is only used in the appropriate patient population:
    - Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation
    - Patient has documented failure with an ICS or ICS combination product or tiotropium
    - Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

Background:

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.[1] COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[2] The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema); the degree to which each type of structural changes contributes to disease varies in each individual. Chronic inflammation causes structural changes and narrowing of the small airways.[1] COPD is the result of cumulative exposures over decades. The most common risk factor for COPD is tobacco smoking. Other risk factors include indoor air pollution, occupational dusts and chemicals, outdoor air pollution, and factors that affect lung growth during gestation and childhood. COPD results from a gene-environment interaction. The

genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin, a circulating inhibitor of serine proteases. COPD has a higher prevalence among men and prevalence increases with age.[2]

COPD is defined as a FEV1/FVC< 0.70 based on a post-bronchodilator FEV1. Patients are stratified into groups (A-D) based on their symptoms and future risk of exacerbations.[2] Many trials for COPD use a surrogate endpoint of change in FEV1 because it is highly reproducible in a majority of patients. However, FEV1 measurements do not always correlate with clinically relevant outcomes such as dyspnea, health status, exercise capacity, quality of life or exacerbations and hospitalization, and changes in lung volume can occur without concomitant changes in FEV1.[3] A change of 5-10% from baseline values is considered to be clinically important when taking into consideration the values that would be considered clinically meaningful by regulators. The American Thoracic Society/European Respiratory Society (ATS/ERS) recommends the change in FEV1 should be ≥20% in short-term trials and ≥15% in long-term trials (≥1 year) to be confident that a clinically meaningful change has occurred. ATS/ERS suggests a minimally important difference of 100-140 ml is an appropriate value, although this value remains poorly defined in COPD patients.[4]

Both pharmacological and non-pharmacological treatment options exist for COPD. Smoking cessation is one of the most effective interventions. Other non-pharmacological options are modification of occupational exposure, reducing or avoiding indoor air pollution, and participating in physical exercise. There are several drug classes available for the relief of airflow obstruction in patients with COPD and to reduce the frequency and severity of COPD exacerbations. These include short- and long-acting beta-2 adrenergic agonists, short- and long-acting anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents (both short-acting and long-acting), combination of LABAs and ICS, as well as methylxanthines and phosphodiesterase-4 (PDE4) inhibitors. There are a small number of drug classes available for reducing COPD exacerbations. These include long-acting anticholinergic agents, combination products containing LABA and ICS, and PDE inhibitors. With the exception of methylxanthines and PDE4 inhibitors, all products are inhaled. Adjunctive therapies include systemic steroids, vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic agents, antitussives and vasodilators. Optimal therapy must factor in the severity of disease, comorbidities, frequency and severity of exacerbations, cost, and general health status.[2,5]

Combination therapy with ICS and long acting agents appears to reduce the risk of exacerbation and improve lung function and health status in patients with moderate to severe COPD. Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, patients who are in Group A (and low risk of exacerbation) should be managed by short or long acting agents, patients in Group B should be on a long acting agent [LABA or long-acting anticholinergic (LAMA)], and patients in Group C and D should be on an ICS and a long acting agent. Drug therapy can be escalated based on patient response and deterioration in lung capacity.[2] The NICE guidelines recommend adding therapy based on an algorithm of breathless ness and FEV1. If patients have intermittent breathlessness, they should use a short-acting agent. Patients with exacerbations or persistent breathlessness should be on a long-acting agent. These guidelines recommend adding an ICS to a long acting agent when a patient's FEV1 is less than 50% predicted or in patients with an FEV1 greater than 50% predicted who remain breathless or have exacerbations despite maintenance therapy with a LABA.[6]

Fluticasone/vilanterol is a new combination inhalation product comprised of a LABA and an ICS and is delivered with the dry powder inhaler Ellipta. Neither component is currently marketed as a single-ingredient inhalation product. Fluticasone furoate is marketed as an intranasal formulation for the treatment of allergic rhinitis. Vilanterol is a new molecular entity and not marketed for any indication. This is the first LABA/ICS product that is approved for once daily dosing. Only one strength is approved (fluticasone/vilanterol 100/25 ug) for the treatment of COPD. It is not approved for use in patients with asthma and carries a safety warning in patients with asthma, as LABAs increase the risk of asthma-related death.[6] Two other combination LABA/ICS products are on the market, fluticasone/salmeterol (Advair®) and budesonide/formoterol (Symbicort®).

Author: Amanda Meeker, Pharm.D.

Methods:
A Medline literature search ending July 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing ipratropium, tiotropium, beclomethasone, ciclesonide, fluticasone, salmeterol, formoterol,budesonide, mometasone, aformoterol, roflumilast, indacaterol, and aclidinium . 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. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.[7],[8] 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 (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, seven systematic reviews, one guideline update, three head to head RCTs, and one new drug were identified.

Systematic reviews:
A recently published high quality systematic review published by the Cochrane Collaboration by Cheyne et al[9] compared the effect of tiotropium to ipratropium in patients with COPD. Two good quality studies with 1,073 participants were included. Both studies used a similar design and inclusion criteria and were of at least 12 weeks duration. One study used tiotropium via the HandiHaler for 12 months and the other studied the Respimat device for 12 weeks. For primary outcomes, this review found that FEV1 increased significantly with tiotropium compared to ipratropium at 3 months (mean difference 109 mL; 95% Confidence Interval (CI) 81 to 137, moderate quality evidence). Fewer people experienced non-fatal serious adverse events on tiotropium compared to ipratropium (odds ratio (OR) 0.5; 95% CI 0.34 to 0.73, high quality evidence). This represents an absolute risk reduction from 176 50 97 per 1000 people over 3 to 12 months. The tiotropium group was also less likely to experience a COPD-related serious adverse event when compared to ipratropium (OR 0.59; 95% CI 0.41 to 0.85, moderate quality evidence). This review shows that tiotropium treatment, when compared with ipratropium, was associated with improved lung function, fewer hospital admissions, fewer exacerbations of COPD and improved quality of life.

A new high quality Cochrane Collaboration systematic review by Chong et al[10] evaluated the use of tiotropium versus LABAs. This review included seven randomized trials with 12,223 participants. All studies were of good methodological quality. However, there was a high amount of heterogeneity among the trials. The primary objective was to compare the relative clinical effects of tiotropium alone versus a LABA alone in quality of life, exacerbations, and lung function in people with chronic stable COPD. Results from six studies showed tiotropium reduced the number of participants experiencing one or more exacerbations compared to the LABA (OR 0.86, 95% CI 0.79 to 0.93). There was no difference seen among the different LABAs. Tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalization compared to LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but there was no difference in overall hospitalizations (OR 0.93; 95% CI 0.57 to 1.54) or mortality (OR 0.82; 95% CI 0.60 to 1.13). Due to the high level of heterogeneity in the quality of life data, the authors did not feel it was appropriate to pool the data. Symptom improvement and changes in lung function were similar between the two groups. Overall, there was insignificant evidence to conclude whether tiotropium or LABAs result in improved quality of life. However, it appears tiotropium may be superior in preventing exacerbations than LABAs (NNT 29; 95% CI 19 to 59). Tiotropium and LABAs appear to be similar in improving lung function, symptom relief, and mortality.

Cope at al[11] evaluated the use of indacaterol 75 µg versus fixed-dose combinations of an ICS and LABA for the treatment of COPD. Fifteen randomized, placebo-controlled trials including COPD patients were evaluated. In the indacaterol studies, patients were allowed to continue receiving inhaled corticosteroids, which was not the case in the ICS/LABA studies. Only a subgroup of patients in the indacaterol studies who did not receive concurrent ICS was included in this analysis,

and the number of those in the subgroup was not reported. All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Outcomes of interest were trough FEV_1 and transitional dyspnea index at 12 weeks. Indacaterol resulted in greater improvement in FEV_1 at 12 weeks compared with budesonide/formoterol 160/9 ug (change from baseline 0.09L; 95% CI 0.04 to 0.13), budesonide/formoterol 320/9 ug (change from baseline 0.07L; 95% CI 0.03 to 0.11), fluticasone/salmeterol 250/50 ug (change from baseline 0.00L; 95% CI -0.07 to 0.07), and fluticasone/salmeterol 500/50 ug (change from baseline 0.01L; 95% CI -0.04 to 0.05). Based on the results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious to budesonide/formoterol and comparable to fluticasone/salmeterol with respect to lung function, but the results of effects on dypsnea are inconclusive with available data.

A review by Dong et al[12] evaluated the overall safety and cardiovascular death for inhaled medications in patients with COPD. Forty-two trials with 52,516 subjects were included. The Cochrane risk of bias tool was used to assess quality of individual trials and two investigators (one pharmacist and one physician) independently evaluated each trial. A mixed-treatment comparison meta-analysis with a fixed effect model indicated tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at higher daily doses. This outcome may be due to severe disease or comorbidities. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium Handihaler or LABA. However, cardiovascular death was a rare, non-predefined outcome in many trials and did not have a consistent definition in clinical trials.

A recent high quality systematic review from the Cochrane Collaboration[13] evaluated the use of LABA and tiotropium combination therapy versus either tiotropium or a LABA therapy alone. A total of five trials were included in the analysis; four studies comparing tiotropium plus LABA to tiotropium alone and one trial comparing to LABA alone. Two studies (moderate quality evidence) used the LABA indacaterol, two used formoterol and one used salmeterol. Results demonstrated moderate quality evidence of improvement in quality of life (as measured by the St. George's Respiratory Questionnaire) with LABA plus tiotropium vs. tiotropium alone (MD -1.61; 95% CI -2.93 to -0.29). Although this was statistically significant, the mean difference is smaller than what is considered a clinically important difference. There was low quality evidence of no significant difference in hospital admission (OR 1.01; 95% CI 0.63-1.61) or mortality (OR 1.56; 95% CI 0.56-4.33). The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. There was no difference in other outcomes of interest, such as mortality and hospital admissions. There is insufficient data to compare tiotropium plus LABA to LABA alone.

Another high quality Cochrane Collaboration review[14] evaluated the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone. Fourteen studies were included, randomizing 11,794 people with COPD. Ten studies assessed fluticasone plus salmeterol and four assessed budesonide plus formoterol. All studies were well designed with a low risk for bias for randomization and blinding, but had high rates of attrition. There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomized 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. When analyzed as the number of people experiencing one or more exacerbations over the course of the study, fluticasone/salmeterol lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. There was no significant difference in the rate of

hospitalizations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, moderate quality evidence). Pneumonia occurred more commonly in people randomized to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Data were inconclusive as to the superiority of ICS/LABA over LABA alone in preventing COPD exacerbations.

Rodrigo et al[15] explored the efficacy and safety of indacaterol in comparison with tiotropium or twice-daily dosed LABAs for the treatment of moderate to severe COPD. Five trials were included in this systematic review. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea (43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat (NNT) = 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; NNT = 10). Trough FEV1 was statistically significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, p = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of achieving an MCID in TDI, p = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, p = .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators. There was moderate quality evidence showing indacaterol may be a useful alternative to tiotropium or twice-daily dosed LABAs.

Rodrigo et al**[16]** evaluated the use of tiotropium plus a LABA ("dual" therapy), LABA/ICS ("combined" therapy), tiotropium plus a LABA/ICS ("triple" therapy), and tiotropium monotherapy in the maintenance treatment of moderate to severe COPD. This was a medium quality systematic review. Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in FEV1, health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV1, HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to harm = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV1, improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21). While treatments with tiotropium plus a LABA and tiotropium plus a LABA/ICS look promising, there is no data to support a recommendation of either therapy over the other. More studies are needed to examine long-term safety and efficacy of these combinations.

New FDA Safety Alerts:
None.

New Guidelines:
An update to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was released in 2013.[2] Recommendations were based on evidence and expert opinion. Levels of evidence were given based on the source of evidence (Evidence A being RCT, B from limited RCTs, C from observational studies, and D from consensus judgement). This update redefines COPD as a mixture of airflow obstruction, alveolar destruction and chronic inflammation. Previous GOLD guidelines classified COPD severity by post-bronchodilator FEV1 alone. Grading was updated to include grades A-D based upon a combination of clinical symptoms, most notably dypsnea, FEV1 and number of yearly exacerbations. Drug therapy options for COPD were addressed. Indacaterol was included as a therapeutic option superior to salmeterol and formeterol, with similar efficacy to tiotropium (level A evidence). Roflumilast was included in the 2011

guidelines, but was again supported with level A evidence for its proven efficacy in reducing exacerbations in patients with severe COPD. Although aclidinium was approved at the time of publication, tiotropium is the only recommended long-acting anticholinergic agent; this may be due to the larger body of evidence on tiotropium. Main recommendations are as followed:

- For group A patients (few symptoms, low risk of exacerbations), a short-acting bronchodilator is recommended as first choice. Alternatively, a long-acting bronchodilator may be used (weak evidence for this recommendation).
- For Group B patients (many symptoms, low risk of exacerbations), long-acting bronchodilators are recommended over short-acting bronchodilators. For patients with severe breathlessness, a combination of long –acting bronchodilators can be used (weak evidence for this recommendation).
- For Group C patients (few symptoms, high risk of exacerbations), the first choice is a ICS/LABA combination or a LAMA. Alternatively, a combination of two long-acting bronchodilators or the combination of ICS/LAMA can be used (based on expert opinion).
- For Group D patients (many symptoms, high risk of exacerbations), the first choice of therapy is an ICS plus a LABA or LAMA, with some evidence of triple therapy with one medication from all three classes (Evidence B).
- Within a class, guidelines do not prefer one agent over another and rather recommend the choice be based on availability, cost of medication, and the patient's response.
- Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators (Evidence A).

Randomized Controlled Trials

A total of six RCT's were identified in the literature search. Of these, there are three potentially relevant head to head clinical trials. Abstracts of these trials are located in Appendix 4.

Study	Comparison	Population	Primary Outcome	Results
Fuhr et al[17]	Aclidinium 400 ug BID with placebo and tiotropium (1:1:1)	Moderate to severe COPD N=30	Mean change from baseline in FEV1 AUC on day 15	Mean change from baseline in FEV1 at day 15 was significantly greater for aclidinium and tiotropium over placebo (p<0.0001)
Sharafkheneh et al[18]	BID budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol pMDI 160/9 ug, or formoterol dry powder inhaler 9 ug (1:1:1)	COPD patients aged >= 40 years with an exacerbation history discontinued medications except ICSs N=1219	Exacerbation rates (number per patient-treatment year)	Budesonide/formoterol 320/9 ug and 160/9 ug reduced exacerbation rates by 34.6% and 25.9%, respectively, versus formoterol (p<= 0.002
Zhong et al[19]	Budesonide/formoterol 320/9 ug BID or budesonide 400 ug BID	Moderate to very severe COPD in Chinese population	FEV1 change from baseline after 24 weeks	Budesonide/formoterol FEV1 improved by 0.18L vs 0.03L in budesonide

		N=308		alone group (p<0.001)

New Drug:

FDA Approved Indication:

Fluticasone/vilanterol is indicated for the long-term, once daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.[20]

Clinical Efficacy:

In trials with an increase in treatment comparisons, even when there are no differences between treatments, there is an increase in expected significance due to chance. Evaluated studies of fluticasone/vilanterol used a pre-specified testing hierarchy to control for this. Level 1 of the hierarchy comprised comparisons of the primary endpoint(s) at the highest dose tested in the study. Significance with a p-value <0.05 was required for these comparisons to allow statistical significance to be inferred for differences with p-value <0.05 for the primary endpoint(s) of lower fluticasone/vilanterol strengths. Inferences could only be made for secondary endpoints if primary endpoints were significant as shown with p-value <0.05. In studies where the highest strength of fluticasone/vilanterol was not statistically significant, the magnitude of effect of subsequent doses cannot be inferred even where information is available.[21–23]

Two similarly designed phase 3, double-blind, double-dummy, multicenter trials were completed (study 2206, study 2207)[21,22] in patients with moderate to severe COPD aged 40 or older. No prior history of COPD exacerbations was required for eligibility. Both studies compared the combination of fluticasone furoate (FF) and vilanterol (VI) to each component and placebo. Of the 2,254 subjects in these trials, 70% were male and 84% were Caucasian. They had an average smoking history of 44 pack years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV1 was 48%, the mean postbronchodilator FEV1/FVC ratio was 47%, and the mean percent reversibility was 14%.[20]

Study 2206 was a fair quality study that included 1030 patients. Patients were randomized to FF/VI 100/25 ug, FF/VI 50/25 ug, VI 25 ug, FF 100 ug, or placebo for 24 weeks. For the co-primary endpoint of mean change in weighted mean (0-4 h post-dose) on day 168, FF/VI 100/25ug, and VI 25 ug were statistically better than placebo; treatment differences were clinically significant at 173 ml and 103 ml, respectively (p <0.001 for both). The FF/VI 50/25 ug arm of the trial is unable to be regarded as statically significant due to the hierarchy employed. When compared to FF alone, the combination of FF/VI resulted in statistically significant changes (120 ml; 95% CI 0.07, 0.17, p-value <0.001). When compared to VI alone, no statistical difference was found for either the higher (70ml; 95% CI 0.021, 0.121, p-value >0.082) or lower strength (90 ml; 95% CI 0.039, 0.140, p-value >0.082) of the combination product. Descriptive differences in symptomatic endpoints such as rescue inhaler use showed a benefit for the higher strength of the combination product, but any symptomatic benefit of adding FF to VI will require further assessment. The primary effect of the ICS component of combination therapy is to reduce COPD exacerbations and control symptoms and generally requires a length of study of one year or more. While COPD exacerbation data was provided for this study, it was not powered or designed to examine exacerbations from an efficacy perspective. Due to the statistical hierarchy, no significance could be inferred for the secondary outcomes. However, no clinically meaningful difference was observed for dyspnea between any active therapy and placebo (as measured by the CRQ-SAS dyspnea domain).[21]

Study 2207 was a fair quality study that randomized 1124 patients to FF/VI 200/25 ug, FF/VI 100/25 ug, VI 25 ug, FF 200 ug, FF 100 ug, and placebo for 24 weeks. For the co-primary endpoint of mean change in weighted mean FEV1 (0-4 h post-dose) on day 168, FF/VI 200/25ug vs placebo (209 ml; 95% CI 0.157, 0.261; p-

value <0.001), FF/VI 200/25 ug vs FF 200 ug (168 ml; 95% CI 0.117, 0.219; p-value <0.001), and VI 25 ug vs placebo (185 ml; 95% CI 0.133, 0.237; p-value <0.001) comparisons were all statistically significant. Due to the pre-defined statistical testing hierarchy, no inference can be drawn for comparisons of lower strengths of FF/VI with placebo or its components as there was no significant difference in the change in lung function between VI and the highest strength of FF/VI (24 ml; 95% CI -0.027, 0.075). Although the number of exacerbations in the corticosteroid-containing regimens was fewer, this study was not designed or powered to examine the impact of fluticasone furoate when added to vilanterol on acute exacerbations. There was a lack of a clinically important change in the dyspnea domain of the CRQ-SAS despite notable improvements in lung function and further study should be done in order to understand the relationship between improvement in the surrogate endpoint FEV1 and improvement in COPD disease state.[22]

Three head-to-head phase 3b, double-blind, double-dummy, multicenter trials compared FF/VI 100/25 ug to salmeterol/fluticasone (Advair®) 250/50 ug for 12 weeks in patients 40 years or older with moderate to severe COPD.[24] None of these studies have been published and therefore could not be assessed for quality. The primary outcome in all three trials was the change from baseline in 0-24 hour weighted mean serial FEV1 on day 84. During study 2352, 511 subjects were randomized and included in the ITT population. The LS mean difference between FF/VI and fluticasone/salmeterol was 29 ml (95% CI -22, 80; p-value = 0.267). 519 subjects were randomized in study 3109. The LS mean difference between treatment groups was 80 ml (95% CI 37,124; p-value <0.001). This difference may be statistically significant, but it is not clinically significant according to consensus expert opinion on the minimal important difference.[5] In study 6974, 828 patients were randomized. The LS mean difference between treatment groups was 0.025 ml (95% CI -0.008, 0.59; p-value = 0.137). Therefore, FF/VI 100/25 ug should be considered non-inferior to fluticasone/salmeterol 250/50 ug after 12 weeks of therapy.

Two year-long studies (2871, 2970) evaluated the rate of exacerbations.[23] Eligible patients entered a 4-week open-label salmeterol/fluticasone (Advair®) 250/50 twice daily treatment phase followed by a 52-week double-blind treatment period with three doses of FF/VI or VI. To account for multiplicity across treatment comparison a step-down procedure was used with testing for high dose combination first, followed by low dose combination, and then other variables. In order to make inferences on secondary endpoints at a given strength, statistical significance at the 5% level had to have been demonstrated at the primary efficacy endpoint for that combination strength; this demonstration also needed to occur in order to make inferences of primary endpoints at a lower strength.[24] COPD exacerbations were defined as worsening of two or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any one major symptom together with any one of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least two consecutive days.[25] COPD exacerbations were considered to be of moderate severity if treatment with systemic corticosteroids and/or antibiotics were required and were considered to be severe if hospitalization was required.[24]

In study 2871, FF/VI 200/25 did not show a statistically significant difference from VI 25 ug alone (LS mean annual rate ratio 0.85; 95% CI 0.70, 1.04; p-value 0.109). The pre-specified statistical analysis plan required statistical significance of the higher dose prior to testing the lower dose which this study failed to accomplish, and therefore we cannot determine the statistical significance of the magnitude of effect of the FF/VI 100/25 ug or FF/VI 50/25 ug doses from this study. The rate of serious adverse events was similar across all treatment groups as was the rate of withdrawal due to adverse events.[23]

Study 2970 showed a statistically significant reduction in exacerbation rates of three doses of FF/VI when compared to vilanterol alone. FF/VI 200/25 ug showed the highest reduction in exacerbation rate compared to VI 25 ug, (LS mean annual rate ratio vs VI 25ug: 0.69; 95% CI 0.56, 0.85; p-value <0.001) followed by FF/VI 100/25 ug (LS mean annual rate ratio vs. VI 25 ug: 0.79; 95% CI 0.64, 0.97; p-value 0.024)and FF/VI 50/25 ug (LS mean annual rate ratio vs. VI 25 ug: 0.81; 95% CI 0.66, 0.99; p-value 0.04). Over half of the subjects in each treatment group did not experience on-treatment exacerbations. The number of subjects with one or more exacerbations was lowest for the FF/VI 100/25 ug and 200/25 ug groups (177 [44%] and 160 [39%] respectively) followed by VI 25ug and FF/VI

50/25 ug (197 [48%] and 198 [48%]).[25] The majority of moderate/sever exacerbations were moderate in intensity (90% in VI 25 ug group and 87-90% in the FF/VI groups). Serious adverse events were similar across all treatments as were withdrawals due to adverse events.

Clinical Safety:

Overall, the most common adverse events seen in trials are pneumonia, decrease in bone mineral density, nasopharyngitis, upper respiratory tract infection, oral candidiasis and headache (all ≥5% of patients). The total incidence of adverse events was comparable across treatment group and respiratory events were the most commonly reported. Rates of patients discontinuing due to an adverse event was also comparable across treatment groups.[20] Two safety findings of interest for inhaled doses of ICS are pneumonia and bone fractures, and both have been seen in previous LABA/ICS combination product development programs for COPD.[25]

An increase in pneumonia was seen in trials, as well as an increased incidence of pneumonias resulting in hospitalization. In two 52-week studies in 3,255 subjects with COPD who had a COPD exacerbation in the prior year, there was a higher incidence of pneumonia reported in subjects receiving FF/VI than subjects receiving vilanterol alone. One subject receiving FF/VI 100/25 ug and six subjects receiving FF/VI 200/25 ug had fatal pneumonia (less than 1% for each treatment group). There were no cases of fatal pneumonia in groups receiving VI 25 ug or FF/VI 50/25 ug.[24,25]

In the same two 52-week studies, an increased risk of fractures was seen with FF/VI compared to VI alone. 15 patients in the FF/VI 50/25 ug arm, 19 in the FF/VI 100/25 ug arm, 13 patients in the FF/VI 200/25 ug arm, and 8 in the VI arm developed fractures.[24, 25]

Due to the LABA component of this combination product, the FDA has issued a safety warning for its use in patients with asthma, as LABAs have been shown to increase asthma exacerbation and asthma-related death. Since COPD is a disease that occurs only in adults, FF/VI has not been specifically studied in the pediatric population, and as such no safety data for this population is available.[25]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

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

Primary Study Endpoint:

1) Mean change from baseline in weighted mean (wm) FEV1 (0-4 h post-dose) on day 168
2) LS mean annual rate of moderate to severe exacerbation

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

Study 2206 Kerwin et al[21,25] 24-week, Phase III, DB, PC, RCT, MC	FV100: FF/VI 100/25 mcg FV50: FF/VI 50/25 mcg V: VI 25 mcg F: FF 100 mcg P: Placebo	Demographics: 221 centers in 9 countries US, EU, other (39% US) Average age: 62.6 yrs Inclusion Criteria: Age ≥ 40 yrs, clinical diagnosis of COPD, smoking hx ≥10 pack yrs, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, score of ≥2 on Modified Medical Research Counil Dyspnea Scale (mMRC) Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD requiring steroid or antibiotics within 6 weeks hospitalization due to poorly controlled COPD within 12 weeks, Lower RTI requiring use of antibiotics within 6 weeks need for long-term oxyge therapy or nocturnal oxygen therapy (≥12 hr/day)	ITT: FV100: 206 FV50: 206 V: 205 F: 206 P: 207 Total Attrition FV100: 55 (26.7%). FV50: 60 (29.1%) V: 62 (30.2%) F: 61 (29.6%) P: 69 (33.3%) Loss to f/u: FV100: 3 (1.4%) FV50: 1 (0.5%) V: 2 (1.0%) F: 0 (0.0%) P: 4 (1.9%)	Mean change from baseline wm FEV1 (0-4 h post-dose) on day 168* FV100 diff from P: 0.17L; 95% CI: (0.12, 0.22) p –value: <0.001 FV50 diff from P: 0.19L; 95% CI: (0.14, 0.24) V diff from P: 0.10L; 95% CI: (0.05, 0.15) F diff from P: 0.05L; 95% CI: (0.00, 0.10) *No significance could be inferred for primary endpoints because of the pre specified statistical hierarch	N/A N/A N/A N/A	Total AEs: FV100: 111 (54%) p-value: 0.279 RR: 1.146 (95% CI: 0.942-1.393) FV50: 114 (55%) p-value: 0.168 V: 111 (54%) p-value: 0.239 F: 123 (60%) p-value: 0.023 P: 100 (48%) SAEs: FV100: 11 (5%) p-value: 1.0 RR: 1.005 95% CI: 0.414, 0.523 FV50: 6 (3%) p-value: 0.322 V: 15 (7%) p-value: 0.425 F: 16 (8%) p-value: 0.328 P: 11 (5%) COPD exacerbations FV100: 19 (9.2%) p –value: 0.868 RR: 0.909 95% CI: 0.481, 1.712 FV50: 12 (6%) p –value: 0.146 V: 22 (10.7%) p –value: 0.873 F: 26 (12.6%) p –value: 0.536 P: 21 (10.1%)	FV100 vs P: ARR: 7.0% NNH: 14 NS NS	**Quality Rating:** Fair **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 33.3% P, 30.2% V, 29.6% F, 29.1% FV50, 26.7% FV100. The majority of patients withdrew due to adverse events, lack of efficacy or withdrawn consent. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a two-week run in period, and a the study was conducted in an outpatient setting Outcomes: The accepted surrogate outcome o FEV1 was used for efficacy measure. No clinically important outcomes measured, including mortality, hospitalizations, and quality of life.

Study 2207 Martinez et al[22,25] 24-week, Phase III, DB, PC, RCT, MC	FV200: FF/VI 200/25 mcg FV100: FF/VI 100/25 mcg V: VI 25 mcg F200: FF 200 mcg F100: FF 100 mcg P: Placebo	Demographics: US, EU, Other (25% US) Average age: 61.6 years Inclusion Criteria: Clinica diagnosis of COPD, age ≥ 40 yrs, smoking hx ≥10 pack yrs, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, score of ≥2 on mMRC Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD within 6 weeks, hospitalization due to poorly controlled COPD within 12 weeks, lower RTI requiring use of antibiotics within 6 weeks need for long-term oxyge therapy or nocturnal oxygen therapy (≥12 hr/day)	ITT: FV200: 205 FV100: 204 V: 203 F200: 203 F100: 204 P: 205 Total Attrition FV200: 50 (24.4%). FV100: 64 (31.4%) V: 50 (24.6%) F200: (23.1%) F100: 53 (30.0%) P: 61 (29.7%) Loss to f/u: FV200: 1 (0.5%) FV100: 2 (1.0%) V: 0 (0.0%) F200: 0 (0.0%) F100: 2 (1.0%) P: 3 (1.5%)	Mean change from baseline in weighted mean (wm) FEV1 (0-4 h post-dose) on day 168 FV200 diff from P: 0.21L; 95% CI: (0.16, 0.26) p <0.001 FV100 diff from P: 0.21L; 95% CI: (0.16, 0.27) V diff from P: 0.19L; 95% CI: (0.13, 0.24) p <0.001 F200 d iff from P: 0.04L; 95% CI: (-0.01, 0.09) F100 diff from P: 0.05L; 95% CI: (-0.01, 0.10)	 N/A N/A N/A N/A	Total AEs: FV200: 93 (45%) p-value: 0.843 FV100: 92 (45%) p-value: 0.766 RR: 0.958 95% CI: 0.768, 1.195 V: 85 (42%) p-value: 0.321 F200: 96 (47%) p-value: 1.0 F100: 78 (38%) p-value: 0.089 P: 96 (47%) SAEs: FV200: 15 (7%) p-value: 0.410 FV100: 12 (6%) p-value: 0.669 RR: 1.2 95% CI: 0.0.494, 2.941 V: 16 (8%) p-value: 0.231 F200: 10 (5%) p-value: 1.0 F100:6 (3%) p-value: 0.445 P: 10 (5%) COPD exacerbations FV200: 14 (6.8%) p-value: 0.289 FV100: 13 (6.4%) p-value: 0.209 V: 18 (8.9%) p-value: 0.737 F200: 10 (4.9%) p-value: 0.060 F100: 4 (2.0%) p-value: 0.001 P: 21 (10.2%)	 NS NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 29.7% P, 24.6% V, 30.0% F100, 23.1% F200, 31.4% FV100, 24.4% FV200. High attrition was similar across all groups and included withdrawal due to adverse events, lack of efficacy, protocol stopping criteria, or withdrawn consent. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a two-week run in period, and a the study was conducted in an outpatient setting Outcomes: The accepted surrogate outcome o FEV1 was used for efficacy measure.

Study 2871 Dransfield et al[23,25] 52-week, Phase III, DB, PC, RCT, MC	FV 200: FF/VI 200/25 ug FV100: FF/VI 100/25 ug FV50: FF/VI 50/25 ug V: VI 25 ug	Demographics: US, EU, Canada, S Africa, Australia, Other (33% US Average age: 63.6 years Inclusion Criteria: Clinica diagnosis of COPD, age ≥ 40 yrs, current smoker or hx ≥10 pack yrs of smoking, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, documented hx of at least 1 COPD exacerbation in 12 months before screening Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD within 6 weeks, hospitalization due to poorly controlled COPD within 12 weeks, lower RTI requiring use of antibiotics within 6 weeks need for long-term oxygen therapy or nocturnal oxygen therapy (≥12 hr/day), subjects at risk of noncompliance, women who are pregnant or breast-feeding or at risk o becoming pregnant during trial, historical or current evidence of uncontrolled or clinically significant disease states	ITT: FV200: 402 FV100: 403 FV50: 408 V: 409 Total Attrition FV200: 101 (25%) FV100: 91 (23 FV50:93 (23%) V: 115 (28%) Loss to f/u: FV200: 5 (1%) FV100:6 (1%) FV50: 7 (2%) V: 11 (3%)	LS mean annual rate of moderate to severe exacerbation FV200: 0.90 FV100: 0.70 FV50: 0.92 V: 1.05 Ratio vs. V* FV200: 0.85 (95% CI 0.70, 1.04; p-value 0.109) FV100: 0.66 (95% CI 0.54, 0.81) FV50: 0.87 (95% CI 0.72,1.0) *No significance could be inferred for primary endpoints for FV100 or FV50 because of the pre-specified statistical hierarch		Total AEs: FV200: 288 (72%) FV100: 301 (75%) p-value: 0.052 RR: 1.090 95% CI: 0.996, 1.190 FV50: 304 (75%) V: 281 (69%) SAEs: FV200: 63 (16%) FV100: 56 (14%) p-value: 0.764 RR: 0.947 95% CI: 0.665, 1.348 FV50: 65 (16%) V: 60 (15%) Death: FV200: 13 (3%) FV100:5 (1%) FV50: 7 (2%) V: 4 (1%)	FV100 vs V: ARR: 6.2% NNH: 16 NS	**Quality Rating:** Fair **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 28% P, 23% FV50, 23% FV100, 25% FV200. Attrition was similar across all groups and due to adverse events, withdrawn consent, lack of efficacy, or protocol deviation. Patients in the FV 200 and V groups also had high rates of attrition due to exacerbations. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a four week run in period and the study was conducted in an outpatient setting. Outcomes: Efficacy and safety of patients were evaluated at study visits at weeks 2, 4, 8 12, 20, 28, 36, 44, and 52.

Study 2970 Dransfield et al[23,25] 52-week, Phase III, DB, PC, RCT, MC	FV 200: FF/VI 200/25 ug FV100: FF/VI 100/25 ug FV50: FF/VI 50/25 ug V: VI 25 ug	Demographics: US, EU, Canada, S Africa, Australia, Other (36% US Average age: 63.7 years Inclusion Criteria: Clinica diagnosis of COPD, age ≥ 40 yrs, current smoker or hx ≥10 pack yrs of smoking, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, documented hx of at least 1 COPD exacerbation in 12 months before screening Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD within 6 weeks, hospitalization due to poorly controlled COPD within 12 weeks, lower RTI requiring use of antibiotics within 6 weeks need for long-term oxygen therapy or nocturnal oxygen therapy (≥12 hr/day), subjects at risk of noncompliance, women who are pregnant or breast-feeding or at risk o becoming pregnant during trial, historical or current evidence of uncontrolled or clinically significant disease states	ITT: FV200: 409 FV100: 403 FV50: 412 V: 409 Total Attrition FV200: 103 (25%) FV100: 112 (28%) FV50:109 (26%) V: 125 (31%) Loss to f/u: FV200: 10 (2%) FV100:6 (1%) FV50: 8 (2%) V: 6 (1%)	LS mean annual rate of moderate to severe exacerbation FV200: 0.79 FV100: 0.90 FV50: 0.92 V: 1.14 Ratio vs. V FV200: 0.69 (95% CI 0.56, 0.85; p-value <0.001) FV100: 0.79 (95% CI 0.64, 0.97; p-value 0.024) FV50: 0.81 (95% CI 0.66,0.99; p-value 0.04)		Total AEs: FV200: 334 (82%) FV100: 320 (79%) p-value: 0.014 RR: 1.105 95% CI: 1.018, 1.196 FV50: 316 (77%) V: 294 (72%) SAEs: FV200: 61 (15%) FV100: 67 (17%) p-value: 0.924 RR: 1.030 95% CI: 0.744, 1.426 FV50: 71 (17%) V: 66 (16%) Death: FV200: 0 FV100:3 (<1%) FV50: 7 (2%) V: 4 (<1%)	FV100 vs V: ARR: 7.5% NNH: 13 NS	**Quality Rating:** Fair **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 31% P, 26% FV50, 28% FV100, 25% FV200. Attrition was similar across all groups and due to adverse events, withdrawn consent, lack of efficacy, protocol deviation, or subject reached protocol defined stopping criteria. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a four week run in period and the study was conducted in an outpatient setting. Outcomes: Efficacy and safety of patients were evaluated at study visits at weeks 2, 4, 8 12, 20, 28, 36, 44, and 52.

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Fluticasone furoate /vilanterol is a combination of an ICS/LABA. Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. It has been shown to bind to the human glucofcorticoid receptor, with approximately 29.9 times more binding affinity than that of dexamethasone and 1.7 times that of fluticasone propionate. The precise mechanism through which fluticasone furoate affects COPD symptoms is unknown. Cortidcosteroids have shown a wide range of actions on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Vilanterol is a LABA. The pharmacologic effects of beta$_2$-agonists are at least in part to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells.

PHARMACOKINETICS

Parameter	Result
Bioavailability	15.2% (fluticasone furoate) 27.3% (vilanterol)
Protein Binding	99% (fluticasone furoate) 94% (vilanterol)
Elimination	Via feces 101% and 90% (fluticasone furoate and vilanterol, respectively)
Half-Life	24 hours (fluticasone furoate) 21.3 hours (vilanterol)
Metabolism	Hepatic via CYP3A4 and p-glycoprotein (fluticasone furoate and vilaterol)

DOSE & AVAILABILITY

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
FF 100/ VI 25 ug	Inh	Q Daily	1 puff	None	None. Monitor for corticosteroid-related side effects	Not indicated	No adjustment	

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning: May cause an increase in asthma-related death, which is considered a class effect of LABA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with fluticasone furoate /vilanterol has been conducted.

Contraindications: Patients with severe hypersensitivity to milk proteins or hypersensitivity to fluticasone foroate, vilanterol or any component of the product.

REMS: none

Warnings and Precautions:

- Should not be initiated in patients during rapidly deteriorating exacerbations.
- Should not be used as a rescue inhaler
- Should not be used more often than recommended, as an overdose may result
- Should not use with any other LABA-containing medication
- May cause thrush; patients should rinse mouth after use
- May cause an increase of pneumonias
- May increase risk of serious infections such as chickenpox, measles, tuberculosis
- Caution should be exercised when considering the coadministration of fluticasone furoate /vilanterol with known strong CYP3A4 inhibitors because increased systemic corticosteroid and increased cardiovascular adverse events may occur
- May cause paradoxical bronchospasm
- May produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and cardiac arrhythmias
- Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids
- Glaucoma and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids
- May cause significant hypokalemia in patients

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Fluticasone furoate may be confused with fluticasone furoate nasal (Veramyst®), fluticasone propionate
Ellipta may be confused with Ella®, Ellence®, eletriptan

Adverse Reactions Table

Adverse Reaction	Placebo (n= 412)	Drug (n=410)	
Infections and infestations			
Nasopharyngitis	8 (1.9%)	9 (2.2%)	
Upper respiratory tract infection	3 (0.7%)	7 (1.7%)	
Oropharyngeal candidiasis	2 (0.5%)	5 (1.2%)	
Headache	5 (1.2%)	7 (1.7%)	

Allergies/Interactions: Breo Ellipta contains lactose, so patients with hypersensitivity to milk proteins should not use this product.

Interactions:

- Inhibitors of CYP3A4
- Monoamine Oxidase Inhibitors and Tricyclic Antidepressants
- Beta blockers
- Non-potassium-sparing diuretics

Current PA with Proposed Changes (Appendix 2):

LABA/ICS Inhalers

Goal(s):

- Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication).
- LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).

Initiative:

- LABA/ICS Step Therapy

Length of Authorization:

Up to 12 months

Requires PA:

- All combination inhaled corticosteroid/long-acting beta-agonist inhalers

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Step Therapy Required Prior to Coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at (www.orpdl.org)

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at www.orpdl.org), DO NOT require prior authorization

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to ~~3~~ **2**	**No:** Go to ~~3~~ **4**
2. Is the medication for Breo Ellipta (fluticasone furoate/vilanterol)	**Yes: Pass to RPH; Deny (Medical appropriateness)**	**No:** Go to **3**
~~2~~3. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days?	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	**No**: **PASS TO RPH** **DENY (Medical Appropriateness).**

~~3~~4. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** Approve for 12 months.	**NO: PASS TO RPH** **DENY (Medical Appropriateness).** Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.

Appendix 3:

Combination Short Acting Bronchodilator Inhalers

Goal(s):

- *Promote preferred drugs that are selected based on evidence based reviews.*
- *To ensure appropriate drug use .*

Initiative: Short Acting Bronchodilator Step Therapy

Length of Authorization: 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.orpdl.org/

Step Therapy Required prior to coverage:

Requires PA: non-preferred combination short acting bronchodilators

Approval Criteria		
1. What diagnosis is being treated?	**Record ICD9 code**	
2. Does the patient have COPD (ICD-9 496)?	**Yes**: Go to #3	**No**: Pass to RPh; Deny (Medical Appropriateness).
3. Will the prescriber change to a preferred product?	**Yes:** Inform provider of covered alternatives in class	**NO:** Go to #4
4. Has patient failed an inhaled Short acting beta agonist (albuterol) OR An inhaled short acting anticholinergic agent (ipratropium)?	**Yes:** Approve for one year	**No:** Pass to RPh, Deny (medical appropriateness)

P&T/DUR Action: 1/31/2013 (MH)
Revision(s): 7/1/2013
Initiated: 9/1/2013

Appendix 4:

Roflumilast

Goal(s):

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior exacerbations.

Length of Authorization: 1 year

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

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

Appendix 5: RCT Abstracts

Furh, R., H. Magnussen, et al. (2012). "Efficacy of aclidinimium bromide 400 ug twice daily compared with placebo and tiotropium in patients with moderate to severe COPD." Chest **141**(3): 745-752.

BACKGROUND: The efficacy and safety of aclidinium bromide bid, a novel, long-acting, muscarinic antagonist, was assessed in patients with moderate to severe COPD.

METHODS: In this phase IIa randomized, double-blind, double-dummy, crossover trial, patients with moderate to severe COPD received aclidinium 400 ug bid, tiotropium 8 ug once daily, and placebo for 15 days, with a 9- to 15-day washout between treatment periods. Treatments were administered through the Genuair or HandiHaler dry powder inhalers. The primary end point was mean change from baseline in FEV(1) AUC(0-12 /12h)(area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged [eg, 0-12 h postdose divided by 12h]) on day 15. Secondary end points were changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), peak FEV(1), and COPD symptom scores.

RESULTS: Thirty patients with COPD were randomized, and 27 completed the study. Mean change from baseline in FEV(1) AUC(12-24/12h) at day 15 was significantly greater for aclidinium and tiotropium over placebo (P < .0001). Mean changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), and peak FEV(1) at day 15 were significantly greater for aclidinium and tiotropium over placebo (P < .0001 for all except P <.001 for FEV(1) AUC(12-24/12h) tiotropium vs placebo). Improvements were significantly greater with aclidinium vs tiotropium on day 1 for all of the normalized AUC values of FEV(1) as well as on day 15 for FEV(1) AUC(12-24/12h) (P < .05 for all). COPD symptoms were significantly improved from baseline with aclidinium vs placebo (P < .05) but not with tiotropium.

CONCLUSIONS: In patients with COPD, aclidinium 400 ug bid compared with placebo provided clinically meaningful improvements in 24-h bronchodilation that generally were comparable to tiotropium 18 ug daily but with significant differences in favor of aclidinium observed in the average nighttime period. Larger studies with longer treatment duration are ongoing to confirm the efficacy of aclidinium 400 ug bid on bronchodilation and COPD symptoms. Trial registry: ClinicalTrials.gov; No.: NCT00868231; URL: www.clinicaltrials.gov.

Sharafkhaneh, A., J. G. Southard, et al. (2012). "Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study." Respiratory Medicine **106**(2):257-268.

BACKGROUND: Treatment of an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.

METHODS: Following a 2-week run-in during which COPD patients aged >=40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol 160/9 ug, or formoterol dry powder inhaler 9 ug. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.

RESULTS: Budesonide/formoterol 320/9 and 160/9 rediced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol (p ,= 0.002). Budesonide/formoterol320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ration (0.788 [95% CI: 0.639, 0.972]; p = 0.026). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol (p <= 0.023). Both budesonide/formoterol 320/9, 160/9 and formoterol groups.

CONCLUSIONS: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NTC00419744).

Zhong, N., J. Zheng, et al. (2012). "Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronicobstructive pulmonary disease. Current Medical Research & Opinion 28**(2):** 257-265**.**

OBJECTIVE: To evaluate the efficacy and safety of budesonide (BUD)/formoterol (FORM) compared with BUD, both administered by way of a dry powder inhaler (Turbuhaler).

METHODS: This was a 6-month, multicenter, randomized, parallel-group, double-blind, double-dummy design study (NCT 00421122). Patients were randomized to either BUD/FORM 160/9 twice daily or BUD 400 ug, twice daily. Improvement of lung function, daily symptoms, reliever use and health-related quality-of-life (St. George's Respiratory Questionaire [SGRQ] score) were compared between the two treatment groups.

RESULTS: A total of 308 patients with moderate to very severe COPD from 12 centers in China were randomized to BUD/FORM (n=156) or BUD (n=152). The primary endpoint, 1-hour post-dose forced expiratory volume in 1 second (FEV1), in the BUD/FORM group improved by 0.18L (from 0.83L at baseline to 1.01L) and this was significantly

better (p<0.001) than the small increase (0.03L) observed in the BUD group after 24 weeks' treatment. Increases in pre-dose and 15-min post-does FEV(1) together with 1-hour post-dose forced vital capacity were also significantly larger with BUD/FORM than BUD (p<0.001 for all). Compared with BUD alone, BUD/FORM improved COPD total symptom scores (-1.04+/-0.16 vs -0.55+/-0.17; p=0.03), reduced reliever use (-0.85+/-0.16 puffs/day vs -0.31+/-0.16 puffs/day; p=0.012) and improved health-related quality-of-life (mean change of total SGRQ score -4.5 points (p=0182). Overall, both treatment groups were well tolerated.

CONCLUSIONS: In Chinese patients with moderate to very severe COPD, fixed combination treatments with BUD/FORM resulted in clinically meaningful improvements in lung function, health-related quality-of-life, COPD symptoms and a reduction in reliever use, compared with BUD use alone and both treatments were well tolerated. Treatment of BNUD/FORM for milder patients with COPD and head to head comparison of Chinese and Caucasians in future studies will be helpful to expand upon the findings of the current clinical trial.

Appendix 6: Abstracts of Meta Analyses

Cheyne L, Irvin-Sellers MJ, White J. "Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews 2013, 9. Art. No.: CD009552.

BACKGROUND: Tiotropium and ipratropium bromide are both recognised treatments in the management of people with stable chronic obstructive pulmonary disease (COPD). There are new studies which have compared tiotropium with ipratropium bromide, making an update necessary.

OBJECTIVES: To compare the relative effects of tiotropium to ipratropium bromide on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in patients with COPD using available randomised controlled trial (RCT) data.

SEARCH METHODS: We identified RCTs from the Cochrane Airways Group Specialised Register of trials (CAGR) and ClinicalTrials.gov up to November 2012.

SELECTION CRITERIA: We included parallel group RCTs of 12 weeks duration or longer comparing treatment with tiotropium with ipratropium bromide for patients with stable COPD.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for inclusion and then extracted data on study quality and outcome results. We contacted trial sponsors for additional information. We analysed the data using Cochrane Review Manager (RevMan 5.2).

MAIN RESULTS: This review included two studies of good methodological quality that enrolled 1073 participants with COPD. The studies used a similar design and inclusion criteria and were of at least 12 weeks duration; the participants had a mean forced expiratory volume in one second (FEV_1) of 40% predicted value at baseline. One study used tiotropium via the HandiHaler (18 µg) for 12 months and the other via the Respimat device (5 µg and 10 µg) for 12 weeks. In general, the treatment groups were well matched at baseline but not all outcomes were reported for both studies. Overall the risk of bias across the included RCTs was low.

For primary outcomes this review found that at the three months trough (the lowest level measured before treatment) FEV_1 significantly increased with tiotropium compared to ipratropium bromide (mean difference (MD) 109 mL; 95% confidence interval (CI) 81 to 137, moderate quality evidence, I^2 = 62%). There were fewer people experiencing one or more non-fatal serious adverse events on tiotropium compared to ipratropium (odds ratio (OR) 0.5; 95% CI 0.34 to 0.73, high quality evidence). This represents an absolute reduction in risk from 176 to 97 per 1000 people over three to 12 months. Concerning disease specific adverse events, the tiotropium group were also less likely to experience a COPD-related serious adverse event when compared to ipratropium bromide (OR 0.59; 95% CI 0.41 to 0.85, moderate quality evidence).

For secondary outcomes, both studies reported fewer hospital admissions in the tiotropium group (OR 0.34; 95% CI 0.15 to 0.70, moderate quality evidence); as well as fewer patients experiencing one or more exacerbations leading to hospitalisation in the people on tiotropium in both studies (OR 0.56; 95% CI 0.31 to 0.99, moderate quality evidence). There was no significant difference in mortality between the treatments (OR 1.39; 95% CI 0.44 to 4.39, moderate quality evidence). One study measured quality of life using the St George's Respiratory Questionnaire (SGRQ); the mean SGRQ score at 52 weeks was lower in the tiotropium group than the ipratropium group (lower on the scale is favourable) (MD -3.30; 95% CI -5.63 to -0.97, moderate quality evidence). There were fewer participants suffering one of more exacerbations in the tiotropium arm (OR 0.71; 95% CI 0.52 to 0.95, high quality evidence) and there was also a reported difference in the mean number of

exacerbations per person per year which reached statistical significance (MD -0.23; 95% CI -0.39 to -0.07, P = 0.006, moderate quality evidence). From the 1073 participants there were significantly fewer withdrawals from the tiotropium group (OR 0.58; 95% CI 0.41 to 0.83, high quality evidence).

AUTHORS' CONCLUSIONS: This review shows that tiotropium treatment, when compared with ipratropium bromide, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD, as proposed in guidelines. We would advise some caution with tiotropium via the Respimat inhaler and suggest waiting for further information from an ongoing head-to-head trial comparing mortality in relation to tiotropium delivery devices and doses.

Chong M. J., C. Karner, et al. (2102). “Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease.” ¨Cochrane Database of Systemic Reviews 2012 9: CD009157.

BACKGROUND: Tiotropium and long-acting beta(2)-agonists (LABAs) are both accepted in the routine management for people with stable chronic obstructive pulmonary disease (COPD). There are new studies which have compared tiotropium with LABAs, including some that have evaluated recently introduced LABAs.

OBJECTIVES: To compare the relative clinical effects of tiotropium bromide alone versus LABA alone, upon measures of quality of life, exacerbations, lung function and serious adverse events, in people with stable COPD. To critically appraise and summarize current evidence on the costs and cost-effectiveness with tiotropium compared to LABA in people with COPD.

SEARCH METHODS: We identified randomized controlled trials (RCTs) from the Cochrane Airwasys Group Specialised Register of trials and economic evaluations from searching NHS EED and HEED (date of last search February 2012). We found additional trials from web-based clinical trial registers.

SELECTION CRITERIA: We included RCTs and full economic evaluations if they compared effects of tiotropium alone with LABAs alone in people with COPD. We allowed co-administration of standard COPD therapy.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for inclusion, then extracted data on study quality and outcomes .We contacted study authors and trial sponsors for additional information. We analyzed data using the Cochrane Review Manager (RevMan 5.1) software.

MAIN RESULTS: Seven clinical studies totaling 12,223 participants with COPD were included in the review. The studies used similar designs and were generally of good methodological quality. Inclusion criteria for RCTs were similar across the included studies, although studies varied in terms of smoking history and COPD severity of participants. They compared tiotropium (which was delivered by HandiHaler in all studies) with salmeterol (four studies, 8936 participants), formoterol (one study, 431 participants) and indacaterol (two studies, 2856 participants). All participants were instructed to discontinue anticholinergic or LABA bronchodilators during treatment, but could receive inhaled corticosteroids (ICS) at a stable dose. Study duration ranged from 3 to 12 months. We extracted data for 11,223 participants. In general, the treatment groups were well matched at baseline. Overall, the risk of bias across the included RCTs was low. In the analysis of the primary outcomes in this review, a high level of heterogenicity amongst studies meant that we did not pool data for St. George’s Respiratory Questionnaire quality of life score. Subgroup analyses based on the type of LABA found statistically significant differences among effects on quality of life depending on whether tiopropium was compared with salmeterol, formoterol, or indacaterol. Tiotropium reduced the number of participants experiencing one or more exacerbations compared with LABA (odds ratio (OR) 0.86; 95% confidence interval (CI) 0.79 to 0.93). For this outcome, there was no difference seen among the different types of LABA. There was no statistical difference in mortality observed between the treatment groups. For secondary outcomes, tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalisation compared with LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but not in the overall rate of all-cause hospitalizations. There was no statistically significant difference in forced expiratory volume in one second FEV(!) or symptom score between tiotropium and LABA-treated participants. There was a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA (OR 0.88; 95% CI 0.78 to 0.99). The tiotropium group was also associated with a lower rate of study withdrawals (OR 0.89; 95% CI 0.81 to 0.99). We identified six full economic evaluations assessing the cost and cost-effectiveness of tiotropium and salmeterol. The studies were based on an economic model or empirical analysis of clinical data from RCTs. They all looked at maintenance costs and the costs for COPD exacerbations, including respiratory medications and hospitalizations. The setting for the evaluations was primary and secondary care in the UK, Greece, Netherlands,

Spain and US> All the studies estimated tiotropium to be superior to salmeterol based on better clinical outcomes (exacerbations or quality of life_ and/or lower total costs. However, the authors of all evaluations reported there was substantial uncertainty around the results.

AUTHORS' CONCLUSIONS: In people with COPD, the evidence is equivocal as to whether or not tiotropium offers greater benefit than LABAs in improving quality of life; however, this is complicated by differences in effect among the LABA types. Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations, although there were no statistical differences between groups in overall hospitalization rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with LABAs. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice-versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different LABAs, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific setting, but there is considerable uncertainty around this finding.

Cope, S., M. Kraemer, et al. (2012). "Efficacy of indacaterol 75 ug versusfixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis." International Journal of Copd 7: 415-420.

BACKGROUND: The purpose of this study was to update our network meta-analysis in order to compare the efficacy of indacaterol 75 µg with that of a fixed-dose combination of formoterol and budesonide (FOR/BUD) and a fixed-dose combination salmeterol and fluticasone (SAL/FP) for the treatment of chronic obstructive pulmonary disease (COPD) based on evidence identified previously in addition to two new randomized clinical trials.

METHODS: Fifteen randomized, placebo-controlled clinical trials including COPD patients were evaluated: indacaterol 75 µg once daily (n = 2 studies), indacaterol 150 µg once daily (n = 5), indacaterol 300 µg once daily (n = 4), FOR/BUD 9/160 µg twice daily (n = 2), FOR/BUD 9/320 µg twice daily (n = 2), SAL/FP 50/500 µg twice daily (n = 4), and SAL/FP 50/250 µg twice daily (n = 1). All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Treatment-by-covariate interactions were included where possible to improve the similarity of the trials. Outcomes of interest were trough forced expiratory volume in 1 second (FEV(1)) and transitional dyspnea index at 12 weeks.

RESULTS: Based on the results without adjustment for covariates, indacaterol 75 µg resulted in a greater improvement in FEV(1) at 12 weeks compared with FOR/BUD 9/160 µg (difference in change from baseline 0.09 L [95% credible interval 0.04-0.13]) and FOR/BUD 9/320 µg (0.07 L [0.03-0.11]) and was comparable with SAL/FP 50/250 µg (0.00 L [-0.07-0.07]) and SAL/FP 50/500 µg (0.01 L [-0.04-0.05]). For transitional dyspnea index, data was available only for indacaterol 75 µg versus SAL/FP 50/500 µg (-0.49 points [-1.87-0.89]).

CONCLUSION: Based on results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious as FOR/BUD (9/320 µg and 9/160 µg) and comparable with SAL/FP (50/250 µg and 50/500 µg) in terms of lung function. In terms of breathlessness (transitional dyspnea index) at 12 weeks, the results are inconclusive given the limited data.

Dong, Y.. –H., H.-H. Lin, et al. (2013). "Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomized controlled trials." ¨Thorax 65(1): 48-56.

BACKGROUND: The active-treatment comparative safety information for all inhaled medications in patients with chronic obstructive pulmonary disease (COPD) is limited. We aimed to compare the risk of overall and cardiovascular death for inhaled medications in patients with COPD.

METHODS: Through systematic database searching, we identified randomised controlled trials of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, long-acting β2 agonists (LABAs), inhaled corticosteroids (ICS), and LABA-ICS combination with at least a 6-month treatment duration. Direct comparison and mixed treatment comparison (MTC) meta-analyses were conducted to estimate the pooled ORs of death for each comparison.

RESULTS: 42 trials with 52 516 subjects were included. The MTC meta-analysis with the fixed effect model indicated tiotropium Soft Mist Inhaler was associated with an universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at a higher daily

dose. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium HandiHaler or LABA. The results were similar for MTC and direct comparison meta-analyses, with less precision in the random effects model.

CONCLUSION: Our study provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution.

Karner, C. & Cates, C. J. "LABAin addition to tiotropium versus either tiotropium or LABAalone for chronic obstructive pulmonary disease." Cochrane Database Syst Rev 4, CD008989 (2012).

BACKGROUND: Long-acting bronchodilators comprising long-acting beta(2)-agonists and the anticholinergic agent tiotropium are commonly used for managing persistent symptoms of chronic obstructive pulmonary disease. Combining these treatments, which have different mechanisms of action, may be more effective than the individual components. However, the benefits and risks of combining tiotropium and long-acting beta(2)-agonists for the treatment of chronic obstructive pulmonary (COPD) disease are unclear.

OBJECTIVES: To assess the relative effects of treatment with tiotropium in addition to LABA compared to tiotropium or LABA alone in patients with chronic obstructive pulmonary disease.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials and clinicaltrials.gov up to January 2012.

SELECTION CRITERIA: We included parallel group, randomised controlled trials of three months or longer comparing treatment with tiotropium in addition to LABA against tiotropium or LABA alone for patients with chronic obstructive pulmonary disease.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion and then extracted data on trial quality and the outcome results. We contacted study authors for additional information. We collected information on adverse effects from the trials.

MAIN RESULTS: Five trials were included in this review, mostly recruiting participants with moderate or severe chronic obstructive pulmonary disease. All of them compared tiotropium in addition to LABA to tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with LABA (formoterol) alone. Two studies used the LABA indacaterol, two used formoterol and one used salmeterol. Compared to tiotropium alone (3263 patients), treatment with tiotropium plus LABA resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). High withdrawal rates in the trials increased the uncertainty in this result, and the GRADE assessment for this outcome was therefore moderate. There were no significant differences in the other primary outcomes (hospital admission or mortality).The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. There were wide confidence intervals around these outcomes and moderate heterogeneity for both exacerbations and withdrawals. The results from the one trial comparing the combination of tiotropium and LABA to LABA alone (417 participants) were insufficient to draw firm conclusions for this comparison.

AUTHORS' CONCLUSIONS: The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus LABA compared to LABA alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Nannin, L. J., T. J. Lasserson, et al. (2012). "Combined corticosteroid and LABA in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews **9: CD006829.**

BACKGROUND: Both inhaled steroids (ICS) and long-acting beta(2)-agonists (LABA) are used in the management of chronic obstructive pulmonary disease (COPD). This updated review compared compound LABA plus ICS therapy (LABA/ICS) with the LABA component drug given alone.

OBJECTIVES: To assess the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone in adults with COPD.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials. The date of the most recent search was November 2011.

SELECTION CRITERIA: We included randomised, double-blind controlled trials. We included trials comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed study risk of bias and extracted data. The primary outcomes were exacerbations, mortality and pneumonia, while secondary outcomes were health-related quality of life (measured by validated scales), lung function, withdrawals due to lack of efficacy, withdrawals due to adverse events and side-effects. Dichotomous data were analysed as random-effects model odds ratios or rate ratios with 95% confidence intervals (CIs), and continuous data as mean differences and 95% CIs. We rated the quality of evidence for exacerbations, mortality and pneumonia according to recommendations made by the GRADE working group.

MAIN RESULTS: Fourteen studies met the inclusion criteria, randomising 11,794 people with severe COPD. We looked at any LABA plus ICS inhaler (LABA/ICS) versus the same LABA component alone, and then we looked at the 10 studies which assessed fluticasone plus salmeterol (FPS) and the four studies assessing budesonide plus formoterol (BDF) separately. The studies were well-designed with low risk of bias for randomisation and blinding but they had high rates of attrition, which reduced our confidence in the results for outcomes other than mortality. Primary outcomes There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomised 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. Our confidence in this effect was limited by statistical heterogeneity between the results of the studies (I(2) = 68%) and a risk of bias from the high withdrawal rates across the studies. When analysed as the number of people experiencing one or more exacerbations over the course of the study, FPS lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. Concerns over the effect of reporting biases led us to downgrade the quality of evidence for this effect from high to moderate. There was no significant difference in the rate of hospitalisations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence due to risk of bias, statistical imprecision and inconsistency). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, downgraded to moderate quality evidence due to statistical imprecision). Pneumonia occurred more commonly in people randomised to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence due to risk of bias in relation to attrition) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Secondary outcomes ICS/LABA was more effective than LABA alone in improving health-related quality of life measured by the St George's Respiratory Questionnaire (1.58 units lower with FPS; 2.69 units lower with BDF), dyspnoea (0.09 units lower with FPS), symptoms (0.07 units lower with BDF), rescue medication (0.38 puffs per day fewer with FPS, 0.33 puffs per day fewer with BDF), and forced expiratory volume in one second (FEV(1)) (70 mL higher with FPS, 50 mL higher with BDF). Candidiasis (OR 3.75) and upper respiratory infection (OR 1.32) occurred more frequently with FPS than SAL. We did not combine adverse event data relating to candidiasis for BDF studies as the results were very inconsistent.

AUTHORS' CONCLUSIONS: Concerns over the analysis and availability of data from the studies bring into question the superiority of ICS/LABA over LABA alone in preventing exacerbations. The effects on hospitalisations were inconsistent and require further exploration. There was moderate quality evidence of an increased risk of pneumonia with ICS/LABA. There was moderate quality evidence that treatments had similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV(1) improved more on ICS/LABA than on LABA, but the average differences were probably not clinically significant for these outcomes. To an individual patient the increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations. More information would be useful on the relative benefits and adverse event rates with combination inhalers using different doses of inhaled corticosteroids. Evidence from head-to-head comparisons is needed to assess the comparative risks and benefits of the different combination inhalers.

Rodrigo, G.J. and H. Neffen (2012). “Comparison of indacaterol with tiotropium or twice-daily long-acting beta-agonists for stale COPD: a systematic review.” Chest 142(5) 1104-1110.

BACKGROUND: Bronchodilators are central to the symptomatic management of patients with COPD. Previous data have shown that inhaled indacaterol improved numerous clinical outcomes over placebo.

METHODS: This systematic review explored the efficacy and safety of indacaterol in comparison with tiotropium or bid long-acting β 2 -agonists (TD-LABAs) for treatment of moderate to severe COPD. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Five trials (5,920 participants) were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea(43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat for benefit [NNTB] 5 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; [NNTB]= 10). Trough FEV 1 was significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, P = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of achieving an MCID in TDI, P = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, P 5 .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators.

CONCLUSIONS: Available evidence suggests that indacaterol may prove useful as an alternative to tiotropium or TD-LABA due to its effects on health status, dyspnea, and pulmonary function.

Rodrigo, G. J., Plaza, V. & Castro-Rodríguez, J. A. "Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review." Pulm Pharmacol Ther **25,** 40–47 (2012).

BACKGROUND: Guidelines recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICS) and their combinations for maintenance treatment of moderate to severe COPD. However, there are limited data supporting combination therapy.

METHODS: This systematic review assessed the efficacy of three therapeutic approaches: tiotropium plus long-acting beta2-agonist (LABA) ("dual" therapy), LABA/ICS ("combined" therapy), and tiotropium plus LABA/ICS ("triple" therapy), all compared with tiotropium monotherapy. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in forced volume in the first second (FEV(1)), health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV(1), HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to treat for harm [NNTH] = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV(1), improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21).

CONCLUSIONS: "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety**.**

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Abbreviated Class Update: Parkinson's Drugs

Month/Year of Review: November 2013
New Drug: rotigotine transdermal system **(**Neupro®)

End of literature search: September 2013
Manufacturer: UCB Pharmaceuticals, Inc.

Current Preferred Agents	Current Non-Preferred Agents
Anticholinergics	
Benztropine tablets	
Trihexyphenidyl tablets/elixir	
COMT Inhibitors*	
Entacapone tablets	Tolcapone (Tamsar®) tablets
Dopaminergic Agents	
Carbidopa/Levodopa tablets	Carbidopa/Levodopa ER tablets
Dopamine Agonists	
Amantadine capsules/syrup/tablets	Bromocriptine (Parlodel®) tablets/capsules
Pramipexole DI-HCL tablets	Ropinirole (Requip®) IR and XL tablets
*MAO- B** Inhibitors*	
Selegiline capsules	Rasagaline (Azilect®) tablets
Combination Product	
	Carbidopa/Levodopa/Entacapone

*COMT = Catechol-O-methyl transferase; **MAO-B = Monoamine oxidase B

PA Criteria: All non-preferred agents require prior authorization to cover preferred products when feasible for covered diagnosis (Appendix 1). OHP does not cover treatment for restless leg syndrome.

Research Questions:

- Is there any evidence about comparative effectiveness of rotigotine transdermal versus other agents for the treatment of Parkinson's Disease (PD) in reducing disability, motor complications, and associated symptoms?
- Is there any evidence about comparative harms of rotigotine transdermal versus other agents in the treatment of PD?
- Are there subpopulations of patients (specifically by race, age, sex, or comorbidities) for which rotigotine is more effective or associated with less harm?

Conclusions:

- There is moderate quality evidence that, compared to placebo, more patients on rotigotine achieve a 20% or greater decrease in UPDRS ADL + Motor scores at 24 weeks (48% vs. 19%; ARR 29%, NNT 4) in the treatment of early Parkinson's Disease (PD).
- There is low quality evidence that rotigotine did not meet non-inferiority in responder rate(at least a 20% decrease in UPDRS ADL + Motor scores) compared to ropinirole in patients with early PD (52% vs. 68%).
- There is moderate quality evidence, that compared to placebo, patients on rotigotine achieved a greater change in total hours "off" from baseline (-2.7 vs. -0.9, p<0.0001) in the treatment of advanced PD over 24 weeks with adjunct levodopa.
- There is low quality evidence that there is no difference between rotigotine and pramipexole in responder rate (at least a 30% decrease in "off" time) in patients with advanced PD over 16 weeks (59.7% vs. 67%; RR 0.9, 95% CI 0.7-1.0); p=0.125).
- Rotigotine is generally well tolerated for up to 6 years with similar side effects as other dopamine agonists, including somnolence, dizziness, nausea, and insomnia. In addition, more patients experienced application site reactions with transdermal rotigotine compared to placebo.
- There is insufficient evidence that rotigotine is more efficacious or safer than other oral dopamine agonists in the treatment of PD. It may be a reasonable option for patients with difficulty swallowing that may be addressed by use of the patch.

Recommendations:

- Rotigotine transdermal patch should be evaluated in executive session for relative cost.

Reason for Review: Oregon reviewed the literature in this class in September 2013 and recommended adding rotigotine transdermal to complete the class

Background:

Rotigotine patch was originally approved for the treatment of PD in 2007 and was the first non-ergot dopamine agonist delivered continuously through a transdermal system. The formation of rotigotine crystals in the transdermal patch resulted in the product being withdrawn from the market in 2008 due to concerns of the impact on the bioavailability and effects on efficacy.[1] It was re-approved by the FDA in April 2012 for the treatment of PD and restless legs syndrome after the manufacturer reformulated the patch. Non-oral routs of delivery can be useful in PD patients scheduled for surgery or those with dysphagia.[2] This review will evaluate its efficacy and safety only in the treatment of PD, as restless leg syndrome is not a covered diagnosis under the Oregon Health Plan.

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most widely used clinical rating scale for PD.[3] It evaluates the key areas of disability and evaluates response to therapy. Many practitioners find it too complicated to use in clinical practice. A total of 199 points are possible with 0 representing no disability and 199 representing total disability. A recent analysis showed that a minimal clinically important difference was 2.3 to 2.7 points on the UPDRS motor score and 4.1 to 4.5 on the UPDRS total score. A moderate clinically important difference was 4.5 to 6.7 points on the UPDRS motor score and 8.5 to 10.3 on the total score. A large difference was 10.7 to 10.8 points on the UPDRS motor score and 16.4 to 17.8 on the UPDRS total score.[4]

Methods:

A MEDLINE OVID search was conducted using rotigotine for Parkinson's disease (PD) and limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans since the date of the literature search conducted for the previous OHA P & T review. The Agency for Healthcare

Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. From the literature search, two systematic reviews were identified as well as 9 randomized controlled trials. Three were excluded due to wrong outcome and/or wrong study design.[5–7]

New Systematic Reviews:

1) A systematic review was conducted to evaluate rotigotine's efficacy in PD, including randomized controlled trials up to July 2012.[2] Trials that used the Unified Parkinson's Disease Rating Scale (UPDRS) score were included. Two authors evaluated trials for quality using the Jadad scale. Six RCTs including 1789 patients were included in the meta-analysis and had Jadad scores that ranged from 4 to 5 (5 being rated as the strongest score). Four trials demonstrated a greater response in UPDRS ADL score with rotigotine compared to placebo (weighted mean difference [WMD] -1.69; 95% CI -2.18 to -1.19; p<0.0001), as well as a greater reduction in motor score (WMD -3.86; 95% CI -4.86 to -2.86; p<0.0001). There was no difference between rotigotine and placebo in overall number of withdrawals (RR 0.88; 95% CI 0.64-1.21; p=0.44) with evidence of heterogeneity (p=0.037, I^2=57.7%). However, rotigotine was associated with a significantly higher rate of withdrawals due to adverse events compared to placebo (11.4% vs. 6.4%, respectively; RR 1.82, 95% CI 1.29-2.59; p=0.0008). Both application site reactions (RR 2.92; 95% CI 2.29-3.72; p<0.0001) and dizziness (RR 1.47, 95% CI 1.12-1.95; p=0.006) occurred with rotigotine significantly more than placebo. The overall magnitude reduction in UPDRS ADL score (-1.69) was slightly greater than that in early PD patients (-1.64) but smaller than that in advanced PD patients (-2.2) when compared to results of previous meta-analyses of dopamine agonists. This review met the DARE scientific quality criteria for a systematic review.

2) Another systematic review evaluated the tolerability and safety of ropinirole versus other dopamine agonists, including rotigotine, in the treatment of PD.[8] A literature search through November 2008 was conducted to identify double-blind randomized clinical trials. Guidelines on systematic reviews from the Cochrane Collaboration were followed and quality of the evidence was assessed using the Jadad criteria. A total of 40 RCTs were identified, including 1 trial comparing ropinirole to rotigotine and 5 trials comparing rotigotine to placebo. In all of the included studies, dopamine agonists exhibited a higher incidence of adverse events than placebo. Rotigotine showed statistically significantly more nausea (RR 2.08, 95% CI 1.30-3.34), dizziness (RR 1.35, 95% CI 1.02-1.9), dyskinesia ((RR 2.29, 95% CI 1.10-4.78), insomnia (RR 1.90, 95% CI 1.22-2.95), vomiting (RR 5.31, 95% CI 2.30-12.27), and hallucinations (RR 4.02, 95% CI 1.23-13.11) compared to placebo. There was not a statistically significant difference in somnolence, headache, confusion, constipation or abdominal pain between rotigotine and placebo. When a direct comparison was made between rotigotine and ropinirole, no significant differences for either dyskinesia or constipation were found.

Guidelines:

National Guideline Clearinghouse (NGC) released treatment guideline on early (uncomplicated) Parkinson's disease. This guideline is an updated version of the therapeutic management of Parkinson's disease by the joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section.[9] Agents available in the US that carried **level A** recommendation for controlling PD's symptoms including Levodopa IR and CR,

pramipexole, ropinirole IR and CR, selegiline and rasagliline. Levodopa also has **level A** recommendation as the most effective symptomatic antiparkinsonian drug; however after a few years of treatment, levodopa is frequently associated with the development of motor complications. Rotigotine is not included in these guidelines.

Clinical Trials:

Early-Stage Parkinson's Disease

A RCT by Giladi et al evaluated the efficacy and safety of the rotigotine patch in the treatment of early PD in 561 patients randomized to rotigotine, ropinirole, or placebo. [10] Patients had mild to moderate disease with a baseline UPDRS ADL score of 9.0 and motor score of 23.2. The primary efficacy variable was the proportion of patients who responded to treatment which was defined as a 20% or greater decrease in the UPDRS parts II (ADL) + parts III (motor) scores from baseline. Compared to placebo, both rotigotine and ropinirole resulted in a significantly higher proportion of responders compared to placebo. The mean decrease from baseline in UPDRS subtotal score was -7.2 for patients receiving rotigotine compared with -2.2 for patients receiving placebo (P<0.0001) and -11.0 for ropinirole (p<0.0001). The changes in motor score and subtotal score are considered clinically significant as well as statistically significant. Results did not show noninferiority of rotigotine and ropinirole (RR 0.8, 95% CI 0.65-0.90); however the study was not powered to show superiority of any active treatment over the other and only 26% of ropinirole patients received the maximum allowed dose of 24mg/day. There were a significant more number of discontinuations due to adverse events in the rotigotine group compared to placebo (17% vs. 5.1%; RR 3.4, 95% CI 1.4-8.8). The majority of those in the rotigotine group were due to application-site reactions (8%). Common adverse events included application-site reactions, nausea, vomiting, somnolence, dizziness, and headache. There was an imbalanced titration (4 weeks vs. 13 weeks) and maintenance (24 weeks vs. 33 weeks) period between the treatment groups, making them hard to compare. This is a short term study; because progression of PD is estimated to be 3 UPDRS points per year, a longer study period is needed to examine long-term effects.

Watts, et al compared rotigotine patch (max dose 6 mg/24h) to placebo for 6 months in patients with early-stage PD.[11] Results demonstrated statistically significant improvements in motor function and activities of daily living (UPDRS II + III score) with rotigotine compared to placebo (-3.98 vs. +1.31; p<0.000.1; mean difference of 5.28 points). The mean rotigotine dose was 5.7 mg/24 h. Superior scoring in the motor examination was the largest contributor to the subtotal improvements. The proportion of responders (at least 20% improvement in UPDRS scores) was higher in the rotigotine group (48% vs. 19%; p<0.0001). Because patients included in the trial were so early in respect to PD disease, it may be difficult to see drastic motor fluctuations as measured by the primary endpoint.

A total of 216 subjects from the Watts trial were enrolled in an open-label long term study with a mean follow-up of 5.3 years. At 2 years, the UPDRS ADL plus motor scores were not different from the double-blind baseline.[12] For the following 4 years, scores worsened but remained within 4 points of the baseline scores. Adjunctive levodopa was started in 74% of patients, making it difficult to determine the long-term efficacy of rotigotine monotherapy.

Advanced Parkinson's Disease:

The PREFER study evaluated the efficacy of rotigotine compared to placebo in patients with suboptimal control of symptoms and significant motor complications.[13] Patients were randomized to rotigotine 8mg/24h, 12mg/24h, or placebo for 24 weeks. Rotigotine 8mg/24h and 12mg/24 hr resulted in a statistically significant reduction in absolute "off" time (-2.7 hrs vs. -2.1 hrs, -0.9hrs, respectively) and an increase in daily "on" time without troublesome dykinesias (3.5 hrs vs. 2.2 hrs vs. 1.1 hrs, respectively) compared to placebo. The primary outcome of changes in daily off time was measured by patient diaries, which can be subjective. UPDRS ADL and motor scores were also significantly increased with both rotigotine doses compared to placebo.

The CLEOPATRA-PD trial[14] was a 24-week randomized trial in PD patients with at least 2.5 hours of daily off-time (advanced PD). Subjects were randomized to rotigotine (max dose of 16mg/24hr), pramipexole (max dose 4.5mg/day), and placebo. The mean daily dose of rotigotine was 12.95 mg/24 h. Daily off-time was reduced by 2.5 hours with rotigotine, 2.8 hours with pramipexole, and 0.9 hours with placebo. Both rotigotine and pramipexole demonstrated statistical significance compared to placebo; however, there was no difference between the two treatment groups. There was also no difference between the rotigotine and ropinirole groups in UPDRS ADL and motor scores or in responder rates.

Open-label extensions of both the CLEOPATRA-PD (n=395) and PREFER (n=258) studies were conducted to evaluate rotigotine over several years of follow-up in patients with advanced PD.[15] Patients were re-titrated do optimal dose (up to 16mg/24h) for 7 weeks. Most patients had moderately severe PD. The majority of subjects reported at least one adverse event, however only 8 and 9% were recorded as severe. The long term efficacy data demonstrated continuing disease progression over the course of studies. UPDRS scores gradually increased over the maintenance periods and were 0.8 points higher than baseline in one study, and 4.1 points higher than baseline in the other. Responder rates also decreased over time to 36% and 25% respectively.

Safety:

Most common adverse events were typical of a dopamine agonist and include nausea, somnolence, dizziness, and headache. Application site reactions also occurred more frequently than placebo in clinical trials. Long term trials have demonstrated rotigotine is generally well tolerated for up to 6 years with the most common adverse reactions of somnolence (54%), falls (33%), peripheral edema (37%), application site reactions (32%), nausea (31%), and dizziness (27%).[12] Case reports of patients experiencing sudden onset of sleep have been reported. In one study of 242 patients, one subject fell asleep while driving a motor vehicle and another reported a brief loss of consciousness while driving. A post-hoc analysis of patients taking low dose rotigotine demonstrated that 4 patients experienced a sleep attack or sudden onset of sleep.

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
Giladi et al[10] DB, PC, RCT	Rot: Rotigotine Rop: Ropinirole Pla: Placebo	Mean age: 61 Male: 58% Caucasian: 97% Mean UPDRS score: -ADL: 9.0 -Motor: 23.2 Mean rotigotine dose 7.2mg/24h Inclusion Criteria: Adults 30 years or older with mild to moderate PD, a score of at least 10 on the UPDRS Exclusion Criteria: Psychiatric disease, h/o skin sensitivity, levodopa use for longer than 6 months, hepatic, renal or cardiac dysfunction, elevated QTc interval	N=215 N=228 N=118 Minimum duration of 33 weeks for rotigotine and 24 weeks for ropinirole based on dose-titration period	<u>Proportion of patients who responded to treatment:</u> Rot: 110 (52%) Rop: 154 (68%) Pla: 35 (30%) P<0.0001 for Rot vs. Pla RR 1.7, 95% CI 1.2-2.4 P<0.0001 for Rop vs. Pla RR 2.3, 95% CI 1.7-3.1 P=0.001 for Rot vs. Rop RR 0.8, 95% CI 0.65-0.90	ARR 22% NNT 5 ARR 38% NNT 3 N/A	<u>Withdrawals due to AEs:</u> Rot: 37(17.2%) Rop: 29 (12.8%) Pla: 6 (5.1%) P=0.002 for Rot vs. Pla RR 3.4, 95% CI 1.4-8.8	ARI= 12.1% NNH 9	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Randomization occurred via interactive voice response system. Patients similar at baseline. <u>Performance:</u> Double-blinded with placebo patches and capsules. Unclear if investigator were blinded during dose titration phase. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Overall high attrition at 29% PLA, 29% ROT, 23% ROP. Mostly due to lack of efficacy and adverse events. **External Validity Review of Bias:** <u>Patient Characteristics:</u> Patients with very mild disease included in study; only 26% of ropinirole patients received the maximum allowed dose of 24 mg/day. <u>Setting:</u> There was an imbalanced titration and maintenance periods between treatment groups, making them hard to compare <u>Outcomes:</u> A responder was defined as a patient with a 20% or greater decrease in the UPDRS parts II + III (ADL + motor) from baseline.

Watts et al.[11] Phase III, MC, R, DB, PC	Rot: Rotigotine Pla: Placebo Rotigotone was started at 2mg/24 hours and titrated to max tolerable dose up to 6 mg/24 hours	Mean age: 63 Males 64% Mean rotigotone dosage: 5.7mg/24 h Inclusion: Age>30, UPDRS motor score of at least 10, MMSE score >25 Exclusion: Prior or current dopamine agonist therapy, epilepsy, seizure history, stroke, TIA, or clinically relevant renal, hepatic, or cardiac dysfunctions	N=181 N=96 24 weeks	<u>Change in UPDRS II+III from baseline:</u> Rot: -3.98 Pla: +1.31 Treatment effect -5.3 P<0.0001 for Rot vs. Pla <u>% of responders</u> Rot: 87 (48%) Pla: 18 (19%) P<0.0001 for Rot vs. Pla RR 2.5, 95% CI 1.6-4.2	N/A ARR 29% NNT 4	<u>Withdrawals due to AEs:</u> Rot: 25 (14%) Pla: 6 (6%) P=0.06 for Rot vs. Pla RR 2.2, 95% CI 0.9-5.9	NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Unclear method of randomization. Patients similar at baseline. <u>Performance:</u> Double-blinded with placebo patches and capsules. Unclear if investigator were blinded during dose titration phase. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Overall attrition at 16% PLA, 22% ROT. High rate due to AE in Rot group. **External Validity Review of Bias:** <u>Recruitment:</u> Unknown <u>Patient Characteristics:</u> Patients had very earl PD <u>Setting:</u> 50 clinical study sites in the US and Canada <u>Outcomes:</u> Primary endpoint was combination of motor and ADL scores, however these patients may be too early in PD disease course to see such drastic motor fluctuations Study funded by Schwarz Pharma

CLEOPATRA PD[14] **(Poewe, et al).** MC, R, DB, DI	Rot: Rotigotine Pram: Pramipexol Pla: Placebo Rotigotine up to 16mg/24 hr Pramipexole up to 3.5mg/day Titration up to 7 weeks Maintenance: 16 weeks	Inclusion Criteria: 30 years or older, stable treatment with levodopa, motor fluctuations of the wearing-off type with an average of at least 2.5 hr per day in the off stage Exclusion criteria: Previous surgery for PD, MMSE <25, hallucinatior or psychosis, h/o MI, prolonged QTc interval	N= 204 N=201 N=101	<u>Absolute change in total hours "off" from baseline</u> Rot: -2.5 Pram: -2.8 Pla: -0.9 P<0.0001 Rot vs. Pla P<0.0001 Pram vs. Pla P=0.003 Rot vs. Pram <u>Responder rate (>30% decrease in off time):</u> Rot: 122 (59.7%) Pram: 135 (67%) Pla: 35 (35%) P<0.0001 Rot vs. Pla RR 1.7, 95% CI 1.3-2.4 P<0.0001 Pram vs. Pla RR 1.9, 95% CI 1.5-2.6 P=0.125 Rot vs. Pram RR 0.9, 95% CI 0.7-1.0	N/A ARR 24.7%/ NNT 4 ARR 32% NNT 3 NS	<u>Withdrawals due to AE:</u> Rot: 11 (5%) Pram: 14 (6%) Pla: 6 (6%) NS One report of sleep attack in pramipexole group	NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Randomization occurred via interactive voice response system. Slightly lower number of men in pramipexole group than other groups. <u>Performance:</u> Double-blinded with placebo patches and capsules. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Overall attrition at 27% PLA, 12% ROT, 17.5% PRAM. Mostly due to lack of efficacy and adverse events. **External Validity Review of Bias:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Patients with more advanced disease; on stable levodopa; almost all patients were white <u>Setting:</u> 77 centers in Europe, South Africa, Australia, and New Zealand <u>Outcomes:</u> Primary outcome of on/off time measured by patient diaries which is very subjective Members of Schwarz Pharma involved in steering committee for the trial design and submitted the manuscript for publication

PREFER[13] (LeWitt, et al) RCT, DB, PG	Rot 8: Rotigotine 8mg/24 hr Rot12: Rotigotine 12mg/24 hr Pla: Placebo	Mean Age: 66 Male 78% PD duration – 7.7 yr Daily "off" – 6.5 hr Inclusion Criteria: at least 30 years old, PD for at least 3 years, on at least 200mg/day of levodopa, inadequate relief of parkinsonism, at least 2.5 hours of "off time"	N=120 N=111 N=120 24 week maintenance phase	<u>Absolute change in total hours "off" from baseline</u> Rot 8: -2.7 Rot 12: -2.1 Pla: -0.9 P<0.0001 Rot 8 vs. Pla P<0.0001 Rot 12 vs. Pla <u>Responder rate (>30% decrease in off time):</u> Rot8: 56.6% Rot12: 55.1% Pla: 34.5% P<0.0001 for both Rot doses compared to placebo	N/A	<u>D/C due to AE</u> Rot8: 18 (15.3%) Rot12: 17 (15.3%) Pla: 11 (9.2%)%	NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Appropriate randomization method and allocation concealment. Similar groups at baseline <u>Performance:</u> Subjects blinded <u>Detection:</u> Unclear if outcome assessors blinded <u>Attrition:</u> Overall attrition of 27.5% ROT 8mg, 27% ROT 12mg, 23% Pla. Mostly due to adverse events in ROT groups and inefficiency in placebo group. **External Validity Review of Bias:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Limited baseline patient characteristics provided; more advanced disease on stable levodopa. Mean dose in 12mg group only 9.5mg. <u>Setting:</u> Clinical sites in the US and Canada <u>Outcomes:</u> Primary outcome of on/off time measured by patient diaries which is very subjective

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix 1: Current PA Criteria

Anti-Parkinsons Agents

Goal(s):

- Cover preferred products when feasible for covered diagnosis. Preferred products are selected on evidence based reviews.
- OPH does not cover treatment for restless leg syndrome (Coverage line 624)

Length of Authorization: 12 months

Requires PA:

Non-preferred drugs

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5.	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome (ICD9-333.94)?	**Yes:** Pass to RPH; Deny, (Not covered by OHP)	**No:** Go to #4
4. RPH only All other indications need to be evaluated as to whether they are above the line or below the line	**Above:** Go to #5	**Below:** Deny, (Not covered by the OHP)
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription

DUR/P&T Board Action: 9/06/10 (DO)
Revision(s):
Initiated: 1/1/11

Appendix 2: Specific Drug Information

PHARMACOKINETICS[16]

Parameter	Result
Oral Bioavailability	Transdermal Formulation
Protein Binding	92%
Elimination	Renally as inactive conjugates
Half-Life	5-7 hours
Metabolism	Multiple CYP isoenzymes, sulfotransferases, and two UDP-glucoronosyltransferases catalyze the metabolism of rotigotine

DOSE & AVAILABILITY[16]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1mg/24h 2mg/24h 3mg/24h 4mg/24h 6mg/24h 8mg/24h	Transdermal	Q24H	Initially, 2mg/24h for early-stage PD or 4mg/24hr for advanced PD. The dose may be increase as needed by 2mg/24 hours at weekly intervals, up to 6 mg/24 hours for early-stage PD and up to 8 mg/24h for advanced-stage disease.	No adjustment needed	No guidance available for patients with severe hepatic impairment.	No information available..	No differences in safety, efficacy or response have been observed among patients of varying age. Skin changes with advanced age may lead to increased rug exposure.	Should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm; the application site should be moved on a daily basis. For discontinuation, the daily dose should be reduced by 2mg/24 hours with a dose reduction preferably every other day, until complete withdrawal.

DRUG SAFETY[16]

Contraindications: Rotigotine is contraindicated in patients who are hypersensitive to rotigotine or any component of the transdermal delivery system.

Warnings and Precautions:

- Sulfite Sensitivity: Rotigotine contains sodium metabisulfite and patient with sulfite sensitivity may experience allergic reactions.
- Falling asleep during activities of daily living/somnolence: Instances of patients falling asleep while engaged in ADL, including operating a motor vehicle, have been reported.
- Hallucinations/Psychotic-like Behavior
- Symptomatic Hypotension
- Syncope
- Impulse Control
- Elevation of blood pressure/heart rate
- Weight gain/fluid retention
- Dyskinesia
- Application Site Reactions: Rotigotine should be discontinued if a generalized skin reaction is observed.
-

Look-alike/Sound-alike Potential:

Rotigotine may be confused with : *rasagiline, rivastigmine, ropinirole*
Neupro may be confused with: *Neupogen, Neurontin*

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

Month/Year of Review: November 2013 **Date of Last Review:** March 2012
PDL Classes: Statins **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: ATORVASTATIN, SIMVASTATIN, LOVASTATIN, PRAVASTATIN
- Non-Preferred Agents: FLUVASTATIN, FLUVASTATIN XL, ROSUVASTATIN (CRESTOR®), LOVASTATIN ER (ALTOPREV®), PITAVASTATIN (LIVALO®), NIACIN/LOVASTATIN (ADVICOR®), EZETIMIBE/SIMVASTATIN (VYTORIN®), AMLODIPINE/ATORVASTATIN (CADUET®), SITAGLIPTIN/SIMVASTATIN (JUVISYNC®)

Key Questions:

- Is there any new evidence about the comparative effectiveness of different statins, reducing long term cardiovascular or cerebrovascular outcomes?
- Is there any new evidence about comparative harms of different statins in patients being treated for the primary or secondary prevention of cardiovascular disease?
- Are there any subpopulations of patients for which one statin is more effective or associate with less harm?

PA Criteria: The standard non-preferred drugs in select PDL classes prior authorization criteria is in place for statins and combinations to ensure that non-preferred drugs are used for an above the line condition.

Conclusions:

- While no evidence based guidelines were found regarding lipid lowering agents for stroke prevention in frail elderly patients, there is evidence to suggest that statins reduce the risk of stroke by 25-47%, major coronary events by 32-37%, and all-cause mortality by 22% in patients over 65 years of age. [1]
- There is more evidence supporting the use of statins for the primary prevention of cardiovascular disease (CVD) with a demonstrated reduction in all-cause mortality (R 0.86, 95% CI 0.79-0.94, NNT 96), fatal CVD events (RR 0.83, 95% CI 0.72-0.96), and fatal coronary heart disease (RR 0.82, 95% CI 0.70-0.96).[2]
- There is moderate quality evidence of an increased risk of developing diabetes mellitus (RR 1.18, 95% CI 1.01-1.39)[2] with statin therapy compared to placebo, with different types and doses of statins having different potentials to increase the incidence of diabetes mellitus.[3]
- There is evidence that statin therapy is not associated with an increased risk of cancer (RR 1.16, 95% CI 0.87-1.54). [2]

Recommendations:

- There is insufficient comparative evidence on long term clinical outcomes or evidence that one agent is safer than another.
- Evaluate comparative costs in executive session.

Previous Conclusions and Recommendation:

- Reductions in cardiovascular (CV) and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available medications. Evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin to improve coronary heart disease clinical outcomes.
- There is no comparative effectiveness data that pitvastatin is more effective or safer than other lipid-lowering agents for managing the risk of CV events in patients with hypercholesterolemia. Make it non-preferred.
- Due to safety concerns, simvastatin 80mg should not be initiated in new patients; implement a prospective dose limit.

Background:

Nine statins have been approved by the FDA since 1987.[4] Reducing high cholesterol is a primary way to reduce the risk of cardiovascular events.[2] There is strong evidence supporting the use of statins for the secondary prevention of cardiovascular events in patients with dyslipidemia. Statins have also been shown to reduce the risk of a first event in individuals at high risk of cardiovascular disease (primary prevention) but selecting appropriate patients for primary prevention is not clearly defined and the potential for harm has also been evaluated.[2] Reductions in cardiovascular and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available medications. There is limited evidence of comparative effectiveness and relative safety among the different statin medications. Head to head studies have shown that a higher dose of a more potent statin reduces lipid levels more than a lower dose of a less potent statin. However, differences in clinical outcomes such as deaths or major coronary events have not been consistently demonstrated between the statins. All statins have also been shown to be generally safe. Simvastatin has shown to have a greater myopathy risk at very high doses. [4]

Methods:

A Medline OVID search for randomized controlled trials (RCTs) was conducted using terms for included drugs. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to October week one 2013. The Cochrane Collection, Agency for Health Care Research and Quality (AHRQ), National Institute for Clinical Evidence (NICE), Canadian Agency for Drugs and Technology in Health (CADTH), Dynamed and Medline OVID were searched for high quality systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.[5,6] 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:

Agency for Healthcare Research and Quality:

At the time of this review, a draft AHRQ review comparing the benefits and harms of combination of statin and other lipid-modifying medication to intensification of statin monotherapy was available, including studies through January 2013.[7] Studies in adults with moderate or high cardiovascular disease (CVD) risk were included. Fifty-eight RCTs were included in the analysis. The strength of evidence was overall variable across comparisons. Only one comparison had high strength of evidence for serious adverse events and nine comparisons had moderate strength of evidence for LDL and HDL outcomes. All other comparisons and outcomes had low or insufficient evidence, including clinical outcomes of mortality, acute coronary events, and revascularization procedures. Other conclusions related to LDL and HDL outcomes are defined below:

Bile acid sequestrants plus statin therapy

- There is moderate quality evidence that combination therapy with bile acid sequestrants and low potency statin therapy lowers LDL cholesterol up to 14% more compared to intensification of statin monotherapy.
- There was insufficient evidence to compare combined bile acid sequestrant and statin therapy with statin monotherapy on the rates of serious adverse events.

Ezetimibe plus statin therapy

- There is moderate quality evidence that combination therapy with ezetimibe in combination with mid potency statin improves LDL-c compared to high potency statin monotherapy and low quality evidence that it improves HDL-c compared with statin monotherapy.
- There is high quality evidence that high potency statin m monotherapy produces fewer serious adverse events than combination of mid potency statin with ezetimibe.
- In patients with preexisting coronary heart disease and in patients with diabetes, there is moderate quality evidence that ezetimibe in combination with mid potency statin more effectively lowers LDL and low quality evidence for raising HDL as compared to high potency statin monotherapy.

Fibrate plus statin therapy

- There is moderate quality evidence that high potency statin monotherapy lowers LDL up to 15% more than mid potency statin in combination with fibrate.
- Moderate quality evidence demonstrates that mid potency statin in combination with fibrate raises HDL up to 10% more than high potency statin monotherapy.
- There is insufficient evidence to compare fibrate plus statin combination therapy to statin monotherapy on the rates of serious adverse events.

Niacin plus statin therapy

- There is low quality evidence that high potency statin monotherapy lowers LDL up to 12% more than mid potency statin in combination with niacin.
- There is low quality evidence that mid potency statin in combination with niacin raises HDL more than high potency statin monotherapy.
- There is insufficient evidence to compare the combination of niacin and statin to statin monotherapy on the rates of serious adverse events.

Omega-3 Fatty Acid plus statin therapy

- There is insufficient evidence to compare the benefits or serious adverse events of combined lipid-modifying therapy with an omega-3 fatty acid and statin to statin monotherapy on LDL-c and HDL-c, regardless of statin potency.

The authors concluded that the evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL levels, including bile acid sequestrants and ezetimibe. However, intensification of statin monotherapy provided benefits or showed little difference with respect to LDL lowering in comparison to combination therapy with fibrates or niacin. There is insufficient evidence to address whether LDL lowering benefits achieved with these medications leads to decreased rates of CV disease. The evidence suggests that providers should tailor therapy based on individual patient needs and concerns for adverse events.

Canadian Agency for Drugs and Technologies in Health (CADTH)

In 2012, CADTH produced a rapid response evaluating the clinical evidence, safety and guidelines of lipid lowering agents for stroke prevention in elderly patients.[1] A literature search was done to identify evidence in geriatric patients on clinical outcomes of mortality, CV outcomes, NNT to prevent on stroke, and adverse events. Overall, two systematic reviews, two meta-analyses, six RCTs, and three non-randomized studies were reviewed. Main conclusions are as followed:

- Evidence suggests statins reduce the risk of all-cause mortality by 22% stroke by 25-47% in patients ≥ 65 years.
- Rosuvastatin reduces the incidence of major coronary events in healthy older persons without hyperlipidemia but with elevated high-sensisitivity CRP levels.
- Evidence suggests atorvastatin reduces the risk of cerebrovascular events and major coronary events (NNT 21 over 4 years).
- Simvastatin therapy in older patients was as safe and effective as younger patients.
- There was no significant difference between rosuvastatin and placebo in serious adverse events among elderly (RR 1.05, 95% CI 0.93 to 1.17).
- The safety profile of atorvastatin was similar between young and older recipients.
- Simvastatin related adverse events were similar between older and younger patients. Renal dysfunction was slightly higher in older patients than younger patients (0.32% vs. 0.14%, respectively; p<0.01).
- Discontinuation of statin therapy was an independent predictor of all cause one year mortality (HR 2.78; 95% CI 1.96 to 3.72; p=0.003).

While no evidence based guidelines were found regarding lipid lowering agents for stroke prevention in frail elderly patients, there is evidence to suggest that statins reduce the risk of stroke by 25-47%, major coronary events by 32-37%, and all-cause mortality by 22% in patients over 65 years of age. Safety profiles were similar, with the most common being muscle weakness, bleeding events, diabetes, and renal, gastrointestinal or hepatic disorders.

Cochrane Collaboration:

A recent Cochrane review assessed the benefits and harms of statins for the primary prevention of CVD.[2] Randomized controlled trials of at least 12 months in duration were included in the analysis. A total of 27 papers reporting on 14 trials were included in the original report and 56 articles on 4 new trials were included in this update. Overall, the 18 included trials involved 56,934 participants with outcomes observed from 1 to 5.3 years. The mean age of the population was 57 years and 60.3% were male. In general, there was low risk of bias although all trials were either fully or partially funded by pharmaceutical companies. Overall, trials showed reductions in all-cause mortality, composite CVD, fatal and non-fatal CVD events, total and LDL cholesterol, and revascularisations. No significant excess of combined adverse events, cancers, myopathy, rhabdomyolysis, liver enzyme elevation, renal dysfunction were found. A slight increased risk of incident diabetes was found in two trials.

Thirteen trials reported on all-cause mortality and overall 4.4% died in the statin group compared with 5.1% in the placebo group (NNT 96, 95% CI 64-244). Only the JUPITER trial showed strong evidence of a reduction in total mortality. Pooled data using a fixed-effect model favored statin treatment (OR 0.86, 95% CI 0.79-0.94). A risk reduction in fatal coronary heart disease (CHD) (1.1% vs. 1.3%; RR 0.82, 95% CI 0.70-0.96), reduction in risk of fatal CVD events (17.4% vs. 20.8%, RR 0.83, 95% CI 0.72-0.96), and non-fatal CVD events (3% vs. 4%, RR 0.77, 95% CI 0.62-0.96) was observed favoring the statin group compared to placebo. A significant risk reduction was also seen in fatal stroke events (17% vs. 22%, RR 0.78, 95% CI 0.68-0.89) and non-fatal strokes (1.3% vs. 2%, RR .69; 95% CI 0.58-0.83) in the statin group compared to placebo group.

Twelve trials reported on adverse events. Overall, there was no difference in event rates between the intervention and control groups (RR 1.00, 95% CI 0.97-1.03) and no differences were observed in the number of participants stopping statin treatment due to adverse events. Heterogeneity was observed in these analyses. Two trials reported new occurrences of type 2 diabetes and demonstrated a relative risk of developing diabetes of 1.18 (95% CI 1.01-1.39). This was driven by the JUPITER trial. There was no evidence of any excess risk of cancer and weak evidence for an increased risk of liver enzyme elevation (RR 1.16, 95% CI 0.87-1.54). There was insufficient data to evaluate patient quality of life. There was limited evidence suggesting that the use of statins for primary prevention is cost-effective.

The authors concluded that the evidence now supports the benefits of statins for primary prevention and further cost-effectiveness analyses are needed to guide the widespread use in these low risk populations.

Navarese et al.

With recent reports indicating that statins are associated with an increased risk for new-onset diabetes mellitus compared with placebo, this recent systematic review evaluated the impact of different types and doses of statins on new-onset diabetes.[3] A literature search was conducted through October 2012 and internal validity of the RCTs was assessed by 2 independent reviewers. Seventeen studies were included in the network meta-analysis. Nine studies evaluated new-onset DM in patients treated with high-dose statins compared with placebo. There were a total of 4,610 cases of new-onset DM (7.28%) in the high-dose statin group and 7.09% in the control group. Treatment with rosuvastatin 20mg/day was associated with a 25% relative increase in the risk for developing DM compared to placebo (OR 1.25, 95% CI 0.82-1.90). Therapy with pravastatin 40 mg/day was associated with the lowest risk (OR 1.07, 95% CI 0.86-1.30).

In patients treated with moderate-dose statins, 81.8% compared with 7.95% in the control group developed new-onset DM. Moderate dose rosuvastatin therapy still created the highest risk (RR 1.11, 95% CI 0.81-1.52) and pravastatin 10 mg/day was associated with a numerically lower risk of DM compared with placebo (RR 0.90, 95% CI 0.71-1.35). The risk was generally increased with higher dose statin regimens compared to moderate dose regimens and there was a gradient for the risk across different types and doses of statins. Numerically, pravastatin was associated with the lowest risk of new-onset DM and rosuvasatin was associated with the highest incidence of DM.

Naci et al.

A meta-analysis was done to determine the comparative effects of individual statins on major cerebrovascular events.[8] A medline search was done to identify literature between 1985 and 2011. Both open-label and double-blind RCTs comparing one statin to another in adults with cardiovascular disease were included. The primary outcome was major cerebrovascular events (defined as fatal- and non-fatal strokes and transient ischemic attacks). A total of 61 trials were identified. Overall, statin therapy was associated with a reduction in the risk of major cerebrovascular events (OR 0.82; 95% CI 0.77-0.87) when compared with control. Atorvastatin, pravastatin, and simvastatin were associated with a significant reduction in major cerebrovascular events compared with control, while fluvastatin, lovastatin and rosuvastatin were not.

There were 11 direct head-to-head studies that demonstrated no significant differences among statins in major cerebrovascular events. However, the evidence for some statins was much stronger and consistent compared to the evidence for others. In addition, a quality assessment of trials was not defined in the systematic review and open-label studies were included. Therefore, comparative results need to be interpreted with caution.

Tolerability and Harms:

A recent meta-analysis was done to evaluate the comparative harms of individual statins.[9] Open-label and double-blind RCTs comparing one statin with another or with control for adults with, or at risk of developing, CV disease were included. A total of 135 trials were included (n=246,955). The overall methodological quality of included trials was moderate, although it was unclear how quality was assessed in this analysis. Results showed that there was no difference in discontinuations because of adverse events between statins as a class and control (OR 0.95, 95% CI 0.83 to 1.08; I^2=21.9%). Simvastatin was significantly more tolerable than atorvastatin (OR 0.61, 95% CI 0.42-0.89; I2=71.9%) and rosuvastatin (OR 0.49; 95% CI 0.27-0.88; I2=0.0%). The network meta-analysis demonstrated that those randomized to pravastatin (OR 1.46, 95% CI 1.10-1.92) and simvastatin (OR 1.34, 95% CI 1.06-1.69) were significantly less likely to stop treatment because of adverse events compared to those randomized to atorvastatin. There was also no overall difference between statins and control in myalgia (OR 1.07; 95% CI 0.89-1.29; I2=22.2%) and those on simvastatin had lower odds of myalagia compared to atorvastatin (OR 0.56, 95% CI 0.42-0.75; I2=0.0%). There was no significant difference in cancer occurrences between statins and control or between individual statins, which a higher incidence of diabetes mellitus with statins compared to control (OR 1.09; 95% CI 1.02-1.16; I2=2.8%). There were no statistically detectable differences between individual statins in terms of diabetes mellitus incidence. The authors concluded that overall, statins as a class are associated with an increased risk of diabetes mellitus and hepatic transaminase elevations, with no statistically significant difference in myalgia, myopathy, rhabomyolysis, and cancer. When compared head-to-head in network meta-analysis, simvastatin and pravastatin are likely to be superior in their safety profile compared to the other agents.

Statin Use in Patients with Chronic Kidney Disease:

A systematic review and meta-analysis was done to evaluate the effects of statins on major clinical outcomes in patients with chronic kidney disease (CKD).[10] A literature search for prospective, RCTs through November 2011 identified 31 included trials (n=48,429). The Jadad scale was used to assess trial quality; 13 trials had a score of 4 and all others had a score of 3 or less. Overall, statin therapy produced a reduction in the risk of CV events (RR 0.77, 95% CI 0.70-0.85, P<0.001) with evidence of heterogeneity in the individual trials. A reduction in CV events was seen when evaluated based on CKD stage, including CKD stage 5 (RR 0.92, 95% CI 0.85-0.99; p=0.031; ARR 2.2%; NNT 46), CKD stage 4 (RR 0.78, 95% CI 0.63-0.96; p=0.017; ARR 2.8%; NNT 36), and CKD stage 3 or stage 2 (RR 0.69, 95% CI 0.63-0.77; p<0.001; ARR 4.2%; NNT 24), with a more pronounced effect in lower CKD stages demonstrating that statin effect was modified by kidney function. There was no significant difference seen in CKD stage 5 – non-dialysis patients (RR 0.82, 95% CI 0.60-1.11), and overall there was a larger benefit in patients not on dialysis (RR 0.70, 95% CI 0.63-0.99) than those on dialysis (RR 0.92, 95% CI 0.85-0.99). Overall, there was no effect of statin therapy on the risk of stroke (RR 0.79, 95% CI 0.56-1.12) with evidence of heterogeneity between trials. Statin therapy also reduced all-cause death (RR 0.92, 95% CI 0.85-0.99) and cardiovascular death (RR 0.91, 95% CI 0.84-0.99). Based on 6 trials, there was no evidence that statins reduced the risk of kidney failure (RR 0.95, 95% CI 0.90-1.01). A subgroup analysis demonstrated that the effect of statin therapy on major CV events was modified by the average baseline kidney function of the subjects in the trials with a progressively smaller relative risk reduction with a lower estimated glomerular filtration rate (GFR). There was no significant difference in the risk of hepatic impairment, muscle pain, increased creatinine kinase level, cancer morbidity, and severe adverse events in the statin-treated groups compared to control. This review combined data from RCTs with data from CKD subgroups which lowers the strength of this review.

A systematic review and meta-analysis by Palmer et al. also evaluated the benefits and harms of statin therapy for adults with CKD.[11] A literature search through February 2012 identified 80 randomized trials comparing the effects of statins with placebo, no treatment, or another statin on mortality and CV outcomes. Two or more authors independently evaluated the trials for quality and evidence was rated using the GRADE method for each outcome.. Many of the included trials reported 1 or more risks of bias. The evidence showed a statistically significantly different treatment effect on mortality according to the stage of CKD (p=0.009). Moderate-to-high quality evidence indicated that stain treatment reduced all-cause mortality (RR 0.81, 95% CI 0.74 to 0.88) and cardiovascular mortality (RR 0.78, 95% CI 0.68 to 0.89) in persons not receiving dialysis but had little or no effect in persons receiving dialysis (RR 0.96, 95% CI 0.88 to 1.04 and RR 0.94, 95%

CI 0.82 to 1.07, respectively). There was low-quality evidence that treatment effects of mortality were uncertain in kidney transplant pateints (RR 1.05, 95% CI 0.84 to 1.31). Strong evidence demonstrated that treatment effects on major CV events were statistically significantly different between the subgroups showing a prevention in major CV events in persons receiving dialysis (RR 0.76, 95% CI 0.73 to 0.80), but little effect in persons receiving dialysis (RR 0.95, 95% CI 0.87 to 1.03). Overall, there was no difference in fatal or nonfatal stroke (RR 0.86, 95% CI 0.62 to 1.20). The authors concluded that the benfits of stain therapy for mortality and CV outcomes differ depending on stage of CKD. Moderate to high quality evidence indicates that statins reduce all-cause and CV mortality and major CV events in persons not receiving dialysis, while having little or no effect in persons receiving dialysis, despite decrease in serum cholesterol levels. There remains insufficient evidence for the use of statins in kidney transplant recipients. This analysis also included data from post hoc analysis of larger trials, which may be less reliable data.

A third systematic review was conducted by Updahyay et al examining the effect of lipid-lowering therapy on clinical outcomes in persons with CKD.[12] A literature search from January 2000 through November 2011 identified 18 RCTs (n=36,528). Lipid lowering agents in addition to statins were included in this review, such as ezetimibe, niacin, colestipol, and cholestyramine. However, 16 of the 18 RCTs evaluated various statins. Overall, there was moderate evidence that lipid lowering therapy was beneficial on all-cause mortality (RR 0.91, 95% CI 0.83 to 0.99; p=0.031), with the upper limit of the 95% CI close to 1.0 and studies having significant heterogeneity. The subgroup of patients with CKD not receiving dialysis was the only subgroup of patients with a statistically significant rate ratio. Trials included participants with different stages of CKD and different baseline risks. The four trials reporting on CV mortality did not show lipid-lowering therapy to be beneficial (RR 0.96, 95% CI 0.87 to 1.06; p=0.41). The authors concluded that the benefit in all-cause mortality was limited to studies in patients with CKD not receiving dialysis and the results were highly heterogeneous. This review also showed that stroke was not prevented by lipid-lowering therapy in patients with CKD.

Guidelines:

In 2012, The Endocrine Society updated the clinical guidelines for the treatment of hypertriglyceridemia.[13] The guidelines recommend that statins not be used as monotherapy for severe or very severe hypertriglyceridemia. However, statins may be useful for the treatment of moderate hypertriglyceridemia when indicated to modify CV risk.

In 2012, the National Heart, Lung, and Blood Institute (NHLBI) expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents was updated.[14] Evidence was graded A-D based on the study design (A from RCTs, D from expert opinion). Statements were given a definition and included: Strong Recommendation, Recommendation, Optional, and No Recommendation. Statins are generally recommended in children ages 11-21 years with elevated LDL-C levels but not specific recommendations are given preferring one statin over another. Although some of the recommendations were based on Grade A evidence, the majority of the evidence is based on efficacy trials evaluating changes in lipid profiles and vascular markers. There is very limited evidence based on reducing the rate of cardiovascular disease events.

New drugs:

None

New Formulations/Indications:

FDA approved a new fixed dose combination product of atorvastatin and ezetimibe (Liptruzet®) in May 2013 for the treatment of hyperlipidemia.

Approval was based on two unpublished RCTs demonstrating that atorvastatin/ezetimibe was equivalent in terms of LDL-C reduction compared to the co-administration of ezetimibe 10mg with atorvastatin 20mg and 40mg.[15] Both studies were similar in design; one evaluated the combination with atorvastatin 20mg, the other with atorvastatin 40mg. Subjects included adults with primary hypercholesterolemia at low, moderate, or moderately high CV risk. The primary objective of the studies was LDL-C lowering efficacy. A total of 406 and 328 subjects were included in each study. The population was mostly Caucasian, 60% female, mean age of 55, and average BMI of 30 kg/m2. The mean baseline LDL-C was 162 mg/dl. The 95% confidence intervals for the changes in LDL-C were within the predefined ± 4%, and therefore the combination tablets were considered pharmacodynamically equivalent to the co-administered tablets.

New FDA safety alerts:
None

New Trials:

The initial literature search resulted in 313 citations. After reviewing abstracts, a total of 8 potentially relevant RCTs were identified and are briefly described in Table 1. Two of these trials were evaluating long term clinical outcomes[16], [17] and the others are head to head trials evaluating lipid lowering outcomes. The abstracts of these trials are included in Appendix 1.

Table 1: Description of Relevant Randomized Controlled Trials

Study	Comparison	Population	Primary Outcome	Results
Mulders et al.[16] RCT, DB, PC	Atorvastatin 20mg vs. placebo	Positive family history for CAD and coronary calcium scoring above the 80th percentile	Cardiovascular events	Cardiovascular Event Ator: 7.2% Pla: 12.5% HR 0.55, 95% CI 0.31-0.97; p=0.04, NNT 19 Cardiovascular Event w/o family history: Ator: 6.6% Pla: 6.8% HR 1.04, 95% CI 0.51-2.13; p=0.912
Ridker et al.[17] Secondary analysis of JUPITER	Rosuvastatin 20 mg vs. placebo	Stratified on the basis of having none or at least one of four major risk factors for developing diabetes	MI, stroke, admission to hospital for unstable angina, arterial revascularization, or CV death	Those with one or more major diabetes risk factor were at higher risk of developing diabetes than those without.
Backes et al.[18]	Rosuvastatin 80mg once	Adults with dyslipidemia	Lipid Changes	Changes in HDL, triglycerides,

RCT, DB	weekly vs. atorvastatin 10 mg daily (n=20)			and CRP were nosignificant and similar between groups.
Hing Ling et al.[19] RCT, DB	Switching to Ezetimibe/simvastatin 10/40 mg vs. atorvastatin 40 mg (doubling dose) (n=250)	Adults at high CV risk with uncontrolled hypercholesterolemia already on atorvastatin 20 mg or its equivalent	Percent change from baseline in LDL-C	<u>Change in LDL-C at 6 weeks:</u> Ezet/Sim: -26.8% Ator 40: -11.8% Treatment Difference = -15.0%, 95% CI -21.15, -8.84% P<0.001
Lee et al.[20] RCT, open-label	Atorvastatin 20mg/day vs. rosuvastatin 10mg/day (n=350)	Statin-naïve auldts with clinically indicated percutaneous coronary intervention	Percent change in total theroma volume (TAV)	<u>Percentage change in TAV:</u> Ator: -3.9% Rosu: -7.4% p=0.018 Usual doses of atorvastatin and rosuvastatin induced significant regression of coronary atherosclerosis in statin-naïve patients, with a greater decrease in favor of rosuvastatin
Lee et al.[21] RCT, open=label	Atorvastatin 20 mg vs. atorvastatin/ezetimibe 5 mg/5 mg (n=78)	Adults with combined hyperlipidemia	Percentage changes in levels of fasting and postprandial TG from baseline to week 8	<u>Change in fasting TG</u> Ator/ez: -30% Ator: -18% P=0.07 <u>Change in postprandial TG</u> Ator/ez: -34% Ator: -13% P=0.03
Pitt et al.[22] Open-label	Rosuvastatin 20 mg vs. rosuvastatin 40 mg vs. atorvastatin 80 mg (n=825)	Adults with acute coronary syndrome	LDL lowering over 6 to 12 weeks	<u>LDL lowering</u> Ros 40: 46.8% Ator 80: 42.7% P=0.02 Ros 20mg was similar to ator 80mg.

Stender et al.[23] RCT, DB, non-inferiority	Pitavastatin (1, 2, and 4 mg) vs. pravastatin (10, 20, and 40 mg) (n=942)	Elderly patients (> or = 65 years) with primary hypercholesterolemia or mixed dyslipidemia	Mean percentage LDL-C reduction at 12 weeks	<u>Mean decrease in LDL:</u> Pitavastatin: 31.4%-44.3% Pravasatin: 22.4-34.0% P<0.001 for all dose comparisons

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Appendix 1: Randomized Controlled Trial Abstracts

- *Mulders, T. A., S. Sivapalaratnam, et al. (2012). "Asymptomatic individuals with a positive family history for premature coronary artery disease and elevated coronary calcium scores benefit from statin treatment: a post hoc analysis from the St. Francis Heart Study." Jacc: Cardiovascular Imaging 5(3): 252-260.*

OBJECTIVES: The goal of this study was to evaluate whether individuals with a positive family history for premature coronary artery disease (CAD) and coronary calcium scoring (CCS) above the 80th percentile might benefit from preventive treatment.
BACKGROUND: First-degree relatives of patients with premature CAD have an increased risk for cardiovascular disease (CVD), whereas events are poorly predicted in these individuals. Surrogate markers, such as CCS, might refine risk scoring. Nevertheless, the outcome of the St. Francis Heart trial, which investigated the effect of atorvastatin 20 mg/day in asymptomatic individuals with CCS above the 80th percentile, did not reach statistical significance.
METHODS: We performed a post hoc analysis on the database of the St. Francis trial to assess efficacy of treatment with atorvastatin 20 mg/day in those with CCS above the 80th percentile and presence (n = 543) or absence (n = 462) of a positive family history for premature CAD. All participants received aspirin 81 mg/day. Primary outcome included coronary death, myocardial infarction, coronary revascularization, stroke, and arterial surgery.
RESULTS: A total of 1,005 individuals, with a mean age of 59.0 +/- 5.9 years and a median absolute CCS of 370 Agatston units (interquartile range: 183 to 662) participated in the trial. After a follow-up of 4.3 (interquartile range: 3.5 to 4.5) years, 7.2% of the treated individuals with a positive family history had a cardiovascular event versus 12.5% of the placebo group (hazard ratio [HR]: 0.55; 95% confidence intervals [CI]: 0.31 to 0.97; p = 0.040). This is comparable with a number needed to treat of 18.9. In individuals without a family history, events were minimally reduced: 6.6% in the treated versus 6.8% in the placebo group (HR: 1.04; 95% CI: 0.51 to 2.13; p = 0.912).
CONCLUSIONS: The combination of a positive family history and CCS above the 80th percentile identifies a subgroup within the primary prevention population that receives greater benefit from statin treatment than the population at large. These results have important implications for future guidelines concerning individuals with a positive family history for premature CAD. Copyright 2012 American College of Cardiology Foundation.

- *Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012 Aug 11;380(9841):565-71. doi: 10.1016/S0140-6736(12)61190-8.*

BACKGROUND:
In view of evidence that statin therapy increases risk of diabetes, the balance of benefit and risk of these drugs in primary prevention has become controversial. We undertook an analysis of participants from the JUPITER trial to address the balance of vascular benefits and diabetes hazard of statin use.
METHODS:

In the randomised, double-blind JUPITER trial, 17,603 men and women without previous cardiovascular disease or diabetes were randomly assigned to rosuvastatin 20 mg or placebo and followed up for up to 5 years for the primary endpoint (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation, or cardiovascular death) and the protocol-prespecified secondary endpoints of venous thromboembolism, all-cause mortality, and incident physician-reported diabetes. In this analysis, participants were stratified on the basis of having none or at least one of four major risk

factors for developing diabetes: metabolic syndrome, impaired fasting glucose, body-mass index 30 kg/m(2) or higher, or glycated haemoglobin A(1c) greater than 6%. The trial is registered at ClinicalTrials.gov, NCT00239681.
FINDINGS:
Trial participants with one or more major diabetes risk factor (n=11,508) were at higher risk of developing diabetes than were those without a major risk factor (n=6095). In individuals with one or more risk factors, statin allocation was associated with a 39% reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47-0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39-1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64-1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07-1·54, p=0·01). Thus, for those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33-0·68, p=0·0001), a 53% reduction in venous thromboembolism (0·47, 0·21-1·03, p=0·05), a 22% reduction in total mortality (0·78, 0·59-1·03, p=0·08), and no increase in diabetes (0·99, 0·45-2·21, p=0·99). For such individuals, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed. In analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin vs 216 on placebo; HR 1·25, 95% CI 1·05-1·49, p=0·01), the point estimate of cardiovascular risk reduction associated with statin therapy (HR 0·63, 95% CI 0·25-1·60) was consistent with that for the trial as a whole (0·56, 0·46-0·69). By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5·4 weeks (84·3 [SD 47·8] weeks on rosuvastatin vs 89·7 [50·4] weeks on placebo).
INTERPRETATION:
In the JUPITER primary prevention trial, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes.

- *Backes, J. M., C. A. Gibson, et al. (2012). "The high-dose rosuvastatin once weekly study (the HD-ROWS)." Journal of Clinical Lipidology 6(4): 362-367.*

BACKGROUND: Alternative dosing is often used clinically to address common barriers with statin therapy, such as intolerance and cost. Previous findings have demonstrated significant and clinically similar reductions in low-density lipoprotein (LDL) cholesterol to daily dosing, when comparing similar total weekly doses.
OBJECTIVE: To determine whether rosuvastatin 80 mg once weekly produced comparable lipid and high-sensitivity C-reactive protein (hsCRP) changes to atorvastatin 10 mg daily, when measured at key points after last dose.
METHODS: This was a randomized, double-blind, parallel group, 8-week pilot study. Eligible subjects, 18 to 65 years of age, had documented dyslipidemia with LDL cholesterol >100 mg/dL and triglycerides <200 mg/dL. Participants were randomized to receive either rosuvastatin 80 mg once weekly (n= 10) or atorvastatin 10 mg daily (n= 10), for 8 weeks. Lipid panels and hsCRP were measured at baseline and 1-4 and 5-8 days after the last dose.
RESULTS: Participants in each arm experienced significant and comparable reductions from baseline in total cholesterol, total cholesterol/high-density lipoprotein cholesterol ratio, non-high-density lipoprotein cholesterol, and overall LDL cholesterol (-29%). Changes in high-density lipoprotein cholesterol, triglycerides, and hsCRP were nonsignificant and similar between groups. Each regimen was well tolerated, with no major adverse events reported.
CONCLUSION: Rosuvastatin 80 mg once weekly produced comparable lipid changes to atorvastatin 10 mg daily when measured at specific points after the last dose. Our findings support previous data demonstrating a significant reduction in LDL-C with once weekly statin dosing.

- *Hing Ling, P. K., F. Civeira, et al. (2012). "Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study." Lipids in Health & Disease 11: 18.*

BACKGROUND: A considerable number of patients with severely elevated LDL-C do not achieve recommended treatment targets, despite treatment with statins. Adults at high cardiovascular risk with hypercholesterolemia and LDL-C >= 2.59 and <= 4.14 mmol/L (N = 250), pretreated with atorvastatin 20 mg were randomized to ezetimibe/simvastatin 10/40 mg or atorvastatin 40 mg for 6 weeks. The percent change in LDL-C and other lipids was assessed using a constrained longitudinal data analysis method with terms for treatment, time, time-by-treatment interaction, stratum, and time-by-stratum interaction. Percentage of subjects achieving LDL-C < 1.81 mmol/L, < 2.00 mmol/L, or < 2.59 mmol/L was assessed using a logistic regression model with terms for treatment and stratum. Tolerability was assessed.
RESULTS: Switching to ezetimibe/simvastatin resulted in significantly greater changes in LDL-C (-26.81% vs.-11.81%), total cholesterol (-15.97% vs.-7.73%), non-HDL-C (-22.50% vs.-10.88%), Apo B (-17.23% vs.-9.53%), and Apo A-I (2.56%vs.-2.69%) vs. doubling the atorvastatin dose (all p <= 0.002), but not HDL-C, triglycerides, or hs-CRP. Significantly more subjects achieved LDL-C < 1.81 mmol/L (29% vs. 5%), < 2.00 mmol/L (38% vs. 9%) or < 2.59 mmol/L (69% vs. 41%) after switching to ezetimibe/simvastatin vs. doubling the atorvastatin dose (all p < 0.001). The overall safety profile appeared generally comparable between treatment groups.
CONCLUSIONS: In high cardiovascular risk subjects with hypercholesterolemia already treated with atorvastatin 20 mg but not at LDL-C < 2.59 mmol/L, switching to combination ezetimibe/simvastatin 10/40 mg provided significantly greater LDL-C lowering and greater achievement of LDL-C targets compared with doubling the atorvastatin dose to 40 mg. Both treatments were generally well-tolerated.

- *Lee, C. W., S.-J. Kang, et al. (2012). "Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild coronary atherosclerotic plaques (from the ARTMAP trial)." American Journal of Cardiology 109(12): 1700-1704.*

High-dose rosuvastatin induces regression of coronary atherosclerosis, but it remains uncertain whether usual-dose statin has similar effects. We compared the effects of atorvastatin 20 mg/day versus rosuvastatin 10 mg/day on mild coronary atherosclerotic plaques (20% to 50% luminal narrowing and lesion length >10 mm) using intravascular ultrasound (IVUS). Three hundred fifty statin-naive patients with mild coronary atherosclerotic plaques were randomized to receive atorvastatin 20 mg/day or rosuvastatin 10 mg/day. IVUS examinations were performed at baseline and 6-month follow-up. Primary end point was percent change in total atheroma volume (TAV) defined as (TAV at 6 months - TAV at baseline)/(TAV at baseline) x 100. Evaluable IVUS was obtained for 271 patients (atorvastatin in 143, rosuvastatin in 128). Clinical characteristics, lipid levels, and IVUS measurements at baseline were similar between the 2 groups. At 6-month follow-up, percent change in TAV was significantly less in the atorvastatin group than in the rosuvastatin group (-3.9 +/- 11.9% vs -7.4 +/- 10.6%, respectively, p = 0.018). In contrast, change in percent atheroma volume was not different between the 2 groups (-0.3 +/- 4.2 vs -1.1 +/- 3.5, respectively, p = 0.157). Compared to baseline, TAV and TAV at the most diseased 10-mm subsegment were significantly decreased in the 2 groups (p <0.001). Changes in lipid profiles at 6-month follow-up were similar between the 2 groups. In conclusion, usual doses of atorvastatin and rosuvastatin induced significant regression of coronary atherosclerosis in statin-naive patients, with a greater decrease in favor of rosuvastatin.

- *Lee, S.-H., S. Park, et al. (2012). "Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipedemia." Journal of Cardiovascular Pharmacology & Therapeutics 17(1): 65-71.*

Postprandial triglyceride (TG) levels are easy to measure and are associated with future cardiovascular risk. The aim of this study was to compare the effects of statin monotherapy and low-dose statin/ezetimibe on lipid parameters including fasting and postprandial TG. After a 4-week dietary run-in period, 78 patients with combined hyperlipidemia were randomized into 1 of 2 treatment groups for 8 weeks: atorvastatin 20 mg or atorvastatin/ezetimibe 5 mg/5 mg. An oral fat load test was performed before and after the drug-treatment period. The low-dose combination had a tendency to decrease fasting TG more than atorvastatin monotherapy. The combination regimen showed a greater reduction in postprandial TG (-13% +/- 42% and -34% +/- 30%, in the atorvastatin and combination groups, respectively, P = .03) and total cholesterol (TC; P = .03). The changes in low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) were not different between the 2 groups. The reduction in apo B/A1 was greater in the combination group (-32% +/- 19% and -42% +/- 13%, in the atorvastatin and combination groups, respectively, P = .02). In conclusion, these results demonstrated a potential beneficial effect of low-dose atorvastatin/ezetimibe combination treatment on postprandial TG control after comparable LDL-C lowering in patients with combined hyperlipidemia.

- *Pitt, B., J. Loscalzo, et al. (2012). "Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study)." American Journal of Cardiology 109(9): 1239-1246.*

Patients with acute coronary syndrome are recommended for early aggressive low-density lipoprotein (LDL) cholesterol-lowering therapy. The LUNAR study compared the efficacy of rosuvastatin with that of atorvastatin in decreasing LDL cholesterol in patients with acute coronary syndrome. Adult patients with coronary artery disease who were hospitalized for an acute coronary syndrome within 48 hours of first symptoms were randomized (n = 825) to an open-label, once-daily treatment with rosuvastatin 20 mg (RSV20), rosuvastatin 40 mg (RSV40), or atorvastatin 80 mg (ATV80) for 12 weeks. Patients were evaluated at weeks 2, 6, and 12. The primary end point was treatment efficacy in lowering LDL cholesterol averaged over 6 to 12 weeks. Changes in other lipoproteins, including high-density lipoprotein (HDL) cholesterol, and safety were evaluated. Analysis of covariance was used to compare least squares mean differences between each rosuvastatin treatment arm and the atorvastatin arm. The efficacy of RSV40 in lowering LDL cholesterol was significantly greater than that of ATV80 (46.8% vs 42.7% decrease, p = 0.02). LDL cholesterol lowering by RSV20 was similar to that by ATV80. Increases in HDL cholesterol were significantly greater with RSV40 (11.9%, p <0.001) and RSV20 (9.7%, p <0.01) than with ATV80 (5.6%). RSV40 was also significantly more effective than ATV80 in improving most other secondary efficacy variables, whereas the effects of RSV20 on these parameters were generally similar to those of ATV80. All 3 treatments were generally well tolerated over 12 weeks. In conclusion, results from the LUNAR study show that RSV40 more effectively decreased LDL cholesterol, increased HDL cholesterol, and improved other blood lipid parameters than ATV80 in patients with acute coronary syndrome.

12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia." European Journal of Preventive Cardiology 20(1): 40-53.
AIM: To compare the safety and efficacy of once-daily pitavastatin (1, 2, and 4 mg) and pravastatin (10, 20, and 40 mg) in elderly patients (>= 65 years of age) with primary hypercholesterolaemia or combined (mixed) dyslipidaemia.
DESIGN: After a 6-8-week washout/dietary period, patients were randomized to six treatment groups (1, 2, or 4 mg pitavastatin vs. 10, 20, or 40 mg pravastatin) in a 12-week multicentre double-blind study. Patients (n = 942; men, 44.3%; Caucasian, 99.3%; mean age, 70 years; age range, 65-89 years) in all groups were well matched for duration of disease and diagnosis.
RESULTS: Mean decreases in low-density lipoprotein cholesterol over 12 weeks were 31.4- 44.3% with pitavastatin 1-4 mg and 22.4-34.0% with pravastatin 10-40 mg (p < 0.001 for all dose comparisons). Compared with pravastatin, pitavastatin provided greater decreases in total cholesterol and apolipoprotein B in all dose groups (p < 0.001) and triglycerides in the low-dose (p = 0.001) and higher-dose (p = 0.016) groups, and greater increases in

high-density lipoprotein cholesterol in the intermediate-dose ($p = 0.013$) and higher-dose ($p = 0.023$) groups. The proportions of patients achieving the European Atherosclerosis Society target with pitavastatin and pravastatin, respectively, were: low doses, 59.9 and 37.9%; intermediate doses, 79.5 and 51.0%; higher doses, 88.1 and 65.7% ($p < 0.001$ for all comparisons). Both statins were well tolerated, with no reports of myopathy or rhabdomyolysis. CONCLUSION: Pitavastatin provides superior efficacy and comparable tolerability to pravastatin in elderly patients.

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Month/Year of Review: November 2013 **Date of Last Review:** May 2006
PDL Classes: Antiemetics, Newer **Source Document:** DERP

Current Status of PDL Class:
- Preferred Agents: ONDANSETRON TAB RAPDIS/SOLUTION/TABLET
- Non-Preferred Agents: APREPITANT/FOSAPREPITANT (EMEND®), DOXYLAMINE SUCCINATE/PYRIDOXINE HCL (DICLEGIS®), DOLASETRON (ANZEMET®), GRANISETRON HCL, GRANISETRON TRANSDERMAL PATCH (SANCUSO®), ONDANSETRON ORAL FILM (ZUPLENZ®), PALONOSETRON (ALOXI®)

Previous Conclusions and Recommendation:
- In patients with post-operative nausea and vomiting (PONV) and chemotherapy induced nausea and vomiting (CINV):
  - Dolasetron, granisetron and ondansetron are equally effective in preventing nausea or vomiting.
  - Palonsetron may be superior to dolasetron and ondansetron for acute/delayed complete response rates.
  - Aprepitant has been studied as an add-on for standard therapy.
- In patients with radiotherapy-induced nausea and vomiting (RINV):
  - Granisetron and ondansetron showed no difference in efficacy.
- In pregnant patients:
  - Ondansetron was not superior to promethazine for effectiveness, but was less sedating.
  - Long term studies show no difference in number of live births, proportion of infant deformities, and birth weight between ondansetron and the active control groups.
- Heterogeneity of trials precludes accurate assessment of comparative tolerability or safety for the newer antiemetic drugs.
- Ondansetron is superior to granisetron for complete response rates in subpopulations based on a predisposition to nausea/vomiting such as motion sickness or previous treatment with emetogenic chemotherapy.

PA Criteria: Prior authorization is in place to: promote preferred drugs, reserve costly antiemetics for appropriate indications, restrict chronic use (> 3 days per week), and if chemotherapy is more frequent than once weekly, approve a quantity sufficient for three days beyond the duration of chemotherapy (Appendix 1).

Conclusions and Recommendations:
- There is evidence that palonsetron may be superior to other 5HT3 antagonists in the treatment of chemotherapy induced nausea and vomiting for moderately emetogenic chemotherapy and that ondansetron, dolasetron, and granisetron are equally effective.
- There is low quality evidence that the combination of doxylamine/pyridoxine led to significantly greater improvement in nausea vomiting symptoms as compared with placebo (-4.8 PUQE score vs. -3.9; p=0.006) but insufficient comparative evidence compared to other available agents. Maintain as non-preferred.
- Evaluate comparative costs in executive session.

Methods:
A recent DERP scan searched Ovid MEDLINE from January 2009 to April 2013 for included drugs and limits for humans, English, and controlled clinical trials. The Cochrane Collection, Agency for Health Care Research and Quality (AHRQ), National Institute for Clinical Evidence (NICE), Canadian Agency for Drugs and Technology in Health (CADTH), 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:
In 2009, the Oregon evidence-based Practice Center completed an update report for DERP on the newer antiemetics. The objective of the review was to evaluate the comparative effectiveness and harms of newer antiemetic drugs including the type 3 serotonin (5-HT3) and substance P/neurokinin 1 (NK1) antagonists. Adults or children with nausea and vomiting related to chemotherapy, radiation, surgery and pregnancy were included. A total of 34 new studies were included in the update (in addition to the 185 from the original report). Main findings were as follows:

Prevention of chemotherapy-induced nausea and vomiting:
- The numbers of patients with complete response were similar with ondansetron, dolasetron, and granisetron, with no consistent statistically significant differences.
- The evidence does not indicate differences between oral and intravenous or between various oral formulations.

Prevention of postoperative nausea and vomiting:
- There were no consistent statistically significant differences in efficacy between dolasetron, granisetron, or the orally disintegrating tablet formulation of ondansetron with traditional ondansetron or in comparisons between dolasetron and granisetron.

Treatment of established nausea and vomiting:
- One trial showed dolasetron was superior to ondansetron in reducing the need for rescue therapy (40% vs. 70%; p=0.004) but there was no difference in the number of nausea and vomiting related hospital admissions.
- One trial demonstrated no statistically significant differences between granisetron and ondansetron in complete response rates (60% for granisetron 0.1 mg, 68% for granisetron 1 mg, 47% for ondansetron).

Tolerability and Safety:
- In chemotherapy patients, 3 trials showed that ondansetron was associated with higher rates of dizziness and abnormal vision than dolasetron and granisetron.
- Dolasetron was associated with higher rates of constipation and diarrhea than ondansetron in 1 trial.
- For the prevention of postoperative nausea and vomiting, no consistent differences were seen for overall adverse events withdrawals due to adverse events, or any particular adverse event.

Canadian Agency for Drugs and Technologies in Health (CADTH)
In February 2013, CADTH produced a rapid response review evaluating ondansetron for the management of chemotherapy induced nausea and vomiting in pediatric patients.[1] A limited literature search was conducted from January 2008 to January 2013. Key findings were as follows:
- For the management of CINV in pediatrics, the effects of ondansetron plus dexamethasone appeared to be better than ondansetron alone or placebo.
- There was no statistically significant difference in antiemetic effect between ondansetron and tropisetron.
- There were some inconsistencies in the results for antiemetic effects of ondansetron compared with granisetron.
- Numerical values suggested that the antiemetic effects of palonsetron was greater compared to ondansetron, however it was unclear if the differences were statistically significant.
- Headache was the most commonly reported adverse event and appeared to be similar for various drug comparisons; however, adverse events were reported in few studies.

Guidelines:
The American Society of Clinical Oncology released an updated practice guideline for antiemetics in Oncology in November 2011.[2] The guideline is based on a systematic review of the literature funded by AHRQ. Recommendations are grouped based on chemotherapy regimens and are as followed:

- *Highly emetogenic agents:* The three-drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended
- *Moderately emetogenic agents:* The two-drug combination of palonosetron and dexamethasone is recommended. If palonosetron is not available, clinicians may substitute a first-generation 5-HT3 receptor antagonist, preferably granisetron or ondansetron. This was based on evidence that supports the equivalency of granisetron and ondansetron and findings that suggested palonsetron provides superior protection against both nausea and vomiting particularly during the period from 24-120 hours after chemotherapy.
- *Low emetogenic agents:* A single 8-mg dose of dexamethasone is suggested.
- Both dexamethasone and a 5-HT3 antagonist are recommended for patients undergoing high-dose chemotherapy.

New drugs:
In April 2013, the combination of doxylamine and pyridoxine (Diclegis®) was approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. This combination was previously available in a fixed-dose combination (Bendectin) for morning sickness, but was voluntarily withdrawn from the US in 1983 because of claims of teratogenicity that have seen been disproven.[3] Approval was based on the results of a 15-day randomized, double-blind placebo-controlled trial in 259 pregnant women with nausea and vomiting not responding to lifestyle changes.[4] Patients were randomized to receive the combination tablets with 10 mg each of doxylamine and pyridoxine or placebo. The combination of doxylamine/pyridoxine led to significantly greater improvement in nausea vomiting symptoms as compared with placebo (-4.8 PUQE score vs. -3.9; p=0.006). Women receiving active treatment were significantly more likely to request continued therapy than those on placebo (48.9% vs. 32.8%; p=0.009).

New Formulations/Indications:
Granisetron transdermal patch (Sancuso®) was FDA approved in September 2008.

Ondansetron oral film (Zuplenz®) was FDA approved in Jul 2010.

New FDA safety alerts:
In December 2012, the FDA notified health care professionals that the 32 mg, single IV dose of ondansetron will no longer be marketed because of the risk of QT interval prolongation, which can lead to Torsades de Pointes. In June 2012, the FDA issued a drug safety communication recommending against the use of a 32 mg IV dose of ondansetron, due to a dose-dependent QT prolongation demonstrated in a QT study. This was an update of a 2011 ongoing safety review and announcement advising against use in those with congenital long QT study. The FDA notes that the lower IV regimen of 0.15 mg/kg every 4 hours for 3 doses may be used in adults with chemotherapy-induced nausea and vomiting, as long as no single dose exceeds 16 mg. The FDA recommended ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or concomitant administration of other QT prolonging medications, while receiving ondansetron.

In September of 2011 the FDA approved a safety labeling change warning for Anzemet (dolasetron mesylate) tablet and injection indicating that it has been shown to cause dose dependent prolongation of the PR and QRS interval and reports

of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients for which it should be used with caution certain patients.

In December 2010, FDA notified healthcare professionals that the injection form of dolasetron should no longer be used to prevent nausea and vomiting associated with chemotherapy in pediatric and adult patients, due to risk of developing torsade de pointes.

New Trials (Appendix 2):

Since the 2009 DERP update, 7 head to head trials were identified. Placebo-controlled trials were not included.

Habib 2011[5]	**Ondansetron vs. apereitant**	**PONV in adults**
Boccia 2011[6]	**Granisetron transdermal vs granisetron**	**Chemotherapy in adults**
Metaxari 2011[7]	**Granisetron vs. ondansetron**	**PONV in adults**
Sidique 2011[8]	**Granisetron vs. ondansetron**	**Chemotherapy in adults**
Basu 2011[9]	**Polonsetron vs. ondansetron vs. granisetron**	**PONV in adults**
Moon 2012[10]	**Polonsetron vs. ondansetron**	**PONV in adults**
Park 2011[11]	**Polonsetron vs. ondansetron**	**PONV in adults**

References:

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9. Basu A, Saha D, Hembrom BP, Roy A, Naaz A. Comparison of palanosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. *J Indian Med Assoc*. 2011;109(5):327–329.

10. Moon YE, Joo J, Kim JE, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. *Br J Anaesth*. 2012;108(3):417–422. doi:10.1093/bja/aer423.

11. Park SK, Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery. *J Int Med Res*. 2011;39(2):399–407.

Appendix 1

Antiemetics, New

Goal(s):

- Promote Preferred drugs.
- Reserve costly antiemetics for appropriate indications.
- Restrict chronic use (> 3 days per week).
- If chemotherapy is more frequent than once weekly, approve a quantity sufficient for three days beyond the duration of chemotherapy.

Length of Authorization: 3 days to 6 months (criteria specific)

Requires PA:

- Non-preferred drugs.

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

Check the Reason for PA:

- Non-preferred drugs will deny on itiation
- Preferred drugs will deny only when maximum dose exceeded (www.orpdl.org)

HICL	Generic	Brand	Quantity Limit
025058	Aprepitant	Emend	3 doses/ 7 days
016576	Dolasetron	Anzemet	9 doses/ 7 days
007611	Granisetron	Kytril Tablets Kytril solution	6 doses / 7 days (30 ml liquid)

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the drug requested preferred?	**Yes:** Go to #4	**No**: Go to #3
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA for <4 days/week. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the ~~Health Resources Commission (HRC).~~Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class and dose limits. If dose > limits, continue to #4.	**No:** Go to #4
4. Is client currently diagnosed with cancer AND receiving chemotherapy or radiation therapy more frequently than every 7 days?	**Yes:** Approve for 3 days past length of therapy (Chemo regimen more frequently than weekly)	**No:** Go to #5

<table>
<tr><td colspan="2">5. Does client have refractory nausea that would require hospitalization or ER visits?</td><td>Yes: Go to #6</td><td>No: go to #8</td></tr>
<tr><td colspan="2">6. Has client tried and failed two conventional antimetics, listed below?

<table>
<tr><th>Generic Name</th><th>Brand Name</th></tr>
<tr><td>Metoclopramide</td><td>Reglan</td></tr>
<tr><td>Prochlorperazine</td><td>Compazine</td></tr>
<tr><td>Promethazine</td><td>Phenergan</td></tr>
</table></td><td>Yes: Approve up to 6 months.</td><td>No: Go to #7</td></tr>
<tr><td colspan="2">7. Does client have contraindications to conventional antiemetics, e.g. Allergy; or cannot tolerate?</td><td>Yes: Document reason and approve up to 6 months.
(Contraindications to required alternative medications)</td><td>No: Pass to RPH; Go to #8</td></tr>
<tr><td colspan="4">8. RPH only:

All other indications need to be evaluated as to whether they are above the line or below the line.

• Above: Deny, (Medical Appropriateness)
• Below: Deny, (Not Covered by the OHP)</td></tr>
</table>

P&T/DUR Action: 9/24/09 (DO/KK), 2/23/06, 2/24/04, 11/18/03, 9/9/03, 5/13/03, 2/11/03
Revision(s): 1/1/10, 7/1/06, 3/20/06, 6/30/04 (added aprepitant), 3/1/04 (removed injectables), 6/19/03
Initiated: ?

Appendix 2: Head to head randomized controlled trials:

Basu, A., D. Saha, et al. (2011). "Comparison of palanosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery." Journal of the Indian Medical Association 109(5): 327-329.
The objective of the study was to compare the efficacy of palanosetron (0.25 mg), granisetron (3.0 mg) and ondansetron (8.0 mg) used as anti-emetics for the prevention of postoperative nausea/vomiting in patients undergoing middle ear surgery. The study was done among 75 adult patients (age group 30-45 years) of which 50 were males and rest (25) females, all of ASA I and ASA II. The patients were randomly allocated into 3 equal groups: Group I (n = 25) received injection palanosetron (0.25 mg) IV, group II (n = 25) received injection granisetron (3 mg) IV and group III (n = 25) received injection ondansetron (8.0 mg) IV at the end of the surgical procedure. A standard general anaesthesia technique was employed. Emetic episodes and safety assessments were performed during two periods of 0-6 hours in the postanaesthesia care unit and 6-24 hours in the ward after anaesthesia. The incidence of emesis-free patients during the 0- 6 hours period was 100% for group I; 72% for group II and 56% for group III. During the 6-24 hours period incidence of emesis-free patients were 96% for group I; 56% for group II and 32% for group III. So to conclude, a single dose of palanosetron (0.25 mg) is a superior anti-emetic to granisetron (3.0 mg) or ondansetron (8.0 mg) in complete prevention of postoperative nausea and vomiting after middle ear surgery during the first 24 hours period.

Boccia, R. V., L. N. Gordan, et al. (2011). "Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study." Supportive Care in Cancer 19(10): 1609-1617.
PURPOSE: A novel transdermal formulation of granisetron (the granisetron transdermal delivery system (GTDS)) has been developed to deliver granisetron continuously over 7 days. This double-blind, phase III, non-inferiority study compared the efficacy and tolerability of the GTDS to daily oral granisetron for the control of chemotherapy-induced nausea and vomiting (CINV).
PATIENTS AND METHODS: Six hundred forty-one patients were randomized to oral (2 mg/day, 3-5 days) or transdermal granisetron (one GTDS patch, 7 days), before receiving multi-day chemotherapy. The primary endpoint was complete control of CINV (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final administration. The prespecified non-inferiority margin was 15%.
RESULTS: Five hundred eighty-two patients were included in the per protocol analysis. The GTDS displayed non-inferiority to oral granisetron: complete control was achieved by 60% of patients in the GTDS group, and 65% in the oral granisetron group (treatment difference, -5%; 95% confidence interval, -13-3). Both treatments were well tolerated, the most common adverse event being constipation.
CONCLUSIONS: The GTDS provides effective, well-tolerated control of CINV associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron.

Habib, A. S., J. C. Keifer, et al. (2011). "A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy." Anesthesia & Analgesia 112(4): 813-818.
BACKGROUND: Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 hours. In addition to causing patient discomfort, the physical act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery,

aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 hours postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia.
METHODS: Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 hours after surgery. Statistical analysis was performed using Wilcoxon's ranked sum test and (2) test. $P < 0.05$ was considered statistically significant.
RESULTS: One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($P = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% vs. 21%, $P = 0.0419$) and 24 hours (14% vs. 36%, $P = 0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs. 60%), nausea scores, need for rescue antiemetics (65% vs. 60%), complete response (no PONV and no rescue, 22% vs. 36%), or patient satisfaction with the management of PONV.
CONCLUSION: The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

Metaxari, M., A. Papaioannou, et al. (2011). "Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents." Journal of Anesthesia 25(3): 356- 362.
PURPOSE: The aim of this double-blind randomized study was to compare the antiemetic efficacy of three 5-hydroxytryptamine type 3 antagonists in terms of the incidence and intensity of postoperative nausea and vomiting (PONV) in a homogenous group of female patients undergoing thyroidectomy.
METHODS: The study cohort consisted of 203 American Society of Anesthesiologists PS I-II female patients randomized into four groups to receive at induction of anesthesia an intravenous (IV) bolus of 5 ml solution of one of the following: normal saline (placebo), granisetron 3 mg, ondansetron 4 mg, or tropisetron 5 mg. Nausea and vomiting were evaluated at five time points: during the first hour in the postanesthesia care unit (PACU) and 6, 12, 18, and 24 h postoperatively. Nausea intensity was measured using a visual analogue scale score (0-10).
RESULTS: Patients in the placebo group displayed a high incidence of nausea in the PACU and at 6, 12, and 18 h postoperatively (44, 60, 50, and 34%, respectively) and of vomiting (26, 42, 30 and 10%). The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 h (26, 18, and 2%, respectively) and vomiting at 6 and 12 h (10 and 6%, respectively). Ondansetron reduced significantly the incidence of nausea and vomiting only at 6 h postoperatively (28 and 12%, respectively). The administration of tropisetron did not affect the incidence of PONV compared to placebo.
CONCLUSION: Among the female patients of this study undergoing thyroid surgery, granisetron 3 mg provided the best prophylaxis from PONV. Ondansetron 4 mg was equally effective, but its action lasted only 6 h, whereas tropisetron 5 mg was found ineffective.

Moon, Y. E., J. Joo, et al. (2012). "Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study.[Erratum appears in Br J Anaesth. 2012 Jun;108(6):1047-8]." British Journal of Anaesthesia 108(3): 417-422.
BACKGROUND: Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking.

This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy.
METHODS: A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue anti-emetics, and adverse effects were evaluated during 0-2 and 2-24 h.
RESULTS: The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, P=0.045). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2-24 h. The only difference in the use of rescue anti-emetics was at 2-24 h (10% with palonosetron compared with 28% with ondansetron, P=0.02).
CONCLUSIONS: Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2-24 h after surgery.

Park, S. K. and E. J. Cho (2011). "A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery." Journal of International Medical Research 39(2): 399-407.
This randomized, double-blind study evaluated the relative efficacy of palonosetron (a new, selective 5-hydroxytryptamine type 3 [5-HT(3)] receptor antagonist) and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 45) or ondansetron 8 mg (n = 45), intravenously, immediately before induction of general anaesthesia. The occurrence of nausea and vomiting and the severity of nausea according to a visual analogue scale were monitored immediately after the end of surgery and during the following 24 h. The incidence of PONV was significantly lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale for nausea. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.

Siddique, R., M. G. Hafiz, et al. (2011). "Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia." Mymensingh Medical Journal: MMJ 20(4): 680-688.
Effect of ondansetron and granisetron were evaluated in sixty (60) children (age 4-11 years) irrespective of sex, diagnosed case of acute lymphoblastic leukemia (ALL) who received high dose methotrexate and did not receive any antiemetic 24 hours prior to HDMTX. This was a prospective, randomized, double-blind, single center study. Of 60 children, 30 received oral ondansetron (4mg) and rest 30 granisetron (1mg) half an hour before therapy. Drugs were randomly allocated with appropriate code. The patients were followed up from day 1 to day 5 of therapy. Episodes of nausea and vomiting were recorded and scorings was done every 24 hours following chemotherapy. No significant difference was found between two groups according to acute emesis (Day-1) (p=0.053). In day two and day three it was significant (p<0.05). In day four it was significant (p=0.002). Early chemotherapy induced nausea and vomiting (CINV) were controlled 90% in children who received granisetron and 70% in children who received ondansetron. Delayed (Day 2-4) CINV were controlled in 80% of children who received granisetron and 43.4% who received ondansetron (p<0.05). Granisetron group required additional doses only 3.3% cases and ondanseton group 30% cases on the second day (p<0.05). Result was significant between two groups. About 36.7% patients had episodes of nausea on day four of chemotherapy in ondansetron group and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself (p=0.001). Maximum episodes of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% (p=0.003). Though adverse effects like headache, constipation, abdominal pain and loose motion were common in both group

of children but their number was much less in children who received granisetron. On second day of therapy score of nausea and vomiting was maximum in ondansetron and minimum in granisetron treated on day 4 and the result was significant. So, to prevent acute and delayed CINV in children with ALL, oral graniseteron can be considered as more effective and well tolerated with minimum adverse effects compared with ondansetrons.

Drug Class Review
on
Newer Drugs for Insomnia

Preliminary Scan Report #3

Last Report: Update 2

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

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

October 2008 (searches through January 2008).

Date of Last Preliminary Update Scan Report

September 2010

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, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of Newer Drugs for Insomnia in treating patients with insomnia?

2. What is the comparative tolerability and safety of Newer Drugs for Insomnia when used to treat patients with insomnia?

3. Are there subgroups of patients for which one Newer Drug for Insomnia is more effective or associated with fewer adverse events based on
    a. demographics (age, racial groups, and gender)?
    b. other medications (e.g., stimulants)?
    c. co-morbidities (including obstructive sleep apnea, other mental disorders)?
    d. pregnancy?
    e. history of substance abuse?

Inclusion Criteria

Populations

Adults and children with insomnia, including (DSM-IV-TR diagnoses):
- Primary insomnia
- Breathing-related sleep disorder (e.g., obstructive sleep apnea)
- Insomnia related to another mental disorder
- Substance-induced sleep disorder, insomnia type
- Sleep disorder due to a general medical condition, insomnia type

Interventions

Table 1.

Generic name	Trade name	Dosage form
Doxepin	Silenor®[a]	Oral tablet
Eszopiclone	Lunesta®	Oral tablet
Ramelteon	Rozarem®	Oral tablet
Zaleplon	Sonata®	Oral capsule
Zolpidem	Ambien®	Oral tablet
	Ambien CR®	Extended release oral tablet
	Edluar®[b]	Sublingual tablet
	Zolpimist®[b]	Oral metered spray
	Intermezzo®[c]	Sublingual tablet

a: interventions found in scan 1, b: interventions found in scan 2, c: interventions found in scan 3 (latest scan)

Effectiveness outcomes

Sleep latency
Sleep duration
Number of awakenings
Sleep quality
Wake time after sleep onset
Daytime alertness
Tolerance
Rebound

Wherever possible, data on duration of therapy (time to tolerance) will be evaluated within the context of comparative effectiveness.

Safety outcomes

Overall adverse effect reports
Withdrawals due to adverse effects
Serious adverse events
Specific adverse events including, but not limited to

- Abuse potential
- Withdrawal symptoms
- Dependency
- Impairment of memory/daytime functioning

Study designs

Effectiveness:

- Controlled clinical trials of an included drug versus placebo or versus any active comparator (including, but not limited to, another included drug, benzodiazepines, trazodone, diphenhydramine, and amitriptyline).
- Good-quality systematic reviews

Adverse Events (dependency and withdrawal symptoms):

- Controlled clinical trials
- Observational studies (case-control, case series, case reports, cohort studies, surveys).

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from September 2010 to June Week 2 2013 using terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

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

RESULTS

New Drugs

New Drugs identified in this Preliminary Update Scan

Intermezzo® sublingual tablet (zolpidem tartrate) was FDA approved in November 2011 for the use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

Limitations of Use: Intermezzo is not indicated for the treatment of middle-of-the-night insomnia when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking.

Identified in previous Preliminary Update Scans

Silenor® (doxepin hydrochloride) was FDA approved in March 2010 for the treatment of insomnia characterized by difficulties with sleep maintenance. Approved doses are 3 mg for adults and 6 mg for elderly patients. A sublingual form of zolpidem tartrate (Edluar®) was approved in March 2009, and an oral spray form of zolpidem tartrate (Zolpimist®) was approved in December 2008.

Awaiting Approval

Suvoroxant (no brand name assigned yet) is an orexin receptor antagonist manufactured by Merck and Co. Merck received a "Complete Response" letter from the FDA in June 2013 informing that it could consider approving 10 mg starting dose for most patients, with 15-20 mg appropriate for patients in whom 10 mg is safe but not effective. FDA had determined that 30 and 40 mg doses were not safe for approval. Merck had proposed that elderly patients start by taking 15 milligrams of the drug and increase that to 30 if necessary, and that non-elderly adults start on 20 milligrams and increase to 40 milligrams if needed. FDA has also requested Merck explore a 5 mg dose for patients taking CYP34A enzyme inhibiting drugs. FDA indicated that if Merck makes a 10 mg dose available the FDA would move quickly to approve it.

New Indications

New indications identified in this Preliminary Update Scan

None identified in this scan.

Identified in previous Preliminary Update Scans

None identified in the previous scans.

New Safety Alerts

Identified in this Preliminary Update Scan

In January of 2013, FDA notified healthcare professionals of the need for lowering the bedtime dose of zolpidem products (Ambien, Ambien CR, and Edluar) because new data showed that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Appendix A contains the detailed safety alerts that were posted on the FDA website.

Identified in previous Preliminary Update Scans
No new safety alerts were obtained in the previous scans

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
No new comparative effectiveness reviews were identified that were produced by AHRQ and CADTH

Reviews identified in previous Preliminary Update Scans
No new comparative effectiveness reviews were identified in the previous scans.

Randomized Controlled Trials

Medline searches resulted in 79 new citations. Of those there are potentially 2 new head to head trials, making a total of three head to head trials since the last update of the full report. Table 2 lists all the potentially relevant head to head trials and abstracts of these trials are included in appendix B.

Table 2. Potentially relevant head to head trials

Author, year	Comparison	Focus
Huang, 2011	Zolpidem, zaleplon	N=48, efficacy, harms
Staner, 2010	Sublingual zolpidem, oral zolpidem	N=70, efficacy, harms
Uchimara, 2012	Zolpidem, eszopiclone	N=72, efficacy, harms, Japanese patients

Shading indicates trials found in this scan.

A cumulative total of 27 placebo-controlled trials have been published since the last full report update, including 16 (including 1 subgroup analysis and a pooled analysis) identified in this latest scan and 11 (including one pooled analysis) from the previous scans. 60% of these trials focused on subgroups. There were 3 trials that were published on the new drug doxepin and one on sublingual zolpidem. The majority of the trials focused on ramelteon and zolpidem. Only 1 trial evaluated the use of zolpidem in children aged 6-17 years. Abstracts from these trials are included in appendix C.

Table 3. Potentially relevant placebo controlled trials

Author, year	Intervention	Subgroup
Ancoli-Israel, 2010	Eszopiclone	Elderly
Blumer, 2009	Zolpidem	Children
Fava, 2009	Zolpidem ER	Generalized anxiety disorder
Fava, 2011	Zolpidem ER	Major depressive disorder
Fava, 2011	Pooled analysis of Eszopiclone	Anxious depression
Goonaratne, 2010	Ramelteon	Older patients with obstructive sleep apnea
Hajak, 2009	Zolpidem	Menopausal women with depression and anxiety
Joffe, 2010	Eszopiclone	
Kohsaka, 2011	Ramelteon	Japanese
Krystal, 2010	Doxepin	Elderly
Krystal 2012	Subgroup analysis of	

	Eszopiclone	
Krystal, 2011	Doxepin	
Lankford, 2012	Doxepin	Elderly
Meyer, 2009	Ramelteon	
McCall, 2010	Eszopiclone	Depressed
McElroy, 2011	Ramelteon	Bipolar 1 disorder with manic symptoms
Menza, 2010	Eszopiclone	Parkinson's disease
Morin, 2009	Zolpidem	
Omvik,2008	Zopiclone	
Pollack, 2011	Eszopiclone	Post-traumatic stress disorder
Randall, 2012	Zolpidem	
Roehrs, 2012	Zolpidem	
Roth, 2008	Sublingual zolpidem	
Uchimara, 2011	Ramelteon	Japanese
Uchiyama, 2011	Ramelteon	Japanese
Uchiyama, 2011	Ramelteon	Japanese
Wang-Weigand, 2009	Ramelteon	

Shading indicates trials found in this scan. Others were found in previous scans.

Appendix A. FDA Safety Alert

Zolpidem Containing Products: Drug Safety Communication - FDA Requires Lower Recommended Doses

Including Ambien, Ambien CR, Edluar, and Zolpimist

[UPDATE 05/14/2013] Today, the U.S. Food and Drug Administration (FDA) is notifying the public that FDA has approved label changes specifying new dosing recommendations for zolpidem products (Ambien, Ambien CR, and Edluar), which are widely prescribed sleep medications. FDA has approved these changes because of the known risk of next-morning impairment with these drugs.

[Posted 01/10/2013]

AUDIENCE: Family Practice, Health Professional, Patient

ISSUE: FDA is notifying the public of new information about zolpidem, a widely prescribed insomnia drug. FDA recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. This announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien, Ambien CR, Edluar, and Zolpimist.

FDA is also reminding the public that all drugs taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia drugs, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia drugs can experience impairment of mental alertness the morning after use, even if they feel fully awake.

For zolpidem products, data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men.

Because use of lower doses of zolpidem will result in lower blood levels in the morning, FDA is requiring the manufacturers of Ambien, Ambien CR, Edluar, and Zolpimist to lower the recommended dose.

FDA is continuing to evaluate the risk of impaired mental alertness with other insomnia drugs, including over-the-counter (OTC) drugs available without a prescription.

FDA prepared a list of questions and answers to provide an additional overview of this safety issue. See the FDA Drug Safety Communication for a Data Summary.

BACKGROUND: Zolpidem is a sedative-hypnotic (sleep) medicine used in adults for the treatment of insomnia. It is marketed as generics and under the brand-names Ambien, Ambien CR, Edluar, Zolpimist, and Intermezzo.

RECOMMENDATION: FDA urges health care professionals to caution all patients (men and women) who use these products about the risks of next-morning impairment for activities that require complete mental alertness, including driving.

The recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR).

For zolpidem and other insomnia drugs, prescribe the lowest dose that treats the patient's symptoms.

Inform patients that impairment from sleep drugs can be present despite feeling fully awake.

The recommended doses of Intermezzo, a lower dose zolpidem product approved for middle-of-the-night awakenings, are not changing. At the time of Intermezzo's approval in November 2011, the label already recommended a lower dosage for women than for men.

Appendix B. Potential relevant head to head trials (n=3)

Huang, Y.-S., S.-C. Hsu, et al. (2011). "A double-blind, randomized, comparative study to evaluate the efficacy and safety of zaleplon versus zolpidem in shortening sleep latency in primary insomnia." Chang Gung Medical Journal **34**(1): 50-56.

BACKGROUND: Benzodiazepines cause a high proportion of adverse effects while non-benzodiazepine compounds have demonstrated high efficacy and less adverse effects in patients with insomnia. The objective of this study was to compare the effectiveness and safety of non-BZ zaleplon and zolpidem in primary insomnia.

METHODS: This was a randomized, double-blind, active-controlled, double-dummy, comparative study. A total of 48 patients were enrolled, of which 45 patients completed the study. Patients who entered the study were required to take the study drug orally once daily at bedtime for two weeks. Each patient kept a sleep diary and answered a questionnaire. We used these documents to measure and evaluate changes from baseline to Week 2 in sleep latency, duration and quality of sleep, the number of awakenings and incidence of rebound insomnia.

RESULTS: The data revealed a significant decrease in sleep latency from baseline to Week 2 for patients receiving zaleplon 10 mg and zolpidem 10 mg. Patients receiving zaleplon exhibited a marginally greater, but not statistically significant, reduction in sleep latency than those who received zolpidem. There was no significant difference in the frequency of adverse effects between the zaleplon and zolpidem groups; however, during this clinical trial there was one lethal event caused by a traffic accident in the zaleplon group.

CONCLUSION: There was no significant difference between zaleplon and zolpidem in the efficacy of reducing sleep latency or adverse effects. A large pharmacovigilance study is needed before concluding that either zolpidem or zaleplon is free from next-day residual effects.

Staner, C., F. Joly, et al. (2010). "Sublingual zolpidem in early onset of sleep compared to oral zolpidem: polysomnographic study in patients with primary insomnia." Current Medical Research & Opinion **26**(6): 1423-1431.

OBJECTIVE: To compare the hypnotic effects of a single dose of a sublingual formulation of zolpidem (Edluar*) 10 mg vs oral formulation (Ambien dagger) 10 mg by polysomnography (PSG) in DSM-IV primary insomnia patients. Primary objective was to compare the two formulations on sleep induction, measured by latency to persistent sleep (LPS), sleep onset latency (SOL) and latency to stage 1 (ST1L). RESEARCH AND METHODS: This was a randomized, double-blind, two-period, cross-over multi-centre study in which each period comprised two successive PSG recording nights. Treatment was administered when PSG recordings started. Subjective sleep and residual effects were assessed the next morning. RESULTS: Seventy female and male patients aged 19-64 were analysed. Sublingual zolpidem significantly shortened LPS by 34% or 10.3 minutes as compared to oral zolpidem (95% CI: -4.3 min to -16.2 min, p = 0.001). SOL and ST1L were also significantly shortened ($p < 0.01$). Furthermore the two formulations were comparable in terms of sleep maintenance properties based on total sleep time (TST). The improvement in subjective sleep and next-day residual effects did not differ between the two treatments. Both routes of administration were well tolerated. CONCLUSIONS: The results demonstrate that sublingual zolpidem is superior to an equivalent dose of oral zolpidem in terms of sleep inducing properties in a carefully selected sample of primary insomnia patients.

Uchimura, N., A. Kamijo, et al. (2012). "A randomized placebo-controlled polysomnographic study of eszopiclone in Japanese patients with primary insomnia." Sleep Medicine **13**(10): 1247-1253.

OBJECTIVES: To evaluate the efficacy and dose-response effect of eszopiclone on sleep latency and sleep maintenance in Japanese patients with primary insomnia.

METHODS: In this randomized, double-blind, five-way crossover study, 72 patients received placebo, eszopiclone 1mg, 2mg, and 3mg, and zolpidem 10mg in random order for two consecutive nights with a washout period between treatments. Objective sleep measures from polysomnography (PSG) and subjective patient reports were collected.

RESULTS: All active treatments produced significant improvement in objective and subjective sleep latency compared with placebo ($P<0.05$ for all comparisons); linear dose-response relationships were observed for eszopiclone. PSG-determined wake time after sleep onset (WASO), sleep efficiency, and number of awakenings (NA), and patient-reported measures of WASO, NA, sleep quality, sleep depth, and daytime functioning significantly improved following treatment with eszopiclone 2mg and 3mg and zolpidem 10mg versus placebo ($P<0.05$). Eszopiclone at all doses increased total sleep time and stage 2 sleep time ($P<0.001$ for both comparisons), but did not alter REM or slow-wave sleep. Eszopiclone was generally well tolerated; the most frequently reported adverse event was mild dysgeusia.

CONCLUSIONS: In Japanese patients with primary insomnia, eszopiclone 2mg and 3mg significantly improved PSG-determined and patient-reported sleep latency and sleep maintenance relative to placebo.

Appendix C. Potentially relevant placebo controlled trials (n=27)

Ancoli-Israel, S., A. D. Krystal, et al. (2010). "A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia." Sleep **33**(2): 225-234.

BACKGROUND: Longer-term pharmacologic studies for insomnia in older individuals are sparse. OBJECTIVE: To evaluate the efficacy and safety of 12 weeks of nightly eszopiclone in elderly outpatients with insomnia. METHODS: Participants (65-85 years) met DSM-IV-TR criteria for insomnia with total sleep times (TST) < or = 6 h, and wake time after sleep onset (WASO) > or = 45 min. Participants were randomized to 12 weeks of eszopiclone 2 mg (n = 194) or placebo (n = 194), followed by a 2-week single-blind placebo run-out. Subject-reported measures of sleep (sTST, sleep latency [sSL], sWASO) and daytime function (alertness, concentration, wellbeing, ability to function) were assessed. AEs were monitored. RESULTS: Subjects treated with 2 mg eszopiclone slept longer at night on average and at every individual time point compared to baseline than placebo subjects, as measured by TST over the 12-week double-blind period (P < 0.0001). Mean sTST over the double-blind period for eszopiclone-treated subjects was 360.08 min compared to 297.86 min at baseline, a mean change of 63.24 min. Over the double-blind period, eszopiclone-treated subjects also experienced a significantly greater improvement in sSL compared to placebo, with a mean decrease of 24.62 min versus a mean decrease of 19.92 min, respectively (P = 0.0014). Eszopiclone subjects also experienced a significantly greater decrease in WASO (mean decrease of 36.4 min) compared to placebo subjects (decrease of 14.8 min) (P < 0.0001). Post-discontinuation, sleep parameters were statistically improved versus baseline for eszopiclone (P-values < or = 0.01), indicating no rebound. The most common AEs (> or = 5%) were headache (eszopiclone 13.9%, placebo 12.4%), unpleasant taste (12.4%, 1.5%), and nasopharyngitis (5.7%, 6.2%). CONCLUSION: In this Phase IV trial of older adults with insomnia, eszopiclone significantly improved patient-reported sleep and daytime function relative to placebo. Improvements occurred within the first week and were maintained for 3 months, with no evidence of rebound insomnia following discontinuation. The 12 weeks of treatment were well tolerated. Clinical Trial Information: A Long-Term Safety and Efficacy Study of Eszopiclone in Elderly Subjects With Primary Chronic Insomnia; Registration #NCT00386334; URL - http://www.clinicaltrials.gov/ct2/show/NCT00386334?term=eszopiclone&rank=24

Blumer, J. L., R. L. Findling, et al. (2009). "Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/ hyperactivity disorder in children 6 to 17 years of age." Pediatrics **123**(5): e770-776.

OBJECTIVE: The goal was to evaluate the hypnotic efficacy of zolpidem at 0.25 mg/kg per day (maximum of 10 mg/day), compared with placebo, in children 6 through 17 years of age who were experiencing insomnia associated with attention-deficit/hyperactivity disorder. METHODS: An 8-week, North American, multicenter, double-blind, placebo-controlled, parallel-group study was conducted. Patients underwent stratification according to age (6-11 years [N = 111] or 12-17 years [N = 90]) and were assigned randomly to receive treatment with the study drug or placebo (in a 2:1 ratio). The primary efficacy variable was latency to persistent sleep between weeks 3 and 6. Secondary efficacy variables also were assessed, and behavioral and cognitive components of attention-deficit/hyperactivity disorder were monitored. Safety was assessed on the basis of reports of adverse events, abnormal laboratory data, vital signs, and physical examination findings. The potential for next-day residual effects also was assessed. RESULTS: The baseline-adjusted mean change in latency to persistent sleep at week 4 did not differ significantly between the zolpidem and placebo groups (-20.28 vs -21.27 minutes). However,

differences favoring zolpidem were observed for the older age group in Clinical Global Impression scores at weeks 4 and 8. No next-day residual effects of treatment were associated with zolpidem, and no rebound phenomena occurred after treatment discontinuation. Central nervous system and psychiatric disorders were the most-frequent treatment-emergent adverse events (>5%) that were observed more frequently with zolpidem than with placebo; these included dizziness, headache, and hallucinations. Ten (7.4%) patients discontinued zolpidem treatment because of adverse events. CONCLUSION: Zolpidem at a dose of 0.25 mg/kg per day to a maximum of 10 mg failed to reduce the latency to persistent sleep on polysomnographic recordings after 4 weeks of treatment in children and adolescents 6 through 17 years of age who had attention-deficit/hyperactivity disorder-associated insomnia.

Fava, M., G. M. Asnis, et al. (2009). "Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder." Journal of Clinical Psychopharmacology **29**(3): 222-230.

A multicenter, double-blind, parallel-group study was designed to assess the efficacy and safety of zolpidem extended-release coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Patients (N = 383) received open-label escitalopram 10 mg/d and were randomized to either adjunct zolpidem extended-release 12.5 mg or placebo. The primary efficacy measure was change from baseline to week 8 in subjective total sleep time. Secondary efficacy measures included subjective sleep onset latency, number of awakenings, wake time after sleep onset, sleep quality, the Hamilton Rating Scale for Anxiety, the Beck Anxiety Inventory, the Sleep Impact Scale, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Sheehan Disability Scale. The last-observation-carried-forward method was used to impute missing values for most efficacy measures. Safety was monitored at each visit. At week 8 and all time points, there was a significant improvement in the zolpidem extended-release/escitalopram group compared with placebo/escitalopram for total sleep time ($P < 0.0001$). Most of the secondary efficacy measures also significantly favored zolpidem at most visits ($P < 0.0001$). The most common treatment-emergent adverse events in both groups were nausea, dizziness, headache, fatigue, and dry mouth. Concurrent zolpidem extended-release/escitalopram, compared with placebo/escitalopram, significantly improved insomnia and sleep-related next-day symptoms, but not anxiety symptoms, in patients with comorbid insomnia and generalized anxiety disorder.

Fava, M., G. M. Asnis, et al. (2011). "Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial." Journal of Clinical Psychiatry **72**(7): 914-928.

OBJECTIVE: This investigation was performed to assess the efficacy and safety of zolpidem extended-release in patients with insomnia associated with major depressive disorder (MDD).

METHOD: Patients (N = 385) received open-label escitalopram 10 mg/d and were randomized to concomitant zolpidem extended-release 12.5 mg/night or placebo for 8 weeks (phase 1) in a randomized, parallel-group, multicenter trial. Responders (>= 50% in 17-item Hamilton Depression Rating Scale [HDRS(17)] score) continued 16 weeks of double-blind treatment (phase 2); escitalopram only was given during a 2-week run-out period. The study was conducted between February 2006 and June 2007. The primary efficacy measure was change from baseline in subjective total sleep time. Secondary efficacy measures included subjective sleep-onset latency, number of awakenings, wake time after sleep onset, sleep quality, sleep-related next-day functioning, HDRS(17), Sleep Impact Scale score, Patient and Clinical Global Impressions of

Insomnia Treatment, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Adverse events were recorded throughout the study; sleep measures were also evaluated during the run-out period.

RESULTS: Throughout phase 1, zolpidem extended-release led to significantly greater improvements in total sleep time (P < .0001), wake time after sleep onset, sleep onset latency, number of awakenings, and sleep quality (P <= .0003), and some measures of sleep-related next-day functioning but not in depressive symptoms or quality of life. During phase 2, improvements with the zolpidem extended-release/escitalopram group occurred for total sleep time (significant [P < .05] at weeks 12 and 16), as well as for a few other secondary efficacy measures but not in depressive symptoms or quality of life. The most common adverse events associated with combination treatment included nausea, somnolence, dry mouth, dizziness, fatigue, and amnesia.

CONCLUSIONS: Zolpidem extended-release administered concomitantly with escitalopram for up to 24 weeks was well tolerated and improved insomnia and some sleep-related next-day symptoms and next-day functioning in patients with MDD but did not significantly augment the antidepressant response of escitalopram.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00296179. Copyright 2011 Physicians Postgraduate Press, Inc.

Fava, M., K. Schaefer, et al. (2011). "A post hoc analysis of the effect of nightly administration of eszopiclone and a selective serotonin reuptake inhibitor in patients with insomnia and anxious depression." Journal of Clinical Psychiatry **72**(4): 473-479.

OBJECTIVE: Patients with major depressive disorder (MDD) and significant anxiety are less responsive to antidepressants than those without anxiety. In this post hoc analysis of patients with insomnia and comorbid anxious depression, eszopiclone cotherapy with a selective serotonin reuptake inhibitor (SSRI) was compared with placebo cotherapy.

METHOD: Data were pooled from 2 randomized, double-blind, 8-week trials. One trial (conducted from January 2004 to October 2004) included patients with DSM-IV insomnia and comorbid MDD treated with fluoxetine concurrently with eszopiclone 3 mg/d or placebo. The other trial (conducted from July 2005 to April 2006) included patients with DSM-IV-TR insomnia and comorbid generalized anxiety disorder treated with escitalopram concurrently with eszopiclone 3 mg/d or placebo. Anxious depression was defined as a baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score >= 14 (excluding insomnia items) and an anxiety/somatization factor score >= 7. Treatment group differences were determined for mean changes in HDRS-17 scores (with and without insomnia items), HDRS anxiety/somatization scores, and response and remission rates. Severity of insomnia was assessed by the Insomnia Severity Index (ISI).

RESULTS: In the combined dataset, 347 of 1,136 patients (30.5%) had insomnia and comorbid anxious depression. Significant improvements in insomnia were observed for eszopiclone cotherapy relative to placebo cotherapy (mean change from baseline on the ISI: -11.0 vs -7.8, respectively; P < .001). There were greater reductions in HDRS-17 scores at week 8 following cotherapy with eszopiclone compared with placebo when the insomnia items were included (mean change: -14.1 vs -11.2, respectively; P < .01) or excluded (-10.6 vs -8.9; P < .01), but not for anxiety/somatization (-4.3 vs -4.1; P = .23). Response rates were greater for eszopiclone cotherapy than for placebo cotherapy (55.6% vs 42.0%, respectively; P = .01; 50.0% vs 44.4% when insomnia items were removed; P = .3). Remission rates were not significantly different (32.6% vs 27.2%, respectively; P = .28).

CONCLUSIONS: In this post hoc analysis of patients with insomnia and comorbid anxious depression

derived from 2 trials, 8 weeks of eszopiclone therapy coadministered with an SSRI resulted in significantly greater improvements in insomnia, significantly greater reductions in HDRS-17 total score, and significantly greater HDRS-17 response rates compared with placebo coadministration. There were no significant differences in response rates (when insomnia items were excluded) and remission rates, as well as in anxiety/somatization scores. Further research is warranted to determine whether these modest antidepressant effects can be replicated, and anxiolytic effects demonstrated, when evaluated in a prospective manner. Copyright 2011 Physicians Postgraduate Press, Inc.

Gooneratne, N. S., P. Gehrman, et al. (2010). "Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study." Journal of Clinical Sleep Medicine **6**(6): 572-580.

STUDY OBJECTIVES: To evaluate the effectiveness of ramelteon, a melatonin receptor agonist, for the treatment of insomnia in older adults starting auto-titrating positive airway pressure (APAP) therapy for sleep apnea.

METHODS: A parallel group, randomized, double-blind, placebo-controlled pilot effectiveness clinical trial. The study enrolled 21 research study participants who were >= 60 years old and had obstructive sleep apnea, defined by an apnea-hypopnea index (AHI) >= 5 events/h, with complaints of insomnia. The primary outcome measure was change in sleep onset latency determined from polysomnography at 4 weeks. Research study participants, all of whom were starting on APAP, were randomized to ramelteon 8 mg (n = 8) or placebo (n = 13).

RESULTS: Ramelteon treatment was associated with a statistically significant difference in sleep onset latency (SOL) as measured by polysomnography of 28.5 min (+/- 16.2 min) compared to placebo (95% C.I. 8.5 min to 48.6 min, effect size 1.35, p = 0.008). This was due to a 10.7 (+/- 17.0) min SOL reduction in the ramelteon arm and a 17.8 (+/- 23.5) min SOL increase in the placebo arm. No change was noted in subjective sleep onset latency (-1.3 min, +/- 19.3 min, 95% C.I.: -21.4 min to 18.7 min). No statistically significant changes were noted in the AHI, sleep efficiency (polysomnography and self-report), APAP adherence, Pittsburgh Sleep Quality Index global score, or Epworth Sleepiness Scale score when comparing ramelteon vs. placebo. Four adverse events occurred in the ramelteon arm and 2 in the placebo arm; none were considered to be related to treatment.

CONCLUSIONS: Ramelteon was effective in improving objective, but not subjective, sleep onset latency even in older adults who were starting APAP therapy for sleep apnea. Further research is warranted in examining the role of ramelteon in the care of older adults with insomnia symptoms and sleep apnea.

Hajak, G., J. Hedner, et al. (2009). "A 2-week efficacy and safety study of gaboxadol and zolpidem using electronic diaries in primary insomnia outpatients." Sleep Medicine **10**(7): 705-712.

OBJECTIVES: To evaluate the efficacy and safety profile of gaboxadol, a selective extrasynaptic GABA(A) agonist (SEGA) previously in development for the treatment of insomnia. METHODS: This was a randomised, double-blind, placebo-controlled, parallel-group, 2-week, Phase III study of gaboxadol 5, 10 and 15mg in outpatients meeting the DSM-IV criteria of primary insomnia (N=742). Zolpidem 10mg was used as active reference. RESULTS: At weeks 1 and 2, significant improvement in total sleep time (sTST) compared to placebo was seen for all doses of gaboxadol (all p<0.05). In addition, gaboxadol 10 and 15mg decreased the number of awakenings (sNAW) (p<0.05) while only gaboxadol 15mg improved wakefulness after sleep onset (sWASO) (p<0.05). At week 1, all doses of gaboxadol significantly improved time-to-sleep onset (sTSO) (p<0.05). At week 2, a sustained effect on sTSO was observed for gaboxadol 15mg. Zolpidem also showed

effect on all of these variables. Gaboxadol and zolpidem improved sleep quality, freshness after sleep, daytime function and energy at both weeks. Transient rebound insomnia was observed following discontinuation of treatment with zolpidem, but not gaboxadol. CONCLUSIONS: Gaboxadol 15mg treatment for 2 weeks significantly improved sleep onset and maintenance variables as well as sleep quality and daytime function, as did zolpidem. Gaboxadol 5 and 10mg also showed benefits on most efficacy variables. Gaboxadol was generally safe and well tolerated, with no evidence of withdrawal symptoms or rebound insomnia after discontinuation of short-term treatment. For zolpidem, transient rebound insomnia was observed.

Joffe, H., L. Petrillo, et al. (2010). "Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial." American Journal of Obstetrics & Gynecology **202**(2): 171.e171-171.e111.

OBJECTIVE: Menopause-associated insomnia is commonly associated with other symptoms (hot flashes, depression, anxiety). Given frequent symptom cooccurrence, therapies targeting sleep may provide an important approach to treatment during midlife. STUDY DESIGN: Peri/postmenopausal women (40-65 years old) with sleep-onset and/or sleep-maintenance insomnia cooccurring with hot flashes and depressive and/or anxiety symptoms were randomized to eszopiclone 3 mg orally or placebo in a double-blinded, crossover 11 week trial. Changes in the Insomnia Severity Index (ISI) scale and secondary outcomes (diary-based sleep parameters, depression/anxiety, hot flashes, quality of life) were analyzed using repeated-measure linear models. RESULTS: Of 59 women, 46 (78%) completed the study. Eszopiclone reduced ISI scores by 8.7 + or - 1.4 more points than placebo (P < .0001). Eszopiclone improved (P < .05) all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and nighttime but not daytime hot flashes. CONCLUSION: Eszopiclone treats insomnia and cooccurring menopause-related symptoms. Our results provide evidence that hypnotic therapies may improve multiple domains of well-being during midlife.

Kohsaka, M., T. Kanemura, et al. (2011). "Efficacy and tolerability of ramelteon in a double-blind, placebo-controlled, crossover study in Japanese patients with chronic primary insomnia." Expert Review of Neurotherapeutics **11**(10): 1389-1397.

The aim of this study was to evaluate the efficacy and safety of ramelteon 4, 8, 16 or 32 mg and placebo in Japanese patients with chronic insomnia using a randomized, double-blind, five-period crossover design. A total of 65 Japanese patients with chronic primary insomnia received ramelteon or placebo for two nights each in sleep laboratories. Changes in sleep parameters were assessed objectively by polysomnography and subjectively by postsleep questionnaires. Safety and tolerability was evaluated by assessment of the occurrence of adverse events, next-day residual effects and laboratory and ECG investigations. Ramelteon 8 and 32 mg significantly shortened the mean latency to persistent sleep in comparison with placebo, and there was a statistically significant trend for linear dose-response for this sleep parameter. Overall changes in sleep architecture were modest (<3% changes vs placebo), with increases in stage 1 and decreases in stage 3/4. Ramelteon was well tolerated, the most common adverse effect being somnolence, which was similar to placebo at doses up to 8 mg, but increased with higher doses. Next-day residual effects occurred no more frequently with ramelteon at any dose than with placebo. When compared with sleep latency data from a similarly-designed US study, there was no evidence of any ethnic differences in the efficacy of ramelteon between Japanese and US patients. Overall, ramelteon 8 mg showed the most favorable balance between sleep-promoting

effects and tolerability. The unique efficacy profile of ramelteon, promoting sleep initiation without affecting other sleep parameters, may be due to its circadian shifting effect.

Krystal, A. D., H. H. Durrence, et al. (2010). "Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia." Sleep **33**(11): 1553-1561.

STUDY OBJECTIVES: to evaluate the efficacy and safety of doxepin 1 mg and 3 mg in elderly subjects with chronic primary insomnia.

DESIGN AND METHODS: the study was a randomized, double-blind, parallel-group, placebo-controlled trial. Subjects meeting DSM-IV-TR criteria for primary insomnia were randomized to 12 weeks of nightly treatment with doxepin (DXP) 1 mg (n = 77) or 3 mg (n = 82), or placebo (PBO; n = 81). Efficacy was assessed using polysomnography (PSG), patient reports, and clinician ratings. Objective efficacy data are reported for Nights (N) 1, 29, and 85; subjective efficacy data during Weeks 1, 4, and 12; and Clinical Global Impression (CGI) scale and Patient Global Impression (PGI) scale data after Weeks 2, 4, and 12 of treatment. Safety assessments were conducted throughout the study.

RESULTS: DXP 3 mg led to significant improvement versus PBO on N1 in wake time after sleep onset (WASO; $P < 0.0001$; primary endpoint), total sleep time (TST; $P < 0.0001$), overall sleep efficiency (SE; $P < 0.0001$), SE in the last quarter of the night ($P < 0.0001$), and SE in Hour 8 ($P < 0.0001$). These improvements were sustained at N85 for all variables, with significance maintained for WASO, TST, overall SE, and SE in the last quarter of the night. DXP 3 mg significantly improved patient-reported latency to sleep onset (Weeks 1, 4, and 12), subjective TST (Weeks 1, 4, and 12), and sleep quality (Weeks 1, 4, and 12). Several global outcome-related variables were significantly improved, including the severity and improvement items of the CGI (Weeks 2, 4, and 12), and all 5 items of the PGI (Week 12; 4 items after Weeks 2 and 4). Significant improvements were observed for DXP 1 mg for several measures including WASO, TST, overall SE, and SE in the last quarter of the night at several time points. Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects; additionally, there were no reports of memory impairment, complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite.

CONCLUSIONS: DXP 1 mg and 3 mg administered nightly to elderly chronic insomnia patients for 12 weeks resulted in significant and sustained improvements in most endpoints. These improvements were not accompanied by evidence of next-day residual sedation or other significant adverse effects. DXP also demonstrated improvements in both patient- and physician-based ratings of global insomnia outcome. The efficacy of DXP at the doses used in this study is noteworthy with respect to sleep maintenance and early morning awakenings given that these are the primary sleep complaints of the elderly. This study, the longest placebo-controlled, double-blind, polysomnographic trial of nightly pharmacotherapy for insomnia in the elderly, provides the best evidence to date of the sustained efficacy and safety of an insomnia medication in older adults.

Krystal, A. D., H. Huang, et al. (2012). "A WASO sub-group analysis of a 6-month study of eszopiclone 3 mg." Sleep Medicine **13**(6): 691-696.

BACKGROUND: Insomnia marked by sleep maintenance difficulty is extremely prevalent. Yet, problems staying asleep have been relatively neglected as a research focus compared to problems falling asleep. Insomnia treatment studies typically have not required participants to have a problem specifically with sleep maintenance. It is possible that exclusion of such subjects limits the detection of treatment effects in the overall trial in general, and of effects on sleep

maintenance specifically. In order to address these issues we conducted a post hoc analysis of a 6-month placebo-controlled trial in which there were no inclusion criteria that specified sleep maintenance difficulties to assess the variable effects of baseline wake time after sleep onset (WASO - the primary maintenance measure) on the efficacy of eszopiclone 3mg.

METHODS: Patients diagnosed with chronic primary insomnia were randomized to eszopiclone 3mg (n=593) or placebo (n=195) nightly for six months. The present analyses of this study consisted of: (1) determination of the distribution of baseline WASO; (2) continuous analysis of the relationship between baseline WASO severity and drug-placebo difference at month 1 and 6; and (3) categorical efficacy analyses of subgroups delimited by the following WASO thresholds: 0, 30, 45, 60, and 90 min.

RESULTS: The baseline WASO distribution was: <= 30=32.2%; >0 to <= 45=41.5%; >30 to <= 90=33.0%; >45 to <= 90=23.7%; >90=22.6%. A relationship between greater baseline WASO severity and a significantly greater drug-placebo difference in efficacy for WASO was evident in both continuous and categorical analyses. Eszopiclone was found to have significant sleep maintenance efficacy at each time point across the entire range of WASO severity studied.

CONCLUSIONS: As illustrated in this analysis, a significant proportion of chronic insomnia patients in efficacy trials that select on the basis of sleep onset latency and total sleep time criteria may have normative-range WASO. However, even in the subgroup with minimal WASO there was a significant sleep maintenance effect. The absence of any sleep maintenance effect in a drug trial may reflect the inclusion of relatively many insomnia patients with no baseline WASO abnormality. However, treatments with therapeutic effects on sleep maintenance, can still demonstrate improvement in sleep maintenance, even in a population not selected for this type of sleep problem, if adequately powered. Future clinical trials intending to examine sleep maintenance should employ WASO selection criteria that would ensure sufficient power to detect a sleep maintenance effect. Drug-placebo difference increased as a function of baseline WASO severity, suggesting that eszopiclone's clinical effectiveness for insomnia may be enhanced in patients with more severe sleep maintenance symptoms.

Krystal, A. D., A. Lankford, et al. (2011). "Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia." Sleep **34**(10): 1433-1442.

STUDY OBJECTIVES: To evaluate the efficacy and safety of doxepin (DXP) 3 mg and 6 mg in adults diagnosed with primary insomnia.

DESIGN AND METHODS: The study was a randomized, double-blind, parallel-group, placebo-controlled trial. Patients meeting DSM-IV-TR criteria for primary insomnia were randomized to 35 days of nightly treatment with DXP 3 mg (n=75), DXP 6 mg (n=73), or placebo (PBO; n=73), followed by 2 nights of single-blind PBO to evaluate discontinuation (DC) effects. Efficacy was assessed using polysomnography (PSG) and patient reports. Efficacy data were examined for Night (N) 1, N15, and N29. Safety assessments were conducted throughout the study.

RESULTS: Compared with PBO, DXP 3 and 6 mg significantly improved wake time after sleep onset (WASO) on N1 (3 mg and 6 mg; P<0.0001), N15 (3 mg P=0.0025; 6 mg P=0.0009), and N29 (3 mg P=0.0248; 6 mg P=0.0009), latency to persistent sleep (LPS) on N1 (3 mg P=0.0047; 6 mg P=0.0007), and total sleep time (TST) on N1 (3 mg and 6 mg P<0.0001), N15 (6 mg P=0.0035), and N29 (3 mg P=0.0261; 6 mg P<0.0001). In terms of early morning awakenings, DXP 3 and 6 mg demonstrated significant improvements in SE in the final quarter of the night on N1, N15, and N29, with the exception of 3 mg on N29 (P=0.0691). Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects, and there were no spontaneous reports of memory impairment,

complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite. Additionally, there was no evidence of rebound insomnia after DXP discontinuation.

CONCLUSIONS: Five weeks of nightly administration of DXP 3 mg and 6 mg to adults with chronic primary insomnia resulted in significant and sustained improvements in sleep maintenance and early morning awakenings (with the exception of SE in the final quarter of the night on N29 for 3 mg [P=0.0691]). These sleep improvements were not accompanied by next-day residual effects or followed by rebound insomnia or withdrawal effects upon discontinuation. These findings confirm the unique profile of sleep maintenance efficacy and safety of DXP observed in prior studies.

Lankford, A., R. Rogowski, et al. (2012). "Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia." Sleep Medicine **13**(2): 133-138.

INTRODUCTION: The efficacy and safety of doxepin (DXP), a histamine H(1) receptor antagonist, was evaluated in elderly adults with sleep maintenance insomnia.

METHODS: This was a randomized, double-blind, placebo-controlled outpatient trial. Elderly adults meeting DSM-IV-TR criteria for primary insomnia were randomized to four weeks of nightly treatment with either DXP 6 mg (N=130) or placebo (PBO; N=124). Efficacy was assessed using patient self-report instruments and clinician ratings. Patient-reported endpoints included subjective total sleep time (sTST), subjective wake after sleep onset (sWASO), latency to sleep onset (LSO), sleep quality, and a Patient Global Impression scale (PGI). The primary endpoint was sTST at week 1.

RESULTS: DXP 6 mg produced significantly more sTST and less sWASO at week 1 (both p-values <0.0001) than PBO. These significant improvements versus placebo were maintained at weeks 2-4 (all p-values <0.05). There were no significant differences in LSO for DXP 6 mg versus PBO. DXP 6 mg significantly improved sleep quality (weeks 1, 3, and 4, p<0.05) and several outcome-related parameters, including several items on the PGI, the severity and improvement items of the Clinician Global Impression scale (CGI; weeks 1 and 2) and the Insomnia Severity Index (ISI; weeks 1-4), all versus PBO. There were no reports of anticholinergic effects (e.g., dry mouth) or memory impairment. The safety profile of DXP 6 mg was comparable to that of PBO.

CONCLUSIONS: In elderly adults with insomnia, DXP 6 mg produced significant improvements in sleep maintenance, sleep duration, and sleep quality endpoints that were sustained throughout the trial. These data suggest that DXP 6 mg is effective for treating sleep maintenance insomnia and is well-tolerated in elderly adults with chronic primary insomnia.

Mayer, G., S. Wang-Weigand, et al. (2009). "Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia." Sleep **32**(3): 351-360.

STUDY OBJECTIVES: Long-duration (> or = 6 months) polysomnographic studies of insomnia medications are lacking. This study evaluated the long-term efficacy of ramelteon, a selective MT1/MT2 melatonin-receptor agonist used for insomnia treatment. DESIGN: Six-month, randomized, double-blind, placebo-controlled study. SETTING: Forty-six investigative sites in the United States, Europe, Russia, and Australia. PARTICIPANTS: Four hundred fifty-one adults (age > or = 18 years) with chronic primary insomnia. INTERVENTIONS: Ramelteon, 8 mg, or placebo 30 minutes before bedtime nightly for 6 months. MEASUREMENTS: Sleep was evaluated by polysomnography and morning questionnaires on the first 2 nights of Week 1; the last 2 nights of Months 1, 3, 5, and 6; and Nights 1 and 2 of the placebo run-out. Next-morning residual effects as well as adverse effects and vital signs were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out. RESULTS: Over the 6 months of

treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at Week 1 and Months 1, 3, 5, and 6 (P < 0.05). Ramelteon significantly reduced subjective sleep latency relative to placebo at Week 1, Month 1, and Month 5 (P < 0.05), with reductions nearing statistical significance at Months 3 and 6 (P < or = 0.08). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity. CONCLUSIONS: In adults with chronic insomnia, long-term ramelteon treatment consistently reduced sleep onset, with no next-morning residual effects or rebound insomnia or withdrawal symptoms upon discontinuation.

McCall, W. V., J. N. Blocker, et al. (2010). "Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression." Journal of Clinical Sleep Medicine **6**(4): 322-329.

STUDY OBJECTIVES: Insomnia is associated with poor health related quality of life (HRQOL) in depressed patients. Prior clinical trials of hypnotic treatment of insomnia in depressed patients have shown improvement in HRQOL, but in these studies HRQOL was relegated to a secondary outcome, and objective measures of sleep were not undertaken. DESIGN: Double-blind, randomized, placebo-controlled clinical trial. SETTING: Outpatient clinic and sleep laboratory. PATIENTS: 60 depressed, insomniac outpatients. INTERVENTIONS: One week of open-label fluoxetine (FLX), followed by 8 more weeks of FLX combined with either eszopiclone (ESZ) 3 mg or placebo at bedtime. MEASUREMENTS: The primary HRQOL measure was the daily living and role functioning subscale (DLRF) of the Basis-32. Other measures included the Q-LES-Q, self-reported sleep, PSG, actigraphy, depression severity (HRSD). RESULTS: At the end of randomized treatment, patients receiving ESZ had lower (better) DLRF scores (0.81 +/- 0.64) than those receiving placebo (1.2 +/- 0.72), p = 0.01. The effect size for DLRF was 0.62, indicating a moderate effect. An advantage for ESZ was also seen in other measures of HRQOL, and most assessments of antidepressant efficacy and sleep. Women reported better end of treatment HRQOL scores than men. CONCLUSIONS: ESZ treatment of insomnia in depressed patients is associated with multiple favorable outcomes, including superior improvement in HRQOL, depression severity, and sleep.

McElroy, S. L., E. L. Winstanley, et al. (2011). "A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance." International Clinical Psychopharmacology **26**(1): 48-53.

This study evaluated the efficacy and tolerability of ramelteon in ambulatory bipolar I disorder with manic symptoms and insomnia. Twenty-one outpatients with bipolar I disorder by Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria with mild-to-moderate manic symptoms and sleep disturbance were randomized to receive either ramelteon (N=10) or placebo (N=11) in an 8-week, double-blind, fixed-dose (8 mg/day) study. Ramelteon and placebo had similar rates of reduction in ratings of symptoms of insomnia, mania, and global severity of illness. However, ramelteon was associated with improvement in a global rating of depressive symptoms. It was also well tolerated and associated with no serious adverse events. The small sample size may have limited the ability of the study to detect potentially clinically important drug-placebo differences. Further studies of ramelteon in subgroups of bipolar patients with sleep disturbance, including those with depression or euthymia, seem indicated.

Menza, M., R. D. Dobkin, et al. (2010). "Treatment of insomnia in Parkinson's disease: a controlled trial of eszopiclone and placebo." Movement Disorders **25**(11): 1708-1714.

Parkinson's disease (PD) is a common neurodegenerative disease affecting up to 1 million individuals in the United States. Sleep disturbances, typically in sleep maintenance, are found in up to 88% of these individuals and are associated with a variety of poor outcomes. Despite being common and important, there are few data to guide clinical care. We conducted a 6-week, randomized, controlled trial of eszopiclone and placebo in 30 patients with PD and insomnia. Patients with other primary sleep disorders (PSG defined) were excluded. The primary outcome was total sleep time (TST), and secondary measures included wake after sleep onset (WASO), number of awakenings, and quality of sleep, among others. The groups did not significantly differ on TST, but significant differences, favoring eszopiclone, did emerge in number of awakenings (P = 0.035), quality of sleep (P = 0.018), and in physician-rated CGI improvement (P = 0.035). There was also a trend toward significance in WASO (P = 0.071). There were no significant differences between groups in measures of daytime functioning. The drug was well tolerated, with 33% of patients on eszopiclone and 27% of patients on placebo reporting adverse events. Although modest in size, this is the first controlled study of the treatment of insomnia in patients with PD. Eszopiclone did not increase TST significantly but was superior to placebo in improving quality of sleep and some measures of sleep maintenance, which is the most common sleep difficulty experienced by patients with PD. Definitive trials of the treatment of sleep disorders in this population are warranted.

Morin, C. M., A. Vallieres, et al. (2009). "Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial." JAMA : the journal of the American Medical Association **301**(19): 2005-2015.

CONTEXT: Cognitive behavioral therapy (CBT) and hypnotic medications are efficacious for short-term treatment of insomnia, but few patients achieve complete remission with any single treatment. It is unclear whether combined or maintenance therapies would enhance outcome. OBJECTIVES: To evaluate the added value of medication over CBT alone for acute treatment of insomnia and the effects of maintenance therapies on long-term outcome. DESIGN, SETTING, AND PATIENTS: Prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia treated at a university hospital sleep center in Canada between January 2002 and April 2005. INTERVENTIONS: Participants received CBT alone or CBT plus 10 mg/d (taken at bedtime) of zolpidem for an initial 6-week therapy, followed by extended 6-month therapy. Patients initially treated with CBT attended monthly maintenance CBT for 6 months or received no additional treatment and those initially treated with combined therapy (CBT plus 10 mg/d of zolpidem) continued with CBT plus intermittent use of zolpidem or CBT only. MAIN OUTCOME MEASURES: Sleep onset latency, time awake after sleep onset, total sleep time, and sleep efficiency derived from daily diaries (primary outcomes); treatment response and remission rates derived from the Insomnia Severity Index (secondary outcomes). RESULTS: Cognitive behavioral therapy used singly or in combination with zolpidem produced significant improvements in sleep latency, time awake after sleep onset, and sleep efficiency during initial therapy (all P<.001); a larger increase of sleep time was obtained with the combined approach (P = .04). Both CBT alone and CBT plus zolpidem produced similar rates of treatment responders (60% [45/75] vs 61% [45/74], respectively; P = .84) and treatment remissions (39% [29/75] vs 44% [33/74], respectively; P = .52) with the 6-week acute treatment, but combined therapy produced a higher remission rate compared with CBT alone during the 6-month extended therapy phase and the 6-month follow-up period (56% [43/74 and 32/59] vs 43% [34/75 and 28/68]; P = .05). The best long-term outcome was obtained with patients treated with combined

therapy initially, followed by CBT alone, as evidenced by higher remission rates at the 6-month follow-up compared with patients who continued to take zolpidem during extended therapy (68% [20/30] vs 42% [12/29]; P = .04). CONCLUSION: In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00042146.

Omvik, S., B. Sivertsen, et al. (2008). "Daytime functioning in older patients suffering from chronic insomnia: treatment outcome in a randomized controlled trial comparing CBT with Zopiclone." Behaviour Research and Therapy **46**(5): 623-641.

The paper presents data from a randomized controlled trial comparing treatment effects of cognitive behavioural therapy (CBT), hypnotic treatment (Zopiclone), and placebo in a sample of insomnia patients. Data from the same trial have already demonstrated that CBT was more efficient in improving sleep than Zopiclone. The novel outcomes that are reported here concern daytime functioning. Forty-six older patients (age >or= 55) qualifying for a diagnosis of primary insomnia were recruited to participate. Assessments were completed at baseline, post-treatment, and at a 6-months follow-up, and measures of worry, anxiety, depression, interpersonal relationships, subjective alertness, vigilance, and quality of life were used. The participants in both treatment conditions scored within the normal range on the outcome measures at baseline with the exception of reporting less alertness, relative to a group of good sleepers. One interaction effect indicated that subjective alertness improved more in the Zopiclone group than the CBT group from baseline to post-treatment, and another that CBT was more effective than Zopiclone in reducing trait anxiety from baseline to follow-up. It was concluded that the treatments yielded only minor effects on the measures of daytime functioning, and that none of them was clearly superior to the other.

Pollack, M. H., E. A. Hoge, et al. (2011). "Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial." Journal of Clinical Psychiatry **72**(7): 892-897.

OBJECTIVE: The development of novel strategies for the treatment of posttraumatic stress disorder (PTSD) represents a critical public health need. We present the first prospective, randomized, double-blind, placebo-controlled trial of a non-benzodiazepine hypnotic agent for the treatment of PTSD and associated insomnia.

METHOD: Twenty-four patients with PTSD by DSM-IV criteria and sleep disturbance were treated in a randomized, double-blind, placebo-controlled crossover study of 3 weeks of eszopiclone 3 mg at bedtime compared to placebo. The primary outcome measures were changes in scores on the Short PTSD Rating Interview (SPRINT) and the Pittsburgh Sleep Quality Index (PSQI). The data were collected from April 2006 to June 2008.

RESULTS: Three weeks of eszopiclone pharmacotherapy was associated with significantly greater improvement than placebo on PTSD symptom measures including the SPRINT (P = .032) and the Clinician-Administered PTSD Scale (P = .003), as well as on measures of sleep including the PSQI (P = .011) and sleep latency (P = .044). Greater improvement with eszopiclone on PTSD measures was present even when specific sleep-related items were excluded. Adverse events were consistent with the known profile of the drug.

CONCLUSIONS: This study provides initial evidence that pharmacotherapy with eszopiclone may be associated with short-term improvement in overall PTSD severity as well as associated sleep disturbance. Longer, more definitive study of eszopiclone in PTSD is warranted.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00120250. Copyright 2011 Physicians Postgraduate

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Randall, S., T. A. Roehrs, et al. (2012). "Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study." Sleep **35**(11): 1551-1557.

STUDY OBJECTIVES: To evaluate the long-term (8 months) efficacy of zolpidem in adults with chronic primary insomnia using polysomnography.

DESIGN: Randomized, double-blind, placebo-controlled clinical trial.

SETTING: Sleep disorders and research center.

PARTICIPANTS: Healthy participants (n = 91), ages 23-70, meeting DSM-IV-TR criteria for primary insomnia.

INTERVENTIONS: Nightly zolpidem, 10 mg (5 mg for patients > 60 yrs) or placebo 30 minutes before bedtime for 8 months.

MEASUREMENTS AND RESULTS: Polysomnographic sleep parameters and morning subject assessments of sleep on 2 nights in months 1 and 8. Relative to placebo, zolpidem significantly increased overall total sleep time and sleep efficiency, reduced sleep latency and wake after sleep onset when assessed at months 1 and 8. Overall, subjective evaluations of efficacy were not shown among treatment groups.

CONCLUSIONS: In adults with primary insomnia, nightly zolpidem administration remained efficacious across 8 months of nightly use.

CLINICAL TRIAL INFORMATION: ClinicalTrials.gov Identifier: NCT01006525; Trial Name: Safety and Efficacy of Chronic Hypnotic Use; http://clinicaltrials.gov/ct2/show/NCT01006525.

Roehrs, T. A., S. Randall, et al. (2012). "Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study." Journal of Psychopharmacology **26**(8): 1088-1095.

Rebound insomnia, worsened sleep when discontinuing use of a hypnotic, is reported in some short-term studies. No study has prospectively assessed, using patient reports or nocturnal polysomnography (NPSG), the likelihood of rebound insomnia with chronic hypnotic use. The objectives of this study was to assess in primary insomniacs the likelihood of experiencing rebound insomnia and a withdrawal syndrome on repeated placebo substitutions over 12 months of nightly zolpidem use. A group of 33 primary insomniacs, without psychiatric disorders or drug and alcohol abuse, 32-65 years old, 15 men and 18 women, were randomized to take zolpidem 10 mg (n = 17) or placebo (n = 16) nightly for 12 months. In probes during months 1, 4, and 12, placebo was substituted for 7 consecutive nights in both the zolpidem and placebo groups. NPSGs were collected and Tyrer Bezodiazepine Withdrawal Symptom Questionnaires were completed on the first two discontinuation nights. Rebound insomnia was not observed on the first two and the seventh discontinuation nights and its likelihood did not increase over the 12 months of nightly zolpidem use. Some individuals did show rebound insomnia, approximately 30-40% of participants, but the percentage of 'rebounders' did not differ between the placebo and zolpidem groups and did not increase across 12 months. No clinically significant withdrawal symptoms on the Tyrer were observed on the discontinuation nights over the 12 months of nightly use. Chronic nightly hypnotic use at therapeutic doses by primary insomniacs does not lead to rebound insomnia or withdrawal symptoms.

Roth, T., S. G. Hull, et al. (2008). "Low-dose sublingual zolpidem tartrate is associated with dose-related improvement in sleep onset and duration in insomnia characterized by middle-of-the-night (MOTN) awakenings." Sleep **31**(9): 1277-1284.

STUDY OBJECTIVES: To evaluate the efficacy and safety of low-dose, sublingual zolpidem tartrate

when taken during a scheduled middle-of-the-night (MOTN) awakening in subjects with insomnia characterized by difficulty returning to sleep following MOTN awakenings. DESIGN: Randomized, double-blind, placebo-controlled, 3-way crossover study. METHODS: Each treatment period consisted of 2 consecutive nights of dosing separated by a washout of 5 to 12 days. Subjects were awakened 4 h after lights out, dosed with sublingual zolpidem tartrate (3.5 mg or 1.75 mg) or placebo, kept awake for 30 min, and then returned to bed for an additional 4 h. Sleep parameters were assessed by polysomnography (PSG) and post-sleep questionnaires. SETTING: Five sleep laboratories. PARTICIPANTS: Adults (24 males, 58 females, mean age 45.9 y) with a diagnosis of DSM-IV primary insomnia and a history of prolonged MOTN awakenings. Baseline difficulties with MOTN awakenings were confirmed by a 10-day screening sleep diary and PSG screening. RESULTS: Low-dose sublingual zolpidem tartrate demonstrated significant dose-related decreases in latency to persistent sleep and total sleep time ($P < 0.001$) compared to placebo after MOTN dosing. All subject reports paralleled PSG observations. Neither dose showed next-morning impairment on the DSST or ratings of sleepiness. The 3.5-mg dose produced improvements in reports of sleep quality ($P < 0.001$), ability to function, and level of refreshed sleep ($P < 0.05$ for both dosages) compared to placebo. Sublingual zolpidem tartrate lozenges were generally safe and well tolerated. CONCLUSIONS: Low-dose sublingual zolpidem tartrate may be suitable for treatment of patients who have difficulty resuming sleep after MOTN awakenings.

Uchimura, N., A. Ogawa, et al. (2011). "Efficacy and safety of ramelteon in Japanese adults with chronic insomnia: a randomized, double-blind, placebo-controlled study." Expert Review of Neurotherapeutics **11**(2): 215-224.

This randomized, double-blind, placebo-controlled study assessed the efficacy and safety of ramelteon 4 and 8 mg in Japanese adults with chronic insomnia. A secondary objective was to evaluate efficacy and safety when doses were uptitrated from placebo, ramelteon 4 and 8 mg to 4, 8 and 16 mg, respectively. Patient-reported sleep data were collected using sleep diaries. There was no statistically significant difference between ramelteon and placebo in the change in subjective sleep latency (sSL) in the full analysis set (n = 1130). Significant improvement was observed in the change in subjective total sleep time with ramelteon 8 mg at week 1. In post hoc analyses, ramelteon 8 mg reduced sSL in individuals with smaller fluctuations (within +/-30 min) of sSL at baseline, in those with a shorter (<1 year) history of insomnia and in individuals who had not used benzodiazepines. Ramelteon up to 16 mg nightly was safe and well tolerated.

Uchiyama, M., M. Hamamura, et al. (2011). "Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia." Sleep Medicine **12**(2): 127-133.

OBJECTIVE: To evaluate the safety of ramelteon, a highly selective MT1/MT2 melatonin receptor agonist, during 24 weeks' treatment of Japanese patients with chronic insomnia.

METHODS: In a single-blind, flexible-titration, multicenter study incorporating placebo run-in and run-out periods, 190 adults with chronic insomnia received ramelteon 4 or 8 mg, titrated up to 16 mg if necessary, for 24 weeks. Primary endpoints included adverse events, residual effects, rebound insomnia, withdrawal symptoms, and dependence. Secondary endpoints included subjective sleep latency and total sleep time.

RESULTS: Drug-related adverse events occurred in 11.6% of patients. No clinically important changes occurred in biochemical, hematological or endocrine parameters. There were no signs of next-day residual effect, rebound insomnia, withdrawal symptoms or dependence. Mean subjective sleep latency decreased significantly, and total sleep time increased significantly; both reached a plateau by week 20 and were sustained thereafter ($P<0.0001$).

CONCLUSIONS: Ramelteon was well tolerated in adult Japanese patients with chronic insomnia and did not cause deterioration of efficacy, residual effects, rebound insomnia, withdrawal symptoms, or dependence after 24 weeks' treatment. Copyright 2011 Elsevier B.V. All rights reserved.

Uchiyama, M., M. Hamamura, et al. (2011). "Evaluation of subjective efficacy and safety of ramelteon in Japanese subjects with chronic insomnia." Sleep Medicine **12**(2): 119-126.

OBJECTIVE: To assess patient-reported efficacy and safety of ramelteon in Japanese patients with chronic insomnia.

METHODS: Randomized, double-blind, placebo-controlled, multicenter trial. After a placebo lead-in period, 987 adults with chronic insomnia received ramelteon 8 mg or placebo once daily for 2 weeks, followed by a placebo run-out period to monitor rebound insomnia. Patient-reported sleep data were collected using sleep diaries.

RESULTS: Ramelteon significantly reduced mean patient-reported sleep latency (primary endpoint) compared with placebo during week 1 (-4.54 min; p=0.001). Ramelteon maintained greater efficacy in sleep latency than placebo at week 2, but the difference did not achieve statistical significance. In a subset of patients who adhered to treatment and completed their diaries as instructed, a statistically significant reduction in subjective sleep latency was sustained through week 2. Compared with placebo, ramelteon also significantly improved mean total sleep time and mean sleep quality during week 1, the number of awakenings during week 2, and overall patient global impression scores. There was no evidence of rebound insomnia. Adverse events were generally mild and transient.

CONCLUSIONS: In Japanese adults with chronic insomnia, ramelteon 8 mg significantly reduced patient-reported sleep latency, increased total sleep time and improved sleep quality after 1 week of treatment. Ramelteon was generally well tolerated with no rebound insomnia. Copyright 2010 Elsevier B.V. All rights reserved.

Wang-Weigand, S., M. McCue, et al. (2009). "Effects of ramelteon 8 mg on objective sleep latency in adults with chronic insomnia on nights 1 and 2: pooled analysis." Current Medical Research & Opinion **25**(5): 1209-1213.

OBJECTIVE: Ramelteon is an MT(1)/MT(2) melatonin receptor agonist indicated for the treatment of insomnia characterized by difficulty with sleep onset. In previous clinical studies, ramelteon reduced latency to persistent sleep (LPS) in subjects with chronic insomnia. The goal of the current analysis was to determine the average reduction in LPS and overall adverse event profile for subjects taking ramelteon 8 mg. RESEARCH DESIGN AND METHODS: This pooled analysis examined four randomized, double-blind, placebo-controlled clinical trials of ramelteon in subjects with chronic insomnia. The analysis included adults (age 18-83 years) with chronic insomnia who took ramelteon 8 mg or placebo. The primary endpoint of each trial was mean LPS, measured by polysomnography (PSG) on nights 1 and 2. Adverse events were collected for all subjects for the duration of each trial. RESULTS: Efficacy data were available for 566 subjects who took ramelteon 8 mg (mean age 46.7 years) and 556 subjects who took placebo (mean age 47.8 years). Mean LPS at baseline was 66.6 min for the placebo group and 66.9 min for the ramelteon group. At nights 1 and 2, mean LPS for the ramelteon 8 mg group (30.2 min) was significantly less than the mean LPS for the placebo group (43.3 min). The least squares mean difference from placebo was -13.1 min ($p < 0.001$). Headache (8.9% ramelteon 8 mg, 8.8% placebo) and somnolence (3.5% ramelteon 8 mg, 0.7% placebo) were the most common adverse events. CONCLUSIONS: Ramelteon 8 mg, on average, reduced LPS by approximately 13 min more than placebo on nights 1 and 2 of treatment in adults with chronic insomnia. Ramelteon was well tolerated with a low incidence of adverse events. This mean reduction in LPS versus

placebo is similar to what has been reported for other classes of insomnia medications. However, these results reflect nights 1 and 2 of treatment and may not be representative of longer treatments.

Drug Use Research & Management Program
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Month/Year of Review: November 2013 **Date of Last Review:** February 2012
PDL Classes: Nonsteroidal Anti-inflammatory Drugs (NSAIDS) **Source Document:** DERP

Current Status of PDL Class:

- Preferred Agents: DICLOFENAC POTASSIUM, DICLOFENAC SODIUM DR, ETODOLAC TABLET, FLURBIPROFEN, IBUPROFEN CAPSULE/DROPS/ORAL SUSP/CHEWABLE/TABLET, INDOMETHASONE CAPSULE, KETOPROFEN, MELOXICAM, NABUMETONE, NAPROXEN TABLET, NAPROXEN DR, NAPROXEN SODIUM, OXAPROZIN, SALSALATE, SULINDAC
- Non-Preferred Agents: CELECOXIB (CELEBREX®), DICLOFENAC TAB ER 24H, DIFLUNISAL, ETODOLAC CAPSULE, ETODOLAC TABLET ER 24H, FENOPROFEN, INDOMETHASONE ORAL SUSPENSION/CAPSULE ER, KETOPROFEN CAPSULE 24H, KETOROLAC TALET, KETOROLAC NASAL SPRAY (SPRIX®), MECLOFENAMATE SODIUM, MEFENAMIC ACID, NAPROXEN CAPSULE, PIROXICAM ,TOLMETIN SODIUM

Previous Conclusions and Recommendation:

- For pain relief, no significant short-term (< 6 months) differences were found among oral NSAIDs.
- For serious harms, celecoxib did not appear to be associated with higher risk of cardiovascular (CV) events and is gastroprotective in the short term compared with nonselective NSAIDs.
- Findings vary by subgroup, depending on age, recent history of gastrointestinal bleeding, and concomitant use of antiulcer medication.
- Nonselective NSAIDs were associated with similar increased risks of serious GI events, and all but naproxen were associated with similar increased risk of serious CV events, but eh partially selective NSAID nabumetone was gastroprotective compared with nonselective NSAIDs.
- Make ketorolac nasal spray (Sprix®) nonpreferred and recommend quantity limit of 5 days.

PA Criteria: Prior authorization is in place to ensure that non-preferred NSAIDs are used for above the line conditions and to restrict ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning (Appendix 1).

Conclusions and Recommendations:

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

References:

1. Peterson, Kim. Drug Effectiveness Review Project: Drug Class Review Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Preliminary Scan Report #1. July 2013.

Analgesics, Non-Steroidal Anti-Inflammatory Drugs 204

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred NSAIDs are used for an above the line condition and restrict ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning.

WARNING - Ketorolac is indicated for the short-term (up to 5 days) management of moderately severe acute pain that requires analgesia at the opioid level. It is not indicated for minor or chronic painful conditions. Ketorolac is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac is indicated, especially when the drug is used inappropriately. Increasing the dose beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Length of Authorization: Up to 12 months

Requires PA:

- Non-preferred NSAIDs
- Ketorolac: Maximum of one claim per 60 days. That claim can be a maximum of 20tablets/5 days, i.e. there is a 5 day maximum per 60 days.

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

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis covered by the Oregon Health Plan? All indications need to be evaluated as to whether they are above the line or below the line.	**Yes:** Go to #3	**No**: Pass to RPH; Deny, (Not covered by the OPH)
3. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	**Yes:** Document prior therapy in PA record. Go to #4	**No**: Go to #5
4. Is request for ketorolac greater than a 5 day supply within 60 days (200mg total over 5 days for tablets, 630mg total over 5 days for the nasal spray)?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness). Review FDA warnings	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the ~~Health Resources Commission (HRC).~~Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.

Revision(s): 5/14/12, 1/1/10
Initiated: ?

Drug Class Review

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Preliminary Scan Report #1

July 2013

Last Report: Update #4 (November 2010)

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

Scan conducted by:
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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #4, November 2010 (searches through June 2010)

Scope and Key Questions

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
2. Are there clinically important differences in short-term harms (< 6 months) between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
3. Are there clinically important differences in long-term harms (≥ 6 months) between NSAIDs, with or without antiulcer medication, when used chronically in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one medication is more effective or associated with fewer harms?

Inclusion Criteria

Populations

Adults with:

- Chronic pain from osteoarthritis
- Rheumatoid arthritis
- Soft-tissue pain
- Back pain
- Ankylosing spondylitis

Interventions

- Oral drugs: celecoxib, diclofenac potassium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketoprofen extended release, ketoprofen sustained release, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen delayed release, naproxen sustained release, naproxen sodium, oxaprozin, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid, and tolmetin
- Topical drugs: diclofenac epolamine 1.3% topical patch, diclofenac sodium 1% topical gel, diclofenac sodium 1.5% topical solution, diclofenac sodium 3% topical gel, and topical diclofenac diethylamine 1.16%.

Outcomes

Effectiveness outcomes

- Pain
- Functional status
- Discontinuations due to lack of effectiveness.

Harms

- Serious gastrointestinal events (gastrointestinal bleeding, symptomatic ulcer disease, perforation of the gastrointestinal tract, and death)
- Serious cardiovascular events (myocardial infarction, angina, stroke, transient ischemic attack, cardiovascular death, hypertension, congestive heart failure, and related measures)
- Tolerability and adverse event (discontinuation due to any adverse event; any serious adverse event; the overall rate of adverse events; the rate of gastrointestinal adverse events; the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, edema, hypertension, or congestive heart failure; and the frequency of, and discontinuations due to, abnormal laboratory tests—primarily elevated transaminases).

Study Designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews
- For harms, controlled clinical trials, good-quality systematic reviews and observational studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2010 through June 26, 2013 using terms for included drugs and conditions. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/) and the Cochrane Collaboration (http://www.cochrane.org/cochrane-reviews). All citations were imported into an electronic database (EndNote X1) 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

Vimovo (naproxen and esomeprazole magnesium fixed-dose combination tablet): Approved on 4/30/10 to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis

New Indications

None.

New Safety Alerts

None.

Comparative Effectiveness Reviews

We identified one new comparative effectiveness review. The abstract of this review is attached in Appendix A, and the link to the full report is listed below.

Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm

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Randomized Controlled Trials

Medline searches resulted in 222 citations. Of those, there were six potentially relevant new randomized controlled trials and one new companion publication (Table 1). Among the new randomized controlled trials, six involved head-to-head comparisons and one was placebo-controlled. Among the head-to-head trials, two involved the new naproxen/esomeprazole magnesium fixed-dose combination product which has not been included in any previous full update DERP report. Abstracts of these trials are attached in Appendix B.

Table 1. New potentially relevant randomized controlled trials

Author Year	Comparison	Focus
Head-to-head trials		
Cryer 2013 (GI-REASONS)	Celecoxib vs NSAIDs	Osteoarthritis
Essex 2012	Celecoxib vs naproxen	Knee osteoarthritis
Kellner 2012 *(companion to CONDOR, Chan 2010)*	Celecoxib vs diclofenac plus omeprazole	Subgroup analysis of elderly patients
Schmitt 1999	Diclofenac sodium dual release capsule vs standard release	Activated osteoarthritis
Cryer 2011/Hochberg 2011	Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib	Knee osteoarthritis
Goldstein 2010	Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib vs naproxen alone	Patients with a history of ulcer
Placebo-controlled trials		
Baraf 2010	Diclofenac sodium topical gel 1% vs placebo	Knee osteoarthritis

Appendix A. Abstracts of potentially relevant new comparative effectiveness reviews of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Structured Abstract

Objectives:
To update a previous report on the comparative benefits and harms of oral non-steroidal anti-inflammatory drugs (NSAIDs) , acetaminophen, over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Data Sources:
Ovid MEDLINE (1996–January 2011), the Cochrane database (through fourth quarter 2010), and reference lists.

Review Methods:
We included randomized trials, cohort studies, case-control studies, and systematic reviews that met predefined inclusion criteria. For each study, investigators abstracted details about the study population, study design, data analysis, followup, and results, and they assessed quality using predefined criteria. We assessed the overall strength of each body of evidence using predefined criteria, which included the type and number of studies; risk of bias; consistency; and precision of estimates. Meta-analyses were not performed, though pooled estimates from previously published studies were reported.

Results:
A total of 273 studies were included. Overall, we found no clear differences in efficacy for pain relief associated with different NSAIDs. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) compared to nonselective NSAIDs. Coprescribing of proton pump inhibitors, misoprostol, and H2-antagonists reduce the risk of endoscopically detected gastroduodenal ulcers compared to placebo in persons prescribed NSAIDs. Celecoxib and most nonselective, nonaspirin NSAIDs appeared to be associated with an increased risk of serious cardiovascular (CV) harms. There was no clear association between longer duration of NSAID use or higher doses and increased risk of serious CV harms. There were no clear differences between glucosamine or chondroitin and oral NSAIDs for pain or function, though evidence from a systematic review of higher-quality trials suggests that glucosamine had some very small benefits over placebo for pain. Head-to-head trials showed no difference between topical and oral NSAIDs for efficacy in patients with localized osteoarthritis, lower risk of

gastrointestinal (GI) adverse events, and higher risk of dermatological adverse events, but serious GI and CV harms were not evaluated. No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs.

Conclusions:
Each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. Choosing the optimal analgesic for an individual with osteoarthritis requires careful consideration and thorough discussion of the relevant tradeoffs.

Appendix B. Abstracts of potentially relevant new randomized controlled trials of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Head-to-Head Trials

Cryer, B., C. Li, et al. (2013). "GI-REASONS: a novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial." American Journal of Gastroenterology **108**(3): 392-400.

OBJECTIVES: Because of the limitations of randomized controlled trials (RCTs) and observational studies, a prospective, randomized, open-label, blinded endpoint (PROBE) study may be an appropriate alternative, as the design allows the assessment of clinical outcomes in clinical practice settings. The Gastrointestinal (GI) Randomized Event and Safety Open-Label Nonsteroidal Anti-inflammatory Drug (NSAID) Study (GI-REASONS) was designed to reflect standard clinical practice while including endpoints rigorously evaluated by a blinded adjudication committee. The objective of this study was to assess if celecoxib is associated with a lower incidence of clinically significant upper and/or lower GI events than nonselective NSAIDs (nsNSAIDs) in standard clinical practice.

METHODS: This was a PROBE study carried out at 783 centers in the United States, where a total of 8,067 individuals aged >= 55 years, requiring daily NSAIDs to treat osteoarthritis, participated. The participants were randomized to celecoxib or nsNSAIDs (1:1) for 6 months and stratified by Helicobacter pylori status. Treatment doses could be adjusted as per the United States prescribing information; patients randomized to nsNSAIDs could switch between nsNSAIDs; crossover between treatment arms was not allowed, and patients requiring aspirin at baseline were excluded. The primary outcome was the incidence of clinically significant upper and/or lower GI events.

RESULTS: Significantly more nsNSAID users met the primary endpoint (2.4% (98/4,032) nsNSAID patients and 1.3% (54/4,035) celecoxib patients; odds ratio, 1.82 (95% confidence interval, 1.31-2.55); P = 0.0003). Moderate to severe abdominal symptoms were experienced by 94 (2.3%) celecoxib and 138 (3.4%) nsNSAID patients (P=0.0035). Other non-GI adverse events were similar between treatment groups. One limitation is the open-label design, which presents the possibility of interpretive bias.

CONCLUSIONS: Celecoxib was associated with a lower risk of clinically significant upper and/or lower GI events than nsNSAIDs. Furthermore, this trial represents a successful execution of a PROBE study, where therapeutic options and management strategies available in clinical practice were incorporated into the rigor of a prospective RCT.

Essex, M. N., P. Bhadra, et al. (2012). "Efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis of the knee: a randomized, double-blind, double-dummy trial." Journal of International Medical Research **40**(4): 1357-70.

OBJECTIVE: To assess the efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis (OA) of the knee.

METHODS: This 6-month, randomized, double-blind, double-dummy trial was conducted at 47 centres in the USA. Patients with OA of the knee were randomized to receive 200 mg

celecoxib orally once daily or 500 mg naproxen orally twice daily. The primary endpoint was defined as a 20% improvement from baseline to 6 months in Western Ontario and McMaster Universities (WOMAC) OA total score.

RESULTS: A total of 586 out of 589 randomized patients received at least one dose of celecoxib (n=294) or naproxen (n=292). The primary endpoint (6-month response rate) was achieved by 52.7% and 49.7% of patients in the celecoxib and naproxen treatment groups, respectively. Significantly fewer discontinuations due to gastrointestinal adverse events occurred in patients receiving celecoxib than in those receiving naproxen (4.1% versus 15.1%, respectively).

CONCLUSIONS: Over the 6month study period, celecoxib provided similar improvements in OA symptoms to naproxen. In addition, celecoxib provided better upper gastrointestinal tolerability than naproxen.

Kellner, H. L., C. Li, et al. (2012). "Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial." Current Medical Research & Opinion **28**(9): 1537-45.

OBJECTIVE: To compare the safety and efficacy of celecoxib versus diclofenac slow release (SR) plus omeprazole in elderly arthritis patients.

RESEARCH DESIGN AND METHODS: Patients aged>=65 years, with osteoarthritis and/or rheumatoid arthritis, at high gastrointestinal (GI) risk who participated in the CONDOR trial (Celecoxib vs. Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) were included in this subanalysis. CONDOR was a 6-month prospective, double-blind, randomized, parallel-group, multicenter, international study comparing treatment with celecoxib 200mg twice daily (BID) versus diclofenac SR 75mg BID plus omeprazole 20mg daily.

MAIN OUTCOME MEASURES: The primary end point was a composite of Clinically Significant Upper and Lower GI Events adjudicated by an independent blinded expert committee. Efficacy was determined by the Patient's Global Assessment of Arthritis.

RESULTS: A total of 2446 patients aged>=65 years were included in the intent-to-treat (ITT) population (n=1219 celecoxib; n=1227 diclofenac). Eight patients in the celecoxib group and 52 in the diclofenac group were adjudicated as having Clinically Significant Upper and Lower GI events (adjusted odds ratio: 6.27; p<0.0001). Clinically significant reductions in hemoglobin (>=2g/dL) and/or hematocrit (>=10%) were observed in 23 patients in the celecoxib group and in 76 in the diclofenac group (relative risk: 3.22 [95% confidence interval: 2.04-5.07]; p<0.0001). Incidence of moderate-to-severe abdominal symptoms and discontinuation of treatment due to GI adverse events (AEs) were lower in the celecoxib group. The Patient's Global Assessment of Arthritis score least squares mean change from baseline to final visit and percentage of patients rating treatment efficacy as good/very good at baseline and final visit were similar in both groups.

LIMITATIONS: The dose of celecoxib used is consistent with the European label for the management of osteoarthritis and may not reflect what is commonly prescribed in current clinical practice in the United States. The data were obtained in a clinical trial setting where patients were enrolled based on specific inclusion and exclusion criteria;

as such, the patients may not be broadly representative of the patient population in a general practice setting.

CONCLUSIONS: Efficacy was comparable in the two treatment groups. There were fewer endpoints as well as fewer GI AEs reported in patients treated with celecoxib compared with diclofenac. These data may help physicians in their treatment decisions for elderly patients with arthritis.

Schmitt, W., K. Walter, et al. (1999). "Clinical trial on the efficacy and safety of different diclofenac formulations: multiple-unit formulations compared to enteric coated tablets in patients with activated osteoarthritis." Inflammopharmacology **7**(4): 363-75.

This double-blind, randomised, multicentre study investigated the efficacy and safety of two different dosages of a diclofenac sodium dual release capsule (150 mg or 75 mg once daily) in comparison to a standard treatment with enteric coated tablets (50 mg t.i.d.) and placebo in patients with activated osteoarthritis. Pain relief as the main efficacy variable was measured through 24 hours by means of a Visual Analogue Scale at baseline and on five assessment days during the 12 weeks of treatment. Efficacy was observed in all treatment groups with a statistically significant difference between the verum groups and placebo. The overall safety and tolerability of the active treatments was good. For the 75 mg group, a lower incidence of liver and biliary system-related side effects was reported. Considering efficacy, safety, and compliance aspects, the once daily administration of diclofenac sodium 75 mg dual release capsule is the appropriate dosage regimen for mid- and long-term treatment of osteoarthritis.

Cryer, B. L., M. B. Sostek, et al. (2011). "A fixed-dose combination of naproxen and esomeprazole magnesium has comparable upper gastrointestinal tolerability to celecoxib in patients with osteoarthritis of the knee: results from two randomized, parallel-group, placebo-controlled trials." Annals of Medicine **43**(8): 594-605.

BACKGROUND. Non-steroidal anti-inflammatory drugs are associated with poor upper gastrointestinal (UGI) tolerability and increased ulcer risk, but patient adherence to gastroprotective co-therapy is frequently inadequate. A fixed-dose combination of enteric-coated naproxen 500 mg and immediate-release esomeprazole magnesium 20 mg was evaluated: efficacy is reported by Hochberg et al. (Curr Med Res Opin 2011;27:1243-53); tolerability findings are reported here. PATIENTS AND METHODS. In two 12-week double-blind, placebo-controlled, multicenter, phase III studies (PN400-307 and PN400-309), patients aged >= 50 years with symptomatic knee osteoarthritis randomly (2:2:1) received naproxen/esomeprazole magnesium BID, celecoxib 200 mg QD, or placebo. Tolerability end-points included: modified Severity of Dyspepsia Assessment (mSODA); heartburn severity; and UGI adverse events (AEs). RESULTS. Overall, 619 (PN400-307) and 615 (PN400-309) patients were randomized; mSODA scores improved (baseline to week 12) in each group, with no significant treatment differences between naproxen/esomeprazole magnesium and celecoxib (95% CIs: PN400-307: -0.4, 1.9; PN400-309: -1.8, 0.6). Naproxen/esomeprazole magnesium-treated patients reported significantly more heartburn-free days versus celecoxib (95% CIs: PN400-307: 2.1, 12.7; PN400-309: 2.5, 13.4). UGI AE incidence (PN400-307: 17.3%;

PN400-309: 20.3%) was similar between treatment groups. UGI AEs resulted in few discontinuations (< 4%, either study). CONCLUSIONS. Naproxen/esomeprazole magnesium has comparable UGI tolerability to celecoxib in patients with osteoarthritis.

Hochberg, M. C., J. G. Fort, et al. (2011). "Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials." Current Medical Research & Opinion **27**(6): 1243-53.

OBJECTIVE: To demonstrate that a fixed-dose combination of enteric-coated naproxen 500mg and immediate-release esomeprazole magnesium 20mg has comparable efficacy to celecoxib for knee osteoarthritis.

RESEARCH DESIGN AND METHODS: Two randomized, double-blind, parallel-group, placebo-controlled, multicenter phase III studies (PN400-307 and PN400-309) enrolled patients aged >=50 years with symptomatic knee osteoarthritis. Following an osteoarthritis flare, patients received naproxen/esomeprazole magnesium twice daily, celecoxib 200mg once daily, or placebo for 12 weeks.

CLINICAL TRIAL REGISTRATION: NCT00664560 and NCT00665431.

MAIN OUTCOME MEASURES: Three co-primary efficacy endpoints were mean change from baseline to week 12 in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain and function subscales, and Patient Global Assessment of osteoarthritis using a visual analog scale (PGA-VAS).

RESULTS: In Study 307, 619 patients were randomized and 614 treated. In Study 309, 615 patients were randomized and 610 treated. Both naproxen/esomeprazole magnesium and celecoxib were associated with improvements (least squares mean change from baseline to week 12) in WOMAC pain (Study 307: -42.0 and -41.8, respectively; Study 309: -44.2 and -42.9, respectively), WOMAC function (Study 307: -36.4 and -36.3, respectively; Study 309: -38.9 and -36.8, respectively), and PGA-VAS (Study 307: 21.2 and 21.6, respectively; Study 309: 29.0 and 25.6, respectively). A prespecified non-inferiority margin of 10mm between naproxen/esomeprazole magnesium and celecoxib was satisfied for each co-primary endpoint at week 12 in both studies. Significant improvements were observed with naproxen/esomeprazole magnesium versus placebo in both studies ($p<0.05$). Celecoxib was significantly different from placebo in Study 307 ($p<0.05$); however, the improvements were not significant in Study 309. Acetaminophen use and patient expectation of receiving active treatment (80% probability) may have contributed to a high placebo response observed.

CONCLUSIONS: Naproxen/esomeprazole magnesium has comparable efficacy to celecoxib for the management of pain associated with osteoarthritis of the knee over 12 weeks.

Goldstein, J. L., M. C. Hochberg, et al. (2010). "Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone." Alimentary Pharmacology & Therapeutics **32**(3): 401-13.

BACKGROUND: Gastroprotective co-therapy may reduce the risk of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, but adherence is suboptimal.

AIM: To compare the incidence of gastric ulcers with PN 400 [enteric-coated (EC) naproxen 500 mg and immediate-release esomeprazole 20 mg], or EC naproxen.

METHODS: Two randomized, double-blind, multicentre studies (PN400-301, PN400-302). Patients [stratified by low-dose aspirin (< or =325 mg) use] aged > or =50 years or 18-49 years with a history of ulcer, received PN 400 BID (301, n = 218; 302, n = 210) or EC naproxen 500 mg BID (301, n = 216; 302, n = 210) for 6 months. The primary endpoint was the cumulative incidence of endoscopic gastric ulcers.

RESULTS: The cumulative incidence of gastric ulcers was significantly lower with PN 400 vs. EC naproxen (301: 4.1% vs. 23.1%, P < 0.001; 302: 7.1% vs. 24.3%, P < 0.001). PN 400 was associated with a lower combined incidence of gastric ulcers vs. EC naproxen in low-dose aspirin users (n = 201) (3.0% vs. 28.4%, P < 0.001) and non-users (n = 653) (6.4% vs. 22.2%, P < 0.001). The incidence of, and discontinuations due to, upper gastrointestinal (UGI) AEs was significantly lower with PN 400 relative to EC naproxen (P < 0.01, both studies).

CONCLUSIONS: PN 400 significantly reduces the incidence of gastric ulcers, regardless of low-dose aspirin use, in at-risk patients, and is associated with improved UGI tolerability relative to EC naproxen (ClinicalTrials.gov, NCT00527782).

Placebo-Controlled Trials

Baraf, H. S., M. S. Gold, et al. (2010). "Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial." Physician & Sportsmedicine **38**(2): 19-28.

Background Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may provide an alternative to oral NSAIDs to relieve pain from osteoarthritis (OA), reducing systemic exposure. This 12-week, randomized, double-blind, parallel-group, multicenter trial examined the efficacy and safety of topical diclofenac sodium 1% gel (DSG) for symptomatic knee OA. Methods Eligible patients were aged >/= 35 years with symptomatic Kellgren-Lawrence grade (KLG) 1 to 3 OA in 1 or both knees for >/= 6 months. Patients meeting entry criteria applied DSG 4 g or vehicle 4 times daily to the symptomatic knee(s). Primary endpoints were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and global rating of benefit at week 12. Pain on movement at week 4 was an additional primary endpoint for European regulatory purposes. Secondary endpoints included primary outcomes at weeks 1, 4, and 8; WOMAC stiffness subscale; spontaneous pain; global rating of disease; and global evaluation of treatment. Subanalyses were performed according to KLG, the number of knees treated, and age. Results Four hundred twenty patients were randomly assigned to DSG (n = 208) or vehicle (n = 212). At week 12, DSG provided significantly greater reductions in WOMAC pain (52.6% vs 43.1%; P = 0.008) and physical function (49.7% vs 39.4%; P = 0.004) versus vehicle and provided significant improvements in most secondary endpoints. Treatment-related adverse events (AEs) were infrequent (DSG, 7.7%; vehicle, 4.2%), with application site dermatitis being the most common AE (DSG, 4.8%; vehicle, 0%). No treatment-related gastrointestinal or serious AEs occurred with DSG. Conclusion Topical DSG treatment provided effective pain relief and functional improvement of OA in 1 or both knees and was well tolerated, irrespective of disease severity or patient age.

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Month/Year of Review: November 2013 **Date of Last Review:** March 2012
PDL Classes: Skeletal Muscle Relaxants **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: BACLOFEN, CYCLOBENZAPRINE HCL, TIZANDINE HCL
- Non-Preferred Agents: CHLORZOXAZONE, METAXALONE, METHOCARBAMOL, DANTROLENE SODIUM, ORPHENADRINE CITRATE, CARISOPRODOL , CYCLOBENZARPINE ER (AMRIX®)

Previous Conclusions and Recommendation:

- The evidence does not support any conclusions about the comparative effectiveness between baclofen, tizanidine, or dantrolene for spasticity. All are effective and equivalent to diazepam. Dantrolene is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions for the comparative efficacy or safety between skeletal muscle relaxants for musculoskeletal conditions.
- Cyclobenzaprine had the largest body of evidence to support its efficacy compared to placebo.
- Chlorzoxazone is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions about the comparative efficacy or adverse effects for different subpopulations of patients such as race, gender, or age.

PA Criteria: Prior authorization is in place to support preferred PDL skeletal muscle relaxants and to cover for OHP above the line diagnoses only. A quantity limit restricts carisoprodol products to less than 56 tablets within 90 days unless the patient has a terminal illness. (Appendix 1).

Conclusions and Recommendations:

- There is limited new evidence since the last review on skeletal muscle relaxants; no further review or research needed.
- Evaluate comparative costs in executive session.

References:

1. Selph, S. Drug Effectiveness Review Project: Drug Class Review on Skeletal Muscle Relaxants. Preliminary Scan Report #5. July 2013.

Skeletal Muscle Relaxants

Goal(s):

- Cover non-preferred drugs only for above the line diagnoses.
- Restrict carisoprodol to short-term use per medical evidence.
    a. There are no long-term studies of efficacy or safety for carisoprodol.
    b. Case reports suggest it is often abused and can be fatal when used in association with opioids, benzodiazepeines, alcohol, or illicit drugs.
    c. Carisoprodol is metabolized to meprobamate.

Length of Authorization: Up to 6 months

Requires PA:

- Non-preferred NSAIDs

Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/
Cyclobenzaprine has the largest body of evidence supporting long-term use and is the preferred product in the muscle relaxant class. For patients that have contraindications to TCAs, NSAIDs, benzodiazepeines or opioids are other alternatives. OHP does not cover pain clinic treatment.

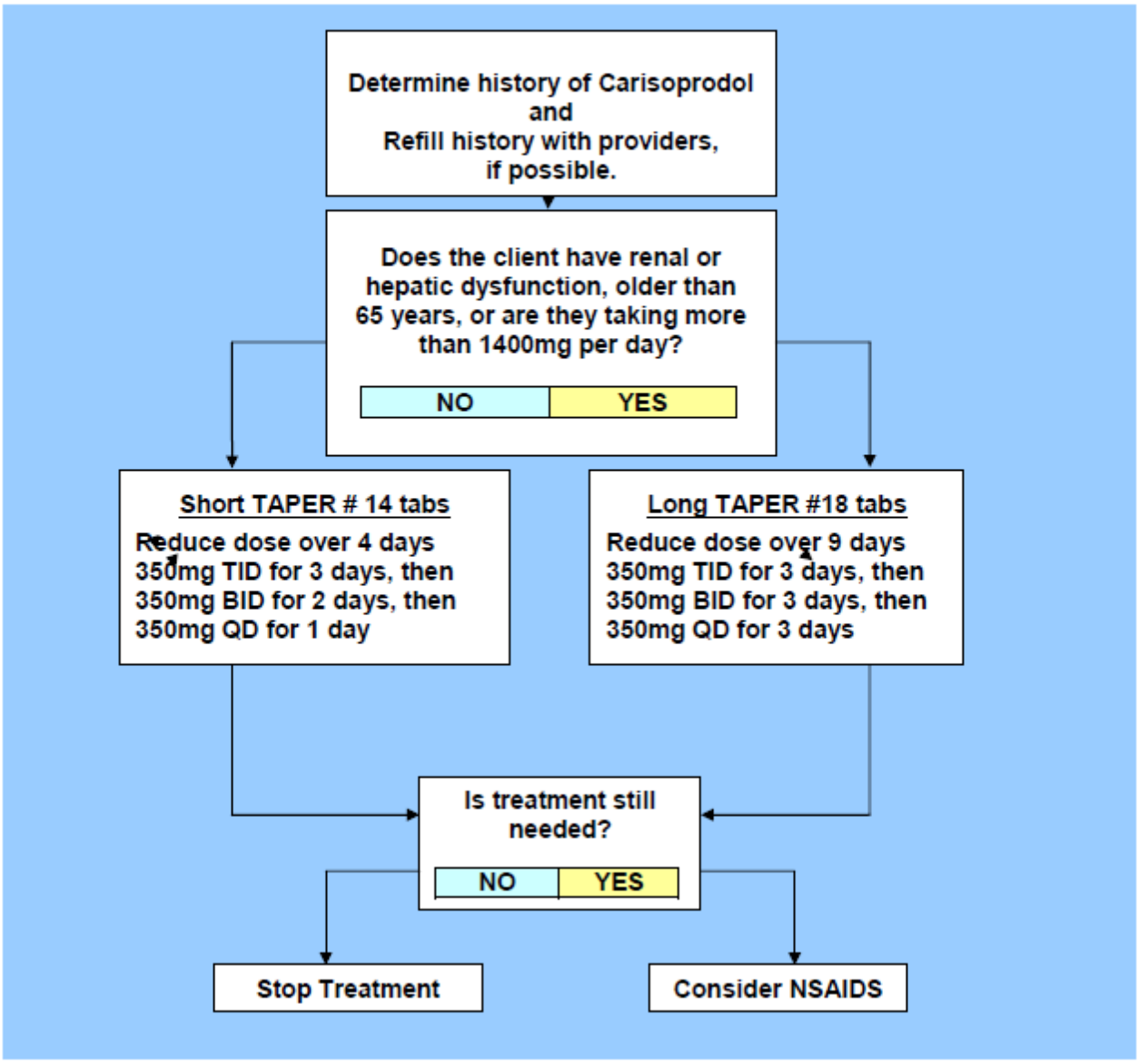
Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is diagnosis covered by the Oregon Health Plan?	Yes: Go to #3.	No: Pass to RPH; Deny, (Not Covered by the OHP)
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC).	Yes: Inform provider of covered alternatives in class	No. Go to #4
4. Is drug requested carisoprodol (Soma®)?	Yes: Go to #5	No. Approve for up to 6 months

5. Does total quantity of carisoprodol (Soma®) products exceed 56 tablets within 90 days? From claims, document product, dose, directions, and amount used during last 90 days:	Yes: Go to #6	No: Approve for up to 6 months
6. Does patient have a terminal illness (e.g. metastatic CA, end stage HIV, ALS)?	Yes: Approve for 6 months.	No: Pass to RPH. Go to #7

7. Pharmacist's Statement:
 	
• Carisoprodol cannot be approved for long term usage.
• Patients are limited to 56 tablets in a 90 day period.
• It is recommended that the patient undergo a "taper" of the Soma (Carisoprodol) product of which a supply may be authorized for this to occur.
• The amount and length of taper depends upon the patient's condition. Does the patient meet one or more of the following?:
  ○ >65 years old
  ○ Renal Failure
  ○ Hepatic failure
 	
Take > 1400mg per day (>3.5 tablets)
	Yes: Document reason and approve long taper:
	
	• Authorize 18 tablets
	• Reduce dose over 9 days
	• 350mg TID X 3 days, then
	• 350mg BID X 3 days, then
	• 350mg QD x 3 days then evaluate
		No: Approve short taper:
		
		• Authorize 10 tablets
		• Reduce dose over 4 days
		• 350 mg tid x 1 day, then
		• 350 mg bid x 2 days, then
		• 350 mg QD x 1 day, then evaluate

221

Tapering Carisoprodol



Drug Class Review
on
Skeletal Muscle Relaxants

Preliminary Scan Report #5

May 2013

Last Report: Update 2 (May 2005)

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

Scan conducted by:
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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Drug Effectiveness Review Project participants with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with consideration of allocating resources. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last scan. Other important studies could exist.

Date of Last Update Report

Original Report: September 2003
Update #1: January 2004
Update#2: May 2005 (searches through November 2004)

Date of Last Preliminary Update Scan Report

Update #3 Preliminary Scan #1: February 2007
Update #3 Preliminary Scan #2: March 2008
Update #3 Preliminary Scan #3: June 2009
Update #3 Preliminary Scan #4: September 2010 (searches through August 2010)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

- Adult or pediatric patients with spasticity or a musculoskeletal condition. We defined spasticity as muscle spasms associated with an upper motor neuron syndrome. Musculoskeletal conditions were defined as peripheral conditions resulting in muscle or soft tissue pain or spasms.
- We included patients with nocturnal leg cramps however, excluded patients with restless legs syndrome or nocturnal myoclonus.
- Obstetric and dialysis patients were also excluded.

Interventions

Table 1. Included interventions

Active Ingredient	Brand name
Baclofen	Lioresal®
Carisoprodol	Soma®
Chlorzoxazone	Lorzone®
Dantrolene	Dantrium®
Metaxalone	Skelaxin®
Methocarbamol	Robaxin®
Orphenadrine	Norflex®
Tizanidine	Zanaflex®

Study designs

- Controlled clinical trials
- Comparative effectiveness reviews

Comparators: Effectiveness and harms of individual skeletal muscle relaxants

- Benzodiazepines were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with any of the skeletal muscle relaxants listed above.
- Other medications used for spasticity but considered to be in another drug class, such as gabapentin (a neuroleptic) and clonidine (an antihypertensive), were also only reviewed when they were directly compared to an included skeletal muscle relaxant.
- Quinine was only included if it was compared to a skeletal muscle relaxant.

Effectiveness outcomes

- Relief of muscle spasms or pain, functional status, quality of life
- Non-clinical outcomes such as electromyogram measurements or spring tension measurements were excluded.

Harms outcomes

- Somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction
- Withdrawal rates and adverse events
- We also paid special attention to reports of serious hepatic injury.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2010 through April Week 3 2013 using terms for included drugs and limited to humans, English language, and controlled clinical trials. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/).

Study Selection

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

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan
None

New drugs identified in previous Preliminary Update Scan(s)
- Cyclobenzaprine (Amrix) Extended Release Oral Capsule 15 mg, 30 mg strengths: Approved 2/1/2007
- Carisoprodol (Soma) Oral Tabled 250 mg: Approved 9/13/2007

New Indications

New indications identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
None

New Safety Alerts

Identified in this Preliminary Update Scan

Dantrium (dantrolene sodium) Oral Capsule: July 2012

BOXED WARNING

- Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving Dantrium. However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications.

WARNINGS

Geriatric Use

- Clinical studies of Dantrium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in the literature has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. As with all patients receiving Dantrium, it is recommended that elderly patients receive the lowest dose compatible with the optimal response. Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving Dantrium. However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications.

Drug Interactions

- Drowsiness may occur with Dantrium therapy, and the concomitant administration of CNS depressants such as sedatives and tranquilizing agents may result in further drowsiness. Cardiovascular collapse in patients treated simultaneously with verapamil and dantrolene sodium is rare. Administration of Dantrium may potentiate vecuronium-induced neuromuscular block.

PRECAUTIONS

- Dantrium should be used with caution in patients with impaired pulmonary function, particularly those with obstructive pulmonary disease, and in patients with severely impaired cardiac function due to myocardial disease. Dantrium is associated with pleural effusion with associated eosinophilia. It should be used with caution in patients with a history of previous liver disease or dysfunction.

Identified in previous Preliminary Update Scan(s)

Table 1. Safety alerts from previous scans

SMR	Date	Alert type	Focus
Carisoprodol	9/07	Label Change: Warnings, Precautions and Adverse Reactions	Risk of sedative properties, drug dependence, withdrawal and abuse
Tizanidine	4/07	Label Change: Contraindications and warnings	When administered with fluvoxamine or ciprofloxacin (CYP1A2 inhibitors), the serum concentration of tizanidine was significantly increased and potentiated its hypotensive and sedative effects

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

None

Reviews identified in previous Preliminary Update Scan(s)

None

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches resulted in 58 citations of which 1was a potentially relevant randomized controlled trial of tizanidine for treatment of chronic low back pain. (See Appendix A for the abstract of this trial) No placebo controlled trials met inclusion criteria. Previous scans have identified three relevant trials published since the last update. (See Appendix B for the abstracts of these three trials.) There are no new head to head trials published since the last full report update.

Table 2. Trials identified in previous preliminary update scan

Author Year	Treatment	Notes
Active-controlled trials (comparators not available in the US)		
Rossi, 2012	*Tizanidine vs Eperisone*	Chronic low back pain

Ketenci 2005	*Tizanidine vs Thiocolchicoside vs tizanidine*	*Low back pain associated with spasm*
Placebo-controlled Trials		
Malanga, 2009	*Cyclobenzaprine ER vs placebo (report of two trials)*	*Low back and neck pain*
Serfer, 2010	*Carisoprodol vs placebo*	*Low back spasm*

Summary

There is little new evidence on skeletal muscle relaxants since the last full report update. This update scan identified only one new active-controlled trial and no comparative effectiveness reviews published since the last preliminary update scan. Since the last full report update in 2005, only 4 new trials have been found, none are head to head comparisons of the drugs in this report.

Appendix A. Abstract of potentially relevant new trial of skeletal muscle relaxants (N=1)

Active controlled trial

Rossi M. Ianigro G. Liberatoscioli G. Di Castelnuovo A. Grimani V. Garofano A. Camposarcone N. Nardi LF. "Eperisone versus tizanidine for treatment of chronic low back pain." Minerva Medica. 103(3):143-9, 2012 Jun.

AIM: Many therapies exist for treatment of chronic low-back pain (LBP) including the use of muscle relaxant and analgesic drugs. The aim of this paper was to compare efficacy and tolerability of eperisone and tizanidine in combination treatment with tramadol in chronic LBP.
METHODS: Sixty patients affected by chronic LBP associated with contractures of paravertebral muscles were randomized in two groups: Group E (30 patients) treated with eperisone; Group T (30 patients) treated with tizanidine. Both groups received tramadol retard 100 mg/day. VAS at rest and with effort were used at baseline (T0) and after 5 (T5), 10 (T10), 15 (T15) and 30 (T30) days of treatment. The Summed Pain Intensity Difference (SPID), the SPID percentage (SPID%) and the Total Pain Relief (TOTPAR), at rest (-r) and with effort (-e) were calculated.
RESULTS: In both groups a statistically significant reduction in VAS-r and VAS-e was observed during the treatment; similar reductions occurred in both groups at every timepoint. SPID-r and -e, SPID%-r and -e and TOTPAR-r and -e resulted similar between groups. A significant difference between groups occurred for incidence of somnolence: 16.6% for Group E versus 43.3% for Group T. Treatment was stopped due to adverse events in 5 patients of Group E and in 9 patients of Group T, without statistically significant difference.
CONCLUSION: Both associations assumed for one month, have shown effective for LBP at rest and with effort. Eperisone/tramadol, reducing discontinuation and allowing a better adherence to the therapy, may be considered a viable option for the treatment of chronic LBP.

Appendix B. Abstracts of potentially relevant new trials of skeletal muscle relaxants (N=3)

Active controlled trial

Ketenci, A., E. Ozcan, et al. (2005). "Assessment of efficacy and psychomotor performances of thiocolchicoside and tizanidine in patients with acute low back pain." International Journal of Clinical Practice 59(7): 764-70.

> Objectives of this study were to assess efficacy and effects on psychomotor performances of thiocolchicoside (TCC) and tizanidine (TZ) compared to placebo. Patients complaining of acute low back pain (LBP) associated with muscle spasm were enrolled in this randomised, double-blind clinical trial, comparing the effects of oral TCC, TZ and placebo on psychomotor performances assessed by a visual analogue scale of tiredness, drowsiness, dizziness and alertness and by psychometric tests after 2 and 5-7 days of treatment. The efficacy assessments, both TCC and TZ, were more effective than placebo in improving pain at rest, hand-to-floor distance, Schober test and decreased paracetamol consumption. There were significant differences among the treatment groups in favour of TCC compared to TZ in visual analog scale-parameters. TZ-induced reduction of psychomotor performances of the patients was confirmed by psychometric tests, which showed significant differences among groups. This study showed that TCC is at least as effective as TZ in the treatment of acute LBP, while it appears devoid of any sedative effect in contrast to TZ.

Placebo-controlled trials

Malanga, G.A., G. E. Ruoff, et al. (2009). “Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design.” Current Medical Research & Opinion **25(**5): 1179-96.

> OBJECTIVE: To evaluate efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15- and 30-mg capsules in patients with muscle spasm associated with acute, painful musculoskeletal conditions. METHODS: Two identically designed, randomized, double-blind, placebo- and active-controlled, parallel-group studies in patients aged 18-75 years with muscle spasm associated with neck or back pain. Patients received CER 15 or 30 mg once daily, cyclobenzaprine immediate release (CIR) 10 mg three times daily, or placebo for 14 days. Primary efficacy measures were patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. Secondary measures were patient's rating of medication helpfulness and physician's clinical global assessment of response (days 8 and 14), relief from local pain, global impression of change, restriction in activities of daily living, restriction of movement, daytime drowsiness, quality of nighttime sleep (days 4, 8, and 14), and quality of life (days 8 and 14). RESULTS: A total of 156/254 randomized patients in study 1 and 174/250 in study 2 completed 14 days of treatment. Significant improvements in patient's rating of medication helpfulness were reported with CER versus placebo (CER 30 mg, study 1, p = 0.007; CER 15 mg, study 2, p = 0.018) at day 4.

Significant improvements with CER 30 mg versus placebo were also seen at day 4 in study 1 for patient-rated global impression of change (p = 0.008), relief of local pain (p = 0.004), and restriction of movement (p = 0.002). Neither study reported differences between study groups on the physician's clinical global assessment. Improvements with CER were comparable to that of CIR. In both studies, daytime drowsiness was reported more frequently in active treatment groups than in the placebo group; however, reports of drowsiness decreased over time in all groups. In general, daytime drowsiness was reported more frequently in CIR groups than in CER groups. More adverse events were reported in the active treatment groups versus placebo and were similar in the CER and CIR groups, except somnolence, which occurred more frequently with CIR. CONCLUSIONS: Once-daily CER 15 mg (study 2) and CER 30 mg (study 1) were effective in treating muscle spasm associated with painful musculoskeletal conditions after 4 days of treatment. Differences between CER and placebo groups did not reach statistical significance on all efficacy measures, and the protocols were not powered to detect differences between active treatment arms. CER was generally safe and well tolerated, with low rates of somnolence.

Serfer, G.T., W. J. Wheeler, et al. (2010). "Randomized, double-blind trials of carisoprodol 250 mg compared with placebo and carisoprodol 350 mg for the treatment of low back spasm." Current Medical Research & Opinion **26**(1): 91-9.

BACKGROUND: Carisoprodol, a centrally active skeletal muscle relaxant, is widely used for the treatment of acute, painful musculoskeletal disorders. When administered at a dose of 350 mg four times daily, carisoprodol demonstrated significant clinical benefit in its early clinical development trials; however, some unfavorable side effects, such as drowsiness and dizziness, were reported. Recently, research was conducted to determine if a lower dose of carisoprodol would retain efficacy but improve tolerability compared to the higher 350-mg dose. OBJECTIVE: The purpose of this multicenter study was to compare the efficacy and safety of carisoprodol 250-mg tablets four times daily to 350-mg tablets four times daily and to placebo in patients with acute, painful musculoskeletal spasm of the lower back. RESEARCH DESIGN AND METHODS: In this 1-week double-blind, placebo-controlled, parallel-group multicenter trial, patients 18 to 65 years of age with moderate to severe back spasm were randomly assigned to treatment with carisoprodol 250-mg tablets (n = 264), 350-mg tablets (n = 273), or matching placebo tablets (n = 269) three times daily and at bedtime. RESULTS: The carisoprodol 250-mg regimen was significantly more effective than placebo as assessed by both patient-rated relief from starting backache (p = 0.0001) and patient-rated global impression of change (p = 0.0046). There were no significant differences between the 250-mg and 350-mg dosages for the coprimary efficacy endpoints, and patients improved with or without sedation. Fewer than 1% of patients in the carisoprodol 250-mg group discontinued prematurely because of treatment-emergent adverse events, and no patient discontinued because of drowsiness. CONCLUSIONS: When administered three times daily and at bedtime, carisoprodol 250 mg was as effective as 350 mg three times daily and at bedtime with a lower incidence of adverse events and fewer discontinuations of therapy due to adverse events. Patients improved whether or not they reported sedation as an adverse event.