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 20th, 2014 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

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

I. CALL TO ORDER
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)
- d. Department Update — L. Saris (OHA)

II. DUR ACTIVITIES
- a. Quarterly Utilization Reports — R. Citron (OSU)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Oregon State Drug Reviews — K. Sentena (OSU)
  1. Update on New Therapies for Treating Major Depressive Disorder (MDD)
  2. New Hepatitis C Antiviral Therapies: How should they be used in clinical practice?

III. DUR OLD BUSINESS
- a. Updated OHP Nutritional Supplement PA Criteria — M. Herink (OSU)
  1. Prior Authorization Criteria
  2. Public comment
  3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS
- a. Pediatric SSRI High Dose Drug Use Evaluation (DUE) — K. Ketchum (OSU)
  1. DUE
  2. Public comment
  3. Discussion of Clinical Recommendations to OHA

- b. ICS/LABA Policy Evaluation — K. Ketchum (OSU)
  1. Policy Evaluation
  2. Prior Authorization Criteria
  3. Quality Improvement Proposal
  4. Public Comment
  5. Discussion of Clinical recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

a. Insomnia Class Update & New Drug Evaluations — K. Ketchum (OSU)
   1. Class Update
   2. Tasimelteon (Hetlioz®) NDE
   3. Suvorexant (Belsomra™) NDE
   4. Public Comment
   5. Discussion of Clinical recommendations to OHA

b. Hormone Replacement Abbreviated Class Update — S. Willard (OSU)
   1. DERP HRT Scan
   2. Conjugated Estrogens/Bazedoxifene (Duavee®) NDE
   3. Public comment
   4. Discussion of Clinical recommendations to OHA

c. Anaphylaxis Rescue Abbreviated Class Review — B. Liang (OSU)
   1. Class Review
   2. Public comment
   3. Discussion of Clinical recommendations to OHA

d. Long Acting Antipsychotic Injectables Abbreviated Class Review — A. Meeker (OSU)
   1. Class Review
   2. Public comment
   3. Discussion of Clinical recommendations to OHA

e. Prenatal Vitamins Abbreviated Review — M. Herink (OSU)
   1. Class Review
   2. Public comment
   3. Discussion of Clinical recommendations to OHA

f. Drug Class Scans — M. Herink / A. Gibler (OSU)
   1. Newer Antiemetics
   2. Skeletal Muscle Relaxants
   3. NSAIDS
   4. Anti-anginal Drugs
   5. Diuretics
   6. Public Comment
   7. Discussion of Clinical recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Corvallis	December 2014
Joshua Bishop, Pharm.D.	Pharmacist	Pharmacy Director	Bend	December 2014
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2014
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2015
William Nunley, M.D.	Physician	Psychiatrist	Portland	December 2015
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Albany	December 2016
James Slater, Pharm.D.	Pharmacist	Associate Pharmacy Director	Beaverton	December 2014
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2015
Kathryn Lueken, M.D., M.M.M.	Physician	Medical Director	Salem	December 2016
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Tuesday, September 23, 2014 1:00-5:00 PM
Wilsonville Training Center
29353 SW Town Center
Wilsonville, OR 97070

MEETING MINUTES

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

Members Present: Cathy Zehrung, RPh; Phillip Levine, PhD; William Origer, MD; Stacy Ramirez, PharmD; Tracy Klein, PhD., FNP; Kathryn Lueken, MD;

Members Present by Phone:

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; Linnea Saris; Amanda Meeker, PharmD; Dee Weston; Kaylin Winden, PharmD Candidate; Andrew Gibler, PharmD;

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

Audience: Deborah Profant (Teva)*; Diana Lein (Bristol-Myers Squibb)*; Lori Howarth (Bayer); Deron Grothe; Camille Kerr (Allergan); Deirdre Monroe (Allergan)*; Jazz Ferreira, Lynda Finch (Biogen Idec)*; Dean Haxby (OSU); Barry Benson (Merck); BJ Cavnor (One in Four)*; Venus Holder (Lilly); Melissa Walsh (Novartis)*; Leslie Mann (Celgene); Jason Alm (Celgene)*; Derek Traister (Biogen Idec); Anne Marie Licos, PharmD (MedImmue)*; Paul Nielsen (AstraZeneca); Paul Bonham (NN1); Scott Larson (BMS); Laura Hill (Abbvie); Cheryl Fletcher (Abbvie); Shane Hall (Purdue); Michelle Bice (Gilead); John Peterson (Gilead)*; Linda Simpson (Gilead); Richard McLeod (Pfizer)*; Arti Baig (Pfizer)*; Brett Marett (BMS); Bill Strynk (J&J); Amy Bauma (Gilead); Brad Peteuck (Gilead); Allison Gille (OSU); Shelley Bailey (Central Drugs); Bob Snediker (J&J)*; Tricia Bourne (Gilead); Dianne Matthews (J&J); Steve Nemirow (Kartini Clinic); Shannon Noel (FCI); Bruce Howard (Acorda); Gina Guinasso (Acorda); Caryn Mickelson (WOAH); Kimberly Blood (WVCH); Stephanie Kendall (J&J); Michael Weingarten (J&J); Michael Estes (Pfizer);

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:00 pm. Introductions of Committee members and staff. Introductions of new committee members included Dr. Kathryn Lueken and Dr. Arturo Salazar.

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

c. Approval of agenda and minutes presented by Dr. Origer (pages 4 - 10)

ACTION: Approved as is.

d. Department updates presented by Trevor Douglass.

II. DUR OLD BUSINESS

a. Hepatitis C Class update (pages 11 - 25)
Dr. Herink presented the following class update:

1. Recommend including additional changes to PA criteria (Appendix 1):
   - Excluding patients who have had previous treatment with an oral direct acting antiviral
   - Requiring an HCV RNA level at week 4 to determine response. If the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the HCV RNA increases or if the 8 week HCV RNA is detectable, discontinue treatment.
   - Excluding GT1 interferon ineligible patients due to insufficient evidence in this population.

2. With evolving pipeline of medications for treatment of hepatitis C, create general Hepatitis C prior authorization criteria to ensure new treatments are being used appropriately until they can be reviewed in full by the Pharmacy & Therapeutics Committee.

3. The sale and distribution of telaprevir has been discontinued; remove from PDL.

Public Comment:
John Peterson from Gilead Sciences.
Steven Nemirow spoke about his treatment using Sovaldi.
BJ Cavnor from One in Four.

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

b. Botulinum Toxins PA Criteria (pages 26 – 29)
Ms. Ketchum presented the following information:

1. Approve updated PA criteria to include overactive bladder syndrome and neurogenic detrusor over-activity.

Public Comment:
Deirdre Monroe from Allergan.

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

III. DUR NEW BUSINESS

a. Synagis ® (pages 30 - 42)
Dr. Sentena presented the following update:

1. Amend the current PA to align recommendations with those of the 2014 AAP guideline.

2. Continue to allow for geographic variations in RSV activity.

3. Remove the requirement in #16 of the PA criteria for a pediatric cardiologist for those with cyanotic heart defects.

Public Comment:
Anne Marie Licos, PharmD from MedImmune.

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

IV. PREFERRED DRUG LIST NEW BUSINESS

a. Drug Class Scans
   1. Parkinson's Medications (pages 43 – 51)
      Dr. Herink presented the following information:

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

      b. Evaluate comparative costs in executive session.

      c. No changes to the PDL.

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

   2. Growth Hormones (pages 52 – 58)
      Dr. Herink presented the following updates:

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

      b. Evaluate comparative costs in executive session.

      c. Update PA criteria to ask physicians to switch to a preferred product in the continuation criteria.

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

   3. Insulins (pages 59 – 84)
      Dr. Herink presented the following updates:

      a. There is low quality evidence of no significant differences in change in HbA1C or overall and severe hypoglycemia between insulin determir and insulin glargine and high quality evidence that insulin determir is associated with less weight gain and low quality evidence of more injection site reactions compared to insulin glargine.

      b. There is no significant new comparative evidence on the efficacy and safety of other agents on the PDL.

c. Continue to include at least one agent from each subgroup (short acting, rapid acting, etc.) as preferred on the PDL and evaluate comparative costs in executive session.

d. Due to no evidence showing an advantage in efficacy or safety with insulin human inhalation powder (Afrezza) when compared to injectable insulin products for which long term data is available, make Afrezza non-preferred.

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

4. Alzheimer Drugs (pages 85 – 114)
   Dr. Herink presented the following updates:

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

   b. Evaluate comparative costs in executive session.

   c. Make Namenda XR® preferred.

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

5. Other Lipotropics (pages 115 – 122)
   Dr. Herink presented the following updates:

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

   b. Evaluate comparative costs in executive session.

   c. Make niacin non-preferred due to lack of cardiovascular outcome benefit and possible harm.

   d. Make fenofibrate tablets preferred and Tricor® and Trilipix® non-preferred.

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

b. Diabetes Class Update (pages 123 – 140)
   Dr. Sentena presented the following updates:

   1. Evidence of SGLT2 inhibitors supports the current PA criteria. Dapagliflozin should be added to the criteria and maintained as non-preferred.

   2. There is no new evidence on the comparative efficacy/ effectiveness or safety for the oral hypoglycemic PDL class. Evaluate comparative costs in executive session.

   3. Make Fortamet and generic equivalents non-preferred

Public Comment:
Bob Snediker form J&J.

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

c. Multiple Sclerosis Class Update (pages 141 – 157)
   Dr. Sentena presented the following updates:

   1. Limited evidence suggests glatiramer 40 mg three times weekly is effective in preventing relapses in patients with RRMS; maintain as non-preferred.

2. Recommend requiring a prior authorization for peginterferon beta-1a.

3. Evaluate costs in executive session.

4. No changes to the PDL.

Public Comment:
Melissa Walsh from Novartis.
Deborah Profant, PhD from Teva.
Lynda Finch from Biogen Idec.

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

d. First Generation Antidepressants (pages 158 – 174)
Dr. Herink presented the following class review:

1. 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.

2. In alignment with treatment guidelines, first and second generation antidepressants should be accessible to patients, with the selection of the individual agent dependent on severity of condition, comorbidities, medication history, and tolerability of side effects for the individual patient.

3. Recommend including first generation antidepressants to the voluntary MH PDL and evaluate costs in executive session. Consider a non-preferred status for MAOIs, given the known safety concerns including high risks of drug-drug and drug-food interactions. Also maintain nefazodone as non-preferred due to hepatic safety concerns.

4. Evaluate costs in executive session.

5. No other changes to the PDL.

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

e. TIMS Class Update (pages 175 – 194)
Dr. Herink presented the following class update:

1. Modify prior authorization criteria to include new FDA approved indications and new medications.

2. Evaluate comparative costs of newly approved agents in executive session.

3. Make Simponi non-preferred.

Public Comment:
Arti Baig from Pfizer.
Jason Alm from Celgene.
Diana Lein from Bristol-Myers Squibb.

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

f. Topical Antifungals Class Update (pages 195 – 208)
Ms. Ketchum presented the following class update:

1. Evaluate comparative costs in executive session.

2. No changes to the PDL.

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

g. Vitamins & Electrolytes Abbreviated Class Review (pages 209 – 216)
Dr. Herink presented the following class review:

1. Evaluate comparative costs in executive session to list specific agents as preferred and non-preferred.

2. Include a formulation of the different potassium salt supplements due to different clinical considerations.

3. Potassium chloride packets make non-preferred on the PMPDP.

4. Potassium gluconate make non-preferred on the PMPDP.

5. Magnesium ER and DR make non-preferred on PMPDP.

6. Magnesium IR make preferred on the PMPDP.

7. Phosphorus make preferred on the PMPDP.

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

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

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Pharmacy Utilization Summary Report: April 2013 - March 2014

Eligibility	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Total Members (FFS & Encounter)	624,719	625,809	625,127	624,642	625,272	625,526	621,935	622,966	613,155	819,426	852,414	899,321	681,693
FFS Members	75,030	75,828	78,595	75,688	78,915	81,973	75,036	76,075	79,453	140,103	133,822	155,785	93,859
OHP Basic with Medicare	26,930	26,793	26,934	26,987	27,103	27,264	27,177	27,343	27,371	27,575	27,629	27,787	27,241
OHP Basic without Medicare	25,029	25,492	27,114	25,664	27,154	28,571	25,347	25,569	27,446	26,374	24,867	24,408	26,086
ACA	22,965	23,434	24,410	22,894	24,587	26,528	22,100	22,925	23,945	83,884	79,176	99,440	39,691
Encounter Members	549,689	549,981	546,532	548,954	546,357	543,553	546,899	546,891	533,702	679,323	718,592	743,536	587,834
OHP Basic with Medicare	36,739	37,009	37,143	37,207	37,215	37,313	37,420	37,665	37,741	37,758	37,903	38,017	37,428
OHP Basic without Medicare	234,763	235,023	232,840	234,071	233,053	230,913	230,687	228,678	222,953	227,448	228,120	227,677	230,519
ACA	277,465	277,341	275,957	277,082	275,479	274,742	278,211	279,977	272,459	413,355	450,189	474,533	318,899

Gross Cost Figures for Drugs	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	YTD Sum
Total Amount Paid (FFS & Encounter)	$32,805,206	$33,575,135	$30,228,303	$33,915,001	$33,234,713	$32,592,899	$34,989,069	$33,786,664	$32,572,219	$38,448,721	$39,991,155	$44,465,012	$420,604,095
Mental Health Carve-Out Drugs	$7,710,456	$7,865,450	$7,177,134	$8,038,148	$7,887,685	$7,599,368	$8,228,070	$7,434,555	$7,908,255	$8,895,952	$8,430,068	$9,406,034	$96,581,176
OHP Basic with Medicare	$41,590	$41,635	$42,562	$44,148	$36,249	$37,419	$21,032	$13,060	$11,010	$9,185	$12,723	$13,217	$323,829
OHP Basic without Medicare	$5,743,232	$5,856,890	$5,358,529	$6,087,537	$5,977,943	$5,767,293	$6,207,813	$5,634,325	$5,987,747	$6,288,711	$5,681,931	$6,125,134	$70,717,085
ACA	$1,873,115	$1,910,538	$1,724,424	$1,848,276	$1,822,789	$1,738,026	$1,938,459	$1,737,438	$1,849,527	$2,573,787	$2,713,480	$3,246,440	$24,976,297
FFS Physical Health Drugs	$2,402,292	$2,400,561	$2,119,978	$2,337,104	$2,233,155	$2,226,880	$2,336,245	$2,205,473	$2,411,354	$3,577,698	$3,470,284	$3,420,928	$31,141,951
OHP Basic with Medicare	$277,790	$263,471	$250,798	$273,512	$269,956	$262,515	$275,323	$251,918	$272,014	$274,156	$247,307	$267,883	$3,186,643
OHP Basic without Medicare	$1,528,036	$1,566,947	$1,346,311	$1,533,939	$1,441,390	$1,465,746	$1,553,249	$1,457,756	$1,645,484	$1,691,373	$1,616,666	$1,524,716	$18,371,612
ACA	$435,904	$418,557	$402,738	$412,983	$410,100	$370,505	$392,983	$386,911	$377,623	$1,550,527	$1,529,187	$1,557,937	$8,245,955
FFS Physician Administered Drugs	$1,355,738	$1,414,525	$1,138,794	$1,296,751	$995,481	$1,095,988	$1,175,394	$1,025,838	$839,384	$1,517,956	$1,129,596	$1,273,843	$14,259,287
OHP Basic with Medicare	$138,688	$102,633	$88,809	$161,719	$136,071	$149,091	$160,967	$156,020	$126,724	$137,692	$103,429	$135,820	$1,597,662
OHP Basic without Medicare	$719,971	$657,507	$578,749	$636,538	$461,475	$607,512	$605,503	$421,141	$427,158	$543,763	$439,559	$393,132	$6,492,007
ACA	$114,040	$256,639	$199,414	$226,672	$175,597	$133,508	$123,621	$162,720	$64,444	$535,988	$350,195	$546,043	$2,888,882
Encounter Physical Health Drugs	$17,778,573	$17,555,067	$16,297,020	$17,893,352	$18,045,222	$17,539,084	$18,864,117	$19,144,092	$17,421,121	$19,241,874	$22,103,040	$25,785,897	$227,668,459
OHP Basic with Medicare	$176,968	$168,551	$167,607	$180,242	$195,525	$197,261	$230,974	$194,496	$243,784	$242,091	$223,754	$187,976	$2,409,230
OHP Basic without Medicare	$11,418,669	$11,324,652	$10,725,011	$11,874,744	$11,913,477	$11,492,182	$12,398,844	$12,485,718	$11,419,862	$11,131,751	$12,028,542	$13,258,953	$141,472,407
ACA	$6,050,825	$5,921,974	$5,284,347	$5,702,613	$5,790,799	$5,717,114	$6,074,397	$6,284,816	$5,627,659	$7,758,359	$9,764,901	$12,230,069	$82,207,871
Encounter Physician Administered Drugs	$3,558,147	$4,339,531	$3,495,377	$4,349,646	$4,073,170	$4,131,578	$4,385,244	$3,976,707	$3,992,106	$5,215,241	$4,858,166	$4,578,309	$50,953,222
OHP Basic with Medicare	$131,838	$137,932	$100,779	$109,851	$123,404	$91,586	$118,215	$85,537	$101,802	$206,931	$173,931	$153,935	$1,535,742
OHP Basic without Medicare	$2,171,633	$2,615,590	$2,158,034	$2,694,047	$2,470,192	$2,504,643	$2,596,096	$2,410,267	$2,386,240	$2,870,546	$2,314,822	$2,043,648	$29,235,758
ACA	$857,384	$915,275	$726,260	$852,016	$916,283	$884,917	$963,682	$853,257	$923,188	$1,556,723	$1,935,654	$2,067,819	$13,452,458

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion

Last Updated: October 23, 2014

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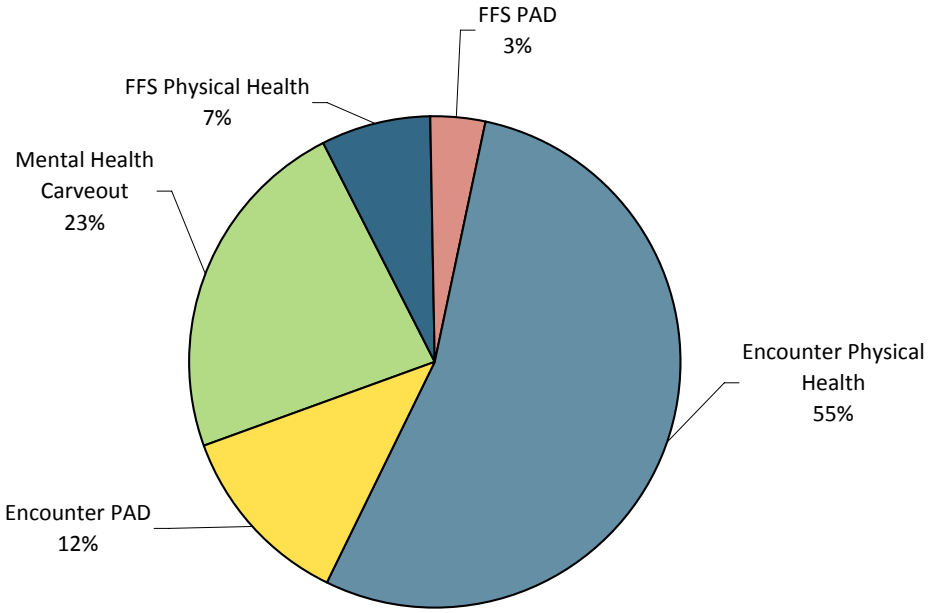
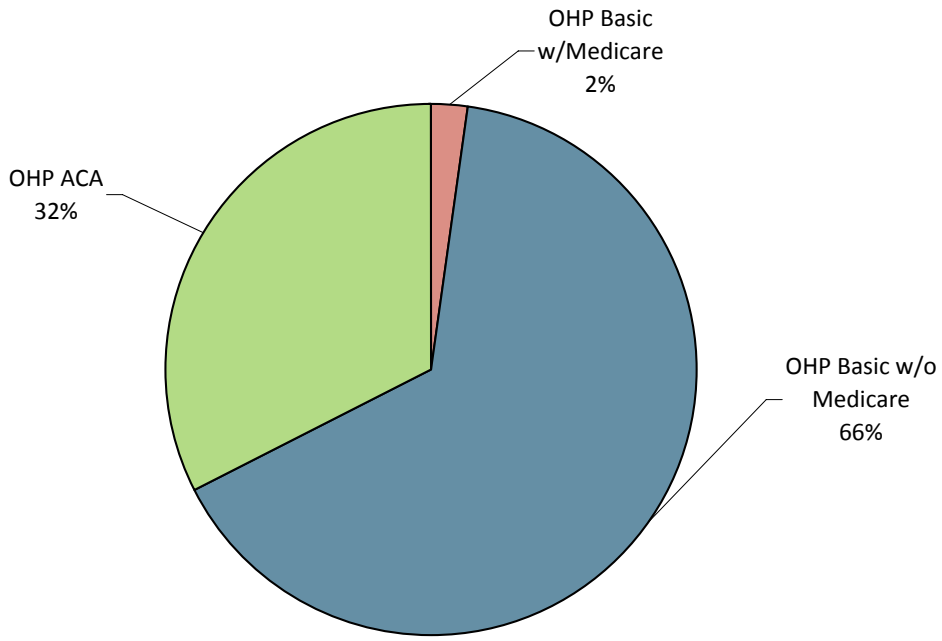
Pharmacy Utilization Summary Report: April 2013 - March 2014

YTD Percent Paid Amounts





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

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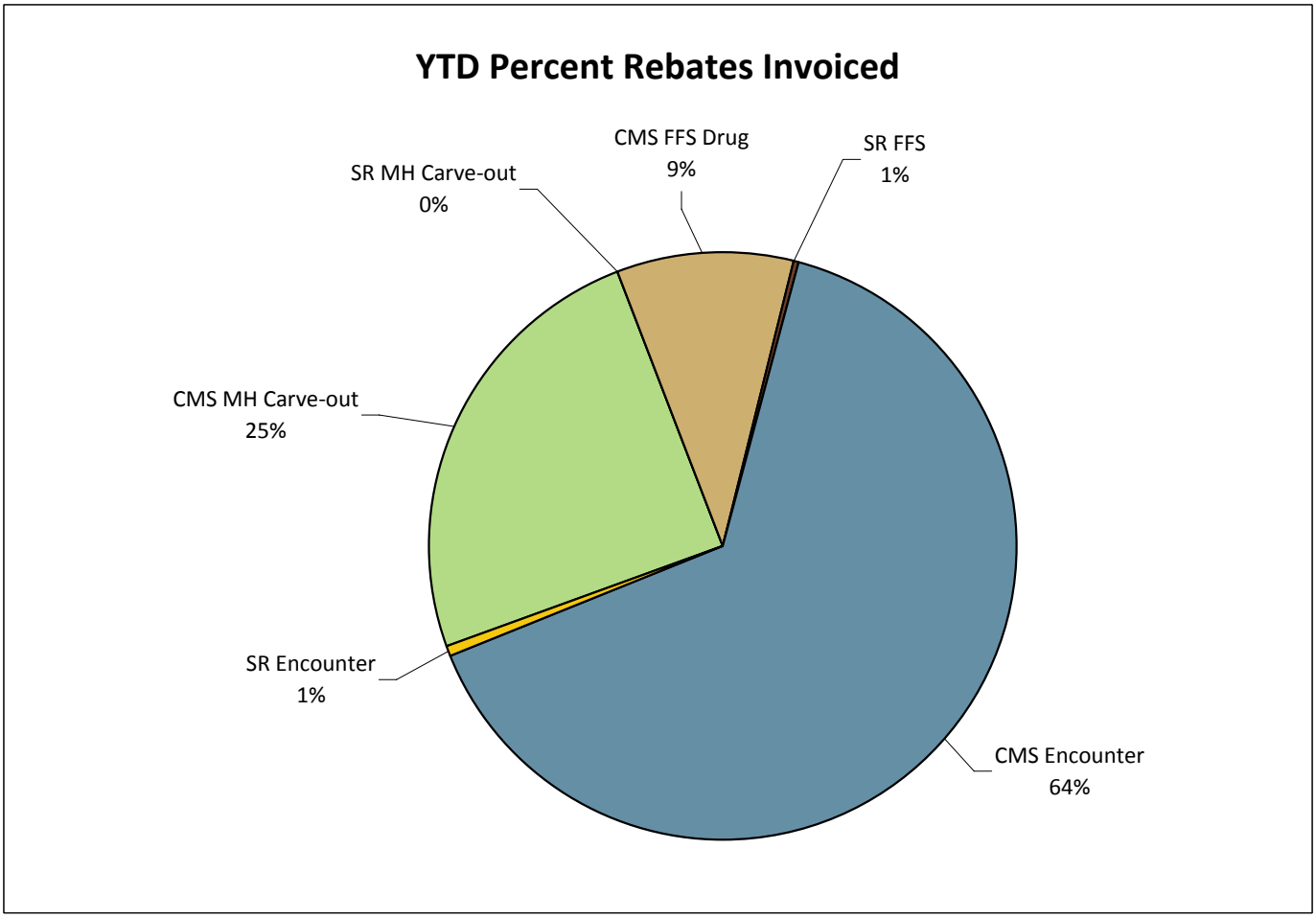
Pharmacy Utilization Summary Report: April 2013 - March 2014

Quarterly Rebates Invoiced	2013-Q2	2013-Q3	2013-Q4	2014-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$50,576,074	$40,883,253	$40,974,375	$61,832,645	$194,266,346
CMS MH Carve-out	$11,511,668	$11,890,992	$11,801,015	$13,045,802	$48,249,477
SR MH Carve-out					$0
CMS FFS Drug	$4,250,177	$4,077,856	$4,206,159	$5,910,601	$18,444,793
SR FFS	$203,962	$169,833	$189,687	$440,510	$1,003,991
CMS Encounter	$34,249,026	$24,615,359	$24,496,481	$41,937,987	$125,298,853
SR Encounter	$361,242	$129,212	$281,034	$497,745	$1,269,233

Quaterly Net Drug Costs	2013-Q2	2013-Q3	2013-Q4	2014-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$46,032,569	$58,859,359	$60,373,578	$61,072,243	$226,337,749
Mental Health Carve-Out Drugs	$11,241,373	$11,634,209	$11,769,865	$13,686,252	$48,331,699
FFS Phys Health + PAD	$6,377,749	$5,937,669	$5,597,842	$8,039,194	$25,952,455
Encounter Phys Health + PAD	$28,413,447	$41,287,481	$43,005,871	$39,346,797	$152,053,595



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

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Pharmacy Utilization Summary Report: April 2013 - March 2014

PMPM Drug Costs (Excludes Rebate)	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$52.51	$53.65	$48.36	$54.30	$53.15	$52.10	$56.26	$54.24	$53.12	$46.92	$46.92	$49.44	$51.75
Mental Health Carve-Out Drugs	$12.34	$12.57	$11.48	$12.87	$12.61	$12.15	$13.23	$11.93	$12.90	$10.86	$9.89	$10.46	$11.94
FFS Physical Health Drugs	$32.02	$31.66	$26.97	$30.88	$28.30	$27.17	$31.13	$28.99	$30.35	$25.54	$25.93	$21.96	$28.41
FFS Physician Administered Drugs	$18.07	$18.65	$14.49	$17.13	$12.61	$13.37	$15.66	$13.48	$10.56	$10.83	$8.44	$8.18	$13.46
Encounter Physical Health Drugs	$32.34	$31.92	$29.82	$32.60	$33.03	$32.27	$34.49	$35.01	$32.64	$28.33	$30.76	$34.68	$32.32
Encounter Physician Administered Drugs	$6.47	$7.89	$6.40	$7.92	$7.46	$7.60	$8.02	$7.27	$7.48	$7.68	$6.76	$6.16	$7.26

Claim Counts	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Total Claim Count (FFS & Encounter)	619,047	612,722	565,041	611,656	603,021	589,198	674,493	617,750	591,560	716,475	742,656	854,430	649,837
Mental Health Carve-Out Drugs	97,933	98,333	89,459	97,153	94,388	90,828	97,399	89,093	93,661	113,575	109,822	124,514	99,680
FFS Physical Health Drugs	65,136	63,284	58,263	62,453	60,482	59,695	63,980	57,440	60,745	77,439	70,913	78,664	64,875
FFS Physician Administered Drugs	8,468	8,670	8,087	8,480	8,499	7,779	7,993	7,465	7,541	16,127	12,940	12,996	9,587
Encounter Physical Health Drugs	411,761	404,522	375,336	406,824	401,996	394,460	462,603	425,398	391,809	454,807	498,332	581,224	434,089
Encounter Physician Administered Drugs	35,749	37,913	33,896	36,746	37,656	36,436	42,518	38,354	37,804	54,527	50,649	57,032	41,607

Amount Paid per Claim (Excludes Rebate)	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$52.99	$54.80	$53.50	$55.45	$55.11	$55.32	$51.87	$54.69	$55.06	$53.66	$53.85	$52.04	$54.03
Mental Health Carve-Out Drugs	$78.73	$79.99	$80.23	$82.74	$83.57	$83.67	$84.48	$83.45	$84.43	$78.33	$76.76	$75.54	$80.99
FFS Physical Health Drugs	$36.88	$37.93	$36.39	$37.42	$36.92	$37.30	$36.52	$38.40	$39.70	$46.20	$48.94	$43.49	$39.67
FFS Physician Administered Drugs	$160.10	$163.15	$140.82	$152.92	$117.13	$140.89	$147.05	$137.42	$111.31	$94.13	$87.29	$98.02	$129.19
Encounter Physical Health Drugs	$43.18	$43.40	$43.42	$43.98	$44.89	$44.46	$40.78	$45.00	$44.46	$42.31	$44.35	$44.36	$43.72
Encounter Physician Administered Drugs	$99.53	$114.46	$103.12	$118.37	$108.17	$113.39	$103.14	$103.68	$105.60	$95.65	$95.92	$80.28	$103.44

Amount Paid per Claim - Multi Source Drugs (Excludes Rebate)	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$23.45	$23.51	$23.15	$23.57	$24.01	$24.21	$22.76	$24.14	$23.69	$22.50	$22.58	$22.02	$23.30
Mental Health Carve-Out Drugs	$36.75	$36.74	$36.08	$39.10	$39.50	$39.94	$39.55	$39.28	$38.63	$34.44	$33.58	$33.47	$37.26
FFS Physical Health Drugs	$20.61	$21.28	$20.59	$21.11	$21.32	$21.03	$20.70	$20.92	$21.69	$21.80	$21.45	$20.96	$21.12
Encounter Physical Health Drugs	$20.82	$20.72	$20.55	$20.33	$20.87	$21.14	$19.60	$21.48	$20.52	$19.67	$20.35	$19.75	$20.48

Amount Paid per Claim - Single Source Drugs (Excludes Rebate)	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$342.40	$349.99	$352.31	$359.69	$360.58	$342.51	$314.94	$348.01	$358.16	$350.44	$386.20	$389.87	$354.59
Mental Health Carve-Out Drugs	$463.19	$476.79	$483.81	$486.01	$485.29	$482.88	$480.01	$480.56	$486.70	$522.92	$527.52	$524.06	$491.64
FFS Physical Health Drugs	$221.48	$226.40	$218.98	$220.11	$215.36	$221.75	$213.68	$241.05	$246.65	$305.52	$344.97	$296.54	$247.71
Encounter Physical Health Drugs	$325.00	$330.08	$332.62	$343.44	$345.21	$320.57	$284.91	$326.82	$335.07	$309.33	$355.18	$369.51	$331.48

Multi-Source Drug Use Percentage	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Multi-Source Drug Use Percentage	92.1%	92.1%	92.2%	92.2%	92.1%	91.8%	91.6%	91.9%	91.9%	91.9%	92.4%	92.6%	92.1%
Mental Health Carve-Out Drugs	90.2%	90.2%	90.1%	90.2%	90.1%	90.1%	89.8%	90.0%	89.8%	91.0%	91.3%	91.4%	90.4%
FFS Physical Health Drugs	91.9%	91.9%	92.0%	91.8%	92.0%	91.9%	91.8%	92.1%	92.0%	91.4%	91.5%	91.8%	91.8%
Encounter Physical Health Drugs	92.6%	92.7%	92.7%	92.7%	92.6%	92.2%	92.0%	92.3%	92.4%	92.2%	92.8%	93.0%	92.5%

Preferred Drug Use Percentage	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Avg Monthly
Preferred Drug Use Percentage	87.03%	84.96%	84.97%	84.97%	84.89%	84.69%	84.60%	84.51%	84.42%	85.95%	86.02%	86.28%	85.3%
Mental Health Carve-Out Drugs	73.08%	71.91%	71.19%	71.10%	71.23%	71.26%	70.92%	71.09%	71.12%	74.11%	74.36%	74.46%	72.2%
FFS Physical Health Drugs	92.29%	91.11%	91.37%	91.24%	91.56%	91.78%	91.47%	91.34%	91.46%	93.72%	93.56%	93.54%	92.0%
Encounter Physical Health Drugs	89.96%	87.71%	87.86%	87.87%	87.67%	87.37%	87.14%	86.99%	87.21%	88.08%	87.93%	88.21%	87.8%

Last Updated: October 23, 2014

Drug Use Research & Management Program
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2014

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$9,681,127	21.2%	11,930	$811	V
2	DULOXETINE HCL	Antidepressants	$4,553,101	10.0%	19,862	$229	V
3	INTUNIV	ADHD Carve Out Drugs	$1,657,076	3.6%	5,824	$285	V
4	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,623,087	3.6%	2,941	$552	V
5	LATUDA	Antipsychotics, 2nd Gen	$1,528,726	3.3%	2,137	$715	V
6	STRATTERA	ADHD Carve Out Drugs	$1,267,914	2.8%	4,560	$278	Y
7	INVEGA SUSTENNA	Injectable Antipsychotics	$862,096	1.9%	646	$1,335	V
8	Factor Viii Recombinant Nos	Physican Administered Drug	$856,608	1.9%	30	$28,554	
9	INVEGA	Antipsychotics, 2nd Gen	$748,718	1.6%	924	$810	V
10	BUPROPION XL	Antidepressants	$709,832	1.6%	13,548	$52	V
11	DIVALPROEX SODIUM ER	Antiepileptics	$623,591	1.4%	3,904	$160	Y
12	RISPERDAL CONSTA	Injectable Antipsychotics	$408,346	0.9%	616	$663	V
13	SERTRALINE HCL	Antidepressants	$390,067	0.9%	32,824	$12	Y
14	MODAFINIL	ADHD Carve Out Drugs	$388,742	0.9%	775	$502	V
15	LAMOTRIGINE ER	Antiepileptics	$381,676	0.8%	789	$484	V
16	FLUOXETINE HCL	Antidepressants	$359,202	0.8%	29,145	$12	Y
17	SAPHRIS	Antipsychotics, 2nd Gen	$336,062	0.7%	697	$482	V
18	PRISTIQ ER	Antidepressants	$330,118	0.7%	1,481	$223	V
19	LANTUS	Insulins	$319,434	0.7%	1,031	$310	Y
20	TRAZODONE HCL	STC 11 - Psychostimulants, Antidepressants	$315,359	0.7%	33,989	$9	
21	ZIPRASIDONE HCL	Antipsychotics, 2nd Gen	$312,625	0.7%	3,186	$98	V
22	HUMIRA	Targeted Immune Modulators	$308,409	0.7%	110	$2,804	Y
23	BUPROPION HCL SR	Antidepressants	$273,167	0.6%	11,435	$24	Y
24	LAMOTRIGINE	Antiepileptics	$270,593	0.6%	18,217	$15	Y
25	ABILIFY MAINTENA	Injectable Antipsychotics	$256,922	0.6%	175	$1,468	V
26	CITALOPRAM HBR	Antidepressants	$251,330	0.6%	30,800	$8	Y
27	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$245,937	0.5%	10,686	$23	Y
28	VENLAFAXINE HCL ER	Antidepressants	$233,909	0.5%	12,228	$19	Y
29	AMITRIPTYLINE HCL	Antidepressants	$226,756	0.5%	16,901	$13	Y
30	CLOZAPINE	Antipsychotics, 2nd Gen	$216,883	0.5%	2,601	$83	Y
31	VIIBRYD	Antidepressants	$212,867	0.5%	1,229	$173	V
32	LORAZEPAM	Benzodiazepine Anxiolytics	$208,986	0.5%	21,263	$10	
33	VENLAFAXINE HCL ER	Antidepressants	$202,958	0.4%	1,543	$132	V
34	Trastuzumab Injection	Physican Administered Drug	$201,198	0.4%	72	$2,794	
35	PROAIR HFA	Asthma Rescue	$195,435	0.4%	3,774	$52	Y
36	RISPERIDONE	Antipsychotics, 2nd Gen	$192,318	0.4%	10,882	$18	Y
37	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$174,711	0.4%	10,190	$17	
38	ENBREL	Targeted Immune Modulators	$167,215	0.4%	79	$2,117	Y
39	ALPRAZOLAM	Benzodiazepine Anxiolytics	$165,888	0.4%	16,581	$10	
40	ATRIPLA	HIV Antivirals	$165,812	0.4%	86	$1,928	
		Aggregate	**$45,683,305**		**675,922**	**$293**	

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

Last updated: October 23, 2014

ProDUR Report for July to September 2014

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	42	15	0	27	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,338	335	0	1,003	1.50%
DD (Drug/Drug Interaction)	Set alert/Pay claim	176	30	0	146	0.20%
ER (Early Refill)	**Set alert/Deny claim**	60,480	11,304	29	49,142	68.01%
ID (Ingredient Duplication)	Set alert/Pay claim	15,828	4,114	4	11,705	17.80%
LD (Low Dose)	Set alert/Pay claim	787	160	0	627	0.88%
LR (Late Refill/Underutilization)	Set alert/Pay claim	125	84	0	41	0.14%
MC (Drug/Disease Interaction)	Set alert/Pay claim	1,598	699	0	897	1.80%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	904	205	0	699	1.02%
PG (Pregnancy/Drug Interaction)	**Set alert/Deny claim**	2,303	1,484	4	815	2.59%
TD (Therapeutic Duplication)	Set alert/Pay claim	5,346	1,558	2	3,783	6.01%
	Totals	**88,927**	**19,988**	**39**	**68,885**	**99.95%**

ProDUR	ProDUR Report for July to September 2014						
Top Drugs in Each DUR Alerts							
DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
DC	Diazepam	75	31	44	10,280	0.7%	41.3%
	Haloperidol	156	42	114	2,035	7.7%	26.9%
	Wellbutrin (Bupropion)	394	48	346	31,570	1.2%	12.2%
DD	Geodon (Ziprasidone)	62	12	50	4,110	1.5%	19.4%
	Celexa (Citalopram)	31	5	26	32,469	0.1%	16.1%
ER	Remeron (Mirtazapine)	732	128	604	6,731	10.9%	17.5%
	Hydrocodone/APAP	388	108	280	9,945	3.9%	27.8%
	Oxycodone	194	82	112	3,415	5.7%	42.3%
	Lorazepam	1,511	333	1,178	22,657	6.7%	22.0%
	Alprazolam	1,161	228	933	18,124	6.4%	19.6%
	Lamictal (Lamotrigine)	2,481	476	2,005	22,631	11.0%	19.2%
	Abilify (Aripiprazole)	1,847	366	1,481	14,458	12.8%	19.8%
	Seroquel (Quetiapine)	2,148	409	1,739	16,260	13.2%	19.0%
	Risperdal (Risperidone)	1,674	351	1,323	13,063	12.8%	21.0%
	Wellbutrin (Bupropion)	2,818	421	2,397	31,570	8.9%	14.9%
	Zoloft (Sertraline)	3,528	629	2,898	35,677	9.9%	17.8%
	Prozac (Fluoxetine)	2,959	571	2,388	32,412	9.1%	19.3%
	Celexa (Citalopram)	2,817	456	2,361	32,469	8.7%	16.2%
	Trazodone	3,653	553	3,100	35,227	10.4%	15.1%
	Cymbalta (Duloxetine)	2,133	355	1,778	23,068	9.2%	16.6%
ID	Lamictal (Lamotrigine)	885	224	661	22,631	3.9%	25.3%
	Seroquel (Quetiapine)	904	238	666	16,260	5.6%	26.3%
	Risperdal (Risperidone)	613	171	442	13,063	4.7%	27.9%
	Zoloft (Sertraline)	853	220	633	35,677	2.4%	25.8%
	Prozac (Fluoxetine)	939	219	720	32,412	2.9%	23.3%
PG	Lorazepam	246	197	49	22,657	1.1%	80.1%
	Alprazolam	182	138	44	18,124	1.0%	75.8%
TD	Lamictal (Lamotrigine)	389	84	306	22,631	1.7%	21.6%
	Depakote (Divalproex Sodium)	269	84	185	12,465	2.2%	31.2%
	Seroquel (Quetiapine)	458	123	339	16,260	2.8%	26.9%
	Zyprexa (Olanzapine)	318	95	223	9,803	3.2%	29.9%
	Risperdal (Risperidone)	268	75	193	13,063	2.1%	28.0%

ProDUR Repo **ProDUR Report for July to September 2014**

Top Drugs in Early Refill

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	5	13	33	1	44	0
	Hydrocodone Bit/APAP	3	2	43	0	26	0
	Oxycodone HCl	8	6	31	0	35	0
	Lorazepam	6	11	106	1	113	0
	Alprazolam	8	9	76	4	53	0
	Diazepam	5	3	42	0	37	0
	Buspar (Buspirone)	10	8	65	0	37	0
	Lamictal (Lamotrigine)	22	23	155	1	134	0
	Depakote (Divalproex Sodium)	3	9	74	1	109	0
	Clonazepam	3	1	20	0	13	0
	Gabapentin	7	2	34	0	28	0
	Abilify (Aripiprazole)	16	16	82	4	135	0
	Seroquel (Quetiapine)	13	22	113	4	138	0
	Risperdal (Risperidone)	12	13	87	3	116	0
	Zyprexa (Olanzapine)	8	10	54	5	107	0
	Geodon (Ziprasidone)	0	7	24	2	25	0
	Albuterol	3	6	17	0	14	0
	Lithium Carbonate	7	4	64	2	59	0
	Wellbutrin (Bupropion)	34	30	91	0	116	0
	Prilosec (Omeprazole)	3	4	19	0	30	0
	Zoloft (Sertraline)	14	28	263	4	147	0
	Celexa (Citalopram)	24	30	131	6	125	0
	Prozac (Fluoxetine)	42	20	159	3	133	0
	Lexapro (Escitaloprim)	11	16	53	1	56	0
	Paxil (Paroxetine)	4	7	34	0	42	0
	Trazodone	19	29	174	7	183	0
	Cymbalta (Duloxetine)	16	19	97	5	94	0
	Effexor (Venlafaxine)	10	22	68	1	50	0
	Amitriptyline	9	13	79	0	57	0
	Straterra (Atomoxetine)	2	1	12	0	20	0
	TOTALS	**327**	**384**	**2300**	**55**	**2276**	**0**

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Retro-DUR Intervention History by Quarter FFY 2013 - 2014

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified		59	61	48
		Profiles Sent		31	38	29
		Responses Received		11	11	9
		Response Rate		35%	29%	31%
		Information Useful or Will Change Practice		6	5	6
		Patient Not With Office		0	0	1
		Already Scheduled		5	10	4
		Will Not Schedule		0	0	0
		Requested No Future Notifications		1	4	1
	Antipsychotic Metabolic Monitoring	Members Identified		707	900	432
		Profiles Sent		706	866	432
		Members With Response		178	52	100
		Response Rate		25%	6%	23%
		Newly Scheduled		95	9	30
		Provider Contacted		76	386	164
		Provider Responses		17	18	47
		Provider Agreed with Recommendation		4	7	15
		Patient Not With Office		22	9	14
	Polypharmacy	Members Identified		404	65	219
		Profiles Sent		387	54	0
		Responses Received		198	22	0
		Response Rate		51%	41%	
		Information Useful or Will Change Practice		37	2	0
		Patient Not With Office		18	3	0
		Not Helpful, waste of time		23	1	

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Retro-DUR Intervention History by Quarter FFY 2013 - 2014

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Profile Review	Children under age 12 antipsychotic	Profiles Reviewed	122	98	108	102
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	33	24	14	34
	Children under age 18 on any psychotropic	Profiles Reviewed	195	92	94	113
	Children under age 6 on any psychotropic	Profiles Reviewed	5	10	10	8
	Lock-In	Profiles Reviewed	41	84	19	
		Letters Sent To Providers	6	3		
		Provider Responses	0	0		
		Provider Agreed / Found Info Useful	0	0		
		Locked In	17	56	19	

Oregon State University
College of Pharmacy

Drug Use Research & Management Program

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2013 - 2014

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	1,356	2,833	48%	1,438	2,889	50%	1,315	2,797	47%			
Five or more concurrent psychotropics	143	9,970	1%	140	10,911	1%	130	10,574	1%			
Three or more concurrent psychotropics	1,992	9,970	20%	1,979	10,911	18%	1,932	10,574	18%			
Two or More Concurrent Antipsychotics	110	9,970	1%	113	10,911	1%	101	10,574	1%			
Under 18 years old on any antipsychotic	2,841	9,970	28%	2,899	10,911	27%	2,804	10,574	27%			
Youth five years and younger on psychotropics	223	9,970	2%	242	10,911	2%	219	10,574	2%			

11/17/2014

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

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

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Update on New Therapies for Treating Major Depressive Disorder (MDD)

By Amanda Meeker, PharmD and Ghazaleh Barkhordarian, PharmD Candidate 2015, all from Oregon State University College of Pharmacy

Depressive disorders, including Major Depressive Disorder (MDD), are common mental health conditions thought to be related to imbalances in serotonin and norepinephrine. Medical management of depressive disorders include first-generation antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second generation antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin/norepinephrine reuptake inhibitors [SNRIs]). Recently, two antidepressants were approved for use in MDD, levomilnacipran (Fetzima®) and vortioxetine (Brintellix®).

Comparative Efficacy

The FDA-accepted primary endpoint of trials evaluating antidepressants for efficacy is change in baseline in an administered depression scale, often the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAMD).[1] Response and remission rates are common outcomes by which antidepressants are clinically evaluated. Response refers to a clinically significant degree of depressive symptom reduction following treatment initiation (generally accepted as a 50% decrease in MADRS or HAMD score).[2,3] Remission is the virtual absence of depressive symptoms (generally accepted as a MADRS score of <10 or HAMD score of <7).[2] The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).[2]

Current evidence suggests that most antidepressants have similar efficacy for the treatment of MDD.[4] SSRIs are used first line because they have their favorable risk-benefit ratio;[5] at the same time, because most SSRIs are generic, they are inexpensive. An AHRQ comparative efficacy review shows that more patients reach response and remission with escitalopram than citalopram, that citalopram may have a faster onset of action than fluoxetine but no greater response or remission rates after 8 weeks, and more patients responded to sertraline than fluoxetine (NNT=14).[4]

Optimal Treatment of First-Episode MDD

The American Psychiatric Association guidelines for depression recommend offering an antidepressant as an initial treatment choice for patients with mild to moderate MDD, and definitely providing an antidepressant to those with severe MDD.[6] After an adequate trial of an antidepressant dose (4-6 weeks), patients should be evaluated for response and antidepressant doses should be increased if a response is not seen.[6] If a patient does not achieve a response after 4-6 weeks on the maximum dose or is unable to tolerate side effects, the trial is considered failed and the patient should be switched to an alternative agent (another SSRI or non-SSRI antidepressant).[6] Once response is achieved, treatment should continue unmodified for 4-9 months before discontinuing therapy to prevent relapse in first episode MDD.[6]

Preferred Antidepressants for Oregon Medicaid

Oregon law prohibits traditional methods of Preferred Drug List (PDL) enforcement for mental health drugs. The Oregon Health Plan (OHP) relies on prescribers to voluntarily choose high value antidepressants for Oregon Medicaid patients. Second generation antidepressants were reviewed for clinical efficacy and safety with specific agents chosen as clinically preferred (table 1). Prescribing preferred antidepressants eliminates patient copays. OHP patients are charged $3 copays for non-preferred branded antidepressants and $1 for non-preferred generic antidepressants (table 2).

Table 1. Current preferred agents on the Voluntary Mental Health PDL

Preferred Agents	
Amitriptyline Tablet	Imipramine Tablet
Bupropion HCl/SR Tablet	Mirtazapine Rapids/Tablet
Citalopram Tablet/Solution	Nortriptyline Capsule/Solution
Escitalopram	Paroxetine Tablet
Fluoxetine	Sertraline Oral Tablet/ Concentrate
Fluvoxamine	Venlafaxine Tablet/ER

Table 2. Current non-preferred agents on the Voluntary Mental Health PDL

Non-preferred Agents	
Bupropion XL /Bupropion HBr (APLENZIN®)	Levomilnacipran (FETZIMA®)
Clomipramine HCl	Nefazodone
Desvenlafaxine (PRISTIQ®, KHEDEZLA®)	Paroxetine HCl (PAXIL CR®), Paroxetine Mesylate (PEXEVA®)
Duloxetine	Selegiline Patch (EMSAM®)
Escitalopram Solution	Vilazodone (VIIBRYD®)
Fluoxetine DR (PROZAC® Weekly)	Olanzapine/Fluoxetine (SYMBYAX®)
Fluvoxamine ER (LUVOX CR®)	Vortioxetine (BRINTELLIX®)

Vortioxetine (Brintellix®)

Vortioxetine, a serotonin modulator and stimulator, was approved in October 2013 for treatment of MDD.[7] A total of 11 short-term studies evaluated the efficacy and safety of vortioxetine in MDD.[8–18] However, FDA approval was based on the results of six good- or fair-quality, randomized, placebo- and active-controlled positive efficacy studies that were conducted in both US and non-US populations.[7] Patients in these trials were mostly white, women, in their mid-40's, and a majority had moderate-to-severe MDD. Extensive exclusion criteria, including patients at risk of suicide, concurrent psychiatric disorders or medical illnesses and patients with treatment-resistant depression, make it hard to generalize findings to a broader population. In trials conducted exclusively in the US, only the 20 mg daily dose demonstrated statistically significant change in baseline score (measured by MADRS or HAMD) over placebo and was therefore chosen as the target daily dose. Nonetheless, lower doses (5 mg and 10 mg) demonstrated improved efficacy compared to placebo in studies conducted in both non-US and US populations.[7]

Overall, response and remission was improved for those on vortioxetine compared to placebo and the effect does not appear to be dose-dependent. Henigsberg et al. studied three doses of vortioxetine and response rates were similar in all arms (relative risks (RR) of 1.9, 1.8, and 2.0 for 1 mg, 5 mg, and 10 mg, respectively)[8]. Remission rates were also similar with RRs of 1.6, 1.7, and 1.6 for the 1-mg, 5-mg and 10-mg groups, respectively.[8] Three of the four studies including a vortioxetine 20-mg arm are unpublished, and two of these studies did not demonstrate that the 20-mg dose was statistically different than placebo, as measured by the MADRS scale (RRs of 1.1 [95% CI 0.9 to 1.5] and 1.4 [95% CI 1.0 to 1.9). Thus one could question the designation of 20 mg as the target dose.

While vortioxetine is being promoted as having a novel mechanism of action, there is no evidence that it is more efficacious than, and some data suggesting it is inferior to, other available second-generation antidepressants. In studies comparing venlafaxine XR or duloxetine to vortioxetine, rates of response and remission were similar to the active comparator.[9–13] At low doses, there were no differences in response rates between vortioxetine and the active comparison, but when compared to 15 and 20 mg doses of vortioxetine, MADRS response rates were higher in the active control arms.[9–13] There were no differences in remission rates at any dose of vortioxetine compared to the active control. There is a need for more

head-to-head trials to truly understand vortioxetine's comparative effectiveness in this class.

The most common adverse events (occurring in >2% of patients and at least 2% greater than placebo) are nausea, diarrhea and dry mouth and the most common serious adverse events are serotonin syndrome, abnormal bruising or bleeding, hypomania, or hypernatremia.[19] It does not appear that side effects are dose-related; however there is an increase likelihood of discontinuation due to adverse events as the dose increases compared to placebo.

Levomilnacipran (Fetzima®)

Levomilnacipran is the active enantiomer of milnacipran (Savella®), an SNRI approved for use in fibromyalgia[20] (but not depression). The approval of levomilnacipran was based on three fair-quality, 8-week randomized, placebo-controlled phase III clinical trials in adults with MDD.[21–23] There are four approved strengths, 20 mg, 40 mg, 80 mg and 120 mg. Dosage adjustment is necessary in moderate to severe renal impairment, and use is not recommended in end stage renal disease.[20]

MADRS response rates appear to be similar for all approved doses.[21–23] MADRS response rates were similar between the two doses of levomilnacipran studied in the Bakish et al. study with RRs of 1.4 (95% CI 1.1-1.9) and 1.3 (95% CI 1.1-1.8) for the 40-mg and 80-mg groups, respectively.[21] MADRS remission RRs were 1.7 (95% CI 1.1-2.5) and 1.80 (95% CI 1.2-2.7) for the 40-mg and 80-mg groups, respectively.[21] In Asnis et al,[22] which studied three doses of levomilnacipran (40 mg, 80 mg, and 120 mg), only the 120 mg group had a statistically significant MADRS response rate (RR 1.4; 95% CI 1.1-1.9), while no dose group was statistically significant for MADRS remission rates. A third short-term efficacy study titrated patients from levomilnacipran sustained-release 25 mg daily to either 75 mg or 100 mg daily based on tolerance; both MADRS response (RR 1.3; 95% CI 1.2-1.7) and MADRS remission (RR 1.8; 95% CI 1.4-2.3) outcomes were statistically significant.[23] No head-to-head trials or comparative studies have been published. There is low quality evidence of no difference in the response rates (around a 40% increase) of all studied doses compared to placebo, but further research is needed before we fully understand this drug's place in therapy and comparative effectiveness.

The most common adverse events (incidence >2% and at least twice the rate of placebo) seen in trials as compared to placebo were nausea, constipation, hyperhidrosis, tachycardia, erectile dysfunction, increased heart rate and vomiting. The two dose-related adverse reactions were urinary hesitation and erectile dysfunction.

Summary

Vortioxetine and levomilnacipran appear to be safe and effective agents for the treatment of MDD based on short-term placebo-controlled trials. However, there is insufficient evidence to determine the most effective treatment dose of vortioxetine and there is a need for more head-to-head trials for both vortioxetine and levomilnacipran to fully understand their efficacy and safety and to determine their place in therapy relative to less expensive alternatives. These drugs may be useful when patients have failed current first- and second-line agents in the treatment of depression, but there is no evidence at this point to support widespread use.

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New Hepatitis C Antiviral Therapies: How should they be used in clinical practice?

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Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and death from liver disease in the United States.[1] The goal of treatment is reduction of cirrhosis, hepatocellular carcinoma, decompensated hepatic disease, liver failure, liver transplant and mortality.[2] Since the 2013 approval of sofosbuvir (SOF) (Solvaldi®) and simeprevir (SMV) (Olysio®), there has been active debate about which patients should receive them due to their high cost. The purpose of this newsletter is to provide evidence for efficacy and safety of these new agents, and identify who is most likely to benefit from treatment.

Progression of HCV is generally slow, but varies significantly among individuals. Over 20 to 30 years, approximately 5% to 20% of individuals who develop chronic HCV infection will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer. [2] Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis. Patients with cirrhosis are at risk of progressing to decompensation, hepatocellular carcinoma or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease and prolonging graft survival in liver transplant recipients. For high risk patients, SOF and SMV show the most benefit in terms of liver events avoided.[3]

Prior standard of care (pegylated interferon (PEG)-based treatment) had lower efficacy rates, high risk for adverse events, difficult administration and high patient burden. Newer treatments were developed to alleviate these limitations. However, this added benefit comes at a significant cost. The wholesale acquisition cost (WAC) of SOF was set at $1,000 per tablet, which translates into $84,000 for 12 weeks of treatment and $168,000 for 24 weeks of treatment.[4] Although therapeutic regimens for other diseases can be just as costly, the sheer number of people afflicted with hepatitis C infection magnifies the issue of cost. Policymakers and clinicians alike are waiting to see if these known and possible other benefits outweigh the cost to the healthcare system.

Sofosbuvir and Simeprevir

Treatment response is measured by the absence of virus (sustained virological response) for 24 weeks (SVR24) or 12 weeks (SVR12) after stopping treatment. SVR has been associated with reduction of virus-related morbidity and mortality and there is evidence that a SVR is equivalent to HCV infection cure.[5,6] HCV genotype 1 (G1) comprises 73% of U.S. chronic HCV cases and has a lower response rate to therapy than genotypes 2 and 3.[7] Short term evidence has shown improved response rates with SOF and SMV compared to previous standard of care (Table 1) in the treatment naive.[2] Still, there is limited evidence directly comparing newer regimens to the older.

Table 1: Response Rates of Hep C FDA Approved Treatment Regimens[2]

Virus Genotype	Treatment Regimen	Response Rate*
Genotype 1	PEG/RBV Dual Therapy x 48 weeks	45%
	PEG/RBV + BOC or TVR Triple Therapy	65-70%
	SOF + PEG + RBV x 12 weeks	89%
	SOF + RBV x 24 weeks	68%
	SOF + SMV +/- RBV 12-24 weeks	90-100%
Genotype 2	PEG/RBV x 24 weeks	75%
	SOF + RBV x 12 weeks	82-95%
Genotype 3	PEG/RBV x 24 weeks	75%
	SOF + RBV x 24 weeks	84%

PEG-pegylated interferon, RBV-ribavirin, BOC-boceprevir, TVR-telaprevir, SOF-sofosbuvir, SMV-simeprevir, *SVR-sustained virological response (12 or 24 wks post tx)

The Oregon Center for Evidence-based Policy recently evaluated the efficacy and safety of SOF for chronic HCV treatment.[2] The available evidence is comprised of ten studies; eight published and two unpublished. However, the majority of the studies are non-comparative and all but one was found to have a high risk of bias. Studies were small, and included few patients that were of clinical interest with less than 14% having cirrhosis and around 10% of African American ethnicity. None of the trials compared SOF to standard of care in HCV G1 patients, and they excluded those patients under 18 years of age, patients with HIV or HBV co-infection, significant alcohol or drug use in the past year, current excessive alcohol use, significant renal (eGFR <60 mL/min), cardiac, pulmonary, or uncontrolled chronic diseases (hypertension and diabetes). The SVR rates in these studies may be strongly influenced by a majority of study of patients having favorable prognostic factors. The relapse rate was not always reported, and trials were not consistent with how they defined relapse. Relapse rates ranged from 5% to 28%, including patients who were fully treated with the SOF regimen.[2]

To date, there are no studies looking at the long-term side effects associated with SOF.[2] The current safety of SOF treatment is based on small studies of short duration with healthier patients than those found in the general HCV population. The adverse events most commonly reported were nausea, fatigue, headache, rash, insomnia, and pain. Overall, discontinuation of active treatment due to adverse events was relatively low in clinical studies (1.4% in patients treated with SOF + RBV).[2] Longer and larger studies or post-marketing follow up data are needed to accurately assess safety.

SMV is a direct-acting-antiviral (DAA) with the same mechanism of action as BOC and TVR, but offers the advantage of being dosed once daily and posing less significant safety concerns. SMV is only FDA approved for use as a triple therapy regimen including PEG and RBV. SMV demonstrated SVR rates ranging from 60-86% and recent studies have shown that SMV triple therapy results in a higher SVR rate compared to PEG plus RBV dual therapy in chronic HCV G1 patients.[8,9] However, with the pipeline of regimens moving away from PEG-based treatment due to side effects, higher discontinuation rates and disease progression, the place in therapy of SMV triple therapy seems limited.

The combination of SMV and SOF has been evaluated and is supported by expert opinion based guidelines.[10] Currently, this recommendation is based on only one small, open-label, randomized, poor quality phase IIa study (COSMOS) evaluating the combination in previous null responders and treatment naïve HCV G1 patients (n=167) with METAVIR F0-F2 fibrosis (Cohort 1) or F3-F4 (Cohort 2).[11] SVR 12 rates in Cohort 1 ranged from 79.2% to 100%, and from 92.6% to 100% in Cohort 2, regardless of whether or not the patient received RBV. More randomized controlled trials evaluating this off-label combination are needed to adequately assess the efficacy and safety in this patient population.

Readiness Assessment and Patient Education

Due to the complexity of the disease and treatment regimens, many psychosocial factors can potentially interfere with treatment adherence, and effectiveness, therefore incurring unnecessary and significant costs. There are higher rates of psychiatric and substance use disorders and cognitive impairment (risk factors for non-adherence) in persons with chronic HCV infection than in the general population.[12] Mental health issues, particularly depression and anxiety disorders, and treatment of addiction should be assessed and managed before initiating treatment. In addition, HCV treatment side effects often result in early treatment discontinuation which reduces rates of cure. The term "readiness" is highlighted as an important concept in an individual's decision-making to undergo treatment, but there is little consensus on its definition.

The use of an initial assessment for readiness to treat has been studied. However, most of the literature occurs in the prison setting[13–15] or in those

with HCV/HIV co-infection.[16–18] Still, standardized protocols or treatment guidelines are lacking. Primary care providers can assess if a patient with chronic HCV is ready for referral to a specialist, as well as identify areas for readiness improvement while waiting to start treatment. The primary topics to address include alcohol and substance use, mental health, and life stability and/or major life events. Validated screening tools such as the SBIRT (http://www.sbirtoregon.org/screening.php) can be used. In addition, it is valuable to assess the willingness of a patient to comply with treatment and all related screening and appointments through a patient consent program.

Key patient educational points include the following: 1) Avoid using alcohol, 2) Avoid using illicit drugs, 3) Get vaccinated for Hepatitis A and B, 4) Talk to your healthcare provider before taking any medications, including over-the-counter and vitamins, 5) Eat a healthy diet, and 6) Work with your healthcare provider in controlling all underlying comorbid illnesses including psychiatric issues. Providing patients with moderate behavioral changes to protect liver health will enable them to be prepared for treatment when it is appropriate.

Ideal Candidates for New Hepatitis C Antiviral Therapy

New guidelines recommend the prioritization of HCV patients for treatment based on disease severity, including those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations.[19,20] Since the next generation of all oral hepatitis C therapy will be available soon, the goal is to identify those patients who need treatment with the current regimens in the next 6-12 months in order to avoid poorer outcomes if treatment is delayed. The Oregon evidence-based policy report recommends using the study inclusion and exclusion criteria to help select patients who are more likely to respond.[2] Common exclusion criteria included decompensated cirrhosis, significant alcohol or drug use within the past 12 months, significant cardiac or pulmonary disease. However, this is based on a lack of evidence in these populations and clinical opinion might help fill in some of these gaps.

Based on clinical expertise from local hepatologists, patient groups who are at higher risk if not treated includes cirrhotic patients (Fibrosis stage 4) without ongoing progressive decompensation (MELD score between 8 and 11), HCV/HIV co-infected patients with cirrhosis (Stage 4), patients with extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulinemia, lymphoma), and HCV infection in the transplant setting (post-transplant with stage 4 fibrosis and pre-transplant in those who it is essential to eradicate the virus). However, there is a lack of evidence in these patient populations so an analysis of risk versus benefit, as well as cost should be involved in the treatment determination. The Oregon prior authorization criterion that prioritizes these high-risk groups can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html.

Conclusion

The slow course of disease progression for those at a lower baseline risk provides ample time for clinicians to select those patients that are most likely to respond and get value from a treatment response with SOF and SMV. Though these recently approved regimens seem to have improved efficacy, much is not known about their safety and their effectiveness in a more heterogenous population than in the clinical trials. The pipeline of medications for the treatment of HCV is extremely robust with newer PEG-free and SOF containing combination therapies expected to be approved in 2014 and 2015. The evidence gaps along with the high cost of these regimens make it prudent to adequately assess patients for readiness to treat and prioritize treatment based on disease severity and risk of progression.

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Nutritional Supplements (Oral Administration Only)

Goal(s):

- Restrict use to clients unable to take food orally in sufficient quantity to maintain adequate weight.
- Require ANNUAL nutritional assessment for continued use.
- Use restriction consistent with DMAP EP/IV rules at: http://www.oregon.gov/oha/healthplan/Pages/home-epiv.aspx

~~http://www.dhs.state.or.us/policy/healthplan/guides/homeiv/main.html~~

These products are not federally rebate-able; Oregon waives the rebate requirement for the class.

Please note:

- **Nutritional formulas, when administered enterally (g-tube), are no longer available through the point of sale system.**
- **Service providers should use the CMS 1500 form and mail to DMAP, P.O. Box 14955, Salem, Oregon, 97309 or the 837P electronic claim form, and not bill through POS.**
- **When billed correctly with HCPCS codes for enterally given supplements, enterally administered nutritional formulas do not require prior authorization. However, the equipment does require a PA (i.e., pump).**
- **Providers can be referred to 800-642-8635 or 503-945-6821 for enteral equipment PAs**
- **For complete information on how to file a claim, go to: http://www.oregon.gov/oha/healthplan/Pages/home-epiv.aspx~~http://www.dhs.state.or.us/policy/healthplan/guides/homeiv/main.html~~**

Length of Authorization:

Up to 12 months

Note: Criteria is divided into: 1) Clients 6 years or older
2) Clients under 6 years

Not Covered:

- Supplements and herbal remedies such as Acidophilis, Chlorophyll, Coenzyme and Q-10 are not covered and should not be approved.

Requires PA:

- All supplemental nutrition products in HIC3 = C5C, C5F, C5G, C5U, C5B (Nutritional bars, liquids, packets, powders, wafers such as Ensure, Ensure Plus, Nepro, Pediasure, Promod).

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

CLIENTS 6 YEARS OF AGE AND OLDER:
Document:

- Name of product being requested
- Physician name
- Quantity/Length of therapy being requested

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the product requested a supplement or herbal product without an FDA indication?	Yes: Pass to RPH; Deny (Medical Appropriateness)	No: Go to #3
3. Is the product to be administered by enteral tube feeding (g-tube)?	Yes: Go to #10	No: Go to #4
4. All indications need to be evaluated as to whether they are above or below the line.	Above the line: Go to #5	Below the line: Pass to RPH; Deny (Not covered by the OHP).
5. Is this request for a client that is currently on supplemental nutrition?	Yes: Go to #6	No: Go to #7
6. Has there been an annual assessment by MD for continued use of a nutritional supplement? Document assessment date.	Yes: Approve for up to 1 year	No: Request documentation of assessment OR Pass to RPH; Deny, (Medical Appropriateness).
7. Client must have a nutritional deficiency identified by one of the following: • Has there been a recent (within year) Registered Dietician assessment indicating adequate intake is not obtainable through regular/liquefied or pureed foods? (Supplement cannot be approved for convenience of client or caregiver.) **OR** • Is here a recent serum protein level < 6?	Yes: ~~Approve up to 1 year~~Go to #9	No: Go to #8
8. Does the patient have a prolonged history (>1 year) of malnutrition and cachexia OR reside in a LTC facility or chronic home care facility? Document: • Residence • Current weight • Normal weight	Yes: Go to #9	No: Request more documentation OR pass to RPH; Deny (Medical Appropriateness).

Approval Criteria		
9. Does the client have: • An increased metabolic need resulting from severe trauma (e.g. Severe burn, major bone fracture, etc.)? OR • Malabsorption difficulties (e.g. Crohns Disease, Cystic Fibrosis, bowel resection/ removal, Short Gut Syndrome, gastric bypass, renal dialysis, dysphagia, achalasia, etc)? OR • A diagnosis that requires additional calories and/or protein intake (e.g. Cancer, AIDS, pulmonary insufficiency, MS, ALS, Parkinson's, Cerebral Palsy, Alzheimers, etc.)	Yes: Approve for up to 1 year	No: Request more documentation OR Pass to RPH; Deny (Medical Appropriateness).
10. Is this request for a client that is currently on supplemental nutrition? • Yes: Approve for 1 month and reply: Nutritional formulas, when administered by enteral tube, are no longer available through the point of sale system. For future use, service providers should use the CMS form 1500 or the 837P electronic claim form and not bill through POS. A one month approval has been given to accommodate the transition. Go to: http://www.oregon.gov/oha/healthplan/Pages/home-epiv.aspx~~http://www.dhs.state.or.us/policy/healthplan/guides/homeiv/main.html~~ • No: Enter an Informational PA and reply: Nutritional formulas, when administered by enteral tube, are no longer available through the point of sale system. For future use, service providers should use the CMS form 1500 or the 837P electronic claim form and not bill through POS. When billed using a HCPCS code, enterally administered nutritional formulas do not require a prior authorization. However, the equipment does require a PA. Providers can be referred to 800-642-8635 or 503-945-6821 for enteral equipment PAs. For complete information of how to file a claim, go to: http://www.oregon.gov/oha/healthplan/Pages/home-epiv.aspx ~~http://www.dhs.state.or.us/policy/healthplan/guides/homeiv/main.html~~		

CLIENTS 5 YEARS and UNDER:
Document:

- Name of product being requested
- Physician name
- Quantity/Length of therapy being requested

Approval Criteria		
1. What diagnosis is being treated that is responsible for needing nutritional support?	Record ICD9 code.	
2. Is the product to be administered by enteral tube feeding (g-tube)?	Yes: Go to #9	No: Go to #3
3. All indications need to be evaluated as to whether they are above or below the line.	Above the line: Go to #4	Below the line: Pass to RPH; Deny (Not covered by the OHP).
4. Is this request for a client that is currently on supplemental nutrition?	Yes: Go to #5	No: Go to #6
5. Has there been an annual assessment by MD for continued use of a nutritional supplement? (No recent weight loss, serum protein level or dietician assessment required if body weight being maintained by supplements due to clients medical condition). Document assessment date.	Yes: Approve for up to 1 year	No: Request documentation of assessment OR Pass to RPH; Deny, (Medical Appropriateness).
6. Is the diagnosis failure to thrive (FTT)? (783.4)	Yes: Approve for up to 1 year	No: Go to #7
7. Does the client have: • An increased metabolic need resulting from severe trauma (e.g. Severe burn, major bone fracture, etc.)? OR • Malabsorption difficulties (e.g. Crohns Disease, Cystic Fibrosis, bowel resection/ removal, Short Gut Syndrome, gastric bypass, renal dialysis, dysphagia, achalasia, etc)? OR • A diagnosis that requires additional calories and/or protein intake (e.g. Cancer, AIDS, pulmonary insufficiency, Cerebral Palsy, etc.)	Yes: Approve for up to 1 year	No: Go to #8
8. Client must have a nutritional deficiency identified by one of the following: • Has there been a recent (within year) Registered Dietician assessment indicating adequate intake is not obtainable through regular/liquefied or pureed foods? (Supplement cannot be approved for convenience of client or caregiver.) OR • Is there a recent serum protein level <6?	Yes: Approve for up to 1 year	No: Request more documentation OR Pass to RPH; Deny (Medical Appropriateness).

Approval Criteria

9. Is this request for a client that is currently on supplemental nutrition?

- Yes: Approve for 1 month and reply:
  Nutritional formulas, when administered by enteral tube, are no longer available through the point of sale system. For future use, service providers should use the CMS form 1500 or the 837P electronic claim form and not bill through POS. A one month approval has been given to accommodate the transition.

Go to: http://www.oregon.gov/oha/healthplan/Pages/home-epiv.aspx~~http://www.dhs.state.or.us/policy/healthplan/guides/homeiv/main.html~~

- No: Enter an Informational PA and reply: Nutritional formulas, when administered by enteral tube, are no longer available through the point of sale system. For future use, service providers should use the CMS form 1500 or the 837P electronic claim form and not bill through POS. When billed using a HCPCS code, enterally administered nutritional formulas do not require a prior authorization. However, the equipment does require a PA. Providers can be referred to 800-642-8635 or 503-945-6821 for enteral equipment PAs.

For complete information of how to file a claim, go to:
http://www.oregon.gov/oha/healthplan/Pages/home-epiv.aspx~~http://www.dhs.state.or.us/policy/healthplan/guides/homeiv/main.html~~

Note: Normal serum protein 6 - 8 g/dl
Normal albumin range 3.2 – 5.0 g/dl

P&T / DUR Action: 2/23/06
Revision(s): 9/1/06, 7/1/06, 4/1/03, 6/22/07, 11/20/14
Initiated:

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

Oregon Health Authority

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

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

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

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

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

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

METHODS

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

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

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

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

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

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

RESULTS

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

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

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

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

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

Table 2 – Initiation by Demographic Distribution

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

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

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

Table 3 – Initiation by Medication

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

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

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

Table 4 – Initiation by Diagnosis

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

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

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

Table 5 – Initiation by Provider Specialty and Geographic Location

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

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

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

DISCUSSION

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

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

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

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

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

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

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

RECOMMENDATION

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

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Appendix 1 – Drugs Included and Classification

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

Appendix 2 – Provider Specialty Groupings

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

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

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

Appendix 3

Initial Pediatric SSRI Antidepressant –Daily Dose Limit

Goal(s):

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

Length of Authorization:

- 12 months

Requires PA:

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

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

Covered Alternatives:

- Doses within recommended age-specific dose.

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

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

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

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Oregon Health Authority

Policy Evaluation: Combination Inhaler Prior Authorization

There has been ongoing controversy about the safety of long-acting beta-agonists over the last decade.[1] A recent meta-analysis found the odds of severe asthma exacerbations were increased with combination inhaler treatment compared to inhaled corticosteroids alone (OR 3.65 95% CI 1.39 – 9.55).[2] A United States Food and Drug Administration (FDA) meta-analysis of over 60,000 patients led to a strengthened public health advisory recommending that long-acting beta-agonists be used only for those who remain symptomatic on other asthma controller medications, for the shortest possible duration and never as a single agent.[3] Combination inhaler recommendations for COPD were not affected by the FDA advisory. The Global Initiative for Chronic Obstructive Lung Disease recommends a stepped approach to COPD treatment with combination inhalers reserved for patients with severe and very severe disease.[4]

Despite the controversy, utilization of combination inhalers has proliferated. In the Oregon fee-for-service Medicaid program, where Advair® was the 9th most costly drug in 2010,[5] only 12% of combination inhaler patients[6] had prior drug claims for any asthma controller in the 90 days prior to therapy initiation contrary to the FDA labeling and practice guidelines.[7] Consequently, the Oregon Medicaid fee-for-service program implemented a prior authorization (PA) policy to align combination inhaler prescribing practices with the FDA guidance and national guidelines.[8] Following implementation, combination inhaler use declined by 45% and inhaled corticosteroid use rose by 6%.[9] The objective of this study was to determine if the PA policy targeting combination inhalers increased short term emergency department or hospital utilization.

METHODS

The Oregon Medicaid fee-for-service program implemented a PA requirement on January 1, 2011. The combination inhaler products affected were all orally inhaled forms of fluticasone/salmeterol, budesonide/formoterol and mometasone/formoterol. PA approval required a trial of inhaled corticosteroid monotherapy or evidence of severe asthma or trial of both an anticholinergic and long-acting beta-agonist inhaler for COPD patients. The policy “grandfathered” (automatically approved payment) all patients with a prior paid claim for a combination inhaler within the previous 90 days, so as not to disrupt current therapy.

This analysis included patients enrolled in the Oregon Medicaid fee-for-service program between January 1, 2010 and August 30, 2011 and that had a minimum of three months continuous Medicaid enrollment before and after an index event. For the

study group, the index event was the earliest date the patient had a combination inhaler claim denied with a message of "PA required" between January 1, 2011 and August 30, 2011. A historical control group was constructed with patients who had a paid combination inhaler claim (the index event) between January 1, 2010 and August 30, 2010, and therefore were not affected by the PA policy. Analogous to the study group grandfathering, control patients were excluded if they had a combination inhaler paid claim in the 90 days prior to their index event.

To ensure the study groups were independent, patients in the study group (2011) were excluded if they had a combination inhaler claim in 2010. To maintain comparability, patients in the control group (2010) were excluded if they had a combination inhaler claim in 2009. Patients were excluded if their demographic data (e.g. age, sex or ethnicity) were not available, they were less than 5 or greater than 64 years old at the time of the index event or if they had dual Medicare eligibility. The asthma treatment guidelines[7] are more clearly defined for patients 5-64 years and Medicare drug claims were not included in the administrative data.

The primary outcome was a composite of an emergency department or hospital claim with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code for asthma or COPD in the primary diagnosis field within 60 days of the index event. The 60 day interval was selected because in comparative studies of combination inhaler medications, time to first exacerbation survival curves typically separate within 60 days.[10,11] The analyses were repeated using a 30 day and 90 day post index event assessment window. The component outcomes also were evaluated individually. The frequency of oral corticosteroid prescriptions during the same period (excluding the day of index event) were examined because it is recommended treatment for acute asthma and COPD exacerbations.[4,7] Finally, the frequency of all-cause emergency department encounters, hospitalizations, or death in the 60 days following an index event was evaluated.

Administrative data in the year before the index event were used to characterize baseline patient demographics and severity of illness. First, patients were classified with respect to the presence of an ICD-9-CM code for asthma (493xx), COPD (491.2x, 492, 492.0, 492.8, 496, 506.4, 518.1, 518.2), both asthma and COPD, and neither asthma or COPD. Asthma and COPD controller and rescue medication use in the 90 days prior to the index event was also characterized (see Appendix A which identifies and classifies the drugs used). As in indicator of severity of illness, the asthma- or COPD-related emergency department encounters and hospitalizations in the year prior to the index event were quantified.[4,7] Asthma disease severity was also assessed using the Healthcare Effectiveness Data Information Set (HEDIS) persistent asthma indicator, a validated measure using pharmacy, medical and hospital claims, from the year prior to the index date.[12] In addition, a ratio of 0.5 (or lower) asthma controller medication claims to total asthma medication claims (controller and rescue) is

associated with a higher risk of using acute asthma services.[13,14,15] Finally, a combined disease severity variable, that included any of the previously mentioned metrics, was created to provide the greatest sensitivity to severe respiratory disease.

Patients in the study group were followed longitudinally to assess if a PA was requested by their prescriber, and the ultimate disposition of any PA requested. Patient demographics, disease severity, and subsequent drug therapy were then characterized by final PA disposition (i.e. not requested, requested and approved or requested and denied).

For, the primary analysis, multivariate logistic regression models were used to adjust for any imbalance in key baseline prognostic variables. The following baseline covariates were explored during the modeling process: age, sex, race, COPD or asthma diagnosis, HEDIS persistent asthma indicator, baseline respiratory controller medication use, baseline emergency department use, baseline hospital utilization and baseline asthma rescue inhaler use. Covariates were selected for inclusion in the final regression models based on a backwards selection process with a p-value set at 0.05. Both unadjusted and adjusted odds ratio (OR) were generated reflecting the relative increase in odds of the modeled outcome (i.e. emergency department visit or hospitalization). The same covariates were used for individual components of composite primary outcome as well as sensitivity analyses at 30 and 90 days. Statistical analyses were conducted with Stata V13 (Stata Corp. College Station, TX).

RESULTS

There were 794 patients with index events for the study group and 662 patients identified with index events for the control group. After excluding patients less than 5 and greater than 64 years old (study n=8, control n=4), those covered by Medicare (study n= 11, control n=18), those with combination inhaler claims in the prior year (study n=324, control n=139), and those without continuous eligibility (study n=154, control n= 150) the final study group was 297 patients and the control group was 351patients.

Table 1 displays the baseline characteristics of the groups. Demographics and baseline diagnostic groups were very similar. The HEDIS persistent asthma indicator, prior emergency department encounters and prior drug use were also similar between groups. However, the controller ratio and prior hospital encounters indicated lower disease severity in the study group.

TABLE 1 – BASELINE CHARACTERISTICS

	Study Group[a] (n=297)	Control Group[b] (n=351)
Demographics	*No. (%)*[c]	*No. (%)*[c]
Mean Age (min-max)	36 (5-64)	36 (5-64)
Age >= 19	224 (75)	250 (71)
Female	192 (65)	223 (64)
Non-White	54 (18)	61 (17)
Diagnostic Group	*No. (%)*	*No. (%)*
Asthma (no COPD[d])	155 (52)	183 (52)
Asthma + COPD	31 (10)	45 (13)
COPD (no Asthma)	46 (15)	54 (15)
No Asthma & No COPD	65 (22)	69 (20)
Disease Severity 1 year prior[e]	*No. (%)*	*No. (%)*
HEDIS[f] Persistent Asthma	62 (21)	82 (23)
Asthma Controller Ratio <0.5	104 (35)	182 (52)
Asthma or COPD Emergency Department Encounter	38 (13)	51 (15)
Asthma or COPD Hospitalization	5 (2)	18 (5)
Any of the Above	141 (47)	210 (60)
Drug Therapy at Index Event (includes 90 days prior) [e]	*No. (%)*	*No. (%)*
Asthma or COPD Controller	84 (28)	95 (27)
Short-Acting Beta-Agonist	138 (46)	162 (46)

[a]*Study Group = Prior authorization required for combination inhaler*
[b]*Control Group = No prior authorization required for combination inhaler*
[c]*Data presented as No. (%) unless otherwise noted*
[d]*COPD = Chronic Obstructive Pulmonary Disease*
[e] *Categories not mutually exclusive*
[f]*HEDIS = Healthcare Effectiveness Data and Information Set*

Table 2 displays the results of primary and secondary outcomes. There were 31 primary outcome events during the 60 day follow-up period, 17 (5.7%) in the study group and 14 (4.0%) in the control group (OR 1.46, 95% confidence interval [CI] 0.71 to 3.02). After statistical adjustment, the OR increased to 2.26 (95% CI 1.01 to 5.06). This was driven primarily by increased odds of emergency department encounters. The adjusted odds of oral corticosteroid use were also 1.81 times higher (95% CI 1.19 to 2.69) in the study group relative to the control group. The secondary safety composite outcome of all cause hospitalization, emergency department encounter or death was similar in both groups. There were no deaths recorded. Results assessed at 30 and 90 days were similar with overlapping confidence intervals (see Appendix 2 that displays these data).

TABLE 2 - PRIMARY AND SECONDARY OUTCOMES 60 DAYS AFTER STUDY ENTRY

	Study Group[a] (n=297)	Control Group[b] (n=351)		
	No. (%)	No. (%)	OR (95% CI[c])	Adjusted[e] OR (95% CI)
Composite Asthma or COPD[d] Emergency Department or Hospital Encounter	17 (5.7)	14 (4.0)	1.46 (0.71 – 3.02)	2.26 (1.01 – 5.06)
Asthma or COPD Emergency Department Encounter	17 (5.7)	12 (3.4)	1.72 (0.81 – 3.65)	2.76 (1.19 – 6.42)
Asthma or COPD Hospital Encounter	4 (1.3)	3 (0.9)	1.58 (0.81 – 3.65)	2.18 (0.43 – 11.21)
All Cause Hospital or Emergency Department or Death	61 (20.5)	74 (21.1)	0.97 (0.66 – 1.42)	0.98 (0.66 – 1.46)
Oral Corticosteroid	42 (14.1)	33 (9.4)	1.59 (0.977 – 2.58)	2.62 (1.54 – 4.45)

[a]*Control Group = No prior authorization required for combination inhaler*
[b]*Study Group = Prior authorization required for combination inhaler*
[c]*CI = Confidence Intervals*
[d]*COPD = Chronic Obstructive Pulmonary Disease*
[e] *Model adjusted for age less than 18, HEDIS Persistent Asthma, Controller Use and Hospitalization at baseline*

Table 3 explores the correlation of drug therapy at 60 days and disease characteristics for patients in the policy group overall and displayed by whether or not a PA was requested by the prescriber on outcomes. Of the 297 study patients affected by the PA requirement, 83 (28%) requested a PA within 14 days and all 83 were approved. Asthma was more prevalent in patients with a PA request than those without (74% versus 59%) and COPD was less prevalent (17% versus 30%). Those with a PA request also appeared to have higher disease severity. The most notable disease severity differences were in the HEDIS persistent asthma indicator (34% versus 16%), prior asthma or COPD hospitalizations (4% versus 1%) and prior controller drug use (48% versus 21%). Of the 83 patients with an approved PA, 65 (78%) had a paid claim for a combination inhaler at 60 days and 9 (11%) had a claim for another controller. There were 214 (72%) patients that did not have a PA request submitted within 14 days of the index event and of these 100 (47%) had a controller medication prescribed at 60 days. Thirty patients without a PA request received a combination inhaler at 60 days either by subsequently enrolling in a Medicaid managed care plan (n=13) or by requesting a PA after 14 days (n=17). Of the remaining 84 patients without a PA request, 52 received a short-acting beta-agonist only and 32 had no paid respiratory drug claims. The incidence of the primary outcome in these subgroups followed disease severity and combination inhaler drug use: 8% of those requesting a PA, 5% of those not requesting a PA. Notably, the rate of all cause hospitalization, emergency department encounters or death was higher for the patients not requesting PA versus those that did (22% versus 16%).

TABLE 3 – ANALYSIS OF STUDY GROUP BY PRIOR AUTHORIZATION REQUEST SUB-GROUP

Study Group[a] (n=297)	Prior Authorization Requested within 14 days (n=83)	No Prior Authorization Requested within 14 days (n=214)
Outcomes at 60 days	*No. (%)*	*No. (%)*
Composite of Asthma or COPD[b] Emergency Department or Hospital Encounter	7 (8)	10 (5)
Asthma or COPD Emergency Department Encounter	7 (8)	10 (5)
Asthma or COPD Hospital Encounter	2 (2)	2 (1)
All Cause Hospital or Emergency Department or Death	13 (16)	48 (22)
Oral Corticosteroid	11 (13)	31 (14)
Drug Use at 60 days	*No. (%)*	*No. (%)*
Combination inhaler	65 (78)	30 (14)
Asthma / COPD Controller	9 (11)	100 (47)
Short-Acting Beta-Agonist only	5 (6)	52 (24)
None of the Above	4 (5)	32 (15)
Diagnostic Group	*No. (%)*	*No. (%)*
Asthma (no COPD)	53 (64)	102 (48)
Asthma + COPD	8 (10)	23 (11)
COPD (no Asthma)	6 (7)	40 (19)
No Asthma & No COPD	16 (19)	49 (23)
Disease Severity 1 year prior [c]	*No. (%)*	*No. (%)*
HEDIS[d] Persistent Asthma	28 (34)	34 (16)
Asthma Controller Ratio <0.5	32 (39)	72 (34)
Asthma / COPD ED	10 (12)	28 (13)
Asthma / COPD Hospital	3 (4)	2 (1)
Any of the Above	49 (59)	92 (43)
Drug Therapy at Index Event (includes 90 days prior [c]	*No. (%)*	*No. (%)*
Asthma / COPD Controller	40 (48)	44 (21)
Short-Acting Beta-Agonist	47 (57)	91 (43)

[a]Study Group = Prior authorization required for combination inhaler
[b]COPD = Chronic Obstructive Pulmonary Disease
[c] Categories not mutually exclusive
[d]HEDIS = Healthcare Effectiveness Data and Information Set

DISCUSSION

In this analysis, patients encountering the PA requirement had 2.26 higher adjusted odds of the primary outcome compared to a historical control group from the previous year. The increased odds of an oral corticosteroid prescription following exposure to the PA policy also suggest an elevated risk for an exacerbation. However, rates of all cause hospitalization, emergency department encounters or death were similar in both groups.

Study group patients whose prescribers requested a PA were more likely to have indicators of severe asthma, suggesting the PA policy was effective at restricting use consistent with the FDA recommendation. Although this study found encountering a PA requirement increased the odds for the primary outcome, it is unclear if the PA caused the increase.

A striking finding was that less than a third of patients encountering a PA requirement subsequently had a PA requested. That is, for a majority of cases no attempt was made by the prescriber to submit a PA request. It is difficult to infer causality between no PA request and subsequent adverse outcomes because having a PA request submitted was associated with increasing disease severity. Despite this limitation, rates of the primary outcome were, in fact, lower in the group of patients who had no PA request (5% versus 8%), although the absolute numbers were small.

The study is unavoidably limited by a small sample size as a result of the policy applying only to newly started patients. New combination inhaler patients represented 37% all combination inhaler patients in 2011 and 22% in 2010. Additionally, the policy was limited to the fee-for-service program which represented just 16% of Oregon Medicaid patients in 2011 and 18% in 2010.

There were a small absolute number of outcome events (31) and it used a historical control. Therefore, the results are potentially sensitive to background changes in prescribing patterns occurring from 2010 to 2011. Although the study periods for the study group and control group were identical, there were 54 fewer patients in the study group. This may reflect a decline in prescribing following the FDA 2010 safety announcements about long-acting beta-agonist use. The number of combination inhaler index events continued to trend downward throughout the study period. Given the nature of the FDA announcement, it was expected prescribers would reserve combination inhalers for patients with more severe disease in the study group. This is supported by the observation that the control group was less severely ill according to several disease severity indicators. In order to maintain adequate sample sizes continuous eligibility was not required beyond the 90 days before and after the index event. Consequently, there may be missing disease severity information and residual confounding may still exist. A frequency plot of index events found them evenly distributed seasonally with a continuous downward trend. However, there was still potential for differences in the control and study groups due to differences in the

availability of promotional drug samples, differences in prescriber access and differences in environmental factors such as forest fires, allergens and circulating viruses from one season to the next.

The combination inhaler PA policy appeared successful at limiting use to patients with moderate to severe asthma or to those not controlled with inhaled corticosteroid monotherapy. The policy was associated with an increased adjusted odds of 2.26 (95% CI 1.19 to 5.08) of emergency department or hospital encounters. The automated PA process was modified to electronically approve for patients with prior claims evidence of asthma (9/1/2011) or COPD (9/28/2012) within 102 days of the PA. However, further policy adjustments may be necessary.

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Appendix 1 – DRUG CLASSIFICATION TABLE

Study Group	Generic Name	Route Code	Asthma Controller	COPD Controller	HEDIS Indicator
ANTICHOL	TIOTROPIUM BROMIDE	IH	0	1	0
ANTICHOL	IPRATROPIUM BROMIDE	IH	0	1	0
ANTICHOL	IPRATROPIUM/ALBUTEROL SULFATE	IH	0	1	0
ComboProducts	GUAIFENESIN/THEOPHYLLINE	PO	0	0	1
ComboProducts	AMINOPHYLLIN/EPHED/POT IOD/PB	PO	0	0	1
ComboProducts	EPHEDRINE SULFATE/GUAIFENESIN	PO	0	0	1
ComboProducts	EPHEDRINE/POTASSIUM IODIDE	PO	0	0	1
ComboProducts	GUAIFEN/AMINOPHYLLIN/EPHED/PB	PO	0	0	1
ComboProducts	GUAIFEN/DYPHYLLINE/P-EPHEDRINE	PO	0	0	1
ComboProducts	GUAIFEN/THEOP ANHYD/P-EPHED	PO	0	0	1
ComboProducts	GUAIFEN/THEOPHYLL/EPHED/PB	PO	0	0	1
ComboProducts	GUAIFENESIN/DYPHYLLINE	PO	0	0	1
ComboProducts	GUAIFENESIN/THEOP SOD GLY	PO	0	0	1
ComboProducts	ISOPROTERENOL/CALCIUM IODIDE	PO	0	0	1
ComboProducts	GUAIFENESIN/OXTRIPHYLLINE	PO	0	0	1
ICS	MOMETASONE FUROATE	IH	1	0	1
ICS	FLUTICASONE PROPIONATE	IH	1	0	1
ICS	FLUNISOLIDE/MENTHOL	IH	1	0	1
ICS	FLUNISOLIDE	IH	1	0	1
ICS	TRIAMCINOLONE ACETONIDE	IH	1	0	1
ICS	CICLESONIDE	IH	1	0	1
ICS	BUDESONIDE	IH	1	0	1
ICS	BECLOMETHASONE DIPROPIONATE	IH	1	0	1
ICS	DEXAMETHASONE SOD PHOSPHATE	IH	1	0	1
ICSLABA	FLUTICASONE/SALMETEROL	IH	0	0	1
ICSLABA	MOMETASONE/FORMOTEROL	IH	0	0	1
ICSLABA	BUDESONIDE/ FORMOTEROL FUMARATE	IH	0	0	1
IgE	OMALIZUMAB	SQ	1	0	1
LABA	SALMETEROL XINAFOATE	IH	1	1	1
LABA	ARFORMOTEROL TARTRATE	IH	1	1	1
LABA	FORMOTEROL FUMARATE	IH	1	1	1
LABA	INDACATEROL MALEATE	IH	0	1	1
leukotriene	ZILEUTON	PO	1	0	1
leukotriene	MONTELUKAST SODIUM	PO	1	0	1
leukotriene	ZAFIRLUKAST	PO	1	0	1

Policy Evaluation: Combination Inhaler Prior Authorization

Study Group	Generic Name	Route Code	Asthma Controller	COPD Controller	HEDIS Indicator
OralSteroids	PREDNISOLONE ACETATE	PO	0	0	0
OralSteroids	CORTISONE ACETATE	PO	0	0	0
OralSteroids	METHYLPREDNISOLONE	PO	0	0	0
OralSteroids	BUDESONIDE	PO	0	0	0
OralSteroids	BETAMETHASONE	PO	0	0	0
OralSteroids	PREDNISOLONE SOD PH/PEAK FLOW	PO	0	0	0
OralSteroids	DEXAMETHASONE	PO	0	0	0
OralSteroids	PREDNISOLONE SOD PHOSPHATE	PO	0	0	0
OralSteroids	TRIAMCINOLONE	PO	0	0	0
OralSteroids	PREDNISONE	PO	0	0	0
OralSteroids	ADRENAL CORTEX (PORCINE)	PO	0	0	0
OralSteroids	HYDROCORTISONE	PO	0	0	0
OralSteroids	HYDROCORTISONE CYPIONATE	PO	0	0	0
OralSteroids	PREDNISOLONE	PO	0	0	0
PDE4I	ROFLUMILAST	PO	0	1	0
SABA	PIRBUTEROL ACETATE	IH	0	0	0
SABA	ALBUTEROL SULFATE	IH	0	0	0
SABA	BITOLTEROL MESYLATE	IH	0	0	0
SABA	ALBUTEROL	IH	0	0	0
SABA	LEVALBUTEROL HCL	IH	0	0	0
SABA	RACEPINEPHRINE HCL	IH	0	0	0
SABA	TERBUTALINE SULFATE	IH	0	0	0
SABA	ISOPROTERENOL HCL	IH	0	0	0
SABA	METAPROTERENOL SULFATE	IH	0	0	0
SABA	EPINEPHRINE BITARTRATE	IH	0	0	0
SABA	EPINEPHRINE	IH	0	0	0
SABA	LEVALBUTEROL TARTRATE	IH	0	0	0
SABA	ISOPROT HCL/PHENYLEPHRINE	IH	0	0	0
THEOPHYLLINE	OXTRIPHYLLINE	PO	1	0	1
THEOPHYLLINE	DYPHYLLINE	PO	1	0	1
THEOPHYLLINE	AMINOPHYLLINE	PO	1	0	1
THEOPHYLLINE	AMINOPHYLLINE	IV	1	0	1
THEOPHYLLINE	THEOPHYLLINE ANHYDROUS	PO	1	0	1
THEOPHYLLINE	THEOPHYLLINE/DEXTROSE 5%-WATER	IV	1	0	1
THEOPHYLLINE	DYPHYLLINE	IM	1	0	1

Appendix 2 – OUTCOMES AT 30-DAYS AND AT 90-DAYS

	Study Group[a] (n=297)	**Control Group[b] (n=351)**		
	No. (%)	No. (%)	OR (95% CI[c])	Adjusted[d] OR (95% CI)
30 Days After Study Entry				
Composite Asthma or COPD[e] Emergency Department or Hospital Encounter	14 (4.7)	7 (2.0)	2.43 (0.97 – 6.11)	4.17 (1.48 – 11.79)
Asthma or COPD Emergency Department Encounter	14 (4.7)	6 (1.7)	2.84 (1.08 – 7.50)	4.69 (1.61 – 13.64)
Asthma or COPD Hospital Encounter	3 (1.0)	1 (0.3)	3.57 (0.37 – 34.52)	4.90 (0.43 – 56.27)
All Cause Hospital or Emergency Department or Death	38 (12.8)	50 (14.2)	0.88 (0.56 – 1.39)	0.88 (0.55 – 1.40)
Oral Corticosteroid	29 (9.8)	16 (4.6)	2.27 (1.21 – 4.26)	3.41 (1.69 – 6.88)
90 Days After Study Entry				
Composite Asthma or COPD Emergency Department or Hospital Encounter	21 (7.1)	15 (4.3)	1.70 (0.86 – 3.37)	2.57 (1.20 – 5.49)
Asthma or COPD Emergency Department Encounter	21 (7.1)	13 (3.7)	1.98 (0.97 – 4.02)	3.08 (1.40 – 6.78)
Asthma or COPD Hospital Encounter	4 (1.3)	3 (0.9)	1.58 (0.34 – 7.13)	2.18 (0.43 – 11.21)
All Cause Hospital or Emergency Department or Death	78 (26.3)	94 (26.8)	0.97 (0.69 – 1.38)	0.97 (0.67 – 1.40)
Oral Corticosteroid	52 (17.5)	49 (14.0)	1.31 (0.86 – 2.00)	1.54 (0.98 – 2.42)

[a] *Control Group = No prior authorization required for combination inhaler*
[b] *Study Group = Prior authorization required for combination inhaler*
[c] *CI = Confidence Intervals*
[d] *Model adjusted for age less than 18, HEDIS Persistent Asthma, Controller Use and Hospitalization at baseline*
[e] *COPD = Chronic Obstructive Pulmonary Disease*

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:

6-12 months

Requires PA:

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

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Step Therapy Required Prior to Coverage:

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

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

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to #2.	**No:** Go to #4.
2. Is the medication for Breo Ellipta™ (fluticasone furoate / vilanterol)?	**Yes:** Pass to RPH; Deny for medical appropriateness.	**No:** Go to #3.

Approval Criteria		
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 (e.g. Fev1 >60% but <80% with some reduction in FEV1/FVC) OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 365~~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).
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.

P&T / DUR Action: *11/20/14, 11/21/13, 5/31/12, 9/24/09 (DO/KK), 2/23/06*
Revision(s): *??, 1/1/14, 9/26/12, 1/1/10*

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Oregon Health Authority

Quality Improvement Proposal: Combination Inhaler Policy

In January 2011, the Oregon Medicaid fee-for-service (FFS) program implemented a prior authorization (PA)[1] for the use of combination inhalers (Appendix 1). A meta-analysis showing an increase in asthma exacerbations with combination inhaler treatment compared to inhaled corticosteroids (ICS) alone (OR 3.65 95% CI 1.39-9.55).[2] The PA was designed to promote appropriate use of asthma controllers according to the most recent evidence-based guidelines.[3,4]

A recent policy evaluation found that those patients who encountered a PA requirement had an increased adjusted odds of experiencing either an emergency department or hospital claim for asthma or COPD within 60 days versus those who did not experience the PA (OR 2.26 95% CI 1.01 - 5.0).[5] Patients with providers requesting the PA had higher asthma disease severity indicating that the purpose of the PA was successful. But, a concerning finding was that less than a third of patients with claims requiring a PA had one requested by a provider.

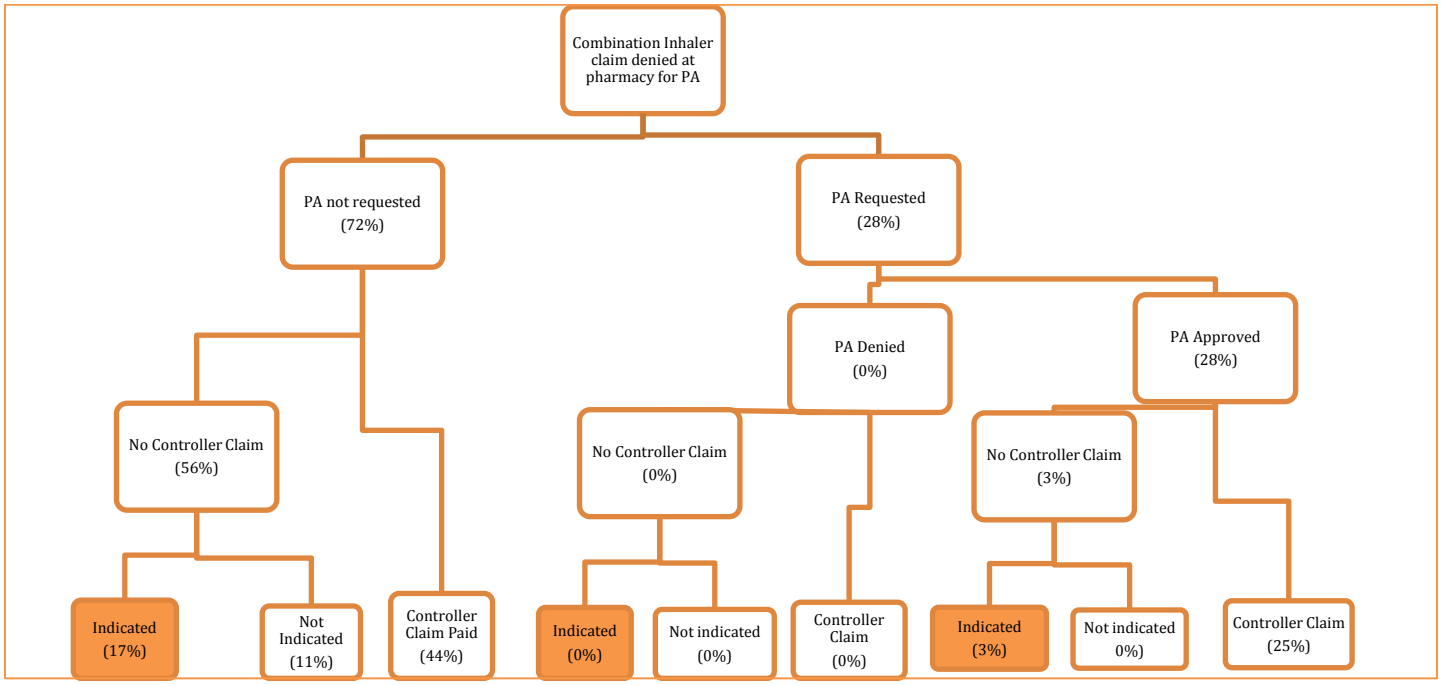
As a result of these findings, this quality improvement project was initiated. The primary objective of this project was to target patients at greatest risk for an adverse outcome associated with the PA policy and develop interventions to prevent them.

Methods:
A schematic was developed using the data from the previous evaluation to identify, categorize and quantify the patients likely at increased risk for adverse outcomes (Figure 1).[2] Patients considered at most risk were those without any paid controller claim within 60 days when it was indicated and despite the PA status. Patients were classified as "indicated" if they had any of the "Disease Severity Indicators" in the year prior to the index PA event in the previous evaluation. Approximately 20% of patients encountering the PA met the "indicated" criteria and did not have a paid controller claim.

Patients were selected for intervention immediately following the claim load into the database each week on Tuesdays and using criteria approximating the "indicated" definitions. Patients were included if they had a *denied* FFS combination inhaler claim within 17-24 days prior with Explanation of Benefit (EOB) code equal to "1056-Prior Authorization Required. " They were excluded if they carried a concurrent EOB of "2017 - Patient enrolled in MCO." EOB 2017 indicated the patient was enrolled in a Medicaid managed care organization (i.e. Coordinated Care Organization) and the claim was submitted to the wrong payer. Patients were excluded if they had a paid FFS or encounter claim for combination inhaler or alternative controller within 14 days after the denied claim. These patients do not need intervention. Patients were also excluded if they had no paid FFS or encounter claim for a short-acting beta-agonist and no prior claims with diagnosis codes for asthma (493.xx), COPD (491.2x, 492, 492.0, 492.8, 496, 506.4, 518.1, 518.2) or any controller medication within the

last 6 months, as it was assumed this indicated less severe disease and no need for intervention (See Table 1). Drugs were identified and classified using the criteria in Appendix 1.

Figure 1 – Schematic of patient disposition at 60 days from policy evaluation



The medical and pharmacy claim profiles of the intervention patients were then manually reviewed by a fourth year Doctor of Pharmacy student each week from June 14 thru July 4, 2014 to determine the accuracy of the selection criteria and assess what types of interventions could be made. The profiles included claims with service dates starting January 1, 2013 thru the present. Patients were placed in one of four categories and computer generated flags were created and manually checked during the reviews (Table 1). The four categories were: 1) Patients with COPD defined as paid FFS or encounter claim in prior 12 months with diagnosis codes 491.2x, 492, 492.0, 492.8, 496, 506.4, 518.1 or 518.2 or a paid FFS or encounter claim for anticholinergic inhaler or phosphodiesterase type 4 inhibitor , 2) Patients with asthma defined as paid FFS or encounter claim in prior 6 months with diagnosis code 493xx or a paid FFS or encounter claim for combination inhaler, inhaled corticosteroid , or leukotriene antagonist , 3) Patients with no FFS or encounter short-acting beta-agonist or controller claims and no medical claims with asthma or COPD diagnosis codes in prior 6 months or 4) Patients with only short-acting beta-agonist claims.

Data were collected from the manual reviews to determine workload and to direct implementation plans. Adjustments to the automated PA policy were made to approve patients at highest risk of adverse outcome (i.e. those with prior claims evidence COPD and moderate severity asthma). These changes were implemented on September 1, 2014. The far right column of Table 1 demonstrates the impact of that change.

An evaluation of the literature identified potential interventions to improve prescribing practices. Other Medicaid programs had success with retrospective letters mailed to physicians or letters targeting both physicians and pharmacists.[6] North Carolina Medicaid used a streamlined PA approval process to prompt

prescribing of preferred proton pump inhibitors and to reduce burden to both pharmacist and physicians seen with the traditional PA process.[7] The process allowed prescribers to document patient-specific approval criteria on a pre-printed prescription form. Both physicians and pharmacists reported a decrease in time required per patient with the streamlined program versus the traditional PA program and both preferred the streamlined PA method.[1] It was also successful at changing prescribing practice. The North Carolina model was adapted for the intervention patient in this project.

Results:

Analysis of the patients identified and reviewed each week revealed that only 32% of patients that experienced the PA had a combination inhaler or alternative controller within 14days (Table 1). This was significantly fewer than at 60 days in the prior evaluation (i.e. 69% from Figure 1). Of the remaining patients who did not get any controller within 14 days (68%), 22% probably were not appropriate for asthma controller therapy as there were no prior claims with asthma or COPD diagnoses and no prior claims for short-acting beta agonists or other controllers. Approximately 10% had prior claims evidence of a COPD diagnosis. Since the safety warnings for long-acting beta agonists do not apply to COPD treatment,the existing automatic PA criteria were modified to better identify these patients. Approximately 24% of patients had prior claims evidence of asthma with or without prior controller use. The existing automatic PA criteria were also modified to better identify these patients for automatic approval at the pharmacy. The remaining 12%, approximately 8 patients per week, with only a history of short-acting beta-agonist were targeted for retrospective review and intervention.

A proposed retrospective intervention was created and called the “Patient Safety Notice: Combination Inhaler” form (Appendix 2). It will be sent to prescribers auto-populated with patient information and prompting use of inhaled corticosteroid over combination inhalers. Prescribers will either return the form to the pharmacy or E-prescribe a new prescription for a preferred inhaled corticosteroid or, they will return fax the form, with exemption criteria documented by the physician, to the Medicaid PA desk where a PA will be approved and the pharmacy notified. This process was adapted from the North Carolina “MD Easy” form which was a pre-populated form that gave providers a choice of three options including: 1) switch to a preferred agent, 2) indicate patient exemption criteria for preferred agent, or 3) utilize the traditional PA process. They would select their preferred option and send the form back to the pharmacy. In the case of North Carolina, the pharmacy was provided a PA override code if appropriate documentation was obtained from the prescriber requesting the need for a non-preferred agent. In contrast, Oregon will not provide the pharmacy with the override code but instruct the providers to fax the form back to the PA desk if a combination inhaler is indicated for PA approval.

Table 1: Patient Selection and Categorization Summary

Patient Selection Flow	6/14/2014 n=	6/21/2014 n=	6/28/2014 n=	Total for all Weeks in June n=		8/30/2014 (after AutoPA adjustment) n=
1) Included patients with denied FFS combination inhaler claim with EOB 1056 – PA Required	102	83	70	255		33
2) Excluded patients with EOB 2017 (this indicates the patient was enrolled in a CCO at the time so the pharmacy billed the wrong insurance)	42	34	24	100		16
3) #1 - #2 = Patients who were affected by the PA policy	60	49	46	155	100%	17
4) Excluded patients with paid claim for combination inhaler or alternative controller within 14 days (no intervention needed)	23	14	13	50	32%	9
5) #3 - #4 = Patients affected by PA policy with no controller therapy	37	35	33	105	68%	8
Patient Categories						
1) Patients with no FFS or MCO short-acting beta-agonist claim, or select medical claims, in prior 6 months (patients that don't need intervention)	10	15	9	34	22%	3
2) Patients with COPD (patients that should be coded for auto-approval)	4	3	8	15	10%	0
3) Patients with prior claims evidence of asthma (patients that should be coded for auto-approval)	14	13	10	37	24%	0
4) Patients with only short-acting beta-agonists (intervention patients)	9	4	6	19	12%	5

Discussion:

This report describes a quality improvement process to address the increased OR of adverse outcomes observed in patients encountering a PA requirement for combination inhalers. Patients were candidates for intervention if they encountered the PA and were not prescribed an alternate controller agent. These patients were determined to be at greatest need of intervention because their asthma was likely poorly controlled which potentially prompted initial prescribing of a combination inhaler. Because these patients did not have a paid claim for a combination inhaler or an alternate controller, their risk of exacerbation or hospitalization is likely greater and warrants intervention. Only 32% of patients were found to have been prescribed any controller agent 17-24 days after encountering the PA.

Approximately 22% of the patients analyzed did not appear to be candidates for combination inhaler therapy. This was determined because their claims data did not have a diagnosis code for asthma, COPD or history of short-acting beta-agonist use. This would indicate that they are likely experiencing less severe symptoms and appropriate initial therapy based on guideline recommendations would include short-acting beta-agonist for as needed use and potentially an inhaled corticosteroid, first line, if symptoms were considered moderate

persistent. It was also noted, there were a small number of patients whose claims history indicated COPD (10%) or asthma (24%) which, based on the PA electronic approval criteria, should have warranted automatic approval. It was discovered that the electronic approval process did not look back far enough to identify COPD and asthma claim history. With this information, adjustment of the approval criteria was indicated and implemented.

The remaining 12% of patients analyzed are those in need of targeted intervention. These patients had a diagnosis of asthma and had previously been prescribed a short-acting beta-agonist. They encountered the PA but were not provided an alternate controller agent.

Recommendation:

1) Implement a weekly review of patients encountering the combination inhaler PA and that meet the criteria established above for intervention. Send prescribers the Patient Safety Notice: Combination Inhaler (Appendix 2) to insure patients a controller, if indicated.

References:

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2. Salpeter SR, Wall AJ, Buckley NS. Long-acting Beta-Agonists with and without Inhaled Corticosteroids and Catastrophic Asthma Events. *Am. J. Med.* 2010;123(4):322-328.e2. doi:10.1016/j.amjmed.2009.07.035.

3. US Department of Health and Human Services, National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma; 2007. *US Dep. Health Hum. Serv. Natl. Heart Lung Blood Inst.* 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed May 23, 2012.

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5. Ketchum KL. Policy Evaluation: Prior authorization of combination inhalers for asthma. 2014.

6. Ho M-J, Venci J. Improving the success of mailed letter intervention programs to influence prescribing behaviors: a review. *J. Manag. Care Pharm. JMCP* 2012;18(8):627–649. http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15780. Accessed September 30, 2014.

7. Vann JCJ, Christofferson S, Humble CG, Wegner SE, Feaganes JR, Trygstad TK. Pharmacist and physician satisfaction and rates of switching to preferred medications associated with an instant prior authorization program for proton pump inhibitors in the North Carolina Medicaid program. *J Manag Care Pharm* 2010;16(4):250–63.

Appendix 1 – Drug identification and classification specifications

Combination Inhalers

HSN	Route Desc	Generic
019963	INHALATION	FLUTICASONE/SALMETEROL
021993	INHALATION	BUDESONIDE/FORMOTEROL FUMARATE
037050	INHALATION	MOMETASONE/FORMOTEROL
040319	INHALATION	FLUTICASONE/VILANTEROL

Alternative controllers:

Group	HSN	Route Desc	Generic
ANTICHOLINERGIC	000057	INHALATION	IPRATROPIUM BROMIDE
ICS	000070	INHALATION	BECLOMETHASONE DIPROPIONATE
ICS	000072	INHALATION	FLUNISOLIDE
ICS	003329	INHALATION	MOMETASONE FUROATE
ICS	006545	INHALATION	BUDESONIDE
LABA	007393	INHALATION	SALMETEROL XINAFOATE
ICS	007873	INHALATION	FLUTICASONE PROPIONATE
ANTICHOLINERGIC	009040	INHALATION	IPRATROPIUM/ALBUTEROL SULFATE
LABA	010747	INHALATION	FORMOTEROL FUMARATE
ANTICHOLINERGIC	024024	INHALATION	TIOTROPIUM BROMIDE
ICS	032691	INHALATION	CICLESONIDE
LABA	034087	INHALATION	ARFORMOTEROL TARTRATE
LABA	037011	INHALATION	INDACATEROL MALEATE
P4I	037123	ORAL	ROFLUMILAST
ANTICHOLINERGIC	039528	INHALATION	ACLIDINIUM BROMIDE
LTA	012321	ORAL	ZILEUTON
LTA	016911	ORAL	MONTELUKAST SODIUM
LTA	011815	ORAL	ZAFIRLUKAST

Short-Acting beta-agonists:

HSN	RouteDesc	Generic
019858	INHALATION	LEVALBUTEROL HCL
002058	INHALATION	METAPROTERENOL SULFATE
002073	INHALATION	ALBUTEROL SULFATE
002075	INHALATION	BITOLTEROL MESYLATE
002076	INHALATION	PIRBUTEROL ACETATE
032814	INHALATION	LEVALBUTEROL TARTRATE

Appendix 2 – Form

Patient Safety Notice: Combination Inhaler

This notice was generated by Oregon Medicaid because your NPI was linked to a denied combination inhaler claim for this patient AND no prior authorization was requested and no alternate controller was filled. For questions call: (888) 202-2126

- Current evidence and the National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma indicate patients with moderately severe asthma that need of controller therapy should be initiated on an inhaled corticosteroid first line. Use of low to medium dose an inhaled corticosteroid is recommended prior to use of combination inhalers of a long acting beta agonist with an inhaled corticosteroid.
- A Food and Drug Administration public health advisory recommending that long-acting beta-agonists be used only for those who remain symptomatic on other asthma controller medications and for the shortest possible duration.

Prescriber Information

Prescriber Name:	
[PRESCRIBER NAME]	
Prescriber Phone:	Prescriber Fax:
[PRESCRIBER PHONE]	[PRESCRIBER FAX]

Patient Information

Patient Name:	Patient DOB:	Patient Medicaid Number:
[PATIENT NAME]	[PATIENT DOB]	[MEMBER ID]

Medication Denial

Requested Medication:	Denial Date:
[Drug Name] [Drug Strength] [Drug Dose] [Day Supply]	[PRESCRIPTION DATE]

Select one of the following two options:

Switch the patient to a preferred inhaled corticosteroid:

- Beclomethasone (Qvar™):40mcg/actuation 1 puff BID
- Beclomethasone (Qvar™):80mcg/actuation 1 puff BID
- Fluticasone (Flovent HFA™): 44mcg /actuation 2 puffs BID
- Fluticasone (Flovent Diskus™) 100mcg/actuation 1 puff BID

To switch to one of the above options, either generate a new ePrescription or complete the faxable prescription on the following page.

Provide information required for approval of [REQUESTED DRUG]

Please check all that apply to this patient:

- ☐ COPD
- ☐ Failure or contraindication to inhaled corticosteroids
- ☐ 2 or more exacerbations requiring oral systemic corticosteroids in the past year
- ☐ Asthma step 3 or higher (2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma)
- ☐ Hospital admission or emergency department visit related to asthma or reactive airway disease in the past 60 days.

If one or more of the above apply, fax this completed form to (888) 346-0178 OR call (888) 202-2126 for immediate authorization of the original prescription.

Prescribers Signature: _____ Date: _____

Prescriber Name : [PRESCRIBER NAME] NPI: [PRESCRIBER NPI]

[CURRENT DATE]

TO:
[PHARMACY NAME]
[PHARMACY ADDRESS]
Telephone: [PHARMACY TELEPHONE]
Fax: [PHARMACY FAX]

FROM:
[PRESCRIBER NAME] NPI: [PRESCRIBER NPI]
[PRESCRIBER ADDRESS]
Telephone: [PRESCRIBER TELEPHONE]
Fax: [PRESCRIBER FAX]

Patient: [Patient Name]
Date of Birth: [Patient DOB]
Medicaid Member ID: [MEMBER ID]
Address: [Patient Address]

Rx

Check one:

- ☐ Beclomethasone (Qvar™): 40mcg/actuation
  Directions: One puff twice daily
  Dispense: One inhaler (120 inhalations)

- ☐ Beclomethasone (Qvar™):80mcg/actuation 1 puff BID
  Directions: One puff twice daily
  Dispense: One inhaler (120 inhalations)

- ☐ Fluticasone (Flovent HFA™): 44mcg /actuation
  Directions: Two puffs twice daily
  Dispense: One inhaler (120 inhalations)

- ☐ Fluticasone (Flovent Diskus™) 100mcg/actuation
  Directions: One puff twice daily
  Dispense: One inhaler (60 blisters)

Refills_____

_____
Physicians Signature

_____

Patient Safety Notice: Combination Inhaler

This notice was generated by Oregon Medicaid because your NPI was linked to a denied combination inhaler claim for this patient AND no prior authorization was requested and no alternate controller was filled. For questions call: (888) 202-2126

- Current evidence and the National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma indicate patients with moderately severe asthma that need of controller therapy should be initiated on an inhaled corticosteroid first line. Use of low to medium dose an inhaled corticosteroid is recommended prior to use of combination inhalers of a long acting beta agonist with an inhaled corticosteroid.
- A Food and Drug Administration public health advisory recommending that long-acting beta-agonists be used only for those who remain symptomatic on other asthma controller medications and for the shortest possible duration.

Prescriber Information

Prescriber Name:	
[PRESCRIBER NAME]	
Prescriber Phone:	Prescriber Fax:
[PRESCRIBER PHONE]	[PRESCRIBER FAX]

Patient Information

Patient Name:	Patient DOB:	Patient Medicaid Number:
[PATIENT NAME]	[PATIENT DOB]	[MEMBER ID]

Medication Denial

Requested Medication:	Denial Date:
[Drug Name] [Drug Strength] [Drug Dose] [Day Supply]	[PRESCRIPTION DATE]

Select one of the following two options:

Switch the patient to a preferred inhaled corticosteroid:

- Beclomethasone (Qvar™):40mcg/actuation 1 puff BID
- Beclomethasone (Qvar™):80mcg/actuation 1 puff BID
- Fluticasone (Flovent HFA™): 44mcg /actuation 2 puffs BID
- Fluticasone (Flovent Diskus™) 100mcg/actuation 1 puff BID

To switch to one of the above options, either generate a new ePrescription or complete the faxable prescription on the following page.

Provide information required for approval of [REQUESTED DRUG]

Please check all that apply to this patient:

- ☐ COPD
- ☐ Failure or contraindication to inhaled corticosteroids
- ☐ 2 or more exacerbations requiring oral systemic corticosteroids in the past year
- ☐ Asthma step 3 or higher (2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma)
- ☐ Hospital admission or emergency department visit related to asthma or reactive airway disease in the past 60 days.

If one or more of the above apply, fax this completed form to (888) 346-0178 OR call (888) 202-2126 for immediate authorization of the original prescription.

Prescribers Signature: _____ Date: _____

Prescriber Name : [PRESCRIBER NAME] NPI: [PRESCRIBER NPI]

[CURRENT DATE]

TO:
[PHARMACY NAME]
[PHARMACY ADDRESS]
Telephone: [PHARMACY TELEPHONE]
Fax: [PHARMACY FAX]

FROM:
[PRESCRIBER NAME] NPI: [PRESCRIBER NPI]
[PRESCRIBER ADDRESS]
Telephone: [PRESCRIBER TELEPHONE]
Fax: [PRESCRIBER FAX]

Patient: [Patient Name]
Date of Birth: [Patient DOB]
Medicaid Member ID: [MEMBER ID]
Address: [Patient Address]

Rx

Check one:

- ☐ Beclomethasone (Qvar™): 40mcg/actuation
  Directions: One puff twice daily
  Dispense: One inhaler (120 inhalations)

- ☐ Beclomethasone (Qvar™):80mcg/actuation 1 puff BID
  Directions: One puff twice daily
  Dispense: One inhaler (120 inhalations)

- ☐ Fluticasone (Flovent HFA™): 44mcg /actuation
  Directions: Two puffs twice daily
  Dispense: One inhaler (120 inhalations)

- ☐ Fluticasone (Flovent Diskus™) 100mcg/actuation
  Directions: One puff twice daily
  Dispense: One inhaler (60 blisters)

- ☐ Other:

Refills_____

_____
Physicians Signature

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 Drugs for Insomnia

Month/Year of Review: November 2014
New drug(s): tasimelteon (Hetlioz™)
suvorexant (Belsomra™)

End date of literature search: August Week 3 2014
Manufacturer: Vanda Pharmaceuticals Inc.
Merck & Co., Inc.

Current Status of Preferred Drug List (PDL) Class:

- Preferred Agents: ZOLPIDEM TABLET
- Non Preferred Agents: ZALEPLON CAPSULE, ZOLPIDEM EXTENDED-RELEASE TABLET, ZOLPIMIST™, LUNESTA™, ROZEREM™, SILENOR™, EDULAR™, INTERMEZZO™

Prior Authorization (PA) Criteria: A quantity limit is in place to prevent chronic daily use of all sedatives (Appendix 2) and to determine if the diagnosis is funded. Treatment of sleep disorders without sleep apnea is not a funded diagnosis (Line 636) by Oregon Health Plan (OHP). Treatment of insomnia contributing to a covered comorbid condition is funded. Electronic step edits were incorporated into the PA process as recommended at the March 2014 P&T meeting to streamline this process. There is also a PA required to prevent a patient from receiving two concurrent oral sedative medications.

Research Questions:

- Is there new comparative effectiveness or safety evidence since the last scan (literature search end date of Week 2, June 2013) of newer drugs for insomnia to warrant a change to the preferred drug list (PDL)?
- Is there evidence that tasimelteon or suvorexant is more effective or safer than currently available newer drugs for insomnia?
- Is there evidence that tasimelteon or suvorexant is more effective of safer for a sub-set of patients with insomnia?

Conclusions:

- There is no new comparative evidence for newer drugs for insomnia since the last scan.
- There is no comparative effectiveness or safety evidence for tasimelteon or suvorexant versus other newer drugs for insomnia.
- There is low level evidence from two small (n= 84, n=20), unpublished, randomized, placebo controlled trials (RCTs) in blind individuals that tasimelteon increases nighttime sleep on the worst 25% of nights by of 50 minutes and decreased daytime sleep on the worst 25% of days by 49 minutes.[1] There is insufficient evidence for adverse drug events of tasimelteon in comparison to placebo.[1]
- There is moderate level evidence from two, unpublished randomized, placebo-controlled trials that suvorexant statistically significantly increases subjective total sleep time by 10-25 minutes and decreases objective waking after sleep onset by 16 -31 minutes.[2] There is low level evidence of no significant adverse drug events for suvorexant in comparison to placebo.[3]

Recommendations:

- As there is no new comparative evidence for the newer drugs for insomnia it is recommended to compare costs in executive session to determine potential changes to the PDL.
- Compare costs of suvorexant in executive session for PDL placement.
- Make tasimelteon non-preferred in the newer insomnia drug class because there is insufficient evidence for insomnia treatment outside the narrow FDA approved indication and require a prior authorization for a funded OHP diagnosis.

Reason for Review: Tasmelteon was approved by the Food and Drug Administration (FDA) in January 2014 for Non-24-Hour Sleep-Wake Disorder (Non-24).[4] Suvorexant was approved in August 2014 for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.[5]

Previous P&T Conclusions (November 2013):[6,7]

- There is insufficient evidence of superiority or significant clinical advantage of Silenor™ and specialized zolpidem formulations (i.e. Edular™ and Zopimist™) over zolpidem tablets.
- There is good quality evidence that zolpidem and zaleplon are similarly effective for subjective sleep latency.
- There is fair quality evidence that there is no significant difference between zolpidem and eszopiclone on measured sleep outcomes.
- There is insufficient comparative evidence about long-term safety.

Background: The 2014 International Classification of Sleep Disorders classifies sleep disorders into seven categories; insomnia, sleep related breathing disorders, central disorders of hypersomnia, circadian rhythm sleep-wake disorders, parasomnias, sleep related movement disorders, and other sleep disorders.[8] Insomnia is a risk factor for many disorders including coronary heart disease, metabolic syndrome and depression. It is recommended that insomnia patients first get adequate treatment for conditions that may be exacerbating their sleep disturbance.[8,9]

Chronic insomniacs ($\geq$ 3 times per week for > 3 months) have an altered perception of sleep quality where subjective measures, such as self-reported sleep latency (time to fall asleep) or wakefulness after sleep onset (WASO) of more than 30 minutes do not correlate well with similar objective sleep measures derived from polysomnography.[10] The goals of treatment are to reduce the distress and anxiety associated with poor sleep, and to improve daytime function.[10] Behavioral approaches are recommended first-line for chronic insomnia.[8,9] There is moderate level evidence that both benzodiazepine and non-benzodiazepine sedatives moderately reduce the time to sleep onset and increase total sleep time.[9] However, the risks include complex sleep-related behaviors, increased risk of falls and abuse potential[9] Sedatives have not been adequately evaluated for risk versus benefit for long-term use.

The orexin signaling pathway, is a newly identified neurobiological pathway alternative pharmacological target to the γ-aminobutyric acid A receptor system targeted by current sedatives. It originates within the lateral hypothalamus and mediates wakefulness. Antagonism of Orexin-α and orexin-β receptors selectively dampens unwanted wakefulness interfering with sleep.[11,12] Suvorexant is the first orexin receptor antagonist approved.

Circadian rhythm disorders (e.g. Non-24) are characterized by patients falling asleep more than 2 hours later than conventional times.[13] These are thought to be caused by a disruption internal circadian system that is regulated by light signals to the suprachiasmatic nucleus which prevents the pineal gland from producing

melatonin, a hormone that otherwise signals "biological night".[14] Common secondary causes of circadian rhythm disorders include shift work and jet lag. There is no consensus on the appropriate dose or timing of exogenous melatonin for circadian rhythm disorders and it is largely ineffective for shift-work or jet-lag caused insomnia.[13] Ramelteon was the first synthetic melatonin agonist approved but is indicated specifically for sleep onset insomnia and has not been evaluated for circadian rhythm disorders. Tasmelteon is a melatonin agonist at the MT1 and MT2 receptors. It is the only drug FDA approved for Non-24 in blind individuals and was granted orphan drug status.[1] Non-24 is a common complaint of blind patients who cannot receive light signals. Measurement of endogenous melatonin level entrainment is a proposed surrogate outcome for melatonin agonist efficacy for Non-24[15] but this has not been reliably correlated to accepted sleep measures (i.e. sleep latency or WASO).[1] Medical treatment of circadian rhythm sleep disorders also falls below the funding line (i.e. Line 636) on the OHP list of prioritized services.

Methods:
A Medline literature search ending August 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing non-benzodiazepine sedatives for the treatment of insomnia was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
None identified.

New Guidelines:
None identified.

Randomized Controlled Trials:
No head to head comparisons were identified.

New Safety Alerts, Indications:

<u>August 2014 - Drug Abuse Warning Network (DAWN)</u>

- "The total estimated number of zolpidem-related emergency department (ED) visits involving overmedication increased for both males and females between 2005-2006 and 2009-2010.
- In 2010, females accounted for two thirds (68 percent) of zolpidem-related ED visits involving overmedication; patients aged 45 to 54 represented the largest proportion of zolpidem-related ED visits involving overmedication.
- More than half of zolpidem-related ED visits involving overmedication in 2010 included other pharmaceuticals combined with zolpidem (57 percent).

- Nearly half (47 percent) of zolpidem-related ED visits involving overmedication resulted in either a hospital admission or transfer in 2010, 26 percent of which were admissions to a critical or intensive care unit."

May 2014 – Ambien™, Ambien CR™ & Edular™

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

FDA is also warning that patients who take the sleep medication zolpidem extended-release (Ambien CR)—either 6.25 mg or 12.5 mg—should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities. This new recommendation has been added to the Warnings and Precautions section of the physician label and to the patient Medication Guide for zolpidem extended-release (Ambien CR)"

May 2014 - Lunesta™

"The U.S. Food and Drug Administration (FDA) is warning that the insomnia drug Lunesta (eszopiclone) can cause next-day impairment of driving and other activities that require alertness. As a result, we have decreased the recommended starting dose of Lunesta to 1 mg at bedtime. Health care professionals should follow the new dosing recommendations when starting patients on Lunesta. Patients should continue taking their prescribed dose of Lunesta and contact their health care professionals to ask about the most appropriate dose for them."

February 2014 - Lunesta™

"6 ADVERSE REACTIONS
6.2 Post-Marketing Experience..added paragraph

In addition to the adverse reactions observed during clinical trials, dysosmia, an olfactory dysfunction that is characterized by distortion of the sense of smell, has been reported during post-marketing surveillance with LUNESTA. Because this event is reported spontaneously from a population of unknown size, it is not possible to estimate the frequency of this event."

New Drug Evaluation: tasimelteon (Hetlioz™)

FDA approved indications: Non-24-Hour Sleep-Wake Disorder (Non-24).

Potential Off-label Use: Chronic insomnia, other circadian rhythm sleep disorders and depression.

Clinical Efficacy Data: There are 5 completed, placebo-controlled, phase 3 studies (1 for Major Depressive Disorder, 2 for Non-24, 1 for adult primary insomnia, 1 for model of insomnia in health volunteers) and one completed phase 2 study for circadian rhythm disorders in health adult volunteers registered at www.clinicaltrials.gov. No results are posted for any trial. The depression trial (NCT01428661, n=507) was not published, but it was reported that it did not meet its primary endpoint of change in the Hamilton Depression Scale after 8 weeks.[15]

The two trials (NCT01163032 and NCT01430754) submitted to the FDA are published as abstracts only and cannot be evaluated for quality. What follows is a summary of the FDA review.[1] NCT01163032 (FDA ID 3201) was a placebo-controlled, double-blind trial of 84 totally blind patients randomized to tasimelteon 20mg or placebo for 6 months and at a time each day when the patient's circadian rhythm was thought to be coming into alignment based upon urinary melatonin. NCT01430754 (FDA ID 3203) was a randomized withdrawal placebo-controlled study designed to evaluated the long-term maintenance effect of tasimelteon versus placebo. After 11 weeks of treatment, 20 patients were randomized to receive tasimelteon 20mg or placebo. The primary endpoint in both studies was an un-validated surrogate of proportion of patients meeting melatonin entrainment. The FDA did not accept the surrogate and based their determinations on the secondary clinical endpoints of the change from baseline of the nighttime sleep duration on the 25% of nights with the least nighttime sleep and the 25% of days with the most daytime sleep. The baseline was a mean of 195 minutes of nighttime sleep and 137 minutes of daytime sleep. The change was nominally significant for the clinical endpoints of interest in both studies. There was a mean increase of 50 minutes of nighttime sleep on the worst 25% of nights and a mean decrease of 49 minutes of daytime sleep on the worst days.

NCT00490945 and NCT00291187 were published together in Lancet.[16] NCT0049045 was a fair quality, phase II study of 39 healthy volunteers. Subjects were randomized to placebo or tasimelteon 10mg, 20mg, 50mg or 100mg. After 2 weeks of a strict 8 hour sleep schedule they were admitted to a sleep facility where external cues to day and night were eliminated and then a 5-hour phase shift was induced using the study drug 1 hour before bedtime for 3 nights. Tasimelteon 50mg and 100mg increased the primary outcome of mean sleep efficiency by 14.6 – 18.4% over placebo. There was not a statistical difference in WASO, a secondary outcome. NCT00291187 was a good quality, phase III study of 411 healthy volunteers. Patients were maintained on a regular 8-hour sleep schedule for 1 week and then admitted for inpatient study where bedtime was advanced by 5 hours for 1 night. Tasimelteon 50mg and 100mg reduced the primary outcome of mean latency to persistent sleep by 22.6 -26.1 minutes more than placebo and the secondary outcome of WASO by 24.1 – 34 minutes. While these studies both indicate the ability of tasimelton 50mg and 100mg to improve adjustment to an induced, 1 time 5-hour phase shift of sleep in a controlled setting in healthy, young volunteers they are difficult to extrapolate to shift-workers and frequent travelers who may be older, less healthy and need to phase shift more routinely. Of note, only the 20mg dose was approved by the FDA and significant findings were produced by the higher 50mg and 100mg doses.

Clinical Safety: Safety was evaluated by the FDA using a database of 1346 subjects that received at least one dose of tasimelteon, 621 of which got the 20mg dose and 111 were treated 6 months. Only 44 were treated for one year. It was judged adequate for an "orphan indication" and overall there were no safety concerns noted.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Sleep Latency as measured by polysomnography
2) Wakefulness after sleep onset as measured by polysomnography

Primary Study Endpoint:

1) Sleep Latency as measured by polysomnography
2) Mean sleep efficiency as measured by polysomnography

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	Safety Results (CI, p-values)	Quality Rating; Internal Validity Risk o Bias/ External Validity Concerns
NCT00490945[16] R-PCT, DB, Phase II 7/14/2004-4/1/2005	-Patients maintained on a regular 8-hour sleep schedule x 2 weeks ther admitted for inpatient study at 2 US sites -single-bed suites free of time cues and had controlled light intensity where induced a 5-hour sleep phase shift x 3 days. Dose of tasimelton varied from 10-100mg	Demographics: 18-50 yrs old mean age: 30's BMI 23-25 Inclusion Criteria: volunteers Exclusion Criteria: -no major sleep disorder - individuals who were adapted to early sleep schedules -good health	ITT: 45 (6 withdrew after the run-in) pbo: 8 t10mg: 9 t20mg: 8 t50mg: 7 t100mg: 7 Attrition: pbo: n=0 (0.00%) t: n=1 (0.03%)	<u>Mean Sleep efficiency Day1 (% of total sleep time asleep as scored by polysomnography):</u> Baseline: 90% pbo: 70.9% p<0.01 vs baseline t10mg: 79.9% t20mg: 82.5% t50mg: 85.5%* t100mg: 89.3%* *p<0.05 vs pbo AD Range: 14.6% - 18.4%) <u>Mean WASO (in minute):</u> Baseline: 34.5 pbo: 106.7 p<0.01 vs baseline t10mg: 79.8 t20mg: 71.9 t50mg: 56.6 t100mg: 41.8	No ADE significantly greater than placebo.	**Quality Rating: Fair** **Internal Validity: RoB** <u>Selection:</u> MOD - unclear process & allocation concealment; stratified by sex <u>Performance:</u> MOD - matched placebo; who was blinded not described <u>Detection:</u> LOW- polysomnography scored by blinded, experienced scorers using standard criteria. <u>Attrition:</u> LOW **External Validity:** <u>Recruitment:</u> volunteers through advertising <u>Patient Characteristics:</u> very young, healthy cohort; probably unrepresentative of shift-workers <u>Setting:</u> model of phase-shift disorder <u>Outcomes:</u> objective polysomnography; a definition of clinically meaningful responders would have been helpful. One night evaluation; unclear if effects would last. **Analysis:** Potentially internally valid, but unclear clinical relevance.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	Safety Results (CI, p-values)	Quality Rating; Internal Validity Risk o Bias/ External Validity Concerns
NCT00291187[16] R-PCT, DB, Phase III 2/9/2006 – 8/21/2006	Patients maintained on a regular 8-hour sleep schedule x 1 weeks -admitted for inpatient study at 20 US sites, 19 of which did assessments. Bedtime advanced 5 hours x 1 night. Dose of tasimelton varied from 10-100mg	Demographics: 21-50 yrs old Inclusion Criteria: volunteers Exclusion Criteria: -no major sleep disorder - people who had previously slept in a sleep clinic -good health	ITT: 411 pbo:103 t20mg: 100 t50mg: 102 t100mg: 106 Attrition: 0	Mean Latency to Persistent Sleep (in minutes): pbo: 44.6 t20mg: 23.1 t50mg: 18.5* t100mg: 22.0* *p<0.01 vs pbo AD range: 22.6 -26.1 minutes Mean WASO (in minutes) pbo: 140.3 t20mg: 116.2* t50mg: 106.3^ t100mg: 122.3 *p<0.05 vs pbo ^p<0.01 vs pbo AD range: 24.1 – 34 minutes	No ADE significantly greater than pcb	**Quality Rating: Good** **Internal Validity: RoB** Selection: LOW – IVR used Performance: MOD: matched placebo; who was blinded not described Detection: LOW- polysomnography scored by blinded, experienced scorers using standard criteria. Attrition: LOW **External Validity:** Recruitment: volunteers through advertising Patient Characteristics: very young, healthy cohort; probably unrepresentative of shift-workers Setting: model of phase-shift disorder Outcomes: objective polysomnography; a definition of clinically meaningful responders would have been helpful. One night evaluation; unclear if effects would last. **Analysis: I**nternally valid, but unclear clinical relevance.

New Drug Evaluation: suvorexant (Belsomra™)

FDA approved indications: Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Potential Off-label Use: None were identified.

Clinical Efficacy Data: There are 3 completed, placebo-controlled, phase 3 studies, all for insomnia or primary insomnia registered at www.clinicaltrials.gov. Only the long-term safety and tolerability study (NCT01021813) was published and is reviewed below.[3] It and two additional trials (NCT01097616 [n= 1023] and NCT01097629 [n = 1019]) were submitted to the FDA but not published. A phase 2, two-period cross-over study (NCT00792298 [n=254]) was also cited in the FDA review and is published.[11]

NCT01021813 was a fair quality, randomized, blinded, placebo-controlled safety and tolerability study of 781 adult patients with primary insomnia. Patients with primary insomnia were treated with suvorexant 30mg (>65yo) or 40mg (<65yo) or matching placebo tablets every night at bedtime for one year, with a 2 month discontinuation study extension. There was no sample size determination for statistical validity. The primary outcomes were predefined events of clinical interest (i.e. cataplexy, sleep onset paralysis, sleep paralysis, complex sleep related behaviors [e.g. sleepwalking], suicidal ideation or behaviors, falls, hypnogogic or hypnopompic hallucinations, excessive daytime sleepiness, and selected events associated with potential for drug abuse) at one year. There were several threats for alpha error and the secondary efficacy outcomes were patient reported time to sleep onset and total sleep time, both in minutes. The least squares mean change from baseline of subjective time to sleep onset was –26.6 minutes for suvorexant versus -17 minutes for placebo, a difference of –9.7 minutes 95% CI (–16.5 to –2.9), p = 0.0055. The least squares mean change from baseline of subjective total sleep time was –60.5 minutes for suvorexant versus -33 minutes for placebo, a difference of 27.5 minutes 95% CI (16.2 to 38.8), p <0.0001.

The two pivotal efficacy trials are described in the FDA briefing document[2] as parallel group, fixed dose studies in which patients with insomnia were randomized to one of two fixed doses of suvorexant (low dose ages 18-<65-20 mg, >65-15mg; high dose ages 18-<65-40 mg, >65-30mg) or placebo for three months. The primary hypothesis compared the high dose on change from baseline on mean Subjective Total Sleep Time (sTST) and change from baseline on objective WASO at Months 1 and 3. The least squares mean difference in sTST was 19.7 minutes for high dose versus placebo, p <0.00001 and 10.7 minutes for low dose versus placebo p = 0.017 at 3 months for study NCT01097616 and 25.1 minutes for high dose versus placebo p <0.00001 and 22.1 minutes for low dose versus placebo, p=0.00004 at 3 months for NCT01097629. The least squares mean difference WASO was -22.9 minutes for high dose versus placebo, p <0.00001 and -16.6 minutes for low dose versus placebo, p=0.000009 at 3 months for NCT01097616 and -29.4 minutes, p <0.00001 for high dose versus placebo and -31.1 for low dose versus placebo, p=0.000009 at 3 months for NCT01097629. Outcomes at 1 month were similar for the high doses in both studies and somewhat larger for low doses in NCT01097616. The clinical significance of the differences is debatable but are nominally similar to the effect size seen with the benzodiazepine and non-benzodiazepine sedatives currently on the market.

NCT00792298[11] was a good quality, randomized, placebo-controlled, 2-period, cross-over trial which consisted of patients who received one of 4 doses of suvorexant (10, 20, 40, or 80 mg) and placebo. Each treatment period was 4 weeks, with a single-blind placebo washout period of at least one week between periods. Patients were assessed with a polysomnography on nights 1 and 28 of each period. The primary outcome was Sleep Efficiency, defined as 100 multiplied by Total Sleep Time (in minutes) divided by Time in Bed (in minutes). The Time in Bed was fixed at 8 hours. Suvorexant showed statistically significant dose-

related improvements versus placebo on the co-primary end points of sleep efficiency at night 1 and night 28 though it is difficult to interpret the clinical relevance of this outcome. Dose-related effects were also observed for secondary outcomes including WASO which declined by 21 – 37 minutes.

Clinical Safety: NCT01021813[3] provided information on safety and tolerability of suvorexant at 1 year. The small sample size, very low event rates and relatively healthy patient population prohibit confident conclusions regarding safety as no outcome reached statistical significance. NCT00792298[11] did not identify any adverse drug events. The FDA briefing document[2] states that "… a total of 2027 patients with insomnia have received at least one dose of suvorexant; 1218 for at least 3 months, 507 for at least 6 months, and 160 for at least one year." It also reports that only somnolence occurred at a significantly higher rate than placebo (e.g. at 3 months placebo 3% vs low dose suvorexant 7% and high dose suvorexant 11%).

The Drug Enforcement Agency placed suvorexant in Schedule IV.[17]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Sleep Latency as measured by polysomnography
2) Wakefulness after sleep onset as measured by polysomnography
3) Withdrawals due to adverse events

Study Endpoint:

1) Sleep Efficiency defined as total sleep time as measured by polysomnography divided by time in bed in minutes
2) Subjective time to sleep onset (sTSO, min), least squares mean change from baseline
3) Subjective total sleep time (sTST, min), least squares mean change from baseline
4) Pre-specified events of clinical interest: cataplexy, sleep onset paralysis, sleep paralysis, complex sleep related behaviors (e. g. sleepwalking), suicidal ideation or behaviors, falls, hypnogogic or hypnopompic hallucinations, excessive daytime sleepiness, and selected events associated with potential for drug abuse.

Ref./Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results	Safety Results (listed in descending order of event rate)	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
NCT01021813[3] R-PCT, DB, Phase III 12/2009 - 8/2011 106 sites in Americas, Australia, Europe, & South Africa The primary objective was to assess the safety and tolerability of suvorexant for up to 1 year.	Intervention: S: 30mg (≥65yo) or 40mg (<65yo) qHS P: matching tablets qHS @ 1 year, S patients randomly assigned in a 1:1 ratio a continuation of their previous dose or to switch to placebo x 2 additional months. P patients remained on placebo. Follow-up: - Patients seen @ week 2 & months 1, 3, 6, 9, 12, 13, 14 with phone calls at each of the intervening months. - Safety assessment self-reported, open-ended questions. - Columbia Suicide Severity Rating Scale, laboratory & ECG @ clinic visits. - Motor Vehicle Accidents and Violations - questionnaire administered at scheduled clinic visits or phone calls - The Quick Inventory of Depressive Symptomatology—Self Report - (QIDS-SR)18 was administered at clinic visits starting at month 1 to assess mood. - Tyrer Withdrawal Symptom Questionnaire was administered before dosing for three consecutive evenings at the start of the randomised discontinuation phase.	Demographics: Age: 61.5 yo (mean) BMI: 27% (overweight) White: 90.5% N.Amer. 61.5% Disease severity measures similar at baseline. Inclusion Criteria: ->18 yo; - primary insomnia assessed by a clinical interview and a structured sleep diagnostic interview Exclusion Criteria: - potentially confounding neurological disorders, major affective or psychotic illness, substance abuse, or an unstable medical disorder.	ITT: S: 522 SS:156 SP:166 P: 259 mITT*: S: 517 SS:152 SP:160 P: 254 *excluded 1 patient in each group who did not take the drug and 4 in each group missing baseline information. Attrition: S: 14/522 (2.7%) P: 12/259 (4.6%) Non-Adherence: S: 200/522 (38.3%) P: 97/259 (37.5%) (reasons similar between groups) Statistical Analysis: -The planned S:500 and P:250 with not >60% in either non-elderly or elderly age groups. -Sample size driven by regulatory guidelines to study at least 100 suvorexant-treated patients in each age group for at least 1 year rather than formal statistical considerations.	Per Protocol Analysis Used: S: 298 P: 147 Subjective total sleep time, least squares mean change from baseline in minutes @ 1 year: S: 60.5 (54.0 to 66.9) P: 33.0 (23.7 to 42.2) Diff: 27.5 (16.2 to 38.8) p <0.0001 Subjective time to sleep onset least squares mean change from baseline in minutes @ 1 year: S: –26.6 (–30.5 to –22.7) P: –17.0 (–22.6 to –11.4) Diff: –9.7 (–16.5 to –2.9) p = 0.0055	Withdrawals d/t ADE: S: 61/522 (11.7%) P: 22/259 (8.5%) RR: 1.38 95% CI (0.86, 2.19) ARI: 3.2% Events associated with potential for drug abuse: S: 18 (3.5%) - P: 10 (3.9%) ARR: 0.4% 95% CI (-3.8%,2.2%) Falls: S: 12 (2.3%) - P: 8 (3.1%) ARR: 0.8% 95% CI (-3.9%,1.5%) Excessive daytime sleepiness: S: 13 (2.5%) - P: 2 (0.8%) ARI: 1.7% 95% CI (-0.5%,3.6%) Suicidal ideation: S: 4 (0.8%) - P: 0 ARI: 0.8% 95% CI (-0.7%,2.0%) Hypnogogic hallucinations: S: 3 (0.6%) - P: 0 ARI: 0.6% 95% CI (-0.9%,1.7%) Sleep onset paralysis: S: 1 (0.2%) - P: 0 ARI: 0.2% 95% CI (-1.3%,1.1%) Sleep paralysis: S: 2 (0.4%) - P: 0 ARI: 0.4% 95% CI (-1.1%,1.4%) Complex sleep-related behaiors: S: 1 (0.2%) - P: 0 ARI: 0.2% 95% CI (-1.3%,1.1%) Hypnopompic hallucinations: S: 1 (0.2%) - P: 0 ARI: 0.2% 95% CI (-1.3%,1.1%) Cataplexy: S: 0 - P: 0	**Quality Rating: FAIR** **Internal Validity: RoB** Selection: LOW - IVR system allocated a computer generated randomisation schedule (2:1, suvorexant:placebo) based on input from a masked Merck statistician. Stratified by age (non-elderly vs elderly) & region. Performance: LOW - Treatment allocation was masked from study investigators, site staff, patients, and Merck monitoring staff throughout the study. Suvorexant or placebo were provided as matching tablets. Detection: LOW - Treatment allocation was masked from study investigators, site staff, patients, and Merck monitoring staff throughout the study. Suvorexant or placebo were provided as matching tablets. An adjudication committee of three non-Merck experts in neurology, psychiatry, and sleep adjudicated prespecified events of clinical interest including events potentially suggestive of intrusion of rapid eye movement (REM),sleep into wakefulness (cataplexy) or initiation of sleep (sleep onset paralysis). Attrition: HIGH – almost 40% non-adherence to protocol/withdrawals. Reasons for withdrawal between groups similar but difficult to assess if randomization was maintained. 5 patients from each group excluded from analysis (i.e. mITT). Sample size was not calculated and multiple outcomes were assessed. **External Validity:** Recruitment: patients identified by investigators; a 1-week single-blind placebo run-in screening phase (295/1076 [27%] failed the screen. High risk of selecting patients more likely to respond favorably. Patient Characteristics: Older, white, healthy population uncharacteristic of general population requesting sleep medications. Setting: academic & private investigational centers may be unrepresentative of ambulatory care population in US. Outcomes: Subjective efficacy outcomes used and efficacy was secondary. Multiple outcomes assessed with high likelihood of multiplicity alpha error given no sample size determination. **Analysis:** Subjective efficacy outcomes of <30minutes difference in total sleep time and <10minutes difference in time to sleep are of questionable clinical relevance. They reach statistical thresholds but there are multiple threats (low sample size, multiple outcomes, secondary outcomes) for alpha error.

Ref./Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results	Safety Results	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
NCT00792298[11] R-PCT, DB, Phase III 11/2008 – 12/2009 29 sites in US & 12 sites in Japan 2-period crossover polysomnography study to assess 4 doses of suvorexant (10, 20, 40, 80 mg) in patients with primary insomnia.	Intervention: 10mg/P P/10mg 20mg/P P/20mg 40mg/P P/40mg 80mg/P P/80mg Patients received the first named treatment in period 1 (up to 4 weeks) and the second named treatment in period 2 (up to 4 weeks), with a 1-week washout between treatment periods.	Inclusion: -18 to 64 years old -good physical & mental health -diagnosed with primary insomnia based on DSM-IV-TR criteria. - confirmed polysomnography of latency to persistent sleep (LPS) of >20 minutes on both night 1 & 7 of run-in period mean WASO of ≥60 minutes on both nights with neither night <45 minutes Exclusion: -reported in supplementary material only Demographics - mean age 44 yo ~BMI 26 ~85-86% US ~70% white Insomnia Severity Score ~17 measured parameters fairly similar at baseline.	ITT: 10mg/P: 31 P/10mg: 32 20mg/P: 33 P/20mg: 32 40mg/P: 32 P/40mg: 32 80mg/P: 31 P/80mg: 31 Total: 254 Attrition: 80mg/P: 1/31 (3.2%) Total: 1/254 (0.4%) Non-Adherence: 10mg/P: 2/31 (6.5%) P/10mg: 2/32 (6.3%) 20mg/P: 3/33 (9.1%) P/20mg: 6/32 (18.8%) 40mg/P: 2/32 (6.3%) P/40mg: 5/32 (15.6%) 80mg/P: 3/31 (9.7%) P/80mg: 3/31 (9.7%) Total: 26/254 (10.2%) Sample Size: The study was planned to enroll approximately 250 randomized patients to yield approximately 208 patients total completing both periods of the crossover study. In order to protect the experiment-wise Type I error of 5%, the highest dose was compared to placebo, and needed to be significant (p=0.05) at both time points (Night 1 and Week 4) in order to test the next highest dose in the same way.	PRIMARY OUTCOMES: Least Squares Mean Change from placebo Sleep Efficiency* Night 1: 10 mg: 5.2 p<0.01 20 mg: 7.6 p<0.001 40 mg: 10.8 p<0.001 80 mg: 12.9 p<0.001 Least Squares Mean Change from placebo Sleep Efficiency* Night 28: 10 mg: 4.7 p<0.01 20 mg: 10.4 p<0.001 40 mg: 7.8 p<0.001 80 mg: 7.6 p<0.001 SECONDARY OUTCOMES: Difference in least squared neans at Night 1 WASO in minutes: 10 mg: -21.2 p<0.001 20 mg: -24.7 p<0.001 40 mg: -33.9 p<0.001 80 mg: -36.8 p<0.001 Difference in least squared neans at Night 28 WASO in minutes: 10 mg: -21.4 p=0.001 20 mg: -28.1 p<0.001 40 mg: -33.2 p<0.001 80 mg: -28.9 p<0.001	Withdrawal d/t ADE: P: 3 (12%) 80mg: 1 (1.6%) No serious ADEs reported. No ADE significantly higher than placebo except somnolence.	**Quality Rating: GOOD** **Internal Validity: RoB** Selection: LOW - assigned to treatment using a computer-generated randomized allocation schedule prepared by Merck and implemented through an interactive voice response system. Randomization was stratified according to country (United States, Japan). Performance: LOW - A double-dummy design was used to maintain blinding. Study investigators, site staff, patients, PSG scorers, and Merck monitoring staff remained blinded to treatment allocation throughout the study. Detection: LOW - Visual scoring of polysomnography data was performed by blinded personnel at Henry Ford Hospital Sleep Disorders and Research Center (Detroit, MI), in 30-second epochs according to the scoring standards developed by the American Academy of Sleep Medicine. Attrition: MOD- sample size was met; per protocol analysis was done excluding ~2% of patients. There was ~10% overall non-adherence to the protocol through-out the short study period increasing chance of dissimilar groups. Multiplicity accounted for with hierarchical testing. Overall small sample with multiple outcomes increases chance for alpha error. **External Validity:** Recruitment: patients identified by investigators; a 1-week single-blind placebo run-in. 469/723 (65%) excluded on screening. High risk of selecting patients more likely to respond favorably. Patient Characteristics: younger, white, healthy population uncharacteristic of general population requesting sleep medications. Setting: Not reported other than ~70 US/30% Japan. Outcomes: Objective outcomes confirmed with polysomnography. Primary outcome difficult to interpret clinically. Secondary WASC outcome effect size similar to other sedatives. Unfortunately, short study duration limits ability to extrapolate results to longer duration. **Analysis:** Probably internally valid but difficult to extrapolate.

* Defined as total sleep time as measured by polysomnography divided by time in bed in minutes [fixed at 480 for this study] multiplied by 100 on night 1 and at the end of week 4.

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Appendix 1: Specific Drug Information Tasimelteon (Hetlioz™) [4]

CLINICAL PHARMACOLOGY

Tasimelteon is a melatonin MT1 and MT2 receptor agonist. These receptors are thought to regulate circadian rhythms.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	NR
Protein Binding	90%
Elimination	80% recovered via metabolites in urine 4% recovered via metabolites in feces
Half-Life	1.3 hours
Metabolism	Extensively metabolized. CYP1A2 and CYP3A4 are the primary isoenzymes involved

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
20mg	Oral	Before bedtime	Tablet		Not studied in patients with severe hepatic impairment (Child-Pugh Class C)	Not established	2x increase in levels	C	-Take without food; -Drug effect may not occur for weeks or months -Smokers metabolize it quicker.

DRUG SAFETY[1]

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

Warnings and Precautions: None

Look-alike / Sound-alike (LA/SA) Error Risk Potential: Halcion, Haldol, Healon, tramadol, trazadone

Appendix: Specific Drug Information - suvorexant (Belsomra™)[5]

CLINICAL PHARMACOLOGY

"The mechanism by which suvorexant exerts its therapeutic effect in insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive."[5]

PHARMACOKINETICS[5]

Parameter	Result
Oral Bioavailability	82% (mean of 10mg)
Protein Binding	>99%
Elimination	23% recovered via metabolites in urine 66% recovered via metabolites in feces
Half-Life	12 hours
Metabolism	Primarily metabolized: primarily by CYP3A with a minor contribution from CYP2C19.

DOSE & AVAILABILITY[5]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	Pregnancy Category	OTHER DOSING CONSIDERATIONS
5 mg 10 mg 15 mg 20 mg	Oral	Before bedtime	Tablet	No dose adjust-ment is required	Not rec. for patients with severe hepatic impairment	Not established	No clinically meaningful differences were observed	C	-Use the lowest effective dose. -Recommended dose is 10 mg, within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. Do not to exceed 20 mg once daily. -Time to effect may be delayed if taken with or soon after a meal.

DRUG SAFETY[5]

Serious (REMS, Black Box Warnings, Contraindications): No REMS or Black Box warnings. Do not use in patients with narcolepsy.

*Warnings and Precautions: "*Daytime somnolence: Risk of impaired alertness and motor coordination, including impaired driving; risk increases with dose; caution patients taking 20 mg against next-day driving and other activities requiring complete mental alertness. Need to evaluate for co-morbid diagnoses: Reevaluate if insomnia persists after 7 to 10 days of treatment."

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

Appendix 3: Current PA Criteria

Central Nervous System (CNS) Sedatives –Quantity Limit

Goal(s):

- Approve only for covered OHP diagnoses.
- Treatment of uncomplicated insomnia is not covered, but insomnia contributing to covered comorbid conditions is.
- Prevent adverse events associated with long-term sedative use.
- Clients coming onto the plan on chronic sedative therapy are grandfathered.(refer to criteria). Also see related Sedative Therapy Duplication edit. The safety and effectiveness of chronic sedative use is not established in the medical literature.

Length of Authorization:

- 6 to 12 months (criteria specific)

Requires PA:

- All CNS sedatives in Standard Therapeutic Class 47 that exceed 15 doses per 30 days.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Trazodone, mirtazapine, diphenhydramine or tricyclic antidepressants may be alternatives for some clients.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does client have diagnosis of insomnia with sleep apnea, ICD9: 780.51?	Yes: Go to #3.	No: Go to #4.
3. Is client on CPAP?	Yes: Approve for up to 1 year. The use of CPAP essentially negates the sedative contraindication and they are often prescribed to help clients cope with the mask.	No: Pass to RPH, Deny, (Medical appropriateness). Due to the depressant effects of sedative/ hypnotics, sedative/hypnotics are contraindicated for this diagnosis and are not approvable.

Approval Criteria		
4. Is the client being treated for co-morbid depression,/ bipolar disorder (296.xx) OR anxiety / panic disorder (300.0x) AND Is there an existing claim history of antidepressants, lithium, antipsychotics, or other appropriate mental health drugs?	Yes: Approve for up to 1 year.	No: Pass to RPH; Go to #5.
5. RPH only: Is diagnosis being treated a covered indication on the OHP and is there medical evidence of benefit of the prescribed sedative? All indications need to be evaluated as to whether they are above the line or below the line.	Above: Document supporting literature and approve up to 6 months with subsequent approvals dependent on f/u and documented response.	Below: Go to #6.
6. RPH only: Is this a request for continuation therapy for client with history of chronic use where discontinuation would be difficult or unadvisable? NOTE: Clients coming onto the plan on chronic sedative therapy are "grandfathered."	Yes: Document length of treatment and last follow-up date. Approve for up to 1 year.	No: Deny, (Medical Appropriateness)

P&T / DUR Action: *11/20/14, 3/27/14, 11/21/13, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Revision(s): *??/??/14; 1/1/07, 7/1/06, 11/15/05*
Initiated: *11/15/02*

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Month/Year of Review: November 2014 **Date of Last Review:** January 2014
PDL Classes: Hormone Replacement Therapy (HRT) **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

Current Preferred Agents	Current Non-Preferred Agents
Oral HRT - Estrogen	
Estradiol	Conjugated Estrogens, Synthetic B (Enjuvia®)
Conjugated Estrogens, Synthetic A	Esterified Estrogens/methyltestosterone
Estropipate	Esterified estrogens (Menest®)
	Estradiol/norethindrone (Activella®)
	Drospirenone/estradiol (Angeliq®)
	Norethindrone acetate/ethinyl estradiol (Jinteli®)
	Estradiol/norethindrone acetate (Mimvey®)
	Estradiol/norgestimate (Prefest®)
	Conjugated estrogens/Medroxyprogesterone (Prempro®, Premphase®)
	Norethindrone acetate/Ethinyl Estradiol (FEMHRT)
Topical HRT - Estrogen	
Estradiol patch (Climara)	Estradiol gel packet (Divigel®)
	Estradiol gel pump (Elestrin®)
	Estradiol patch (Estraderm®)
	Estradiol patch (Estrasorb®)
	Estradiol gel pump (EstroGel®)
	Estradiol spray (Evamist®)
	Estradiol patch (Vivelle-dot®)
	Estradiol/norethindrone acetate patch (Combipatch®)
	Estradiol/levonorgestrel patch (Climara Pro®)
Vaginal HRT - Estrogen	
Estradiol tablet	Estradiol vaginal cream (Estrace®)
Conjugated Estrogen cream	Estradiol vaginal ring (femring®)

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend including one or more agents from this category
- Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence.
- Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.
- There are insufficient data to assess the risk of long term hormone therapy use in perimenopausal women or postmenopausal women younger than 50 years of age.
- Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestin to reduce the risk of endometrial hyperplasia.
- There were no consistent differences by age and comorbidities in subgroup analyses.

- Despite of lacking randomized clinical trials evidence for potential favorable thromboembolic risks using transdermal formulation of hormone therapy, several national guidelines recommended transdermal route of administration over oral route.

Research Questions:

- Is there any new comparative evidence in reducing symptoms of menopause, preventing low bone density, or preventing fractures?
- Is there any new comparative safety evidence of the different preparations?
- Are there subpopulations of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Methods:

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

Conclusions and Recommendations:

- There is high quality evidence that estrogens are the most effective agents at relieving common symptoms associated with menopause, including vasomotor symptoms and quality of life, with no significant differences between doses or mode of administration. There is high strength of evidence that vaginal estrogen reduces pain during intercourse and insufficient evidence for oral estrogen.
- There is no new significant comparative evidence on the efficacy or safety of hormone replacement therapy medications; no further review or research needed.
- Evaluate comparative costs in executive session.

Systematic Reviews:

A draft AHRQ report reviewing the evidence evaluating the comparative effectiveness of treatments for menopausal symptom relief and long term harms was available.[2] It is unknown when the final review will be completed. Menopausal symptoms that were evaluated include vasomotor symptoms, quality of life, psychological symptoms, sexual function, urogenital atrophy, and sleep dysfunction. The most commonly studied agents were estrogens, isoflavones, and SSRI/SNRIs. Overall, the authors concluded that there is good evidence available showing that estrogens are the most effective at relieving common symptoms associated with menopause, and there are no significant differences between doses or mode of administration. There is high strength of evidence that estrogen is the most effective agent in relieving vasomotor symptoms (SMD -0.7 or lower compared with placebo) and high strength of evidence that difference doses of estrogen are equally effective. There is high strength of evidence that vaginal estrogen reduces pain during intercourse compared to placebo (SMD -0.50; 95% CI -0.71 to -0.29) and insufficient evidence that oral estrogen reduces pain. Estrogens are also accompanied by other potential long-term benefits and harms that require consideration. Compared with estrogen, other agents have lesser efficacy and limited evidence on long-term benefits and harms. There is low strength evidence that estrogen alone reduces breast cancer risk. There is moderate strength evidence that estrogen has no effect on coronary heart disease and high strength of evidence that estrogen therapy increases the risk of venous thromboembolic events. There is moderate strength evidence that estrogen therapy reduces the risk of osteoporotic fractures.

References:

1. Peterson K. Drug Effectiveness Review Project: Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage. Preliminary Scan Report #5. July 2014.

2. Agency for Healthcare Research and Quality. Menopausal Symptoms: Comparative Effectiveness Review of Therapies. Draft Comparative Effectiveness Review. Available at: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1022

Drug Class Review
on
Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage

Preliminary Scan Report #5

July 2014

Last Report Update #3 (October 2007)

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

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

Scan prepared 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 only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA since the last report. Other important studies could exist.

Date of Last Update Report:

Update #3 was completed in October 2007, with searches through March 2007.

Date of Previous Update Scans:

Scan #1: May 2009
Scan #2: June 2010
Scan #3: November 2011
Scan #4: September 2013

Scope and Key Questions

The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?

2. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for preventing low bone density and fractures?

3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?

4. What is the comparative safety of different hormone therapy preparations for long-term use (5 or more years)?

5. Are there subgroups of patients based on demographics, other medications, co-morbidities, length of use, or initiation of use relative to onset of menopause, for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

- Study participants include women recruited from any health care setting or a population-based sample experiencing menopause. When possible, data are considered separately for women with natural versus surgical menopause (oophorectomy) and for postmenopausal women versus women in the menopausal transition stage.
- Women in the menopausal transition stage are those transitioning through natural menopause who have had irregular menstrual periods within the last 12 months.
- Postmenopausal women are those with surgical or natural menopause and amenorrhea for more than 12 months.

Interventions

Interventions include oral and transdermal estrogen monotherapy or estrogen plus progestin/progesterone preparations listed below for all symptoms, bone density and fracture outcomes, and vaginal tablet or cream for urogenital atrophy, administered as sequential or continuous regimens. Included products are shown in Table 1.

Table 1. Included estrogen products

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Oral estrogens			
17b Estradiol	Gynodiol (generic) Estradiol (generic) Estrace	0.5, 1, 1.5, 2 mg 0.5, 1, 2 mg 0.5, 1, 2 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar or vaginal atrophy, topical vaginal products should be considered. 3. Treatment of Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen dependant carcinoma of the prostrate (for palliation only). 6. Prevention of osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Estradiol acetate	Femtrace	0.45, 0.9, 1.8 mg	Treatment of moderate to severe vasomotor symptoms associated with the menopause.
Esterified estrogens	Menest Neo-Estrone	0.3, 0.625, 1.25, 2.5 mg 0.3, 0.625, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Atrophic vaginitis. 3. Kraurosis Vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. 7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 8. Prostatic carcinoma-palliative therapy of advanced disease.
Estropipate	Estropipate (generic) Ogen Ortho-est	0.75, 1.5, 3 mg 0.75, 1.5, 3 mg 0.75, 1.5 mg	1. Signs and symptoms of naturally occurring or surgically induced estrogen deficiency states associated with menopausal and post-menopausal symptoms, e.g., hot flashes, sleep disturbances and urogenital atrophy. 2. Osteoporosis induced by estrogen deficiency states in conjunction with other pertinent measures.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Conjugated equine estrogens (CEE)	Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only). 6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Synthetic conjugated estrogens	Cenestin Enjuvia C.E.S Congest PMS-Conjugated	0.3, 0.45, 0.625, 0.9, 1.25 mg 0.625, 1.25 mg 0.3, 0.625, 0.9, 1.25 0.3, 0.625, 0.9, 1.25, 2.5 mg 0.3, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause: 0.45mg, 0.625mg, 0.9mg, 1.25mg 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 0.3 mg
Estrogen-progestin combinations			
CEE, medroxyprogesterone	Prempro Premplus Premphase	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg 2.5/0.625 mg, 5/0.625 mg 0.625 mg CEE, 5.0 mg progesterone	1. Treatment of moderate to severe symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
17b-estradiol, norgestimate	Ortho-Prefest	1 mg estradiol/0.9 mg norgestimate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
			vaginal atrophy associated with the menopause. When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17-b estradiol, norethindrone acetate	Activella	1 mg estradiol/0.5 mg norethindrone acetate	1.0 mg/0.5mg and 0.5mg/0.1mg 1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. 1.0mg/0.5mg 3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
17b-estradiol, drospirenone	Angeliq	1.0 mg estradiol, 0.5 mg drospirenone	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Ethinyl estradiol, norethindrone acetate	FemHRT	5 mcg ethinyl estradiol/1 mg norethindrone acetate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Transdermal estrogens			
17b-estradiol matrix patch	Alora Climara Esclim Vivelle Vivelle-Dot Menostar Estradot Oesclim 17-b estradiol (generic)	0.025, 0.05, 0.075, 0.1 mg/d 0.025, 0.05, 0.06, 0.075, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 0.05, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 14 mcg/d 25, 37.5, 50, 75, 100 µg/d 25, 50 µg/day 25, 50, 100 µg/d 0.1, 0.05 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol reservoir patch	Estraderm	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risks of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol, norethindrone acetate patch	Combi-Patch Estalis Estalis Sequi Estracomb	0.05 mg estradiol/0.14 mg norethindrone, 0.05/0.25 mg 140 µg norethindrone acetate/50 µg estradiol-17β/day, 250/50 µg/day 0.05 mg estrogen twice/week (Vivelle 50 patch) for 2 weeks, then 9 or 16 cm^2 Estalis patch twice/week for 2 weeks 0.05 mg estrogen twice/week for 2 weeks, then 0.05 mg estrogen + 0.25 mg progesterone for 2 weeks	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
17b-estradiol, levonorgestrel patch	Climara Pro	0.045 mg estradiol/0.015 mg levonorgestrel	Treatment of moderate to severe vasomotor symptoms associated with menopause
17b-estradiol transdermal gel	EstroGel Elestrin Divigel	1.25 g (0.75 mg estradiol) 0.87 g (0.52 mg estradiol) 0.25, 0.5, 1.0 g (0.25, 0.5, 1.0 mg estradiol)	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate topical emulsion	Estrasorb	1.74 g (0.5 mg estradiol)	Estrasorb is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause**.**
Topical products			
17b-estradiol vaginal cream	Estrace vaginal cream	0.1 mg estrogen/g	Treatment of vulvar and vaginal atrophy.
CEE cream	Premarin vaginal cream	0.625 mg estrogen/g	Treatment of atrophic vaginitis and kraurosis vulvae.
Esterified estrogen cream	Neo-Estrone vaginal cream	1 mg estrogen/g	1. Treatment of menopausal and post menopausal symptoms. 2. Should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.
17-b estradiol intravaginal ring	Femring Estring	0.05 mg estradiol, 0.1 mg/d 2 mg (7.5 µg estradiol/day)	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate vaginal tablet	Vagifem	25 µg	Treatment of atrophic vaginitis.
Related Drugs			
Conjugated estrogens/bazedoxifene	Duavee®	0.45 mg conjugated estrogens and 20 mg bazedoxifene	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Prevention of postmenopausal osteoporosis.
Paroxetine	Brisdelle™	7.5 mg	Treatment of moderate to severe vasomotor symptoms associated with menopause.
Ospemifene	Osphena™	60 mg	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

*Shading indicates new drugs identified in the present scan.

Effectiveness Outcomes

- Hot flashes or flushes defined as any otherwise unexplained sensation of flushing/sweating experienced by the woman being studied. Studies will be included if they measured frequency, severity, presence versus absence, or a combination measure of frequency and severity as either primary or secondary outcomes at baseline, 3 months, and/or the end of the study.
- Symptoms such as sleep disturbances/night sweats, mood changes (depression), sexual function, urogenital atrophy, and quality-of-life measures.
- Prevention of osteoporosis measured by improvement in bone density and fracture outcomes after at least 1 year of use.

Harms Outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Withdrawals due to specific adverse effects

  For short-term use
  - Atypical bleeding; endometrial hypertrophy
  - Nausea and vomiting
  - Breast tenderness
  - Headaches
  - Weight changes
  - Dizziness
  - Thrombosis (including relationship to estradiol levels)
  - Cardiovascular events
  - Rash and pruritus
  - Cholecystitis
  - Effects on the liver

  For long-term use
  - Cardiovascular events
  - Breast cancer
  - Thrombosis
  - Cholecystitis
  - Ovarian cancer
  - Endometrial cancer

Study Designs

1. Symptoms: Double-blind, randomized controlled trials of at least 3 months duration of one hormone therapy preparation versus another hormone therapy preparation or versus placebo.
2. Prevention of osteoporosis: Double-blind or open, randomized controlled trials of postmenopausal women who are treated for at least 1 year versus another hormone therapy preparation or versus placebo.
3. Good quality systematic reviews and meta-analyses.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from June 2013 through June 20, 2014 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials. To identify recent comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm) We also searched the US Food and Drug Administration website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and boxed warnings.

Study Selection

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

RESULTS

New Drugs

New drugs from this scan report

Although we found no new estrogen or estrogen plus progestin/progesterone products for this scan, we identified three new related products:

Ospemifene (Osphena™): FDA approved on 2/26/13 for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

Paroxetine (Brisdelle™): FDA approved on 6/28/2013 for the treatment of moderate to severe vasomotor symptoms associated with menopause

Conjugated estrogens/bazedoxifene (Duavee®): FDA approved on 10/3/2013 for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis

New drugs from previous scan reports

EvaMist® (estradiol transdermal spray): Approved for the treatment of moderate to severe vasomotor symptoms due to menopause (7/27/2007).

Divigel® (estradiol 0.1% transdermal gel): Approved for the treatment of moderate to severe vasomotor symptoms due to menopause (6/4/2007).

Synthetic conjugated estrogens A, vaginal cream: Approved for the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia (11/28/2008).

New Indications

New indications from this scan report
No new indications for included drugs were identified.

New indications from previous scan reports
Premarin® (conjugated estrogren): (1) new indication, the treatment of moderate to severe dyspareunia, (2) new dosing regimen for this indication, 0.5 g Premarin vaginal cream twice weekly) (11/7/2008).

New Boxed Warnings

Boxed warnings from this scan report
No new boxed warnings were identified.

Safety alerts from previous scan reports
Premarin: 10/28/2011 (oral); 02/14/2012 (topical); 04/11/2012 (injectable)
Prempro, Premphase: 02/02/2012 (oral)

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. (See **WARNINGS, Malignant Neoplasms, Endometrial cancer**.)

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is

unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast cancer**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Comparative Effectiveness Reviews

Reviews identified in this scan report

In this scan, we identified 5 new comparative effectiveness reviews. Their citations are listed below and the key questions and abstracts are provided in Appendix A. The AHRQ review that was previously identified has not yet been published.

1. Hayes, Inc. Bioidentical hormone replacement therapy for menopausal symptoms. 2013. http://www.hayesinc.com/hayes/htareports/directory/bioidentical-hormone-replacement-therapy-for-menopausal-symptoms/

2. Lai K, Cui J, Ni S, Zhang Y, He J, Yao K. The effects of postmenopausal hormone use on cataract: a meta-analysis. *PLoS ONE.* 2013;8(10):e78647. http://www.ncbi.nlm.nih.gov/pubmed?term=24205286

3. Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2013;6:CD008613. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008613.pub2/abstract

4. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. *Menopause.* Oct 2013;20(10):1098-1105. http://www.ncbi.nlm.nih.gov/pubmed?term=23799357

5. Yang D, Li J, Yuan Z, Liu X. Effect of hormone replacement therapy on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS ONE.* 2013;8(5):e62329. http://www.ncbi.nlm.nih.gov/pubmed?term=23667467

Reviews identified in previous scan reports

A comparative effectiveness review of therapies for menopausal symptoms that is currently in progress was identified from the AHRQ Effective Healthcare Program website. Amendments were made to the protocol on May 30, 2013. The key questions for this review are included in Appendix B and the protocol is available at:
http://www.effectivehealthcare.ahrq.gov/ehc/products/353/1022/menopause-protocol-130612.pdf

Randomized Controlled Trials

Medline searches for this scan resulted in 110 new citations. Of those, there was only 1 new potentially relevant trial. The newly identified trial compares the effects of conjugated equine estrogen 0.625 mg/medroxyprogesterone acetate 2.5 mg to tibolone and no treatment on the vaginal outcomes in postmenopausal women after six months. Along with the 58 trials identified in previous update scans, there are now 59 potentially relevant new trials for this drug class with 8 previously identified head-to-head trial, 10 total active-controlled trials, 37 previously identified placebo-controlled or no treatment-controlled trials, and 4 previously identified studies of various doses of the same included drug. Table 2 summarizes the new and previously identified studies (see Appendix C for abstracts of new and previously identified studies).

In addition, new studies pertaining to related drugs listed in Table 1 were identified through Medline searches. A total of 17 new trials were identified, with 15 pertaining to Duavee®, 1 pertaining to Brisdelle™, and 1 pertaining to Osphena™. Information pertaining to these trials is available upon request.

Table 2. Potentially relevant trials of hormone therapy

Study Year	Comparison(s)	N Duration	Focus
Alhola 2010	Estrogen + progestin Placebo	32 6 months	Cognitive function
Bachmann 2008a	Vaginal estradiol (E2) vs. placebo	230 12 weeks	Atrophic vaginitis
Bachmann 2008b	Transdermal 17-beta-estradiol/levonorgestrel vs. placebo	425 12 weeks	Moderate-severe vasomotor symptoms
Bachmann 2009a	Conjugated estrogens vaginal cream vs placebo	423 12 weeks	Atrophic vaginitis
Bachmann 2009b	Transdermal 17-beta estradiol (low dose or micro-dose) vs placebo	121 12 weeks	Vulvovaginal symptoms
Baksu 2009	Oral conjugated estrogen vs intranasal estradiol hemihidrate vs no treatment	100 1 year	Climacteric symptoms, anxiety and depression
Buster 2008	Transdermal estradiol spray vs. placebo	454 12 weeks	Moderate-severe vasomotor symptoms
Cameron 2006	Continuous transdermal estradiol/levonorgestrel vs. interrupted estradiol patch x 4 days followed by estradiol/levonorgestrel patch	59 6 months	Incidence of amenorrhea and relief of vasomotor symptoms
Carmignani 2010	Estradiol 1 mg/0.5 mg norethisterone vs Soy isoflavone 90 mg vs Placebo	60 16 weeks	Psychological, somatic, and urogenital menopausal symptoms
Chlebowski, 2010 WHI	CEE 0.625 mg + medroxyprogesterone acetate 2.5 mg Placebo	16,608 Intervention 5.6 years Followup 7.9 years	Breast cancer incidence and breast cancer mortality
Cieraad 2006	17-beta estradiol/dydrogesterone vs. conjugated equine estrogen/norgestrel	169 6 months	Lipids, vasomotor symptoms, bleeding, tolerability
De Franciscis 2007	17-beta estradiol/dydrogesterone vs. dydrogesterone	120 4 weeks	Vasomotor symptoms, bleeding
Endrikat 2007	Estradiol valerate/dienogest vs. placebo	324 12 weeks	Moderate-severe vasomotor symptoms
Fahlen 2011	Estradiol+Progestogen No treatment control	75 1 year	Quality of life in breast cancer survivors
Fonseca 2007	17-beta estradiol/norethisterone vs. placebo	40 cross over at 6 months	Sexual function and vasomotor symptoms

Study Year	Comparison(s)	N Duration	Focus
Freedman 2009	Synthetic conjugated estrogens vaginal cream vs placebo	305 12 weeks	Vulvovaginal atrophy
Gambacciani, 2011	17-estradiol 1 mg + drospirenone 2 mg Calcium	70 3 months	Quality of life
Gast 2009	Oral low-dose conjugated estrogens plus conjugated estrogens vaginal cream vs placebo cream and placebo tablet	285 6 weeks	Sexual function and quality of life
Genazzani, 2011a	DHEA 10 mg Estradiol 1 mg + dihydrogesterone 5 mg Tibolone 2.5 mg	48 12 months	Sexual function
Hachul 2008	Estrogen/progesterone vs. placebo	24 12 weeks	Sleep and cognition
Haines 2009	Micro-dose transdermal estradiol vs placebo	165 12 weeks	Asian women, hot flashes
Hassa 2010	Conjugated equine estrogen 0.625 mg vs Transdermal 17 beta-estradiol patch 3.9 mg every other week vs Placebo	N not reported in abstract 6 months	Vasomotor symptoms
Hayashi 2011	All initially taking Estriol + medroxyprogesterone then randomized to same or to raloxifene 60 mg	32 52 weeks	Bone-mineral density
Hedrick 2009	Various doses of estradiol gel 0.1% vs. placebo	488 12 weeks	Vasomotor symptoms, vaginal atrophy
Heiss 2008	Conjugated equine estrogen/medroxyprogesterone vs Calcium	16,608 Mean 2.4 years of follow-up	To report health outcomes at 3yrs after intervention was stopped (WHI)
Honjo 2009	Low-dose oral estradiol vs placebo	211 8 weeks	Japanese women, hot flashes
Huang 2007	Transdermal estradiol vs. placebo	382 12 months	Bone turnover and BMD (appears to be post-hoc analysis from ULTRA trial)
Huang 2009	CEE vs placebo	2763 1 year	Secondary analysis from HERS study data, risk of coronary heart disease
Kalleinen 2008	Cyclic estrogen-progestin vs. placebo	25 6 months (before-after)	Sleep
Lee 2007	Estradiol/drospirenone vs. placebo	90 4 months	Vasomotor symptoms

Study Year	Comparison(s)	N Duration	Focus
Lin 2011	Drospirenone 2 mg + 17-estradiol Placebo	244 4-28 day cycles	Hot flushes in Chinese women
Limpaphayom 2006	Various doses of conjugated estrogen/medroxyprogesterone	1028 24 weeks	Quality of life in 9 ethnic groups of Asian women
Long 2006	Oral vs. vaginal conjugated equine estrogen	57 3 months	Sexual function
Maki 2007	Conjugated equine estrogen/medroxyprogesterone vs. placebo	180 4 months	Cognition, sexual function, quality of life, sleep
Maki 2009	CEE vs black cohosh vs red clover vs placebo	66 1 year	Cognition
Marinho 2008	17-beta estradiol vs. placebo	74 NR	Cognitive function, depression
Mattsson 2007	Various doses of oral estradiol valerate/medroxyprogesterone (continuous HRT)	459 12 months	Moderate-severe vasomotor Symptoms
Merz 2010	Norethindrone 1 mg + ethinyl estradiol 10 mcg Placebo	35 12 weeks	Chest pain
Michael 2010	CEE vs placebo	1458 6 years	Secondary analysis of WHI data, physical function in women ages 65 to 79 years at enrollment
Mizunuma 2010	Oral estradiol 0.5 mg or 1.0 mg, with or without levonorgestrel 40 mcg vs Placebo	152 52 weeks	Bone mineral density
Moriyama 2008	Estradiol valerate vs. exercise	44 6 months	Health-related quality of life, vasomotor symptoms
Panay 2007	Various doses of low dose 17-beta estradiol/norethisterone vs. placebo	577 6 months	Vasomotor symptoms
Pefanco 2007	Micronized 17-beta estradiol vs. placebo	57 3 years	Cognitive function including depression
Pitkin 2007	Various doses of continuous combined HRT consisting of estradiol valerate/medroxyprogesterone	NR 12 months	Health related quality of life
Prior 2007	Conjugated equine estrogen vs. medroxyprogesterone	41 12 months	Vasomotor symptoms
Resnick 2009	CEE vs placebo	886 3 years	Secondary analysis of WHI data, cognition in women age 65 years and older

Study Year	Comparison(s)	N Duration	Focus
Saeideh 2010	Tibolone + Cal+D vs. CEE/MPA + Cal+D vs. Cal+D	150 6 months	Onset of vaginal bleeding and vaginal maturation value
Samsioe 2007	Transdermal vs. oral estradiol/norethisterone	677 1 year	Harms (safety), tolerability
Schierbeck 2012	Intact uterus: triphasic estradiol and norethisterone acetate No uterus: 2 mg estradiol vs No treatment controls	1006 Intervention stopped after 11 years but followed for up to 16 years	Long term effect of HRT on cardiovascular outcomes
Simon 2007	Transdermal estradiol gel vs. placebo	484 12 weeks	Vasomotor symptoms, vaginal atrophy
Simon 2006	Topical micellar nanoparticle estradiol emulsion vs. placebo	200 12 weeks	Moderate-severe vasomotor symptoms
Simon 2008	Synthetic conjugated estrogen vs. placebo	42 12 weeks	Vulvovaginal atrophy
Stevenson 2010	17 beta-estradiol 0.5 mg/dydrogesterone 2.5 mg vs 17 beta-estradiol 1 mg/dydrogesterone 5 mg vs Placebo	313 52 weeks	Vasomotor symptoms
Valen-Sendstad 2010	Estradiol 1 mg + norethisterone 0.5 mg Placebo	65 12 month	Depressive symptoms and cognitive function in women with Alzheimer disease
Veerus 2008	Continuous combined HRT vs. no treatment, or hormone therapy vs. placebo	1823 mean follow-up 3.6 yrs	Vasomotor symptoms, quality of life
Welton 2008	Conjugated equine estrogen/medroxyprogesterone vs. placebo	3721 12 months	Health related quality of life, emotional and physical symptoms using scales
Yang 2007	Various doses of transdermal 17-beta estradiol gel vs. estriol	120 12 months	Bone mass
Zaborowska 2007	Transdermal placebo vs. estrogen, or estrogen, acupuncture, or placebo	102 12 weeks	Vasomotor symptoms
Ziaei 2010	CEE 0.625 mg + medroxyprogesterone + Ca+D Tibolone 2.5 mg + Ca+D Ca+D	140 6 months	Climacteric symptoms and sexual function

Cal+D, Ca+D = calcium + vitamin D tablet
*Shading indicates new trials identified in the present scan.

Appendix A. Potentially relevant new comparative effectiveness reviews (N=5)

1. Hayes, Inc. Bioidentical hormone replacement therapy for menopausal symptoms. 2013.

Key Questions:

- Are FDA-approved bioidentical estrogen hormonal products (e.g., estradiol, estrone) or progesterone hormonal products (e.g., micronized oral progesterone, progesterone creams) safer or more effective than nonbioidentical hormonal products for the treatment of menopausal symptoms?
- Is compounded BHRT safe and effective for the treatment of menopausal symptoms?
- Have definitive patient selection criteria been established for use of bioidentical hormones for treatment of menopausal symptoms?

2. Lai K, Cui J, Ni S, Zhang Y, He J, Yao K. The effects of postmenopausal hormone use on cataract: a meta-analysis. *PLoS ONE*. 2013;8(10):e78647.

Abstract:

BACKGROUND

Cataract is the leading cause of blindness worldwide. Many observational studies assessed the relationship between postmenopausal hormone replacement therapy (HRT) and risk of cataract development, but the reported results were controversial. The aim of present meta-analysis was to evaluate the association of postmenopausal hormone replacement therapy with risk of cataract development.

METHODS

The eligible observational studies, including cross-sectional, case-control and cohort studies, were identified by searching PubMed and Embase during March of 2013. Either a fixed- or a random-effects model was used to calculate the pooled odds ratio (OR) with its 95% confidence interval (95%CI). Subgroup analysis on cataract types was performed.

RESULTS

A total of four cohort and five case-control or cross-sectional studies were finally included into this meta-analysis. Overall, a significant decreased risk of developing any type of cataract was found in ever HRT group as compared with non-HRT group among cohort studies (OR 0.83; 95% CI: 0.71,0.97) and case-control or cross-sectional studies (OR 0.74; 95% CI: 0.59,0.93). Subgroup analysis on cataract types determined that the significantly decreased risk of nuclear cataract in current HRT group (OR 0.72; 95% CI: 0.61,0.85) and also a critically reduced risk of nuclear cataract in ever HRT group (OR 0.80; 95% CI: 0.64,1.01) were found among case-control or cross-sectional studies, as compared with non-HRT group. No association of HRT with risk of cortical and posterior subcapsular cataract was observed.

CONCLUSIONS

The results of present meta-analysis indicate that postmenopausal hormone use may play a protective role in cataract development.

3. Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2013;6:CD008613.

Abstract:

BACKGROUND

There is conflicting information about the impact of the menopause on glycaemic control amongst women with type 1 diabetes. Some menopausal women with type 1 diabetes are treated with hormone replacement therapy (HRT) but the effects of this treatment have, to date, not been established.

OBJECTIVES

To assess the effects of HRT for women with type 1 diabetes mellitus.

SEARCH METHODS

We searched *The Cochrane Library*, MEDLINE, EMBASE, CINAHL and PsycINFO from their inception to June 2012. The last search was run for all databases on 18 June 2012.

SELECTION CRITERIA

We selected randomised controlled trials or controlled clinical trials that involved peri- or postmenopausal women with type 1 diabetes undergoing HRT as an intervention.

DATA COLLECTION AND ANALYSIS

Two researchers independently applied the inclusion criteria to the identified studies and assessed risk of bias. Disagreements were resolved by discussion or by intervention by a third party. Descriptive analysis was conducted for the review.

MAIN RESULTS

Ninety-two publications were screened. No studies met the inclusion criteria exclusively but one study that included both type 1 and type 2 diabetes participants was considered. This randomised clinical trial (RCT) compared HRT (N = 27) with placebo (N = 29) over 12 months. The outcome measures were cardiovascular risk factors, including lipid profile, glycaemic control, blood pressure and body weight. No significant differences between placebo and HTR were detected. Patient-important outcomes like all-cause mortality, cardiovascular disease, diabetic complications or health-related quality of life were not investigated.

AUTHORS' CONCLUSIONS

There is a lack of evidence around the use of HRT in women with type 1 diabetes. The one study that has been undertaken in this area is underpowered. More RCTs are required in the area to examine the impact of HRT on glycaemic control and cardiovascular outcomes.

4. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. *Menopause.* Oct 2013;20(10):1098-1105.

Abstract:

OBJECTIVE
Given the complexity of the literature on quality of life (QOL) and hormone therapy (HT) among women in the menopausal transition and postmenopause, the purposes of this integrative review were to (1) define QOL as a multidimensional construct; (2) review validated instruments for measurement of QOL; (3) review results of HT and QOL clinical trials that have used validated instruments; and (4) assess the effectiveness of HT on QOL, including health-related QOL (HRQOL), menopause-specific QOL (MSQOL), and global QOL (GQOL).

METHODS
The literature on HT and QOL was searched for definitions of QOL and validated instruments for measuring QOL, and the results were summarized. The purposes of this integrative review were to evaluate the effects of HT on HRQOL, differentiating the effects of HT on GQOL, HRQOL, and MSQOL. As a basis for this review, we searched for published controlled clinical trials in which the effects of HT on QOL were studied using validated QOL instruments, in particular menopause-specific validated instruments.

RESULTS
Clear definitions are elucidated. Validated instruments for the measurements of HRQOL, GQOL, and MSQOL are summarized, and the necessity of their incorporation into future research and clinical practice is emphasized. The published effects on QOL of estrogens and progestogens administered to symptomatic and nonsymptomatic women in the menopausal transition and beyond are reviewed.

CONCLUSIONS
The impact of various health state-related symptoms on HRQOL and GQOL is now an integral component of contemporary health care. Effects of HT include GQOL and HRQOL and should be menopause-specific. There is clearly a need for further studies on menopause and menopause-related therapies using appropriate and validated instruments. Literature review shows that HT provides a significant benefit for MSQOL in midlife women, mainly through relief of symptoms, but treatment also may result in a global increase in sense of well-being (GQOL). HRQOL benefits are contingent on symptom status, as are MSQOL outcomes. Women who are severely symptomatic experience a significant improvement in HRQOL and MSQOL, although this improvement is not significant among women without severe symptoms at baseline measures in clinical trials.

5. Yang D, Li J, Yuan Z, Liu X. Effect of hormone replacement therapy on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS ONE*. 2013;8(5):e62329.

Abstract:

BACKGROUND
Hormone replacement therapy (HRT) is widely used to controlling menopausal symptoms and prevent adverse cardiovascular events. However, the benefit and risk of HRT on cardiovascular outcomes remains controversial.

METHODOLOGY AND PRINCIPAL FINDINGS
We systematically searched the PubMed, EmBase, and Cochrane Central Register of Controlled Trials databases for obtaining relevant literature. All eligible trials reported on the effects of HRT on cardiovascular outcomes. We did a random effects meta-analysis to obtain summary effect estimates for the clinical outcomes with use of relative risks calculated from the raw data of included trials. Of 1903 identified studies, we included 10 trials reporting data on 38908 postmenopausal women. Overall, we noted that estrogen combined with medroxyprogesterone acetate therapy as compared to placebo had no effect on coronary events (RR, 1.07; 95% CI: 0.91-1.26; P=0.41), myocardial infarction (RR, 1.09; 95% CI: 0.85-1.41; P=0.48), stroke (RR, 1.21; 95% CI: 1.00-1.46; P=0.06), cardiac death (RR, 1.19; 95% CI: 0.91-1.56; P=0.21), total death (RR, 1.06; 95% CI: 0.81-1.39; P=0.66), and revascularization (RR, 0.95; 95% CI: 0.83-1.08; P=0.43). In addition, estrogen therapy alone had no effect on coronary events (RR, 0.93; 95% CI: 0.80-1.08; P=0.33), myocardial infarction (RR, 0.95; 95% CI: 0.78-1.15; P=0.57), cardiac death (RR, 0.86; 95% CI: 0.65-1.13; P=0.27), total mortality (RR, 1.02; 95% CI: 0.89-1.18; P=0.73), and revascularization (RR, 0.77; 95% CI: 0.45-1.31; P=0.34), but associated with a 27% increased risk for incident stroke (RR, 1.27; 95% CI: 1.06-1.53; P=0.01).

CONCLUSION/SIGNIFICANCE
Hormone replacement therapy does not effect on the incidence of coronary events, myocardial infarction, cardiac death, total mortality or revascularization. However, it might contributed an important role on the risk of incident stroke.

Appendix B. Potentially relevant comparative effectiveness review currently in progress (N=1)

Title: Menopausal Symptoms: Comparative Effectiveness Review of Therapies (Protocol submitted April 3, 2012; Amended May 30, 2013)

Key Question 1
What is the comparative effectiveness of different treatments for reducing symptoms of menopause (vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy, and sexual dysfunction) and for improving quality of life? Individual agents will be compared to the extent permitted by the evidence.

Treatments of interest include:

- Hormone therapies
    - Oral estrogen only or combined with progestin (or androgen)
    - Transdermal estrogen or combined with progestin
    - Vaginal estrogen
    - Combined estrogen-progestin and progestin-only contraceptives (for women desiring contraception)
    - Compounded menopausal hormone therapy
    - Evidence evaluating hormone therapies will be considered separately for women with and without a uterus. Women with breast cancer are excluded.
- Nonhormone therapies
    - Prescription
        - Antidepressants—SSRIs and SNRIs
        - Eszopiclone
        - Clonidine
        - Methyldopa
        - Gabapentin, pregabalin
    - Nonprescription/complementary and alternative therapies
        - Isoflavones, including red clover (*Trifolium pratense*)
        - Black cohosh (*Cimicifuga racemosa*)
        - St. John's wort (*Hypericum perforatum*)
        - Ginseng
        - Flax seed
        - Vitamin E
        - Dong quai (*Angelica sinensis*)
        - Dehydroepiandosterone

Key Question 2
What are the effects of hormone therapy preparations on coronary heart disease, stroke, or thromboembolism; cholecystitis; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancers? Exposure will be examined according to duration of use and initiation relative to age and onset of menopause. (For women desiring contraception, combined estrogen-progestin and progestin-only contraceptives are included.)

Key Question 3
What are the effects of nonhormone therapy preparations on coronary heart disease, stroke, or thromboembolism; cholecystitis; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer? Exposure will be examined according to duration of use and initiation relative to age and onset of menopause. What are the significant agent-specific harms/adverse effects of nonhormone therapies?

Key Question 4
Does effectiveness and adverse effects vary among subgroups of patients defined by demographics, symptom severity, other medications, and comorbidities or according to agent, preparation, or dose?

Appendix C. Abstracts of potentially relevant new and previously identified trials of estrogens (N=59)

*Shading indicates new trials identified in the present scan.

Head-to-head (N=8)

Cameron, S. T., A. F. Glasier, et al. (2006). "Comparison of a transdermal continuous combined and an interrupted progestogen HRT." Maturitas **53**(1): 19-26.

OBJECTIVES: Pilot study to compare the effects of a continuous combined hormone replacement therapy (HRT) regimen with an interrupted progestogen regimen administered transdermally, upon the endometrium of postmenopausal women, the incidence of amenorrhoea and relief of menopausal symptoms. METHODS: Fifty-nine postmenopausal women aged 50-63 years were randomised to either (i) continuous combined regimen: combined oestrogen/progestogen skin patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) or (ii) interrupted regimen: oestrogen-only patches (releasing 80 microg estradiol/day) for 4 days followed by combined oestrogen/progestogen patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) for 3 days, for 6 months. An endometrial biopsy was performed at end of treatment for histological analysis. RESULTS: Thirty-three women (56%) completed the study. Significantly higher rates of amenorrhoea were observed with the interrupted than continuous combined regimen (P<0.0001; 25% versus 7% at 6 months). The interrupted regimen was also associated with fewer days of bleeding overall (total 20 versus 44 days during months 4-6; P=0.001). Both regimens improved vasomotor symptoms. No endometrial hyperplasia or atypical changes were observed in endometrial biopsies. CONCLUSIONS: Although significantly less bleeding was observed with the interrupted regimen, it did not have a sufficiently high incidence of amenorrhoea to render it clinically useful.

Cieraad, D., C. Conradt, et al. (2006). "Clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms." Archives of Gynecology & Obstetrics **274**(2): 74-80.

A clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms. OBJECTIVE: The objective of the study was to compare the effects of sequential 17beta-oestradiol/dydrogesterone and conjugated equine oestrogens (CEE)/norgestrel on lipid parameters, climacteric symptoms, bleeding patterns and tolerability. STUDY DESIGN: This double-blind study was conducted in 193 peri- and post-menopausal women randomised to receive six, 28-day cycles of oral sequential oestradiol 1 mg/dydrogesterone 10 mg or CEE 0.625 mg/norgestrel 0.15 mg. The change from baseline in serum lipids and hot flushes was analysed using a two-way analysis of variance. RESULTS: After 24 weeks there was a statistically significant increase in high-density lipoprotein (HDL) cholesterol in the oestradiol/dydrogesterone group and a significant reduction in the CEE/norgestrel group. The difference between the groups was significant (P=0.001). The number of hot flushes was reduced by 86% in both groups; this improvement was supported by the Greene Climacteric Symptom Scale score, the patients' opinion and quality of life assessments. The percentage of women experiencing cyclic bleeding was greater with CEE/norgestrel, as was the mean duration and severity of bleeding. Both treatments were well tolerated. CONCLUSION: Oestradiol/dydrogesterone and CEE/norgestrel were equally effective in treating climacteric

symptoms, but oestradiol/dydrogesterone showed some advantages in terms of lipid profile and incidence of bleeding.

De Franciscis, P., L. Cobellis, et al. (2007). "Low-dose hormone therapy in the perimenopause." International Journal of Gynaecology & Obstetrics **98**(2): 138-42.

OBJECTIVE: To evaluate the effects of low-dose hormone therapy (LD-HT) on bleeding pattern and vasomotor symptoms in perimenopausal women. METHODS: In a prospective, open-label study at an University clinic, 120 perimenopausal women suffering from irregular menstrual cycles and hot flushes were randomized to micronized 17beta-estradiol 1 mg plus dydrogesterone 10 mg sequential added (LD-HT; group A: 60 subjects) or dydrogesterone 10 mg from day 15 to 28 (group B: 60 subjects). Number and severity of hot flushes and bleeding pattern were assessed throughout the study. RESULTS: Women in group A experienced a significant reduction in number of hot flushes while no significant variation was observed in group B. The incidence of cyclic bleeding was 86% in group A and 76% in group B, the mean duration was significantly lower in group A than in group B. CONCLUSIONS: LD-HT may control both irregular bleeding and hot flushes in perimenopausal women.

Hassa, H., H. M. Tanir, et al. (2010). "Is placebo as effective as estrogen regimens on vasomotor symptoms in women with surgical menopause?" Clinical & Experimental Obstetrics & Gynecology **37**(2): 135-137.

OBJECTIVE: To evaluate the short-term effects of two hormone therapy (HT) regimens and placebo on the Greene Climacteric Scale (GCS) of women with surgical menopause following six months of treatment. METHODS: This 6-month, prospective, randomized, parallel-group, masked evaluator study compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (group I), 3.9 mg transdermal 17beta-estradiol patch applied every week (group II) and placebo (group III). Mean GCS before and after six months of treatment in each group was compared. RESULTS: In groups I and II, vasomotor symptoms ($p < 0.005$, $p < 0.05$), somatic symptoms ($p < 0.05$, $p < 0.05$) and total score ($p < 0.005$, $p < 0.01$) significantly reduced from baseline values respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, vasomotor ($p < 0.05$), subscore and total score ($p < 0.05$) decreased significantly while other subscore reductions were not significant. CONCLUSIONS: Estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Additional larger prospective randomized studies need to be conducted in an aim to look at not only short-term but also long-term effects on climacteric symptoms, in comparison to both placebo arms and different dose and mode of HT use.

Long, C.-Y., C.-M. Liu, et al. (2006). "A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women.[see comment]." Menopause **13**(5): 737-43.

OBJECTIVE: To compare the effects of oral and vaginal estrogen therapy (ET) on the vaginal blood flow and sexual function in postmenopausal women with previous hysterectomy. DESIGN: Fifty-seven women were randomized to receive either oral (0.625 mg of conjugated equine estrogens per tablet; n = 27) or topical (0.625 mg conjugated equine estrogens per 1 g vaginal cream; n = 30) estrogen administered once daily. All women underwent estradiol measurements, urinalysis, pelvic examination, introital color Doppler ultrasonographies, and personal interviews for sexual symptoms using a validated questionnaire before and 3 months after ET. RESULTS: A higher serum level of estradiol was noted in the oral group compared with the topical group after 3 months of ET. There were significant increases in the number of vaginal vessels and the minimum diastole (P <

0.01), and marked decreases of pulsatility index values (P < 0.01) in both groups after ET. Regarding the systolic peak, we found a significant decrease only in the topical group (P < 0.05). Although the post-ET prevalence of anorgasmia decreased significantly in both groups (P < 0.05), changes in other domains, including the rates of low libido and coital frequency, were not statistically significant (P > 0.05). In the topical group, ET improved sexual function on the vaginal dryness and dyspareunia domains in a statistically significant manner (P < 0.05), but this was not the case in the oral group (P > 0.05). However, the efficacy of oral ET for vaginal dryness and dyspareunia reached 80% and 70.6%, respectively. The corresponding figures of the topical ET were 79.2% and 75%. CONCLUSIONS: The results of our study suggest that ET alone in hysterectomized postmenopausal women increases the vaginal blood flow and improves some domains of sexual function, but it may not have an impact on diminished sexual desire or activity. Compared with systemic therapy, topical vaginal preparations are found to correlate with better symptom relief despite the lower serum level of estradiol.

Mizunuma, H., Y. Taketani, et al. (2010). "Dose effects of oral estradiol on bone mineral density in Japanese women with osteoporosis." Climacteric **13**(1): 72-83.

OBJECTIVES: This 2-year study compared 0.5 and 1.0 mg oral estradiol (E(2)), with or without levonorgestrel (LNG), for the treatment of postmenopausal osteoporosis in Japanese women. METHODS: Japanese women with osteoporosis after natural menopause or bilateral oophorectomy were randomized to receive E(2) 0.5 or 1.0 mg/day with LNG 40 microg as required, or placebo, for 52 weeks. Women treated with E(2) in the first year continued therapy at the same doses in the second year. Efficacy, safety and pharmacokinetics were assessed. RESULTS: There were 73 women randomized to E(2) 0.5 mg, 157 to E(2) 1.0 mg and 79 to placebo. Lumbar bone mineral density at 52 weeks increased significantly more with E(2) 1.0 mg (p < 0.001) and 0.5 mg (p < 0.001) than with placebo (no change). After 2 years, a 10% increase in bone mineral density with E(2) 1.0 mg was significantly greater than with E(2) 0.5 mg (8%; p = 0.008). E(2) was associated with an acceptable safety and tolerability profile, with slightly more adverse events with E(2) 1.0 than 0.5 mg. Serum E(2) concentration increased in a dose-dependent manner. CONCLUSION: This study showed that E(2), at both 1.0 mg and 0.5 mg doses, was effective in increasing bone mineral density with an acceptable safety and tolerability profile in Japanese postmenopausal women with osteoporosis but that the bone mineral density response was higher with the 1.0 mg dose.

Prior, J. C., J. D. Nielsen, et al. (2007). "Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy." Clinical Science **112**(10): 517-25.

Oestrogen therapy is the gold standard treatment for hot flushes/night sweats, but it and oestrogen/progestin are not suitable for all women. MPA (medroxyprogesterone acetate) reduces hot flushes, but its effectiveness compared with oestrogen is unknown. In the present study, oral oestrogen [CEE (conjugated equine oestrogen)] and MPA were compared for their effects on hot flushes in a planned analysis of a secondary outcome for a 1-year randomized double-blind parallel group controlled trial in an urban academic medical centre. Participants were healthy menstruating women prior to hysterectomy/ovariectomy for benign disease. A total of 41 women {age, 45 (5) years [value is mean (S.D.)]} were enrolled; 38 women were included in this analysis of daily identical capsules containing CEE (0.6 mg/day) or MPA (10 mg/day). Demographic variables did not differ at baseline. Daily data provided the number of night and day flushes compared by group. The vasomotor symptom day-to-day intensity change was assessed by therapy assignment. Hot flushes/night sweats were well controlled in both groups, one occurred on average every third day and every fourth night. Mean/day

daytime occurrences were 0.363 and 0.187 with CEE and MPA respectively, but were not significantly different (P=0.156). Night sweats also did not differ significantly (P=0.766). Therapies were statistically equivalent (within one event/24 h) in the control of vasomotor symptoms. Day-to-day hot flush intensity decreased with MPA and tended to remain stable with CEE (P<0.001). In conclusion, this analysis demonstrates that MPA and CEE are equivalent and effective in the control of the number of hot flushes/night sweats immediately following premenopausal ovariectomy.

Samsioe, G., V. Dvorak, et al. (2007). "One-year endometrial safety evaluation of a continuous combined transdermal matrix patch delivering low-dose estradiol-norethisterone acetate in postmenopausal women." Maturitas **57**(2): 171-81.

OBJECTIVE: To evaluate the safety and endometrial protection of low-dose transdermal estradiol (E2)/norethisterone acetate (NETA) patches (Estalis 25/125) in terms of post-treatment incidence of endometrial hyperplasia/cancer after 1 year of treatment in postmenopausal women with intact uteri. METHODS: Patients were randomized to receive either transdermal E2/NETA (delivering daily doses of E2 25 microg and NETA 125 microg; applied every 3-4 days) or oral E2/NETA (E2 1mg and NETA 0.5 mg; given daily) in this open-label study. The primary variable was the incidence of endometrial hyperplasia/cancer based on endometrial biopsies; secondary variables included vaginal bleeding/spotting patterns, patch adhesion, safety and tolerability. RESULTS: Six hundred and seventy-seven patients were randomized (507 in the transdermal group and 169 in the oral group; one did not receive study drug) and >80% completed the study. There were no cases of endometrial hyperplasia or cancer in either group and the upper limit of the one-sided 95% confidence interval in the transdermal group was 0.85%. Over time, both treatments were associated with a decreasing frequency of spotting/bleeding days. The overall incidence of adverse events (AEs) was comparable in both groups, and the majority was mild-to-moderate in intensity. Breast tenderness was the most frequently reported AE (transdermal 19.9% versus oral 28.4%). AEs related to the gastrointestinal system were more frequent with oral E2/NETA, and episodes of spotting and bleeding were more frequent with transdermal E2/NETA. Local skin tolerability of the transdermal matrix system was good. CONCLUSIONS: Transdermal E2/NETA (25 and 125 microg) provided adequate endometrial protection in postmenopausal women when evaluated according to CPMP/CHMP criteria, achieved a high rate of amenorrhea, and was well tolerated.

Active-controlled (N=10)

Carmignani, L. O., A. O. Pedro, et al. (2010). "The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: a randomized controlled trial." Maturitas **67**(3): 262-269.

OBJECTIVES: To compare the effects of daily ingestion of dietary soy supplementation, l ow-dose hormone therapy (HT) and placebo on psychological, somatic and urogenital symptoms in postmenopausal women. STUDY DESIGN: A double-blind, randomized, controlled trial. Sixty healthy, symptomatic, postmenopausal women of 40-60 years of age were allocated to use dietary soy supplementation (containing 90 mg of isoflavone) or HT (1mg estradiol and 0.5mg norethisterone acetate) or placebo. Main outcome measures: the Menopause Rating Scale (MRS) was used to assess menopausal symptoms at baseline and after 16 weeks of treatment. Intention-to-treat analyses were performed using the chi-square test, Fisher's exact test, the Kruskal-Wallis non-parametric test and analysis of variance (ANOVA). RESULTS: No statistically significant differences were found between the

groups with respect to baseline clinical and sociodemographic characteristics. The psychological, somatic and urogenital symptoms analyzed in the MRS improved during treatment in all the groups, except for urogenital symptoms in the placebo group in which no significant changes were detected. Comparison between groups revealed a statistically significant improvement in somatic symptoms (hot flashes and muscle pain) in the users of HT (-45.6%) and dietary soy supplementation (-49.8%). Urogenital symptoms (vaginal dryness) improved significantly in HT users (-38.6%) and in users of the dietary soy supplementation (-31.2%). There was no statistically significant difference between the groups with respect to overall MRS score or to scores obtained in the psychological symptoms subscale. CONCLUSION: Dietary soy supplementation may constitute an effective alternative therapy for somatic and urogenital symptoms of the menopause.

Gambacciani, M., G. Rosano, et al. (2011). "Clinical and metabolic effects of drospirenone-estradiol in menopausal women: a prospective study." Climacteric 14(1): 18-24.

OBJECTIVES: To describe the effects of low-dose hormonal replacement therapy (HRT) on quality of life, metabolic parameters and blood pressure in postmenopausal women.
METHODS: Postmenopausal women untreated with HRT or sex steroids in the previous 12 months were randomized to treatment with 17-estradiol (1mg/day) plus drospirenone (2mg/day) (E2+DRSP) or to calcium (controls). Quality of life was evaluated by the Women's Health Questionnaire (WHQ) at baseline and after 6 and 12 weeks of treatment. Anthropometric, metabolic and blood pressure measurements were performed before and after 3 months of treatment.
RESULTS: WHQ domain scores for vasomotor and somatic symptoms, anxiety/fears, depressed mood, sexual behavior and sleep problems decreased significantly in the E2+DRSP group relative to both baseline and control values ($p<0.05$). Body mass index was unchanged, while waist circumference decreased significantly ($p<0.001$) after E2+DRSP treatment. Significant decreases were also observed after E2+DRSP treatment for blood insulin values, insulin resistance (estimated by homeostasis model assessment) and systolic blood pressure ($p<0.001$, all). In subjects with systolic blood pressure<130mmHg at baseline, no changes in systolic values were registered, while women with baseline high-normal systolic blood pressure (130-139mmHg) showed significant decreases ($p<0.0069$). E2+DRSP did not modify diastolic blood pressure values. In the calcium-treatment group, there were no significant changes in WHQ scores or in anthropometric, metabolic or blood pressure measurements.
CONCLUSION: In postmenopausal women, E2+DRSP administration improves vasomotor symptoms and general aspects of quality of life and may positively influence cardiovascular risk factors.

Genazzani, A. R., M. Stomati, et al. (2011). "Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality." Climacteric 14(6): 661-668.

BACKGROUND: Sexual desire is affected by endocrine and psychosocial factors. Menopausal hormonal changes are relevant to the causes of sexual dysfunction during reproductive aging.
AIM: To evaluate the effects of different types of hormonal replacement therapy (HRT) on sexual function, frequency of sexual intercourse, and quality of relationship in early postmenopausal women. We recruited 48 healthy postmenopausal women aged 50-60 years (mean age 54.5 +/- 3.3 years). Women with climacteric symptoms were uniformly randomized into three groups receiving either dehydroepiandrosterone (DHEA 10 mg) daily, or daily oral estradiol (1 mg) plus dihydrogesterone (5 mg), or daily oral tibolone (2.5 mg)

for 12 months. Women who refused hormonal therapy were treated with oral vitamin D (400 IU). Efficacy was evaluated using the McCoy Female Sexuality Questionnaire before treatment and after 12 months. We evaluated the hormonal profile before treatment and after 3, 6 and 12 months.
RESULTS: The groups receiving DHEA or HRT reported a significant improvement in sexual function compared to baseline ($p < 0.001$ and $p < 0.01$, respectively) using the McCoy total score. The quality of relationship was similar at baseline and after 3, 6 and 12 months of treatment. There were significant increases in the numbers of episodes of sexual intercourse in the previous 4 weeks in women treated with DHEA, HRT and tibolone in comparison with the baseline value ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). No changes in the McCoy score occurred in women receiving vitamin D.
CONCLUSIONS: Daily oral DHEA therapy at the dose of 10 mg, HRT and tibolone all provided a significant improvement in comparison with vitamin D in sexual function and in frequency of sexual intercourse in early postmenopausal women.

Hayashi T, Ina K, Maeda M, Nomura H. (2011). "The effects of selective estrogen receptor modulator treatment following hormone replacement therapy on elderly postmenopausal women with osteoporosis. " Nitric oxide. 24(4):199-203, 2011 May.

OBJECTIVES: A comparison between the atheroprotective and osteoprotective effects of the selective estrogen receptor modulator (SERM) raloxifene and those of hormone replacement therapy (HRT) has not been made in elderly women., METHODS: A randomized prospective controlled trial was performed in a cohort of 32 elderly Japanese women with osteoporosis receiving HRT (estriol plus medroxyprogesterone) for more than 1 year. In 16 randomly selected subjects, HRT was changed to raloxifene therapy (60mg/day, 71.4+/-3.4 years, SERM group). The other 16 patients were continued on HRT (71.8+/-2.9 years, HRT group). As a control group, 14 subjects were enrolled, did not take any medications and were age-matched to experimental patients (72.5+/-3.3 years, control group). Plasma lipids, TNF[alpha], adiponectin, NO metabolites (NOx:NO2(-) and NO3(-)), cyclicGMP and bone-mineral density (BMD) were evaluated at baseline and at 26 and 52 weeks after enrollment., RESULTS: SERM (Raloxifene) increased high-density-lipoprotein cholesterol levels and tended to decrease low-density-lipoprotein cholesterol levels (P=0.058) compared with baseline. Adiponectin, NOx and cGMP levels were significantly increased after 6 months compared with baseline or the HRT group. TNF[alpha] was decreased by raloxifene. In control subjects, no significant changes were observed in any of these markers. Bone-mineral density was higher at baseline in the raloxifene and HRT groups than in the control group, and BMD increased 12 months after baseline in the HRT and control group.
CONCLUSION: SERM improved BMD and endothelial function in elderly postmenopausal women with osteoporosis who had received HRT, and these effects were comparable to or slightly stronger than those of HRT. Changes in adiponectin and TNF[alpha] may underlie the improvements in endothelial function, such as NO signaling.

Heiss, G., R. Wallace, et al. (2008). "Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin.[see comment]." JAMA **299**(9): 1036-45.

CONTEXT: The Women's Health Initiative (WHI) trial of estrogen plus progestin vs placebo was stopped early, after a mean 5.6 years of follow-up, because the overall health risks of hormone therapy exceeded its benefits. OBJECTIVE: To report health outcomes at 3 years (mean 2.4 years of follow-up) after the intervention was stopped. DESIGN, SETTING, AND PARTICIPANTS: The intervention phase was a double-blind, placebo-controlled, randomized trial of conjugated equine estrogens (CEE) 0.625 mg daily plus

medroxyprogesterone acetate (MPA) 2.5 mg daily, in 16,608 women aged 50 through 79 years, recruited by 40 centers from 1993 to 1998. The postintervention phase commenced July 8, 2002, and included 15 730 women. MAIN OUTCOME MEASURES: Semi-annual monitoring and outcomes ascertainment continued per trial protocol. The primary end points were coronary heart disease and invasive breast cancer. A global index summarizing the balance of risks and benefits included the 2 primary end points plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. RESULTS: The risk of cardiovascular events after the intervention was comparable by initial randomized assignments, 1.97% (annualized rate) in the CEE plus MPA (343 events) and 1.91% in the placebo group (323 events). A greater risk of malignancies occurred in the CEE plus MPA than in the placebo group (1.56% [n = 281] vs 1.26% [n = 218]; hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.04-1.48). More breast cancers were diagnosed in women who had been randomly assigned to receive CEE plus MPA vs placebo (0.42% [n = 79] vs 0.33% [n = 60]; HR, 1.27; 95% CI, 0.91-1.78) with a modest trend toward a lower HR during the follow-up after the intervention. All-cause mortality was somewhat higher in the CEE plus MPA than in the placebo group (1.20% [n = 233] vs 1.06% [n = 196]; HR, 1.15; 95% CI, 0.95-1.39). The global index of risks and benefits was unchanged from randomization through March 31, 2005 (HR, 1.12; 95% CI, 1.03-1.21), indicating that the risks of CEE plus MPA exceed the benefits for chronic disease prevention. CONCLUSIONS: The increased cardiovascular risks in the women assigned to CEE plus MPA during the intervention period were not observed after the intervention. A greater risk of fatal and nonfatal malignancies occurred after the intervention in the CEE plus MPA group and the global risk index was 12% higher in women randomly assigned to receive CEE plus MPA compared with placebo.

Maki, P. M., L. H. Rubin, et al. (2009). "Effects of botanicals and combined hormone therapy on cognition in postmenopausal women." Menopause **16**(6): 1167-77.

OBJECTIVE: The aim of this study was to characterize the effects of red clover, black cohosh, and combined hormone therapy on cognitive function in comparison to placebo in women with moderate to severe vasomotor symptoms. METHODS: In a phase II randomized, double-blind, placebo-controlled study, 66 midlife women (of 89 from a parent study; mean age, 53 y) with 35 or more weekly hot flashes were randomized to receive red clover (120 mg), black cohosh (128 mg), 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (CEE/MPA), or placebo. Participants completed measures of verbal memory (primary outcome) and other cognitive measures (secondary outcomes) before and during the 12th treatment month. A subset of 19 women completed objective, physiological measures of hot flashes using ambulatory skin conductance monitors. RESULTS: Neither of the botanical treatments had an impact on any cognitive measure. Compared with placebo, CEE/MPA led to a greater decline in verbal learning (one of five verbal memory measures). This effect just missed statistical significance (P = 0.057) in unadjusted analyses but reached significance (P = 0.02) after adjusting for vasomotor symptoms. Neither of the botanical treatment groups showed a change in verbal memory that differed from the placebo group (Ps > 0.28), even after controlling for improvements in hot flashes. In secondary outcomes, CEE/MPA led to a decrease in immediate digit recall and an improvement in letter fluency. Only CEE/MPA significantly reduced objective hot flashes. CONCLUSIONS: Results indicate that a red clover (phytoestrogen) supplement or black cohosh has no effects on cognitive function. CEE/MPA reduces objective hot flashes but worsens some aspects of verbal memory.

Moriyama, C. K., B. Oneda, et al. (2008). "A randomized, placebo-controlled trial of the effects of physical exercises and estrogen therapy on health-related quality of life in postmenopausal women.[see comment]." Menopause **15**(4 Pt 1): 613-8.

OBJECTIVE: The purpose of this study was to evaluate the isolated and associated effects of estrogen therapy (estradiol valerate 1 mg/d orally) and physical exercise (moderate aerobic exercise, 3 h/wk) on health-related quality of life (HRQOL) and menopausal symptoms among women who had undergone hysterectomy. DESIGN: A 6-month, randomized, double-blind, placebo-controlled clinical trial with 44 postmenopausal women who had undergone hysterectomy. The interventions were physical exercise and hormone therapy (n = 9), being sedentary and hormone therapy (n = 14), physical exercise and placebo (n = 11), and being sedentary and placebo (n = 10). HRQOL was assessed by a Brazilian standard version of the Medical Outcome Study Short-Form Health Survey and symptoms by Kupperman Index at baseline and after 6 months. RESULTS: There was a decrease in symptoms in all groups, but only groups who performed physical exercise showed an increase in quality of life. Analysis of variance showed that changes in physical functioning (P = 0.001) and bodily pain (P = 0.012) scores over the 6-month period differed significantly between women who exercised and women who were sedentary, regardless of hormone therapy. Hormone therapy had no effect, and there was also no significant association between physical exercise and hormone therapy in HRQOL. CONCLUSIONS: Physical exercises can reduce menopausal symptoms and enhance HRQOL, independent of whether hormone therapy is taken.

Saeideh, Z., M. Raziyeh, et al. (2010). "Comparing the effects of continuous hormone replacement therapy and tibolone on the genital tract of menopausal women; a randomized controlled trial." Journal of Reproduction & Infertility **11**(3): 183-187.

INTRODUCTION: Many postmenopausal women who are on hormone replacement therapy discontinue medications due to vaginal bleeding. Tibolone, a synthetic steroid, has minimal stimulatory effect on the endometrium. The aim of this study was to assess the effects of continuous HRT regimen and tibolone on the onset of vaginal bleeding and vaginal maturation value.

MATERIALS AND METHODS: A total of 150 healthy women in postmenopausal period were randomly enrolled in this controlled clinical trial. Patients were randomly allocated into three groups, and were followed for six months. The first 50 women received 2.5 mg tibolone plus a Cal+D tablet (500 mg Calcium and 200 IU vitamin D) daily, the second 50 women received 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate (CEE/MPA) plus one Cal+D tablet daily, and the remaining 50 received only one Cal+D tablet per day and served as the control group. Symptoms were recorded using a questionnaire that assessed vaginal bleeding or spotting, vaginal dryness and intention to continue the medications. Vaginal maturation value was assessed by examining vaginal smears before and after the treatment. The results for the three groups were analyzed using statistical methods.

RESULTS: In comparison with the control group, CEE/MPA and tibolone increased vaginal maturation value and decreased the frequency of vaginal dryness ($p < 0.01$). Women in tibolone group were more likely to continue the treatment regimen than those in the CEE/MPA or the control groups ($p < 0.01$).

CONCLUSION: Tibolone can serve as an appropriate choice for HRT as it has low rates of vaginal bleeding/ spotting episodes and high acceptance rate in postmenopausal women.

Zaborowska, E., J. Brynhildsen, et al. (2007). "Effects of acupuncture, applied relaxation, estrogens and placebo on hot flushes in postmenopausal women: an analysis of two prospective, parallel, randomized studies.[see comment]." Climacteric **10**(1): 38-45.

OBJECTIVE: To assess if transdermal or oral estrogens, acupuncture and applied relaxation decrease the number of menopausal hot flushes/24 h and improve climacteric symptoms, as assessed by the Kupperman index, more than transdermal placebo treatment. SETTING: An outpatient clinic at a Swedish university hospital. METHODS: A total of 102 postmenopausal women were recruited to two studies performed in parallel. In Study I, the women were randomized between transdermal placebo or estrogen treatment and, in Study II, between oral estrogens, acupuncture or applied relaxation for 12 weeks. Climacteric symptoms were measured with daily logbooks on hot flushes. Women completed the assessment questionnaire for the Kupperman index at baseline and after 12 weeks. RESULTS: The number of flushes/24 h decreased significantly after 4 and 12 weeks in all groups except the placebo group. Both at 4 and 12 weeks, acupuncture decreased the number of flushes more ($p<0.05$; $p<0.01$, respectively) than placebo. At 12 weeks, applied relaxation decreased the number of flushes more ($p<0.05$) than placebo. The Kupperman index score decreased in all groups except the placebo group. The decrease in score was significantly greater in all treatment groups than in the placebo group ($p<0.01$). CONCLUSION: Acupuncture and applied relaxation both reduced the number of hot flushes significantly better than placebo and should be further evaluated as alternatives to hormone therapy in women with menopausal vasomotor complaints.

Ziaei, S., M. Moghasemi, et al. (2010). "Comparative effects of conventional hormone replacement therapy and tibolone on climacteric symptoms and sexual dysfunction in postmenopausal women." Climacteric 13(2): 147-156.

OBJECTIVE: To compare the effects of tibolone with those of conventional hormone replacement therapy on climacteric symptoms and sexual function in postmenopausal women.

MATERIALS AND METHODS: In a randomized, controlled trial, 140 postmenopausal women were allocated into three groups. Of the subjects included, 47 women received 2.5 mg tibolone + one Cal+D tablet (500 mg calcium and 200 IU vitamin D) daily; 46 women received 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone (CEE/MPA) + one Cal+D tablet daily; and 47 women received only one Cal+D tablet as the control group. The Greene Climacteric Scale (GCS) questionnaire was used to detect the efficacy of treatment on climacteric symptoms. Rosen's Female Sexual Function Index (FSFI) was used for sexual function evaluation. Sex hormone binding globulin (SHBG), free estradiol index (FEI) and free testosterone index (FTI) were measured before and after treatment. The women were followed up for 6 months

RESULTS: After treatment, all subscores in the GCS improved in the tibolone and CEE/MPA groups ($p < 0.01$), except the sexual subscore in the CEE/MPA group, compared with baseline. There were significant differences in the FSFI in the tibolone and CEE/MPA groups in comparison to the control group after treatment. Tibolone, in comparison to CEE/MPA, significantly lowered SHBG levels and increased the FTI and FEI and improved the desire, arousal and orgasm sexual domains of the FSFI ($p < 0.001$).

CONCLUSION: Tibolone may be an alternative to conventional hormone replacement therapy in the treatment of climacteric symptoms and sexual dysfunction in postmenopausal women.

Placebo- controlled or no treatment-controlled (N=37)

Alhola, P., H. Tuomisto, et al. (2010). "Estrogen + progestin therapy and cognition: a randomized placebo-controlled double-blind study." Journal of Obstetrics & Gynaecology Research 36(4): 796-802.

AIMS: The use of hormone therapy (HT) is a relevant and topical issue in the treatment of menopausal symptoms in women. Information regarding the effects of combination treatment with estrogen and progesterone as well as treatment timing on cognitive function is lacking and was evaluated in healthy pre- and postmenopausal women.
METHODS: Sixteen premenopausal (45-51 years) and 16 postmenopausal (58-70 years) women were randomly assigned to receive either estrogen + progestin therapy (HT) or placebo (PL) for six months. The study was double-blind. Cognitive performance was measured at baseline and follow up with tests of verbal and visuomotor functions, verbal and visual memory, and attention.
RESULTS: In premenopausal women, cognitive attention, when compared to baseline, improved with HT but declined slightly with PL in the two-choice reaction time task (P = .049), while PL was associated with better performance in tests of shared attention (P = 0.024) and auditory attention (P < 0.05). In postmenopausal women, HT was associated with improved performance in verbal episodic memory (P = 0.024) and a minor decline in auditory attention (P = 0.025).
CONCLUSIONS: HT, with estradiol valerate and norethisterone, in healthy women showed only minor effects on attention around the menopausal transition and on memory in postmenopause.

Bachmann, G., C. Bouchard, et al. (2009a). "Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally." Menopause **16**(4): 719-27.

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of low-dose conjugated estrogens (CE) cream for treatment of atrophic vaginitis. METHODS: Postmenopausal women (N = 423) with moderate-to-severe vaginal atrophy were randomized to CE cream 0.3 mg or placebo once daily (21 days on/7 days off) or twice weekly for 12 weeks, followed by open-label treatment with CE cream for 40 weeks consistent with their prior regimen. Primary endpoints were changes in vaginal maturation index (VMI; percentage of superficial cells), vaginal pH, and severity of participant-reported most bothersome symptom (vaginal dryness, itching, burning, or dyspareunia) at week 12. Endometrial safety was assessed by transvaginal ultrasound and endometrial biopsy for 52 weeks. RESULTS: At week 12, improvements in VMI with daily and twice-weekly use of low-dose CE cream (27.9% and 25.8%, respectively) were significantly greater compared with placebo (3.0% and 1.0%, respectively; P < 0.001). Improvements in vaginal pH with daily and twice-weekly CE cream (-1.6 for both) were also significantly greater relative to placebo (-0.4 and -0.3, respectively; P < 0.001). VMI and vaginal pH responses were sustained through 52 weeks. Both CE cream regimens significantly reduced most bothersome symptom scores compared with placebo (P < or = 0.001), including those for dyspareunia (P < or = 0.01). There was no report of endometrial hyperplasia or carcinoma. Adverse events occurred with similar frequency among the active and placebo groups during the double-blind phase. CONCLUSIONS: Daily and twice-weekly use of low-dose CE cream was equally effective in relieving symptoms of vulvovaginal atrophy. Both regimens showed endometrial safety and sustained efficacy during 1 year of therapy.

Bachmann, G., R. A. Lobo, et al. (2008). "Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial." Obstetrics & Gynecology **111**(1): 67-76.

OBJECTIVE: To evaluate the efficacy of two vaginal doses of estradiol (E2) compared with placebo in the treatment of atrophic vaginitis. METHODS: In a multi-center, randomized, double-blind, parallel-group study, 230 postmenopausal women received treatment with 25 mcg or 10 mcg E2 or placebo for 12 weeks. Efficacy was measured through composite score of three vaginal symptoms and grading of vaginal health. Additional analyses included maturation of vaginal and urethral mucosa. Safety assessments included endometrial biopsy, adverse events, changes in laboratory tests, and physical examinations. After 12 weeks of treatment, all patients were switched to the open-label extension and received treatment with 25 mcg E2 up to week 52. RESULTS: Vaginal tablets with 25 mcg and 10 mcg E2 showed significant (P<.001) improvement in composite score of vaginal health. Other results with 10 mcg E2 were not entirely consistent with those for 25 mcg E2. Over 12 weeks, both active treatments resulted in greater decreases in vaginal pH than placebo. There were no significant differences between the 25 mcg and 10 mcg E2 groups in terms of improvements in maturation value or composite score of three vaginal symptoms. The efficacy was maintained to week 52 with 25 mcg E2. CONCLUSION: Vaginal tablets with 25 mcg and 10 mcg E2 provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and increased maturation of the vaginal and urethral epithelium. Those improvements were greater with 25 mcg than with 10 mcg E2. Both doses were effective in the treatment of atrophic vaginitis.

Bachmann, G. A., M. Schaefers, et al. (2007). "Lowest effective transdermal 17beta-estradiol dose for relief of hot flushes in postmenopausal women: a randomized controlled trial.[see comment]." Obstetrics & Gynecology **110**(4): 771-9.

OBJECTIVE: To investigate the efficacy of micro-dose transdermal estrogen in relieving menopausal vasomotor symptoms. METHODS: A randomized, double-blind, placebo-controlled, multi-center trial. Healthy postmenopausal women with at least seven moderate or severe hot flushes per day for at least 1 week, or at least 50 per week, applied transdermal patches with a nominal delivery of 0.023 mg/d 17beta-estradiol and 0.0075 mg/d levonorgestrel (low-dose E2/levonorgestrel; n=145), 0.014 mg/d E2 (micro-dose; n=147), or placebo (n=133) for 12 weeks. The coprimary efficacy variables were the mean changes from baseline in frequency and severity of moderate and severe hot flushes at the week 4 and 12 endpoints. RESULTS: At the week 12 endpoint, mean weekly frequencies of moderate and severe hot flushes were significantly reduced compared with placebo with low-dose E2/levonorgestrel (-51.80; P<.001) and micro-dose E2 (-38.46; P<.001). Severity scores were also significantly reduced with both treatments compared with placebo. At week 12 endpoint, 41.3% of women receiving micro-dose E2 were treatment responders (75% or more reduction from baseline in hot flush frequency; P=.003 compared with 24.2% placebo). In this group, the mean reduction in moderate and severe hot flushes from baseline was approximately 50% after 2, 70% after 4, 90% after 8, and 95% after 12 weeks. There were no differences between active treatments and placebo regarding adverse events. CONCLUSION: Micro-dose E2 (0.014 mg/d) was clinically and statistically significantly more effective than placebo in reducing the number of moderate and severe hot flushes, with a 41% responder rate, supporting the concept of the lowest effective dose.

Bachmann, G. A., M. Schaefers, et al. (2009b). "Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women." Menopause **16**(5): 877-82.

OBJECTIVE: The aim of this study was to investigate the effectiveness of microdose transdermal 17beta-estradiol (E2) therapy in postmenopausal women with moderate to severe vulvovaginal symptoms. METHODS: This report is based on a subset of 121 women who reported most bothersome moderate or severe vulvovaginal symptoms at baseline, from a previous randomized, double-blind, placebo-controlled, multicenter study of 425 healthy, symptomatic, postmenopausal women. Recruits had experienced at least 7 moderate or severe hot flushes daily for at least 1 week or at least 50 moderate or severe hot flushes per week for at least 1 week. Effects on coprimary efficacy variables have been reported previously. Participants received low-dose transdermal E2 plus levonorgestrel (n = 43; nominal delivery 0.023 mg/d E2/0.0075 mg/d levonorgestrel), microdose E2 (n = 42; nominal delivery 0.014 mg/d), or placebo (n = 36) for 12 weeks. Secondary efficacy variables reported herein include mean change from baseline in vaginal pH and vaginal maturation index, the proportion of women with symptoms of vulvar and vaginal atrophy at baseline and week 12, and the proportion of women with moderate-to-severe symptoms of vulvar and vaginal atrophy. RESULTS: Microdose transdermal E2 treatment was associated with a consistent benefit versus placebo in women with vulvovaginal atrophy. There was a statistically significant difference between both E2 versus placebo for changes in vaginal pH and vaginal maturation index. CONCLUSIONS: Microdose transdermal E2 offers a useful addition to the therapeutic armamentarium for postmenopausal women in whom vulvovaginal symptoms are particularly troublesome.

Baksu, B., A. Baksu, et al. (2009). "Do different delivery systems of hormone therapy have different effects on psychological symptoms in surgically menopausal women? A randomized controlled trial." Maturitas **62**(2): 140-5.

OBJECTIVE: To compare the influence of different delivery forms of estrogen therapy on menopausal and psychological symptoms in surgically menopausal women. STUDY DESIGN: Surgically menopausal women were assigned to a 1-year-therapy with oral conjugated estrogen 0.625mg/day (n=35), intranasal 300microg/day estradiol hemihidrate (n=33), percutaneous gel 1.5mg/day estradiol hemihidrate (n=32) or no treatment (control group, n=32). Serum E(2) and FSH levels, Kupperman's Scale used to assess climacteric symptoms, Hamilton Depression Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) scores were assessed before and after 1-year-therapy. RESULTS: After 1 year, the greatest increase in E(2) was in the oral group, followed by the transdermal gel, and then the intranasal group (oral vs transdermal gel: p=0.022: oral vs intranasal: p=0.0001; transdermal gel vs intranasal: p=0.0001). All treatment groups improved significantly in total Kupperman index score and HARS ($p<0.05$) with no difference between the groups. With regard to HDRS, all treatment groups improved significantly ($p<0.05$) with the greatest improvement in the oral group, and no difference between transdermal gel and intranasal groups (oral vs transdermal gel: p=0.015; oral vs intranasal: p=0.001; transdermal gel vs intranasal: p=0.735). Control group scored worse in all tests after study ($p<0.05$). All scores correlated significantly with post-treatment serum E(2) and FSH levels ($p<0.001$). CONCLUSION: Oral, intranasal and percutaneous gel estradiol therapies significantly improve menopausal and psychological symptoms in surgically menopausal women with oral route better than transdermal gel and intranasal modalities against depressive mood.

Buster, J. E., W. D. Koltun, et al. (2008). "Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial." Obstetrics & Gynecology **111**(6): 1343-51.

OBJECTIVE: To investigate the safety and efficacy of a transdermal estradiol (E2) spray in women with postmenopausal vasomotor symptoms. METHOD: A randomized, double-blind, placebo-controlled, multicenter, parallel-group clinical trial was conducted. Postmenopausal women (N=454) with at least eight moderate-to-severe hot flushes per day applied daily, one, two, or three E2 (90 microliter spray contains 1.53 mg E2) or matching placebo sprays. The primary efficacy endpoints were mean change from baseline in frequency and severity of

moderate-to-severe hot flushes at weeks 4 and 12. RESULTS: All three E2 groups showed a significant decrease in hot flushes at weeks 4 and 12 compared with their placebo groups (P<.010). The mean change in frequency at week 12 was eight fewer flushes per day for women in the E2 groups and between four and six fewer flushes for women in the placebo groups. Women in the three- and two-E2 spray groups demonstrated significant (P<.050) reductions in severity score at weeks 4 and 12; women in the one-spray group showed significant reductions at week 5. At week 12, the majority (74-85%) of women on E2 showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group. The systemic E2 delivery rates at week 12 were approximately 0.021 mg/d, 0.029 mg/d, and 0.040 mg/d for the one-, two-, and three-spray doses, respectively. Common adverse events were similar to those previously reported with other transdermal products. Treatment-related application site reaction rate was similar to placebo (1.3% compared with 1.8%). CONCLUSION: The three dose levels of E2 spray achieved efficacy at 0.021-0.040 mg/d delivery rates. The spray is a well-tolerated, new, convenient method of delivering low-dose E2 transdermally.

Chlebowski, R. T., G. L. Anderson, et al. (2010). "Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women." JAMA 304(15): 1684-1692.

CONTEXT: In the Women's Health Initiative randomized, placebo-controlled trial of estrogen plus progestin, after a mean intervention time of 5.6 (SD, 1.3) years (range, 3.7-8.6 years) and a mean follow-up of 7.9 (SD, 1.4) years, breast cancer incidence was increased among women who received combined hormone therapy. Breast cancer mortality among participants in the trial has not been previously reported.
OBJECTIVE: To determine the effects of therapy with estrogen plus progestin on cumulative breast cancer incidence and mortality after a total mean follow-up of 11.0 (SD, 2.7) years, through August 14, 2009.
DESIGN, SETTING, AND PARTICIPANTS: A total of 16,608 postmenopausal women aged 50 to 79 years with no prior hysterectomy from 40 US clinical centers were randomly assigned to receive combined conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo pill. After the original trial completion date (March 31, 2005), reconsent was required for continued follow-up for breast cancer incidence and was obtained from 12,788 (83%) of the surviving participants.
MAIN OUTCOME MEASURES: Invasive breast cancer incidence and breast cancer mortality.
RESULTS: In intention-to-treat analyses including all randomized participants and censoring those not consenting to additional follow-up on March 31, 2005, estrogen plus progestin was associated with more invasive breast cancers compared with placebo (385 cases [0.42% per year] vs 293 cases [0.34% per year]; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; P = .004). Breast cancers in the estrogen-plus-progestin group were similar in histology and grade to breast cancers in the placebo group but were more likely to be node-positive (81 [23.7%] vs 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23-2.58; P = .03). There were more deaths directly attributed to breast cancer (25 deaths [0.03% per year] vs 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00-4.04; P = .049) as well as more deaths from all causes occurring after a breast cancer diagnosis (51 deaths [0.05% per year] vs 31 deaths [0.03% per year]; HR, 1.57; 95% CI, 1.01-2.48; P = .045) among women who received estrogen plus progestin compared with women in the placebo group.
CONCLUSIONS: Estrogen plus progestin was associated with greater breast cancer incidence, and the cancers are more commonly node-positive. Breast cancer mortality also appears to be increased with combined use of estrogen plus progestin.

Endrikat, J., T. Graeser, et al. (2007). "A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous-combined hormone therapy preparation containing 1mg estradiol valerate/2mg dienogest on hot flushes in postmenopausal women." Maturitas **58**(2): 201-7.

OBJECTIVES: To evaluate the effects of an estrogen-reduced, continuous-combined hormone therapy preparation (HT) containing 1mg estradiol valerate (1EV) and 2mg dienogest (2DNG) on the number of moderate and severe hot flushes. METHODS: This study compared the effects of an oral continuous-combined HT containing 1mg EV and 2mg DNG (1EV/2DNG) with those of placebo. The planned treatment duration was 12 weeks. Data were obtained from 324 postmenopausal women. The primary efficacy variable was the individual relative change of the mean number of moderate and severe hot flushes per week. Weeks 5-12 of treatment were compared with the 2 weeks preceding the treatment phase. RESULTS: Moderate and severe hot flushes were reduced by 80.8+/-30.9% in the 1EV/2DNG group and by 41.5+/-39.4% in the placebo group. This difference was statistically significant ($p<0.0001$; Wilcoxon's rank sum test). The incidence of all types of hot flushes (mild+moderate+severe) was reduced by 75.2+/-30.2% under 1EV/2DNG and by 35.3+/-37.0% under placebo. In the subset of non-hysterectomized women, exposure to 1EV/2DNG led to 2.4+/-6.2 days with bleeding in the reference period of 84 days of treatment, versus 0.3+/-1.3 days in the placebo group. The safety profile of 1EV/2DNG was very similar to that of placebo. CONCLUSIONS: Continuous-combined HT preparation with 1mg EV and 2mg DNG induced a significant reduction of moderate and severe hot flushes compared to placebo ($p<0.0001$). Thus, this low-estrogen preparation is an effective and safe option for HT.

Fahlen, M., B. Wallberg, et al. (2011). "Health-related quality of life during hormone therapy after breast cancer: a randomized trial." Climacteric 14(1): 164-170.

AIM: To study the effects of menopausal hormone therapy (HT) on health-related quality of life in women after breast cancer.

PATIENTS AND METHODS: In the Stockholm trial, breast cancer survivors were randomized to HT (estradiol and progestogen) or to a control group (no treatment). A subgroup of 75 women was studied (38 with HT, 37 controls). Fifty patients were on concomitant tamoxifen. Patients completed three questionnaires (EORTC QLQ C-30, EORTC QLQ-BR 23 and the Hospital Anxiety and Depression Scale (HADS)) during 1 year of treatment.

RESULTS: A significant group-by-time interaction was found for improvement of insomnia in the HT group ($p<0.001$). Within the HT group, but not in the control group, there was significant improvement for HADS anxiety, HADS depression, emotional, cognitive, and social functions and global quality of life. When HT was added to tamoxifen, the increase in global quality of life was significant ($p<0.01$).

CONCLUSION: The effects of HT on quality of life in breast cancer survivors have not previously been reported. The present data suggest that this controversial treatment may improve quality of life after breast cancer.

Fonseca, A. M., V. R. Bagnoli, et al. (2007). "Monophasic estrogen-progestogen therapy and sexuality in postmenopausal women." Clinical Drug Investigation **27**(2): 131-7.

OBJECTIVE: This study aimed to evaluate the effects of monophasic estrogen-progestogen therapy on the sexuality and climacteric symptoms of postmenopausal women. PATIENTS AND METHODS: A prospective, randomised, double-blind, crossover, placebo-controlled,

single-centre study was carried out over a total of 12 consecutive months in 40 postmenopausal women with an intact uterus who had no contraindications to hormone therapy. Patients received 17beta-estradiol 2mg in combination with norethisterone acetate 1mg (Cliane) daily for 6 months or one placebo tablet daily for 6 months. The tablets were identical in appearance. After 6 months, the groups were crossed over and the patients were followed up for another 6 months. The groups were homogenous with respect to age, height, bodyweight, body mass index and race. For the statistical analysis, the group receiving hormone therapy was referred to as group A and the placebo group was designated group B, irrespective of the placebo/hormone therapy sequence. RESULTS: In group A there were fewer hot flashes ($F=22.85$, $p<0.01$) and an improvement in sexual interest ($F=5.55$, $p<0.05$). The sequence in which the medication was received resulted in a statistically significant difference with respect to dyspareunia ($F=9.65$, $p<0.01$) and satisfaction with the duration of penetration ($F=6.58$, $p<0.05$). In the intrapatient analysis of variation with respect to orgasmic capability and the presence of dialogue with partner regarding the couple's sexual life, whether the placebo was taken prior to or following hormone therapy was significant ($F=17.12$, $p<0.001$ and $F=7.10$, $p<0.05$, respectively). CONCLUSIONS: Monophasic estrogen-progestogen therapy has a beneficial effect on sexuality and on hot flashes in postmenopausal women.

Freedman, M., A. M. Kaunitz, et al. (2009). "Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy." Menopause **16**(4): 735-41.

OBJECTIVE: The aim of this study was to evaluate low-dose synthetic conjugated estrogens A (SCE-A) cream administered twice weekly for the treatment of moderate to severe vulvovaginal atrophy (VVA) in a symptomatic postmenopausal population. METHODS: In a multicenter, double-blind, randomized, placebo-controlled study, 305 women with symptoms of VVA were treated with either 1 g SCE-A cream (n = 150) or matching placebo (n = 155) for a period of up to 12 weeks. Participants had to have a vaginal pH of greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and at least one of five symptoms of VVA (dryness, soreness, irritation, pain with intercourse, and bleeding after intercourse) that was moderate or severe in intensity. Women had to select one moderate or severe symptom as the most bothersome. RESULTS: Efficacy was assessed at 2, 3, 4, 8, and 12 weeks and included the change from baseline in the severity of the most bothersome symptom (MBS), maturation index, and pH. Most women identified vaginal dryness as the MBS (48%) followed by pain with intercourse (31.3%). A statistically significant increase in the maturation index and significant decreases in pH and severity of the MBS were observed for those treated with SCE-A vaginal cream compared with placebo. CONCLUSIONS: A low dose (1 g = 0.625 mg) of SCE-A vaginal cream administered twice weekly was shown to be effective compared with placebo in treating VVA in postmenopausal women for the three coprimary efficacy measures of maturation index, pH, and severity of the MBS.

Gast, M. J., M. A. Freedman, et al. (2009). "A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women." Menopause **16**(2): 247-56.

OBJECTIVE: To evaluate the effects of combined vaginal and oral low-dose estrogen plus progestogen therapy (EPT) on the frequency and severity of dyspareunia, sexual function, and quality of life in recently postmenopausal women. METHODS: This outpatient, double-blind, randomized, placebo-controlled trial enrolled 285 healthy, sexually active postmenopausal women aged 45 to 65 years. Women received either one daily oral low-dose conjugated estrogens (0.45 mg)/medroxyprogesterone (1.5 mg) tablet for six 28-day cycles along with 1 g conjugated estrogens vaginal cream (0.625 mg), intravaginally for the first 6 weeks of the trial or a placebo cream and placebo tablet. Efficacy was evaluated using the McCoy Female Sexuality Questionnaire, self-reported daily diary cards, the Brief Index of Sexual Functioning-Women

(BISF-W), and the Women's Health Questionnaire. RESULTS: The EPT group had a significant decrease in the frequency of dyspareunia compared with baseline and placebo in an analysis of responses to the McCoy Female Sexuality Questionnaire. Also, EPT was associated with a significant improvement in a woman's level of sexual interest, frequency of orgasm, and pleasure of orgasm. There was no effect of EPT use on coital frequency. The EPT group had significant improvement in receptivity/initiation and relationship satisfaction, although not in other BISF-W domains, versus placebo (BISF-W analysis) and significant improvement versus placebo on most Women's Health Questionnaire responses. CONCLUSIONS: EPT provided a statistically significant improvement compared with placebo in dyspareunia, sexual experience, and quality of life as measured in this study. In general, EPT also improved self-reported sexual perception and enjoyment significantly compared with placebo.

Hachul, H., L. R. A. Bittencourt, et al. (2008). "Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women." International Journal of Gynaecology & Obstetrics **103**(3): 207-12.

OBJECTIVE: To investigate the effects of estrogen and progesterone on sleep in postmenopausal women. METHOD: The 33 participants were randomly assigned to an estrogen or placebo group after undergoing clinical and hormonal assessments and a polysomnogram, and they underwent the same tests again after 12 weeks. Then, while still taking estrogen or placebo, they all received progesterone for another 12 weeks and underwent a final polysomnogram. RESULTS: Estrogen plus progesterone was more effective than estrogen alone in decreasing the prevalence of periodic limb movement (PLM) (8.1% vs 2.8%), hot flashes (14.2% vs 0%), and bruxism (11.1% vs 0%) at night, or somnolence and attention difficulty during the day. The prevalences of breathing irregularities, arousal from sleep, anxiety, and memory impairment were decreased in both groups following progesterone treatment. CONCLUSION: While not significantly affecting sleep quality, hormone therapy decreased the prevalence of arousal in both groups and that of PLM in the group treated with estrogen plus progesterone.

Haines, C., S. L. Yu, et al. (2009). "Micro-dose transdermal estradiol for relief of hot flushes in postmenopausal Asian women: a randomized controlled trial." Climacteric **12**(5): 419-26.

OBJECTIVES: To compare the effect of micro-dose transdermal estradiol and placebo on the incidence and severity of menopausal symptoms and well-being in postmenopausal Asian women with vasomotor symptoms. DESIGN: Multicenter, double-blind, randomized, placebo-controlled study. RESULTS: Of 165 subjects randomized to estradiol 0.014 mg/day or placebo for 12 weeks, 80 per group were included in the analysis. Groups were comparable at baseline, although time since menopause was slightly shorter in the estradiol group. There was a greater reduction in mean weekly hot flushes at week 12 in the estradiol group (55%) than the placebo group (40%; $p < 0.01$), which was evident by week 4. A similar pattern was seen for moderate and severe hot flushes (-58% vs. -39%, respectively). Reductions were statistically significant at weeks 4, 8, and 12. Vaginal pH fell significantly in the estradiol group by week 4 and then remained stable throughout the treatment period, but there were no significant changes in the placebo group. Vaginal maturation value increased more in the estradiol than the placebo group ($p < 0.001$). Few subjects had vaginal bleeding or spotting. Quality of life improved similarly in both groups. Urogenital symptoms improved considerably from baseline in both treatment groups, with no significant differences. Eight subjects experienced treatment-related adverse events (seven in the estradiol group). CONCLUSIONS: In Asian women, micro-dose estradiol was significantly superior to placebo in improving vasomotor symptoms. The bleeding profile was comparable with that of placebo. Micro-dose estradiol was safe and well tolerated in Asian women.

Hedrick, R. E., R. T. Ackerman, et al. (2009). "Transdermal estradiol gel 0.1% for the treatment of vasomotor symptoms in postmenopausal women." Menopause **16**(1): 132-40.

OBJECTIVE: The objective of this study was to evaluate the efficacy and safety of three doses of estradiol gel 0.1% (Divigel, a novel formulation consisting of 1 mg estradiol per 1 g transdermal gel) to reduce the frequency and severity of vasomotor symptoms and signs of vulvar and vaginal atrophy associated with menopause. DESIGN: A total of 488 postmenopausal women were evaluated in a 12-week study comparing placebo with estradiol gel 0.1% at doses of 1.0, 0.5, and 0.25 mg/day, with estimated daily deliveries of 0.027, 0.009, and 0.003 mg of estradiol, respectively. Primary endpoints were the change from baseline in daily frequency and severity of moderate to severe vasomotor symptoms. Change from baseline in the signs of vulvar and vaginal atrophy (vaginal pH and percentage of superficial cells) was also assessed. RESULTS: Treatment with estradiol gel 0.1% showed statistically significant reductions in frequency and severity of vasomotor symptoms from baseline compared with placebo as early as Week 2 that were maintained throughout treatment. Signs of vulvar and vaginal atrophy were also significantly improved from baseline with all three doses of estradiol gel 0.1% compared with placebo. CONCLUSIONS: Low-dose transdermal estradiol gel 0.1% is an effective treatment for relief of vasomotor symptoms, as well as signs of vulvar and vaginal atrophy, associated with menopause. Estradiol gel 0.1% offers multiple dosing options to individualize patient therapy, including the lowest available effective dose (0.25 mg estradiol, delivering 0.003 mg/d estradiol) to treat the vasomotor symptoms of menopause.

Honjo, H. and Y. Taketani (2009). "Low-dose estradiol for climacteric symptoms in Japanese women: a randomized, controlled trial." Climacteric **12**(4): 319-28.

OBJECTIVES: To investigate two different doses of oral estradiol to reduce the number of hot flushes in Japanese women with climacteric symptoms. METHODS: Women (n = 211) aged 40-64 years who had experienced natural menopause or bilateral oophorectomy, with > or = three moderate/severe hot flushes per day in the week before study, were randomized to receive micronized estradiol (E2) 0.5 or 1.0 mg or placebo once daily for 8 weeks. The primary efficacy endpoint was percentage change in mean daily number of hot flushes over 7 days from baseline to final examination. RESULTS: Percentage change in mean daily number of hot flushes at final examination was similar for E2 0.5 mg and E2 1.0 mg (-79.58 +/- 28.29% vs. -82.49 +/- 25.31%, p = 0.555) but was significantly lower with placebo (-57.89 +/- 34.15%, p < 0.001 vs. E2, both doses). There was no significant difference in number of treatment-related adverse events occurring in the E2 0.5 and 1.0 mg groups (25% and 36.6%, respectively). The higher E2 dose showed more pronounced effects on symptom severity. CONCLUSIONS: The dose of 0.5 mg/day was effective as the oral E2 starting dose for treatment of hot flushes in Japanese women.

Huang, A. J., B. Ettinger, et al. (2007). "Endogenous estrogen levels and the effects of ultra-low-dose transdermal estradiol therapy on bone turnover and BMD in postmenopausal women." Journal of Bone & Mineral Research **22**(11): 1791-7.

In a randomized controlled trial of a 0.014 mg/d transdermal estradiol patch, serum bone turnover markers decreased to a greater degree in postmenopausal women with lower versus higher endogenous estradiol levels. This suggests that the protective effects of ultra-low-dose estrogen therapy on the postmenopausal skeletal health may depend critically on women's endogenous estrogen levels before treatment. INTRODUCTION: Postmenopausal women with very low or undetectable estradiol levels have lower BMD, increased bone turnover, and increased risk of hip and vertebral fracture. We assessed whether the effects of ultra-low-dose 0.014 mg/d transdermal estradiol (Menostar; Berlex, Montvale, NJ, USA) on bone turnover and BMD are influenced by endogenous estradiol levels. MATERIALS AND METHODS:

We analyzed data from postmenopausal women (mean age, 66 yr) randomized to an 0.014-mg/d transdermal estradiol patch or placebo in the ultra-low-dose transdermal estrogen (ULTRA) trial. The free estradiol index (FEI), calculated as the ratio of total estradiol (by mass spectometry) to sex hormone-binding globulin (SHBG; by immunoradiometric assay) x 100, was used to estimate bioavailable estradiol at baseline. Among the 382 women who adhered to >or=80% of study medication, we examined change in serum osteocalcin and bone-specific alkaline phosphatase levels at 12 mo and total hip and lumbar spine BMD at 24 mo in each quintile of FEI. RESULTS: Compared with women in the highest quintile of FEI, those in the lowest quintile of FEI had a 26% greater reduction in bone-specific alkaline phosphatase and 15% greater reduction in osteocalcin in response to ultra-low estradiol treatment (p for trend across quintiles < 0.05). There was a trend toward greater improvement in total hip BMD (p = 0.06) but not spine BMD (p = 0.90) in those with lower versus higher FEI levels. CONCLUSIONS: The beneficial effects of ultra-low-dose 0.014-mg/d transdermal estrogen therapy on skeletal health may depend critically on women's endogenous estrogen levels before treatment.

Huang, A. J., G. F. Sawaya, et al. (2009). "Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women." Menopause **16**(4): 639-43.

OBJECTIVE: The aim of this study was to examine interactions between hot flushes, estrogen plus progestogen therapy (EPT), and coronary heart disease (CHD) events in postmenopausal women with CHD. METHODS: We analyzed data from the Heart and Estrogen/Progestin Replacement Study, a randomized, placebo-controlled trial of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate in 2,763 postmenopausal women with CHD. Hot flushes were assessed at baseline using self-administered questionnaires; women reporting bothersome hot flushes "some" to "all" of the time were considered to have clinically significant flushing. Cox regression models were used to examine the effect of EPT on risk of CHD events among women with and without significant flushing at baseline. RESULTS: The mean age of participants was 66.7 +/- 6.8 years, and 89% (n = 2,448) were white. Sixteen percent (n = 434) of participants reported clinically significant hot flushes at baseline. Among women with baseline flushing, EPT increased risk of CHD events nine-fold in the first year compared with placebo (hazard ratio = 9.01; 95% CI, 1.15-70.35); among women without baseline flushing, treatment did not significantly affect CHD event risk in the first year (hazard ratio = 1.32; 95% CI, 0.86-2.03; P = 0.07 for interaction of hot flushes with treatment). The trend toward differential effects of EPT on risk for CHD among women with and without baseline flushing did not persist after the first year of treatment. CONCLUSIONS: Among older postmenopausal women with CHD, EPT may increase risk of CHD events substantially in the first year of treatment among women with clinically significant hot flushes but not among those without hot flushes.

Kalleinen, N., O. Polo, et al. (2008). "The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women." Climacteric **11**(3): 233-43.

OBJECTIVE: In this prospective randomized, placebo-controlled and double-blind study, the objective was to investigate the effects of estrogen-progestin treatment (EPT) on sleep in pre- and postmenopausal women. DESIGN: Seventeen premenopausal (aged 45-51 years) and 18 postmenopausal (aged 58-70 years) women were studied in a sleep laboratory for two nights (one night for adaptation and one study night) before and after 6 months of treatment with EPT or placebo. During the treatment period, premenopausal women received cyclic EPT or placebo and the postmenopausal women continuous EPT or placebo. Polysomnography and questionnaires were used to evaluate sleep and well-being. RESULTS: At the end of the treatment period, premenopausal women receiving EPT had more awakenings from stage 1

sleep (p = 0.047) and postmenopausal women with EPT had a greater total number of awakenings (p = 0.031) than the corresponding placebo group. Further, sleepiness decreased less in the premenopausal EPT group than in the placebo group (p = 0.031). In postmenopausal women, EPT decreased and placebo slightly increased slow wave activity during the second non-rapid eye movement sleep episode (p = 0.046). CONCLUSIONS: In premenopausal and late postmenopausal women, EPT had only random and marginal effects on sleep. Although the limited findings were mostly unfavorable for EPT, one cannot conclude that EPT deteriorates sleep. Further, neither middle-aged cycling premenopausal women nor older postmenopausal women benefit from estrogen-progestin treatment in terms of their sleep quality.

Lee, B. S., B. M. Kang, et al. (2007). "Efficacy and tolerability of estradiol 1 mg and drospirenone 2 mg in postmenopausal Korean women: a double-blind, randomized, placebo-controlled, multicenter study." Maturitas **57**(4): 361-9.

OBJECTIVES: The aim of this study was to demonstrate that the therapeutic efficacy of an estradiol 1mg/drospirenone 2mg (E2/DRSP) preparation is superior to a placebo in postmenopausal Korean women with hot flushes and other climacteric symptoms, and to demonstrate that this treatment is both safe and tolerable. METHODS: This was a double-blind, randomized, placebo-controlled, multicenter study over four 28-day treatment cycles. A total of 158 subjects were screened and 90 women were randomized into two treatment groups (E2/DRSP group, n=45; placebo group, n=45). The primary efficacy parameter was the individual relative change of hot flushes. The secondary efficacy parameters such as other climacteric, urogenital symptoms and vaginal bleeding patterns were also evaluated, and the occurrence of any adverse events was noted. In addition, physical, gynecological examinations and laboratory analyses were performed at the beginning and end of the study. RESULTS: The mean number of hot flushes per week during treatment weeks 3-16 decreased by 48.1% during treatment with placebo, and by 84.4% during treatment with E2/DRSP (p<0.001). The E2/DRSP combination also reduced the incidence and intensity of menopausal symptoms in postmenopausal women. Most of adverse events was mild or moderate degree of intensity. None of the parameters measured in the study, including laboratory analyses, physical and gynecological examinations, vital signs, and weight, led to any concerns of safety. CONCLUSIONS: The E2 1mg/DRSP 2mg combination tested in the study was efficacious and safe in the treatment of hot flushes and other climacteric symptoms in postmenopausal Korean women.

Lin, S. Q., L. Z. Sun, et al. (2011). "Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women." Climacteric 14(4): 472-481.

OBJECTIVES: Drospirenone is a novel progestogen that, combined with 17-estradiol, reduces the frequency and severity of menopausal vasomotor symptoms (VMS) in different populations. This double-blind, multicenter study compared the efficacy, safety and tolerability of 2 mg drospirenone/1 mg estradiol (DRSP/E2) vs. placebo in Chinese postmenopausal women with moderate to severe VMS.

METHODS: Women, aged 45-65 years, were randomized to DRSP/E2 (n=183) or placebo (n=61) once daily for four 28-day cycles. Changes in the frequency and severity of hot flushes were analyzed as primary variables, together with other climacteric and urogenital symptoms, clinical global improvement, adverse events and physical/gynecological parameters.

RESULTS: Relative changes in numbers of hot flushes/week were -80.4% for DRSP/E2 vs. -51.9% for placebo (treatment difference -28.5%, p<0.0001). There were trends toward a

greater reduction in severity of hot flushes with DRSP/E2 treatment. Patients treated with DRSP/E2 were more often free from sweating episodes (p<0.0001) and vaginal dryness (p=0.0008). Other climacteric symptoms, including nervousness and pollakisuria, followed a trend of greater response with DRSP/E2. Similar to other combination HRT regimens, DRSP/E2 increased occurrences of bleeding, but these decreased over time. Adverse events in patients treated with DRSP/E2 were mostly mild to moderate and withdrawal rates were low.
CONCLUSIONS: Daily treatment of postmenopausal Chinese women with DRSP/E2 for 16 weeks significantly reduced the incidence of hot flushes and demonstrated advantages vs. placebo for other climacteric symptoms. These results indicate that DRSP/E2 is effective, safe and well tolerated in postmenopausal Chinese women.

Maki, P. M., M. J. Gast, et al. (2007). "Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial." Neurology **69**(13): 1322-30.

OBJECTIVE: To evaluate the effects of hormone therapy (HT) on cognition and subjective quality of life (QoL) in recently postmenopausal women with cognitive complaints. METHODS: Cognitive Complaints in Early Menopause Trial (COGENT) was a randomized, double-blind, placebo-controlled, multicenter, pilot study of 180 healthy postmenopausal women aged 45 to 55 years, randomly assigned to receive either placebo or conjugated equine estrogen 0.625 mg/medroxyprogesterone acetate 2.5 mg for 4 months. Outcome measures included memory, subjective cognition, QoL, sexuality, and sleep, which were assessed at baseline and month 4. RESULTS: The study was terminated before the expected final sample size of 275 due to a decrease in enrollment coinciding with the publication of findings from the Women's Health Initiative. There were no differences between groups on any cognitive or QoL measures, except for an increase in sexual interest and thoughts with HT. Modest negative effects on short- and long-term verbal memory approached significance ($p < 0.10$). Women with baseline vasomotor symptoms (VMS) showed a decrease in VMS and an improvement in general QoL, but no cognitive benefit vs placebo. CONCLUSIONS: With the power to detect an effect size of >or=0.45, this study suggests potential modest negative effects on verbal memory that are consistent with previous hormone therapy trials in older women.

Marinho, R. M., J. M. Soares, Jr., et al. (2008). "Effects of estradiol on the cognitive function of postmenopausal women." Maturitas **60**(3-4): 230-4.

OBJECTIVE: To analyze the effect of estrogen on the cognitive function of postmenopausal women through psychometric tests. METHODS: Seventy-four postmenopausal women were divided into two groups: (G1) estrogen group (n = 34), treated with 2 mg 17 beta-estradiol; (G2) placebo group (n = 31), treated with inactive substance. All the participants were submitted, before and after treatment, to psychometric tests, Greene's Scale of Climacteric Symptoms and the Hamilton Scale for depression. Statistical analysis was performed using the Mann-Whitney test and Student's t-test. In order to evaluate the degree of improvement of symptoms or depression after estrogen treatment, Spearman's correlation coefficient was calculated. RESULTS: A few psychometric tests (immediate and late recall of story, Trailmaking A and B, FAS, Stroop, Bells tests) showed post-intervention improvement, but these were not significant when compared to the placebo group's data. The estrogen group's climacteric symptoms were mitigated in comparison to placebo's, but there was no significant difference between the two groups on the Hamilton Scale. Reduction in climacteric symptoms was associated with improvement in executive function performance as evaluated

by the Stroop test. CONCLUSION: Our results suggest estrogen improves the cognitive function, possibly due to a decrease in vasomotor symptoms.

Merz, C. N. B., M. B. Olson, et al. (2010). "A randomized controlled trial of low-dose hormone therapy on myocardial ischemia in postmenopausal women with no obstructive coronary artery disease: results from the National Institutes of Health/National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE)." American Heart Journal 159(6): 987.e981-987.

BACKGROUND: Compared with men, women have more evidence of myocardial ischemia with no obstructive coronary artery disease. Although low endogenous estrogen levels are associated with endothelial dysfunction, the role of low-dose hormone therapy has not been fully evaluated. We postulate that a 12-week duration of low-dose hormone replacement therapy is associated with myocardial ischemia and endothelial dysfunction.
METHODS AND RESULTS: Using a multicenter, randomized, placebo-controlled design, subjects were randomized to receive either 1 mg norethindrone/10 microg ethinyl estradiol or placebo for 12 weeks. Chest pain and menopausal symptoms, cardiac magnetic resonance spectroscopy, brachial artery reactivity, exercise stress testing, and psychosocial questionnaires were evaluated at baseline and exit. Recruitment was closed prematurely because of failure to recruit after publication of the Women's Health Initiative hormone trial. Of the 35 women who completed the study, there was less frequent chest pain in the treatment group compared with the placebo group (P = .02) at exit. Women taking 1 mg norethindrone/10 microg ethinyl estradiol also had significantly fewer hot flashes/night sweats (P = .003), less avoidance of intimacy (P = .05), and borderline differences in sexual desire and vaginal dryness (P = .06). There were no differences in magnetic resonance spectroscopy, brachial artery reactivity, compliance, or reported adverse events between the groups.
CONCLUSIONS: These data suggest that low-dose hormone therapy improved chest pain symptoms, menopausal symptoms, and quality of life, but did not improve ischemia or endothelial dysfunction. Given that it was not possible to enroll the prespecified sample size, these results should not be considered definitive.

Michael, Y. L., R. Gold, et al. (2010). "Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial." Menopause **17**(2): 295-302.

OBJECTIVE: Although estrogen may be linked to biological pathways that maintain higher physical function, the evidence is derived mostly from observational epidemiology and therefore has numerous limitations. We examined whether hormone therapy affected physical function in women 65 to 79 years of age at enrollment. METHODS: This study involves an analysis of the Women's Health Initiative randomized controlled trials of hormone therapy in which 922 nondisabled women who had previous hysterectomies were randomized to receive estrogen therapy or a placebo and 1,458 nondisabled women with intact uteri were randomized to receive estrogen + progestin therapy or a placebo. Changes in physical function were analyzed for treatment effect, and subgroup differences were evaluated. All women completed performance-based measures of physical function (grip strength, chair stands, and timed walk) at baseline. These measures were repeated after 1, 3, and 6 years. RESULTS: Overall, participants' grip strength declined by 12.0%, chair stands declined by 3.5%, and walk pace slowed by 11.4% in the 6 years of follow-up (all P values <0.0001). Hormone therapy, as compared with placebo, was not associated with an increased or decreased risk of decline in physical function in either the intention-to-treat analyses or in analyses restricted to participants who were compliant in taking study pills. CONCLUSIONS: Hormone therapy provided no overall protection against functional

decline in nondisabled postmenopausal women 65 years or older in 6 years of follow-up. This study did not address the influence of hormone therapy for women of younger ages.

Panay, N., O. Ylikorkala, et al. (2007). "Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief." Climacteric **10**(2): 120-31.

OBJECTIVE: To evaluate the efficacy of two ultra-low-dose 17beta-estradiol plus norethisterone acetate (NETA) treatment regimens for relieving menopausal symptoms. DESIGN: A total of 577 postmenopausal women were enrolled, in three treatment groups in a double-blind, randomized, placebo-controlled study of 0.5 mg 17beta-estradiol + 0.1 mg NETA or 0.5 mg 17beta-estradiol + 0.25 mg NETA or placebo. Participants returned at weeks 4, 8, 12 and 24 for climacteric complaint evaluation based on a daily diary vasomotor symptom record. Patients were assessed by the Greene Climacteric Scale and urogenital symptoms were also evaluated. RESULTS: Treatment with ultra-low-dose 0.5 mg 17beta-estradiol + 0.1 mg NETA (0.1 Group) or 0.5 mg 17beta-estradiol + 0.25 mg NETA (0.25 Group) effectively reduced the severity and number of hot flushes within the initial weeks of therapy. Compared to placebo, a rapid, statistically significant decrease in the frequency and severity of hot flushes was achieved by week 3, followed by further improvement which continued throughout the study. There were no statistically significant differences between the active treatment arms. CONCLUSIONS: The data show that both ultra-low-dose regimens are effective in reducing the severity and number of hot flushes compared to placebo, with good safety profiles.

Pefanco, M. A., A. M. Kenny, et al. (2007). "The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women." Journal of the American Geriatrics Society **55**(3): 426-31.

OBJECTIVES: To evaluate the effect of ultra-low-dose (0.25 mg/d) micronized 17beta-estradiol on cognitive function in older postmenopausal women. DESIGN: Randomized, placebo-controlled trial conducted for 3 years. SETTING: Academic health center in greater Hartford, Connecticut. PARTICIPANTS: Fifty-seven healthy, community-dwelling, older postmenopausal women. INTERVENTION: Women received 0.25 mg/d of micronized 17beta- estradiol (estrogen therapy (ET), n=32) or placebo (n=25); all women who had not had a hysterectomy received 100 mg/d of oral micronized progesterone for 2-week periods every 6 months. MEASUREMENTS: Neuropsychological measures of memory, language, mood, and executive function were collected at baseline, 3 months, and 36 months. Measures of executive function included the Controlled Oral Word Association Test, the Trail Making Test, and the Wisconsin Card Sorting Test. The Boston Naming Test was used to measure language skills. The Symbol Digit Modalities Test was used as a measure of sustained attention. Measures of memory included the Complex Figure Test, Fuld Object Memory Test, and a selected subtest from the Wechsler Memory Scale. Scores from the Geriatric Depression Scale and the Beck Anxiety Inventory were used to assess symptoms of depression. RESULTS: No differences were found between ET and placebo on any of the neurocognitive measures or depression instruments, nor were there any differences when the groups were stratified according to age. CONCLUSION: This small study, which had adequate power to detect change in some but not all domains of cognition tested, revealed that low-dose estrogen neither benefits nor harms cognitive function in older women after 3 years of treatment, but confirmation is needed from larger trials.

Resnick, S. M., M. A. Espeland, et al. (2009). "Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy." Journal of Clinical Endocrinology & Metabolism **94**(11): 4152-61.

CONTEXT: Different menopausal hormone therapies may have varied effects on specific cognitive functions. We previously reported that conjugated equine estrogens (CEE) with medroxyprogesterone acetate had a negative impact on verbal memory but tended to impact figural memory positively over time in older postmenopausal women. OBJECTIVE: The objective of the study was to determine the effects of unopposed CEE on changes in domain-specific cognitive function and affect in older postmenopausal women with prior hysterectomy. DESIGN: This was a randomized, double blind, placebo-controlled clinical trial. SETTING: The study was conducted at 14 of 40 Women's Health Initiative (WHI) clinical centers. PARTICIPANTS: Participants were 886 postmenopausal women with prior hysterectomy, aged 65 yr and older (mean 74 yr), free of probable dementia, and enrolled in the WHI and WHI Memory Study (WHIMS) CEE-Alone trial for a mean of 3 yr and followed up for a mean of 2.70 yr. INTERVENTION: Intervention was 0.625 mg of CEE daily or placebo. MAIN OUTCOME MEASURES: Annual rates of change in specific cognitive functions and affect, adjusted for time since randomization, were measured. RESULTS: Compared with placebo, unopposed CEE was associated with lower spatial rotational ability ($P < 0.01$) at initial assessment (after 3 yr of treatment), a difference that diminished over 2.7 yr of continued treatment. CEE did not significantly influence change in other cognitive functions and affect. CONCLUSIONS: CEE did not improve cognitive functioning in postmenopausal women with prior hysterectomy. CEE was associated with lower spatial rotational performance after an average of 3 yr of treatment. Overall, CEE does not appear to have enduring effects on rates of domain-specific cognitive change in older postmenopausal women.

Schierbeck, L. L., L. Rejnmark, et al. (2012). "Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial." BMJ 345: e6409.

OBJECTIVE: To investigate the long term effect of hormone replacement therapy on cardiovascular outcomes in recently postmenopausal women.
DESIGN: Open label, randomised controlled trial.
SETTING: Denmark, 1990-93.
PARTICIPANTS: 1006 healthy women aged 45-58 who were recently postmenopausal or had perimenopausal symptoms in combination with recorded postmenopausal serum follicle stimulating hormone values. 502 women were randomly allocated to receive hormone replacement therapy and 504 to receive no treatment (control). Women who had undergone hysterectomy were included if they were aged 45-52 and had recorded values for postmenopausal serum follicle stimulating hormone.
INTERVENTIONS: In the treatment group, women with an intact uterus were treated with triphasic estradiol and norethisterone acetate and women who had undergone hysterectomy received 2 mg estradiol a day. Intervention was stopped after about 11 years owing to adverse reports from other trials, but participants were followed for death, cardiovascular disease, and cancer for up to 16 years. Sensitivity analyses were carried out on women who took more than 80% of the prescribed treatment for five years.
MAIN OUTCOME MEASURE: The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.
RESULTS: At inclusion the women on average were aged 50 and had been postmenopausal for seven months. After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint compared with 33 in the control group (hazard ratio 0.48, 95% confidence interval 0.26 to 0.87; P=0.015) and 15 died compared with 26 (0.57, 0.30 to 1.08; P=0.084). The reduction in cardiovascular events was not associated with an increase in any cancer (36 in treated group v 39 in control group, 0.92, 0.58 to 1.45; P=0.71) or in breast cancer (10 in treated group v 17 in control group, 0.58, 0.27 to 1.27; P=0.17). The hazard ratio for deep vein thrombosis (2 in treated group v 1 in control group)

was 2.01 (0.18 to 22.16) and for stroke (11 in treated group v 14 in control group) was 0.77 (0.35 to 1.70). After 16 years the reduction in the primary composite outcome was still present and not associated with an increase in any cancer.
CONCLUSIONS: After 10 years of randomised treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.

Simon, J. A., C. Bouchard, et al. (2007). "Low dose of transdermal estradiol gel for treatment of symptomatic postmenopausal women: a randomized controlled trial.[see comment]." Obstetrics & Gynecology **109**(3): 588-96.

OBJECTIVE: To investigate safety and efficacy and identify the lowest effective dose of a new transdermal estradiol (E2) gel for relief of menopausal symptoms in a population of postmenopausal women. METHODS: This study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Postmenopausal women with at least 60 hot flushes per week applied 0.87 g/d (n=136), 1.7 g/d (n=142), or 2.6 g/d (n=69) E2 gel or placebo gel (n=137) topically for 12 weeks. The changes from baseline in hot flush frequency and severity at 4 and 12 weeks and changes from baseline in vaginal atrophy symptoms at 12 weeks were examined. RESULTS: With increasing E2 doses, mean trough serum E2 increased from 17 to 29 pg/mL. By weeks 3-5, E2 gel reduced moderate-to-severe hot flush rate by at least seven hot flushes per day (P<.001) and reduced the severity score (P<.01). The numbers needed to treat for benefit for an 80% and 100% decrease in hot flush number were 3.2 and 6.3 for the 0.87-g/d group and 1.3 and 2.3 for the 2.6-g/d group. At week 12, vaginal pH was more acidic and vaginal maturation index more mature compared with placebo (P<.001). The lowest dose improved most bothersome vulvovaginal atrophy symptoms (P<.05). Estradiol gel was well tolerated at the site of application and produced no unexpected adverse effects. The 0.87 g/d dose produced fewest adverse events.
CONCLUSION: The 0.87 g/d dose of this new transdermal E2 gel, which delivers an estimated 0.0125 mg E2 daily, delivered the lowest effective dose for treatment of vasomotor symptoms and vulvovaginal atrophy in a population of postmenopausal women.

Simon, J. A. and E. S. Group (2006). "Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms." Menopause **13**(2): 222-31.

OBJECTIVE: To assess the efficacy and safety of topical micellar nanoparticle estradiol emulsion (MNPEE; Estrasorb; Novavax, Inc., Malvern, PA) in postmenopausal women with moderate to severe vasomotor symptoms. DESIGN: A multicenter, randomized, double-blind, placebo-controlled study was conducted in 200 postmenopausal women with seven or more moderate to severe hot flushes per day. The study consisted of a 3-week screening period followed by a 1-week placebo emulsion run-in period and a 12-week active or placebo treatment period. Women were randomized (1:1) to receive MNPEE (3.45 g daily dose of emulsion containing 8.6 mg estradiol) or matching placebo emulsion. The primary efficacy variable was the change from baseline in the frequency of moderate and severe hot flushes at weeks 4 and 12. Adverse events were monitored throughout the trial. RESULTS: Topical micellar nanoparticle estradiol emulsion was statistically significantly superior to placebo emulsion in reducing the mean frequency of moderate to severe vasomotor symptoms by week 3 (P = 0.003), with superiority to placebo maintained from weeks 4 to 12 (P < 0.001). At week 12 (peak benefit), MNPEE reduced mean daily frequency of hot flush count by 11.1 (P < 0.001 vs placebo). MNPEE significantly reduced mean symptom severity from weeks 4

to 12 (P < 0.001) compared with placebo. At endpoint, mean serum concentrations of estradiol and estrone were 63 and 89 pg/mL, respectively, in the MNPEE group. The mean endpoint ratio of estradiol to estrone in these patients was 0.774. MNPEE was safe and well tolerated. CONCLUSION: Once-daily application of 3.45 g of micellar nanoparticle estradiol emulsion containing 8.6 mg of estradiol was safe and effective in providing significant relief of vasomotor symptom frequency and severity in postmenopausal women.

Simon, J. A., K. Z. Reape, et al. (2008). "Randomized, multicenter, double-blind, placebo-controlled trial to evaluate the efficacy and safety of synthetic conjugated estrogens B for the treatment of vulvovaginal atrophy in healthy postmenopausal women." Fertility & Sterility **90**(4): 1132-8.

OBJECTIVE: To evaluate the safety and efficacy of synthetic conjugated estrogens B (SCE-B; 0.3 mg/d) for 12 weeks in the treatment of vulvovaginal atrophy in symptomatic, postmenopausal women. DESIGN: Prospective, randomized, multicenter, double-blind, placebo-controlled trial. SETTING: Forty-two participating sites in the United States. PATIENT(S): Postmenopausal women with at least one moderate to severe symptom of vaginal atrophy. INTERVENTION(S): Daily oral administration, in a randomized, placebo-controlled setting, of SCE-B (0.3 mg) or of placebo for 12 weeks. MAIN OUTCOME MEASURE(S): Mean changes in vaginal maturation index, percentage of parabasal and superficial cells, vaginal pH, and severity of the most bothersome symptom (MBS) between baseline and predetermined time points were assessed. Safety and tolerability were evaluated. RESULT(S): A total of 310 women (mean age, 58.6 y) were enrolled. Synthetic conjugated estrogens B yielded statistically significantly greater differences in vaginal maturation index and vaginal pH from baseline to the end of treatment. Vaginal dryness (44.4%) and pain during intercourse (30.2%) were the symptoms most commonly identified as the MBS. A statistically significant mean reduction in the severity of the MBS was noted for SCE-B. There were no clinically significant differences observed between the two groups for findings related to safety. CONCLUSION(S): Synthetic conjugated estrogens B (0.3 mg/d) was effective in treating vulvovaginal atrophy in symptomatic postmenopausal women. Significant improvement was seen in vaginal maturation index, vaginal pH, and severity of MBS from baseline to the end of treatment.

Stevenson, J. C., G. Durand, et al. (2010). "Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17beta-oestradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: results from a double-blind, controlled study." Maturitas **67**(3): 227-232.

OBJECTIVES: Guidelines recommend using the lowest effective dose of oestrogen for the management of vasomotor symptoms in postmenopausal women. The primary aim of this double-blind, multi-centre, randomised study was to assess the efficacy of oral ultra-low dose continuous combined hormone replacement therapy with 17beta-oestradiol and dydrogesterone. STUDY DESIGN: 313 women with >=50 moderate to severe hot flushes during the previous week were randomised to 0.5 mg 17beta-oestradiol/2.5 mg dydrogesterone (E 0.5 mg/D 2.5 mg), 1mg 17beta-oestradiol/5mg dydrogesterone (E 1mg/D 5 mg) or placebo for 13 weeks. The placebo group then switched to E 0.5 mg/D 2.5 mg for a further 39 weeks, whilst the other groups continued on the same treatment. RESULTS: After 13 weeks, the reduction in the number of moderate to severe hot flushes/day in the E 0.5 mg/D 2.5 mg group was greater than in the placebo group (-6.4 vs. -4.9, p<0.001) and comparable to that in the 1/5 mg group (-6.3). E 0.5 mg/D 2.5 mg and E 1mg/D 5 mg significantly improved the total Menopause Rating Scale score. The number of bleeding/spotting days was lower with E 0.5 mg/D 2.5 mg than with E 1 mg/D 5 mg. The overall amenorrhoea rate with E 0.5 mg/D 2.5 mg was 81%; this increased to 91% in months 10-12. CONCLUSIONS: Continuous combined 0.5 mg 17beta-oestradiol and 2.5mg dydrogesterone was effective in alleviating vasomotor symptoms and improving quality of life,

and was associated with a high amenorrhoea rate and a good tolerability profile. Copyright Copyright 2010 Elsevier Ireland Ltd. All rights reserved.

Valen-Sendstad, A., K. Engedal, et al. (2010). "Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone." American Journal of Geriatric Psychiatry 18(1): 11-20.

OBJECTIVE: To elucidate the effects of low-dose 17beta-estradiol and norethisterone (hormone therapy [HT]) versus placebo in women with Alzheimer Disease (AD) on cognition, depressivesymptoms, and activities of daily living.
DESIGN: A 12-month randomized, double-blind, placebo-controlled study, stratified by apolipoprotein E (ApoE) genotype (with versus without the epsilon4 allele), duration of education (< or =9 versus >9 years), and age (< or =75 versus >75 years) performed during 2000-2004.
SETTING: Ambulatory memory clinic in a general hospital.
PARTICIPANTS: Sixty-five female outpatients aged 65-89 years who met criteria for probable AD according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition and International Classification of Diseases, tenth edition. Ten patients were excluded, resulting in 55 participants who had at least one posttreatment efficacy evaluation.
INTERVENTION: Randomly assigned to receive either 1-mg estradiol and 0.5-mg norethisterone or placebo once daily.
MEASUREMENTS: Cognitive variables were the Dementia Rating Scale, tests from Consortium toEstablish a Registry for AD, Global Deterioration Scale (GDS) and Barthel Index.
RESULTS: When only treatment effects were compared by analysis of variance, there were nonsignificant differences between treatment groups for all efficacy variables. A linear model analysis, including stratifying factors in addition to treatment in the model, revealed a significant main effect on mood. The depressive symptoms were lower in the HT group than in the placebo group. Those treated with HT without the ApoE epsilon4 allele had better mood, Word Learning Memory score, and GDS score. Those in the HT group with a higher level of education obtained a better GDS score. Adverse events did not differ between the groups.
CONCLUSION: HT interacts with ApoE genotype in women with AD. Women without an ApoE epsilon4 allele may get better mood and cognition with HT. HT may reduce depressive mood a nd give less cognitive decline.

Veerus, P., K. Fischer, et al. (2008). "Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial." BMC Women's Health **8**: 5.

BACKGROUND: The aim of the study was to determine the effect of postmenopausal hormone therapy on women's symptom reporting and quality of life in a randomized trial.
METHODS: 1823 women participated in the Estonian Postmenopausal Hormone Therapy (EPHT) Trial between 1999 and 2004. Women were randomized to open-label continuous combined hormone therapy or no treatment, or to blind hormone therapy or placebo. The average follow-up period was 3.6 years. Prevalence of symptoms and quality of life according to EQ-5D were assessed by annually mailed questionnaires. RESULTS: In the hormone therapy arms, less women reported hot flushes (OR 0.20; 95% CI: 0.14-0.28), sweating (OR 0.56; 95% CI: 0.44-0.72), and sleeping problems (OR 0.66; 95% CI: 0.52-0.84), but more women reported episodes of vaginal bleeding (OR 19.65; 95% CI: 12.15-31.79). There was no difference between the trial arms in the prevalence of other symptoms

over time. Quality of life did not depend on hormone therapy use. CONCLUSION: Postmenopausal hormone therapy decreased vasomotor symptoms and sleeping problems, but increased episodes of vaginal bleeding, and had no effect on quality of life.

Welton, A. J., M. R. Vickers, et al. (2008). "Health related quality of life after combined hormone replacement therapy: randomised controlled trial.[see comment]." BMJ **337**: a1190.

OBJECTIVE: To assess the effect of combined hormone replacement therapy (HRT) on health related quality of life. DESIGN: Randomised placebo controlled double blind trial. SETTING: General practices in United Kingdom (384), Australia (94), and New Zealand PARTICIPANTS: Postmenopausal women aged 50-69 at randomisation; 3721 women with a uterus were randomised to combined oestrogen and progestogen (n=1862) or placebo (n=1859). Data on health related quality of life at one year were available from 1043 and 1087 women, respectively. INTERVENTIONS: Conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5/5.0 mg or matched placebo orally daily for one year. MAIN OUTCOME MEASURES: Health related quality of life and psychological wellbeing as measured by the women's health questionnaire. Changes in emotional and physical menopausal symptoms as measured by a symptoms questionnaire and depression by the Centre for Epidemiological Studies depression scale (CES-D). Overall health related quality of life and overall quality of life as measured by the European quality of life instrument (EuroQol) and visual analogue scale, respectively. RESULTS: After one year small but significant improvements were observed in three of nine components of the women's health questionnaire for those taking combined HRT compared with those taking placebo: vasomotor symptoms (P<0.001), sexual functioning (P<0.001), and sleep problems (P<0.001). Significantly fewer women in the combined HRT group reported hot flushes (P<0.001), night sweats (P<0.001), aching joints and muscles (P=0.001), insomnia (P<0.001), and vaginal dryness (P<0.001) than in the placebo group, but greater proportions reported breast tenderness (P<0.001) or vaginal discharge (P<0.001). Hot flushes were experienced in the combined HRT and placebo groups by 30% and 29% at trial entry and 9% and 25% at one year, respectively. No significant differences in other menopausal symptoms, depression, or overall quality of life were observed at one year. CONCLUSIONS: Combined HRT started many years after the menopause can improve health related quality of life.

Varying dose studies (N=4)

Limpaphayom, K. K., M. S. Darmasetiawan, et al. (2006). "Differential prevalence of quality-of-life categories (domains) in Asian women and changes after therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: the Pan-Asia Menopause (PAM) study." Climacteric **9**(3): 204-14.

OBJECTIVES: To assess the prevalence of four categories (domains) of menopausal symptoms as markers for quality of life in nine ethnic groups of Asian women. To evaluate changes in quality of life (MENQOL scores) in Asian women following hormone therapy. METHODS: A prospective, randomized, double-blind, multinational clinical trial in 1028 healthy postmenopausal women of nine ethnic groups from 11 Asian countries/regions. Following 2 weeks of baseline observation, the women received one of three conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) doses (in mg) daily for 24 weeks: 0.625/2.5, 0.45/1.5, or 0.3/1.5. At baseline and at the end of weeks 4, 12 and 24 following the start of therapy, the study participants were asked to record, on a menopause-specific quality of life (MENQOL) questionnaire, 29 menopausal symptoms, as experienced during the preceding month. The symptoms were categorized into four domains: vasomotor,

psychosocial, physical and sexual. RESULTS: The baseline (pretreatment) symptom scores in each of the four domains varied substantially among the different ethnic groups, ranging from 2.21 to 5.71 in the vasomotor, 2.37-5.96 in the psychosocial, 2.66-5.39 in the physical, and 2.11-6.55 in the sexual domain. Overall, Vietnamese and Pakistani women had the highest baseline scores, i.e. were most afflicted by each set of symptoms in a given domain, and Indonesian, Malay, Taiwanese and Thai women were least afflicted. In the overall population, intervention resulted in statistically significant decreases in the scores of all four domains within 4 weeks of intervention. The beneficial effects were similar in the three dose groups. CONCLUSIONS: The prevalence of four domains of menopausal symptoms, representative of quality of life as recorded on a MENQOL questionnaire, varies considerably among ethnic groups of Asian women. The MENQOL scores in the overall population were significantly lowered in the course of the study, indicating an improvement in quality of life. In the absence of a placebo group, the relative contribution of hormones and placebo in our intervention is unknown.

Mattsson, L. A., S. Skouby, et al. (2007). "Efficacy and tolerability of continuous combined hormone replacement therapy in early postmenopausal women." Menopause International **13**(3): 124-31.

OBJECTIVE: Continuous combined hormone replacement therapy (ccHRT) based on estradiol valerate (E2V) and medroxyprogesterone acetate (MPA) is effective for relief of menopausal symptoms three years or more after the menopause. This study was undertaken to examine the efficacy and tolerability of ccHRT in early postmenopausal women (last menstrual period 1.3 years before study entry). STUDY DESIGN: This was a 52-week, randomized, double-blind, multinational study of ccHRT comprising three different dose combinations of E2V/MPA in 459 early postmenopausal non-hysterectomized women experiencing 30 or more moderate to severe hot flushes a week and/or vasomotor symptoms requiring treatment. MAIN OUTCOMES MEASURES: The primary endpoint was change in frequency and severity of moderate to severe hot flushes at 12 weeks. Secondary outcome measures included number of bleeding days and evaluation of tolerability. RESULTS: The frequency of hot flushes was reduced by >or=70% after one month (P<0.001 for all doses at week 2 onwards), with little evidence of statistically different dose effects. Severity of flushing was also attenuated by ccHRT. Mean number of bleeding days fell to <1 per 28-day cycle at 52 weeks. Rates of amenorrhoea approached 80-90% at the end of the study, but were significantly lower at several time points with the highest-dose regimen (2 mg E2V + 5 mg MPA) than with the lower-dose options (1 mg E2V + 2.5 mg MPA and 1 mg E2V + 5 mg MPA; P<0.05). Adverse events declined in frequency over time with all regimens but throughout the study were more numerous with the highest-dose regimen than with lower doses (P= 0.0002). CONCLUSIONS: Continuous combined HRT was effective for the relief of climacteric symptoms in early postmenopausal women and was well tolerated.

Pitkin, J., V. P. Smetnik, et al. (2007). "Continuous combined hormone replacement therapy relieves climacteric symptoms and improves health-related quality of life in early postmenopausal women." Menopause International **13**(3): 116-23.

OBJECTIVE: Hormone replacement therapy (HRT) relieves menopausal symptoms but its effect on health related quality of life (HRQoL) is uncertain. The aim of this study was to assess the effect of three dose regimens of continuous combined HRT, consisting of estradiol valerate (E2V) and medroxyprogesterone acetate (MPA) on HRQoL in early postmenopausal women (last menstrual period 1-3 years before study entry). STUDY DESIGN: This was a 52-week, randomized, double-blind, multinational study comparing E2V (1 mg or 2 mg) plus MPA (2.5 mg or 5 mg) in different dose combinations. The intention-to-treat population

comprised 459 women (average age 51.5 years). MAIN OUTCOME MEASURES: HRQoL was assessed by the Women's Health Questionnaire (WHQ), the 15D Questionnaire and a visual analogue scale (VAS). RESULTS: There were improvements on eight of the nine domains of the WHQ with all dose regimens during the first 12 weeks (P<0.0001) and an I mprovement in the remaining domain (menstrual symptoms) with the lower-dose regimens (P<0.05). These initial improvements in HRQoL were then maintained or augmented over the remainder of the study (P<0.0001 for change from baseline at 52 weeks for all domains and dose regimens). Mean 15D total score had improved meaningfully and significantly by 12 weeks (P<0.0001 versus baseline) in all treatment groups and this improvement was maintained thereafter. This improvement in 15D total score was most marked among previous non-users of HRT (P<0.05 versus previous users). VAS scores recorded significant (P<0.05) reductions in hot flushes, sweating and sleep disturbances in all groups after week 1 and highly significant (P<0.0001) relief of all climacteric symptoms at week 52. CONCLUSION: Continuous combined HRT was associated with pronounced improvement of vasomotor symptoms and HRQoL in this population of early postmenopausal women.

Yang, T.-S., Y.-J. Chen, et al. (2007). "A clinical trial of 3 doses of transdermal 17beta-estradiol for preventing postmenopausal bone loss: a preliminary study.[see comment]." Journal of the Chinese Medical Association: JCMA **70**(5): 200-6.

BACKGROUND: It is well documented that a daily oral dose of 0.625 mg of conjugated equine estrogen or 1-2 mg of 17beta-estradiol is needed to prevent postmenopausal bone loss. Recent studies have indicated that a lower dose of estrogen maybe as effective in maintaining bone mass. The purpose of this study was to evaluate the effects of 3 dosages of transdermally administered 17beta-estradiol gel in postmenopausal women stratified by oophorectomy and natural menopause. METHODS: One hundred and twenty postmenopausal women were randomly selected to form 4 groups. Three groups of women were treated with a transdermal administration of estradiol gel at a daily dosage of 1.25, 2.5 and 5.0 g (containing 0.75, 1.5, and 3 mg of 17beta-estradiol/day), respectively. The 4th group of women, receiving estriol 2 mg/day p.o., was studied concurrently as a control. Bone mineral density was measured by quantitative computed tomography of the vertebrae from T12 to L3 at baseline, then at 6-month intervals for 1 year. RESULTS: Women in all groups receiving 17beta-estradiol gel obtained a significant increase in bone mass, with the exception of the 1.25 g/day group, which showed a minimal increment at the 6-month period, compared with the control group. Comparisons of the increments in bone mass after estrogen therapy for both natural and surgical menopausal subjects found that there was a more prominent response in surgical menopausal women receiving a dosage of 2.5 g/day. CONCLUSION: Estradiol gel at the dosage of 1.25 g/day, equivalent to 17beta-estradiol 0.75 mg/day, effectively prevented bone loss in postmenopausal women after a 12-month treatment period. The therapeutic effect of estradiol gel on bone mass was more prominent in the surgical menopausal groups at the dosage of 2.5 g/day. The atrophic ovaries may therefore play a crucial role in the subsequent decades of postmenopausal women.

Drug Use Research & Management Program
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New Drug Evaluation: Delayed Release Duavee® (conjugated estrogens/bazedoxifene)

Month/Year of Review: November 2014
Generic Name: conjugated estrogens/bazedoxifene
PDL Class: HRT-Estrogen, Oral

End date of literature search: March 1, 2014
Brand Name (Manufacturer): Duavee® (Wyeth)
Dossier Received: Pending

United States Food and Drug Administration (FDA) Approved Indication:
Conjugated estrogens/bazedoxifene (CE/BZA) is indicated for treating moderate to severe vasomotor symptoms associated with menopause or for preventing postmenopausal osteoporosis in women with a uterus. [1]

Research Questions:
- Is there evidence CE/BZA is superior to hormone therapy (e.g. conjugated estrogens/medroxyprogesterone acetate [CE/MPA]) in treating postmenopausal vasomotor symptoms or improving health-related quality of life or menopause-related quality of life (MSQOL) for postmenopausal women with vasomotor symptoms?
- Is there evidence CE/BZA is safer than hormone therapy for treating postmenopausal vasomotor symptoms?
- Is CE/BZA superior to bisphosphonates, other selective estrogen receptor modulators (SERMs), or hormone therapy for preventing osteoporosis and hip, vertebral, or other fractures?
- Is CE/BZA safer than bisphosphonates, other SERMs, or hormone therapy for preventing osteoporosis?
- Are there sub-groups where CE/BZA is more effective or safer than current therapies for postmenopausal symptoms or osteoporosis prevention?

Conclusions:
- CE/BZA has not been compared with current therapies for postmenopausal vasomotor symptoms. Only one phase 3 poor quality trial (SMART 2) and one supportive poor quality sub-study (SMART 1) comparing CE/BZA with placebo provide low quality evidence. CE/BZA significantly reduced the number and severity of hot flushes (mean difference in the daily number of moderate and severe hot flushes between CE/BZA and placebo was –2.71 in SMART 2 and -6.29 in sub-study SMART 1).

- Evidence that CE/BZA improves health-related quality of life (HRQOL) is insufficient. One combined analysis provides low quality evidence that CE/BZA, vs placebo, results in a meaningful change in the vasomotor functioning score of MSQOL.

- The poor quality SMART 5 trial provides low quality evidence CE/BZA significantly increases lumbar spine and total hip bone mineral density (BMD) compared with placebo (placebo subtracted difference 1.51% for the lumbar spine and 1.21% for the total hip). However, the researchers observed no statistically significant difference between the CE/MPA subgroup and CE/BZA and did not evaluate fracture risk.

- Clinical trials provide low quality evidence for the CE/BZA indications: treatment of vasomotor symptoms and prevention of osteoporosis. The incidences of all-cause mortality, serious adverse events, venous thromboembolism (VTE), and endometrial hyperplasia or endometrial malignancy in patients taking CE/BZA were similar to placebo. However, the adverse effects associated with use in a general, menopausal population remain unexplored. The potential implications of

discontinuing CE/BZA, such as the rapid bone loss associated with CE-alone use, are unclear. CE/BZA comes with the CE-related risk of VTE and ischemic stroke, and the benefits of oral hormone therapy (HT) are more likely to outweigh the risks before age 60 or within 10 years of menopause.

- According to prescribing information and National Osteoporosis Foundation (NOF) guidelines, CE/BZA use should be limited to women at significant risk of osteoporosis after considering alternatives not containing estrogen. The Global Consensus Statement on Menopausal Hormone Therapy places further limitations on the use of hormonal therapy by stating menopausal hormone therapy is effective and appropriate for preventing osteoporosis-related fractures in at-risk women who are <60 years of age or within 10 years of the start of menopause.

Recommendations:

- Make CE/BZA non-preferred due to insufficient evidence comparing it with currently available therapies and low quality evidence of efficacy compared with placebo.
- Limit use to women who
  - are postmenopausal and are within 10 years of menopause
  - are <60 years of age
  - have an intact uterus
  - failed or contraindicated to
    - conventional hormone therapy(for Prevention of vasomotor symptoms), OR
    - bisphosphonates (for Prevention of osteoporosis)

Reason for Review:
The tissue specific estrogen complex CE/BZA was approved by the FDA October 3, 2013.

Background:
CE/BZA is the first FDA-approved estrogen/SERM combination. The drug's estrogen component provides vasomotor symptom relief and increases bone density, while the SERM potentially mitigates the endometrial cancer risk that arises when women who have a uterus receive estrogen unopposed by a progestogen. The SERM also may mitigate the risk of breast cancer. BZA monotherapy has been approved in 35 countries and marketed in six countries—including Japan, Korea, Canada, and Australia—for the treatment and prevention of post-menopausal osteoporosis. [2, 3]

Treatment of Vasomotor Symptoms:
Women with menopause-related vasomotor symptoms experience reduced sleep quality, irritability, difficulty concentrating, and reduced quality of life.[4, 5] Several studies have reported the use of HT can improve menopause-related symptoms.[4, 6, 7]

Estrogen therapy (ET) with a progestogen, which is required in women with a uterus, or without a progestogen is considered the most effective treatment for moderate to severe menopause-related vasomotor symptoms and their consequences.[5 ,8] The risk of VTE and ischemic stroke increases with oral HT, but the absolute risk is rare in those <60 years old. Therefore, the benefits are more likely to outweigh the risks in women <60 years of age or within 10 years of menopause.[8, 9]

Postmenopausal Osteoporosis Prevention:
Based on 2010 statistics, an estimated 10.2 million Americans ≥50 years old have osteoporosis, and 42.5 million have low bone mass at the femoral neck or lumbar spine. Combined, these figures represent about 54% of the population who are >50 years old. . [10]

Osteoporosis diagnosis is established by bone mineral density (BMD) measurement or the occurrence of adulthood hip or vertebral facture, in the absence of metabolic bone diseases and major trauma. Osteoporosis is defined by BMD at the hip or lumbar spine that is ≤2.5 standard deviations (SD) below the mean BMD of a young-adult reference population as measured by dual-energy x-ray absorptiometry (DXA), which assesses bone density at various skeletal sites using radiation exposure. [10]

Although those with the lowest BMD have the highest fracture risk, patients with low bone mass, rather than those with osteoporosis, have the most factures. The most common fractures occur at the spine, hip (proximal femur), and wrist. [10]

NOF guidelines[10] recommend pharmaceutical treatment for women with:

- clinical or asymptomatic hip or vertebral fractures;
- DXA T-scores ≤ –2.5 SD at the femoral neck, lumber spine, and total hip; or
- postmenopausal women with low bone mass (DXA T-score between –1 and –2.5 SD) at the femoral neck, total hip, or lumbar spine and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on US-adapted WHO absolute fracture risk (FRAX). [10]

FDA-approved options for osteoporosis prevention are bisphosphonates, SERMs, and HT. Non-pharmacologic recommendations include adequate calcium and vitamin D and weight-bearing and muscle-strengthening exercise.[10] The NOF guidelines state that approved non-estrogen treatment is first-line, before considering HT when solely used for preventing osteoporosis.[10] According to the Global Consensus Statement on Menopausal Hormone Therapy, menopausal HT is effective and appropriate for preventing osteoporosis related fractures in at-risk women who are <60 years of age or within 10 years after menopause.[8] According to the North American Menopause Society (NAMS), when alternate osteoporosis therapies are not appropriate or cause adverse effects, the extended use of HT is an option for women at high risk for osteoporosis-related fractures. The NAMS also considers HT or oral contraceptives, unless contraindicated, appropriate for women who have early menopause and need to prevent bone loss, until reassessment when they reach the normal age of menopause.[5] However, the benefits of HT on bone mass and fracture rapidly wane after discontinuing treatment, requiring transition to osteoporosis treatments that preserve bone mass. In the WHI, the ET and placebo groups had the same cumulative incidence of hip fracture within a few years of discontinuing ET.[5] In contrast, bisphosphonates may have residual effects after treatment is discontinued.[10] The NOF recommends CE/BZA's use for women who are at significant risk of osteoporosis after considering alternatives that do not contain estrogen, while other guidelines have yet to address this product.[10]

According to the NOF, the need for continuing osteoporosis medication should be reviewed annually.[10] After the initial three to five years of treatment, a comprehensive risk assessment should be performed. Comprehensive assessment should include fracture history, new chronic diseases or medications, height measurement, BMD testing, and vertebral imaging if there has been any documented height loss during the treatment period.[10]

Clinical Efficacy:

Clinical efficacy data is included only for the approved dose (CE 0.45 mg/BZA 20 mg). The acronym CE/BZA refers to the approved dose. The dosage for unapproved dosage forms are noted when addressed.

Treatment of Vasomotor Symptoms:

Approval of CE/BZA for treating moderate to severe vasomotor symptoms was based on pivotal Trial 305 (Selective Estrogens, Menopause, And Response to Therapy 2 or SMART 2), with supporting evidence from a sub-study of Trial 303 (SMART 1 sub-study). [2]

In SMART 2 (Trial 305)—a poor quality study—CE/BZA significantly reduced the number and severity of hot flushes over 12 weeks. SMART2 was a multicenter, double-blind, three parallel group, placebo-controlled study that randomized 332 (n=310 modified intent to treat [mITT], defined below) healthy postmenopausal women who were age 40 to 65 and had intact uteruses. The women sought treatment for hot flushes and reported seven moderate to severe hot flushes per day or 50 per week. Subjects were randomized 2:2:1 to received daily CE 0.625 mg/BZA 20 mg, CE/BZA, or placebo. The co-primary endpoints were reduction in the average daily number of moderate and severe hot flushes and reduction in daily severity of hot flushes at weeks 4 and 12 compared with placebo. The daily severity score was calculated as follows: [(# mild hot flushes) + (# moderate hot flushes x 2) + (# severe hot flushes x 3)] ÷ [total # hot flushes]. The mITT population and last observation carried forward (LOCF) were used for the primary analysis at weeks 4 and 12. The mITT population was defined as those who had taken ≥1 dose, had ≥5 days of data at baseline, and had ≥5 days of data for ≥1 on-therapy week. At week 12, CE/BZA reduced the average number of daily moderate and severe hot flushes from baseline by 74% (mean change from baseline –7.63) vs 47%] (mean change from baseline –4.92) for placebo, resulting in a difference from placebo of –2.71 (CI: –3.84 to –1.57, p<0.001). This exceeded the >2 hot flushes per day criterion in 2003 FDA Guidance. The FDA noted the magnitude of effect was numerically lower than approved

CE/progestogen preparations: CE/MPA mean reduction of –10.8 hot flushes per day for a placebo-subtracted decrease of –4.8. With regard to severity of hot flushes, CE/BZA reduced the average daily severity from baseline by 38% (mean change from baseline –0.87) vs 11% (mean change from baseline –0.26) for placebo (difference from placebo –0.60, CI: –0.86 to –0.35, p<0.001). The greatest mean decrease in symptoms (frequency and severity) occurred 5 to 6 weeks after treatment onset.[2,11]

SMART 1 was a poor quality supportive study evaluating the effects of CE/BZA on menopausal symptoms. The main study of this multicenter, double-blind, placebo- and active-controlled phase 3 trial enrolled 3,397 healthy, primarily white women who had been postmenopausal for at least 1 year, were ages 40 to 75, and had an intact uterus. Subjects were randomized 1:1:1:1:1:1:1:1 to receive CE (0.625 mg or 0.45 mg)/BZA (10mg, 20mg, or 40 mg) or raloxifene 60 mg or placebo. Subjects also were directed to maintain a consistent daily intake of dietary and supplemental calcium (1000 to 1600 mg) and vitamin D (200 to 400 IU). The primary endpoint of the main study was the incidence of endometrial hyperplasia at 12 months, while the primary endpoint for the indication was the mean change in the number of hot flushes from baseline at week 12 using LOCF for the efficacy evaluable population (EE1, n=216), defined as subjects who had taken at least 1 dose, had screening endometrial biopsy, or had hyperplasia diagnosed before the time point and who reported at least seven moderate or severe hot flushes daily or 50 weekly during screening. Subjects recorded hot flushes in daily diaries and the mean daily number of hot flushes was calculated using moderate and severe hot flushes and the mean daily severity of hot flushes was calculated using mild, moderate, and severe (assigned intensities of 1, 2, and 3, respectively). At baseline, the mean number of hot flushes were 11.44, 12, and 14.32 for the CE/BZA (n=28), raloxifene (n=24), and placebo (n=33) arms and the mean severity of hot flushes was 2.45, 2.37, and 2.37, respectively. CE/BZA significantly reduced the frequency and severity of hot flushes compared with placebo. At week 12, the mean daily change in the number of hot flushes from baseline were –8.74, –5.29, and –2.45 for CE/BZA, raloxifene, and placebo, resulting in percentage decreases of 76%, 44%, and 17%, respectively. The mean change in severity of hot flushes was –1, –0.22, and –0.21, respectively, for a placebo subtracted difference of –0.60 (CI: –0.86 to –0.35) for CE/BZA.[2, 12]

Abraham et al[13] analyzed the changes in total and domain scores on the 29-item self-administered Menopause-specific Quality of Life questionnaire (MENQOL) across SMART 1, SMART 2, and SMART 5 (a trial for the approved osteoporosis indication), as well as SMART 3, a trial conducted for the unapproved indication vulvar/vaginal atrophy. MSQOL was prospectively evaluated among several secondary endpoints in these studies, mostly without adjusting for multiplicity. The studies reported scores for the vasomotor, physical, sexual, and psychosocial functioning domains and the aggregated score for CE/BZA. Subjects indicated their symptom experiences in the last month on a scale from 1 (not experienced) to 8 (extremely bothered). The differences in total MENQOL and physical, psychosocial, and sexual functioning domains between CE/BZA and placebo did not exceed the defined Clinically Important Differences (CID). The differences in vasomotor functioning exceeded the CID for SMART 2 at 3 months (–1.69, p<0.001) and SMART 5 at 12 months (–1.65, p<0.001), but not for SMART 1 at any time point and not for SMART 5 at 3 months.

The evidence for CE/BZA's efficacy in treating vasomotor symptoms is of low quality. The evidence is comprised of one main study and one sub-study with small patient numbers, with the average number of patients per treatment arm per study center being less than one for the SMART 1 sub-study and less than three for SMART 2. Although CE/BZA is indicated for women who are post-menopausal up to the age of 75, the populations in the studies were generally healthy and likely would not reflect a true population. High discontinuation rates across the SMART 1 main study's treatment arms (29.8% for CE/BZA, 35.7% for RAL, and 35.4% for PLA) indicate CE/BZA's usefulness may be limited. Also a fixed-dose formulation of CE/BZA may limit its use in women who require higher or lower doses of estrogen. Numerous internal validity concerns also were evident in these studies:

- Mild hot flushes were included in the assessment of the change in moderate and severe hot flushes, which may inflate the baseline severity.
- A clinically significant reduction in the severity of hot flushes was not defined. 31.3% of subjects had protocol violations in SMART 1 and 25.2% in SMART 2.
- The SMART 2 mITT population had subjects who did not meet the entry criteria for the requisite number of hot flushes.
- The distribution by race/ethnicity was uneven across study groups for the SMART 1 sub-study
- An imbalance in the number of hot flushes at baseline existed across study groups in the SMART 1 sub-study.
- Enrollment in the SMART1 main study was not based on hot flush frequency or severity requirement.
- The number of subjects in the SMART 1 sub-study was not predefined.

Finally, CE/BZA's ability to improve quality of life has not been adequately demonstrated. One poorly quality assessment of MSQOL has been performed. This assessment equivocally supports the vasomotor symptom indication; however, it does not support CE/BZA's ability to improve other measures of the MSQOL and does not address HRQOL.

Postmenopausal Osteoporosis Prevention: [2]
An osteoporosis sub-study (OSS) of SMART 5 (Trial 3307) and two supportive sub-studies (OP1 and OP2) of SMART 1 (Trial 303) served as the basis for CE/BZA's indication for the prevention of postmenopausal osteoporosis. The primary endpoints for the sub-studies were the mean changes in BMD at the lumbar spine at month 12 for SMART 5 OSS and at 24 months for the SMART1 OP1 and OP2.

SMART 5 was a poor quality, multicenter, randomized, double-blind, and placebo- and active-controlled study in generally healthy women who were age 40 to 64, had an intact uterus, were ≤5 years postmenopausal, and were seeking treatment for menopausal symptoms. The study evaluated the endometrial safety and BMD effects of daily CE (0.45 mg or 0.625 mg)/BZA 20 mg vs BZA 20 mg alone, CE 0.45 mg/MPA 1.5 mg, and placebo. The primary endpoint for the main study was incidence of endometrial hyperplasia. The percent change in lumbar spine BMD and in total hip BMD from baseline at month 12 were primary and secondary endpoints, respectively, of the OSS. The OSS was performed at sites with DXA machines and included 119 of 445, 56 of 230, 59 of 220, and 139 of 474 subjects in the CE/BZA, BZA, CE/MPA, and placebo arms of the main study, respectively.

The CE/BZA, BZA, and CE/MPA subgroups had significantly greater increases in lumbar spine and total hip BMD compared with the placebo subgroup at 12 months:
OSS lumbar spine: 0.24% for CE/BZA (p<0.001), 0.07% for BZA (p=0.0026), 1.30% for CE/MPA (p< 0.001), –1.28% for placebo
OSS total hip: 0.50% for CE/BZA (p< 0.001); 0.47% for BZA (p< 0.001); 0.71% for CE/MPA (p-value not reported); –0.72% for placebo

The placebo subtracted mean percent change in BMD at the lumbar spine and total hip for the CE/MPA subgroup was numerically greater than for the CE/BZA subgroup but was not statistically different: 2.57% (CI: 1.72 to 3.43) vs 1.51% (CI: 0.82 to 2.2), respectively, for the spine and 1.42% (CI: 0.85 to 1.99) vs 1.21% (CI: 0.76 to 1.67) for the hip. The placebo group had progressive bone loss over 12 months.

SMART 1—a poor quality, 24-month, multicenter, placebo- and active-controlled study—evaluated the effects of CE/BZA on BMD in women at risk for osteoporosis. Included were healthy postmenopausal women who were age 40 to 75 and had intact uteruses and acceptable endometrial biopsy at baseline. The subjects were randomized 1:1:1:1:1:1:1:1 into eight groups: CE (0.45 mg or 0.625 mg)/BZA (10 mg, 20 mg, or 40 mg), raloxifene 60 mg, and placebo. Subjects were prospectively enrolled into one of two sub-studies based on menopausal status: (1) Osteoporosis Prevention I sub-study (OPI 1) if >5 years post-menopausal and a BMD T-score at the lumbar spine or total hip between –1 and –2.5 and ≥1 additional osteoporosis risk factor (2) Osteoporosis Prevention 2 and Metabolic sub-study (OP2) if ≤5 years postmenopausal and ≥1 osteoporosis risk factor. Baseline characteristics were similar across study groups except for maternal history of fracture: 5.56% for CE/BZA, 6.95% for raloxifene, 8.15% for placebo group for OP1 and 3.6% for CE/BZA, 7.5% for raloxifene, 6.5% for placebo group for OP2. The mean years since menopause for OP1 was about 11 years and for OP2 was about 3 years, the mean age of subjects was 58 for OP1 and 52 for OP2, the mean age of the last menses was about 48 for OP1 and 50 for OP2, the baseline mean lumbar spine T-score was –1.47 for OP1 and in the normal range (–0.83) for OP2. About 55% of women in OP2 were osteopenic by T-score. Subjects in both sub-studies had their daily calcium and vitamin D intake assessed at baseline and received calcium carbonate 600 mg plus vitamin D_3 if their calcium intake was <1000 mg.

The primary endpoint of the main study was the incidence of endometrial hyperplasia after 1 year—a surrogate endpoint for endometrial cancer—using the EE population (subjects who had taken at least 1 dose, had screening endometrial biopsy, or had hyperplasia diagnosed before the time point). The main secondary endpoint evaluated by the FDA was the mean percent change from baseline BMD of the lumbar spine after 2 years of therapy between CE/BZA groups and placebo using the mITT population (subjects who took ≥1 dose and had baseline and ≥1 on-therapy BMD) and LOCF. Among the other secondary endpoints was BMD of the hip (mean percent change at all time points). Responder rates were compared between CE/BZA groups and placebo using mITT, defined as all subjects who took at least one dose and had baseline and at least one on-therapy BMD.

In both sub-studies, the CE/BZA group had a significantly greater least square (LS) mean percent change in lumbar spine and total hip BMD from baseline to 24 months than the placebo group and a significantly greater percent change in lumbar spine BMD than the raloxifene group (p≤0.001 for all vs placebo):

- OP1 lumbar spine: 1.64% for CE/BZA, 0.75% for raloxifene, –1.47% for placebo

total hip: 1.07% for CE/BZA, 0.87% for raloxifene, 1.53% for placebo

- OP2 lumbar spine: 1.72% for CE/BZA, 0.13% for raloxifene, –1.90% for placebo
  total hip: 0.46% for CE/BZA, –0.27% for raloxifene, –1.41% for placebo

The responder rates for no change or increase in BMD for the lumbar spine at month 24 were significantly greater for CE/BZA and RAL than PLA: 68% and 59% vs. 30%, respectively, ($p<0.001$ for both). The FDA did not use responder figures in their review.

The evidence for the efficacy of CE/BZA in preventing osteoporosis is of low quality. The indication is based on sub-studies with small patient numbers and surrogate, secondary, and sub-study endpoints. Also, the efficacy of CE/BZA in improving fracture risk has not been addressed. CE/BZA is indicated for women with osteoporosis who are up to age 75. At this age, many women are likely to have acquired or be subject to a variety of health issues. However, the populations used in the CE/BZA studies were generally healthy women who had been prescreened for endometrial abnormalities. Furthermore, women primarily ≤65 years of age served as subjects in the SMART 1 trial; 45% of subjects in SMART 1 OP2 had a mean lumbar T-score within the normal range; the maximum years of age and years since menopause of patients in SMART 5 were about 62 and 5.5, respectively; and the mean T-score was within the normal range for SMART 5. Also limiting external validity were high discontinuation rates across the SMART 1 main study's treatment arms (29.8% for CE/BZA, 35.7% for RAL, and 35.4% for PLA) and the use of two different formulations for phase 3 trials, neither of which was the marketed formulation. However, the FDA was satisfied the formulations were bioequivalent. Internal validity concerns included an uneven history of maternal fracture across study groups for SMART 1 OP1 and OP2, an imbalance in discontinuation rates in SMART 5, and a lack of direct statistical comparisons between CE/MPA and raloxifene and CE/BZA.
Outstanding questions: How long should therapy be continued? What is CE/BZA's place in therapy relative to other osteoporosis prevention therapies? Is CE/BZA more safe and effective than CE/MPA for long-term use?

Clinical Safety: [1]
CE/BZA's safety was evaluated in four phase 3 clinical trials including a total of 1,224 patients treated with CE/BZA and 1,069 patients treated with placebo, as well as calcium (600-1200 mg) and vitamin D (200-400 IU) daily in SMART 1 and 5. The incidences of all-cause mortality and serious adverse events were 0% and 3.5%, respectively, in the CE/BZA group and 0.2% and 4.8%, respectively, in the placebo group. The percentage of subjects discontinuing treatment due to adverse reactions was 7.5% in the CE/BZA group and 10% in the placebo group. Hot flush, upper abdominal pain, and nausea were the most common adverse reactions leading to discontinuation. The most common adverse reactions (incidence ≥ 5%) more frequently reported in subjects treated with CE/BZA than placebo are presented in the appendix table Adverse Reactions.

SMART 1 and SMART 5 assessed the effects of CE/BZA on endometrial hyperplasia or endometrial malignancy and on uterine bleeding or spotting. The EE population (patients who had taken at least one dose of CE/BZA, had baseline and post-baseline endometrial biopsies, or had been diagnosed with hyperplasia) had an incidence of endometrial hyperplasia or malignancy <1% at 24 months and 12 months for SMART 1 and 5, respectively. The cumulative amenorrhea at 12 months was 83% and 88% for the CE/BZA groups in SMART 1 and 5, respectively, vs 85% and 84% for the placebo groups.

VTE was reported in 0% of patients taking CE/BZA and 0.1% of patients taking placebo. Because both groups had low VTE event rates, conclusions cannot be drawn about the risk of VTE with CE/BZA relative to that seen with other estrogen therapies.

The risks associated with the use of CE alone should be assumed to be similar for CE/BZA until shown otherwise.

Unanswered safety questions include the following:
What effects does discontinuing therapy have on bone loss? What are the risks of long-term use of CE/BZA and are the risks different depending on the age of the patient, number of years of use, and years since the start of menopause? What are the risks of developing hyperplasia for patients with significantly higher BZA clearance? Will women who take CE/BZA initially for vasomotor symptoms experience rapid bone loss upon discontinuation due to resolution of vasomotor symptoms?

What are the risks of CE/BZA use in the general population of postmenopausal women, including those who may not be healthy, have not had uterine biopsy prior to use, and are older and are several years past the start of menopause?

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COMPARATIVE CLINICAL EFFICACY

Treatment of Vasomotor Symptoms: [2, 11, 12]

Relevant Endpoints:
1) Health Related Quality of Life and Menopause Specific Quality of Life (see Clinical Efficacy section regarding MSQOL)
2) Serious adverse reactions
3) Mean daily number of moderate and severe hot flashes
4) Mean daily severity of hot flushes

Primary Study Endpoint:
1) Incidence of endometrial hyperplasia at 12 months (primary endpoint of the SMART 1 main study)
2) Mean change from baseline in average daily number of moderate and severe hot flushes at week 4 (SMART 2) and week 12 (SMART 1 sub-study and SMART 2)
3) Mean change from baseline in average daily severity of hot flushes at week 4 (SMART 2) and week 12 (SMART 1 sub-study and SMART 2): [(# mild hot flushes) + (# moderate hot flushes x 2) + (# severe hot flushes x 3)] ÷ [total # hot flushes]

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (p-values), LOCF	ARR/ NNT	Safety Results (CI, p-values)	ARR, NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. SMART 1 (Trial 303) supportive sub-study Lobo (2009) and FDA Med Review Phase 3, MC (94), DB, PC, AC, RCT Note: This study included 8 arms, 6 for CE/BZA, 1 for RAL, and 1 for PLA. Only the	1. CE 0.45 mg/BZA 20 mg daily 2. RAL 60 mg daily 3. PLA daily Duration: 12 weeks Note: SMART1 evaluated CE/BZA for treating vasomotor symptoms and preventing osteoporosis, so 3397 were randomized, but only patients meeting EE1 criteria (n=216	**Demographics:** SMART 1 EE1 population (CE/BZA, RAL, PLA, respectively): · Age (mean): 54.6, 55.6, 54 · Ethnic origin (%) White: 82.1, 87.5, 87.9 Black: 14.3, 4.2, 3 Other: 3.6, 8.3, 6.1 (1 subject missing from data for PLA ethnicity) · BMI (mean): 25.7, 25.7, 24.7 · Years since last menstruation (mean):	**EE1** 1. 28 2. 24 3. 33 Total trial randomization: N=3544 CE 0.625 mg/BZA 10 mg: 430 CE 0.625 mg/BZA 20 mg: 414 CE 0.625 mg/BZA 40 mg: 417 CE 0.45 mg/BZA	**Mean daily change in # of moderate and severe hot flushes at week 12:** 1. CE/BZA: –8.74, SE 1.14 (p=0.001) 2. RAL: –5.53, SE 1.18 (p=0.049) 3. PLA: –2.45, SE 1.02 (Efficacy is a difference of	NA	For the safety population (CE/BZA n=433, RAL n=423, PLA n=427): **Any SAE at month 24:** CE/BZA: 6% RAL: 7.6% PLA: 8% **Any TEAE at month 24:** CE/BZA: 92.6% RAL: 92.4%	NA NA	**Quality rating:** Poor-Fair **Internal Validity:** Selection: · The distribution by race/ethnicity is uneven across study groups · An imbalance in the number of hot flushes at baseline existed across groups with 11.4 hot flushes for CE/BZA and 14.3 for PLA. · Subjects who had ≥7 moderate o severe hot flushes per day or ≥50 per week during the screening week were prospectively included

approved dose (CE 0.45 mg/BZA 20 mg) is addressed in this efficacy evaluation.	total) were selected for the evaluation of vasomotor symptoms post-randomization. The safety evaluation includes all subjects taking the approved CE/BZA dose, raloxifene, and placebo.	6.7, 6.6, 6.8 · Mean # mod + severe HF: 11.44, 12, 14.32 · Mean severity HF: 2.45, 2.37, 2.39 **Inclusion Criteria:** · Healthy, postmenopausal women, age 40 to 75, with intact uterus · FSH >30 IU/mL and 17β-estradiol <183.5 pmol/L · Last menstruation ≥12 months before screening · BMI ≤32.2 kg/m^2 · Acceptable endometrial biopsy results at screening · ≥7 to 10 moderate or severe hot flushes daily or ≥50 weekly during the screening week · ≥5 years postmenopausal **Exclusion Criteria:** · Estrogen-dependent neoplasia · Endometrial hyperplasia · Malignancy in last 10 y, except basal cell skin cancer · Thrombophlebitis, thrombosis, thromboembolic disorders · Cerebrovascular accident, stroke, or TIA	10 mg: 417 CE 0.45 mg/BZA 20 mg: 433 CE 0.45 mg/BZA 40 mg: 423 RAL 60 mg: 423 PLA: 427	>2 hot flushes daily) **in severity of hot flushes at week 12:** 1. CE/BZA: –1, SE 0.15 (<0.001) 2. RAL: –0.22, SE 0.17 3. PLA: –0.21, SE 0.14	NA	PLA: 91.8% **Venous thromboembolism at month 24:** CE/BZA: <1% RAL: <1% PLA: <1% **Cardiovascular AEs at month 24:** CE/BZA: <1% RAL: <1% PLA: <1% **Discontinuation due to AEs:** CE/BZA: 10.6% RAL: 13.9% PLA: 14.3%	NA NA NA	in the sub-study. However, the number of subjects was not predefined. <u>Performance:</u> · 31.3% of subjects had protocol violations, including use of prohibited medications affecting lipids or coagulation and use of prohibited medications affecting bone metabolism. · Blinding of researchers was described for the main study but not the sub-study <u>Detection:</u> <u>Attrition:</u> · The discontinuation rate was high across all 8 arms for the main study, ranging from 29.8% to 35.7%, and was 29.8% for CE 0.45 mg/BZA 20 mg, 35.7% for RAL, and 35.4% for PLA specifically. Discontinuation rates for the sub-study were: 28% CE 0.45 mg/BZA 10 mg; 14% CE 0.45 mg/BZA 20 mg; 38% CE 0.625 mg/BZA 40 mg; 57% PLA; 25% RAL · Used LOCF **External Validity:** <u>Recruitment:</u> <u>Patient Characteristics:</u> · The study was limited to healthy postmenopausal women who had uterine biopsy performed <u>Setting:</u> · The average number of patients per study center was very small. Therefore, any determinations about setting are likely not

		· Neuro-ocular disorder · MI or ischemic heart disease · Chronic renal or hepatic disease · Gall bladder disease · Use of oral estrogen, progestin, androgen, or SERM medications withou washout · Presence of unresolved abnormal mammogram or pap smear; endocrine disease; LFT >1.5xULN; BP >160/100; alcohol or drug abuse						possible. <u>Outcomes:</u> · This study is of insufficient duration to assess or support the assessment of CE/BZA efficacy or safety beyond 12 weeks. · What constitutes a clinically meaningful reduction in the severity of hot flushes was not defined. · These results are from a sub-study of a main study investigating the incidence of endometrial hyperplasia. · Enrollment in the total sub-study was small (n=216 over 94 study centers). · Enrollment in the main study was not based on hot flush frequency or severity requirement. · Mild hot flushes were included in the assessment of the severity of hot flushes, which may inflate the baseline severity and confound the efficacy results, because mild hot flushes usually respond without treatment. · Safety is difficult to determine because of exclusion of subjects with conditions that may predispose them to unwanted side effects of estrogen therapy **Analysis:** · The results of this sub-study supports the indication with regard to the reduction in the number moderate and severe hot flashes by >2 per day. While this sub-study also supports a statistically significant

								improvement in severity of hot flushes, no indication of the clinical significance of this is evident. ・This sub-study is of insufficient duration to support the assessment of CE/BZA efficacy beyond 12 weeks or to assess the effect of discontinuation on severity of menopausal symptoms. Furthermore, the study population is unlikely to reflect the population considered for this therapy. ・This sub-study is of insufficient duration to assess or support the assessment of CE/BZA safety.
2. SMART 2 (Trial 305) Pinkerton (2009) and FDA Med Review Phase 3, MC (43), DB, PC, RCT	1. CE 0.45 mg/BZA 20 mg daily 2. PLA daily Duration: 12 weeks	CE/BZA (n=127), PLA (n=63), respectively, for safety population: ・ Age (mean): 53.6, 53.6 ・Ethnic origin (%) White: 88.2, 84.1 Black: 8.7, 11.1 Hispanic: 7.9, 4.8 Other: 3.2, 4.8 ・BMI (mean): 26.4, 26 ・Years since last menstruation (mean): 4.7, 4.8 for mITT population: ・Daily # mod + severe hot flushes (mean±SD): 10.3±5.38, 10.5±4.96 ・Daily severity score of hot flushes (mean±SD): 2.3±0.31, 2.3±0.33	**mITT** 1. 122 2. 63 Total randomized: CE 0.45 mg/ BZA 20 mg: 133 CE 0.625 mg/ BZA 20 mg: 133 PLA: 66	**Mean daily change in # moderate and severe hot flushes at week 4:** 1. CE/BZA: –5.9, (p=0.001) 2. PLA: – 2.84 Difference: –3.07 (–4.40 to –1.73) (Efficacy is a difference of >2 hot flushes per day) **in severity of hot flushes at week 4:** 1. CE/BZA: –0.58 (p<0.001) 2. PLA: –0.09	NA	**SAE:** CE/BZA: 2% PLA: 0% **Venous thromboembolism:** CE/BZA: 0% PLA: 0% **Discontinuation due to AEs:** CE/BZA: 3.9% PLA: 9.5%	NA NA NA	**Quality rating:** Poor-Fair **Internal Validity:** <u>Selection:</u> ・The mITT population had subjects who did not meet the entry criteria for the requisite number of hot flushes. <u>Performance:</u> ・25.2% (n=80) of subjects had protocol deviations. 23.3% (n=74) had protocol deviations due to inclusion/exclusion violations. 8.8% (n=28) had protocol violations while on study drug. There was an uneven distribution of overall deviations across treatment groups. ・6.3% of subjects were taking concomitant therapy to treat VMS symptoms. ・ Blinding of researchers was not described.

		Inclusion Criteria: · Age: 40 to 56 · Intact uterus · At least 12 months postmenopausal · Seeking treatment for hot flushes · Experienced ≥7 moderate to severe hot flushes daily or ≥50 weekly · BMI ≤34 kg/m^2 **Exclusion criteria:** · history of disease (e.g., endometrial hyperplasia, estrogen-dependent neoplasia; undiagnosed vaginal bleeding; chronic renal or hepatic disease; thromboembolic disorders; cerebrovascular accident; neuro-ocular disorders; ischemic heart disease; gallbladder disease; malignancy, except skin cancer · endometrial thickness >4 mm, focal endometrial abnormality, ovarian cyst complex or >20 mm · active endocrine disease, alcohol or drug abuse, heavy smoking, use of an IUD w/in 12 weeks before screening		Difference: –0.48 (–0.70 to –0.27) **Mean daily change in # moderate and severe hot flushes at week 12; mean difference from PLA (CI):** 1. CE/BZA: –7.63 (p<0.001) 2. PLA: – 4.92 Difference: –2.71 (–3.84 to –1.57) **in severity of hot flushes at week 12:** 1. CE/BZA: –0.87 (p<0.001) 2. PLA: –0.26 Difference: –0.60 (–0.86 to –0.35)	NA NA NA			Attrition: For the safety population: 11%, 13%, and 16% of those taking CE 0.45 mg/BZA 20 mg (n=127), CE 0.625 mg/BZA 20 mg (n=128), and PLA (n=66) discontinued, respectively. **External Validity:** Recruitment: Patient Characteristics: · The population was generally healthy and had been assessed for endometrial hyperplasia. Setting: · The average number patients per study center was very small. Therefore, any determinations about setting are likely not possible. Outcomes: · The study enrolled small patient numbers spread over numerous centers · The study was of short duration **Analysis:** · The results of this sub-study supports the indication with regard to the reduction in the number of moderate and severe hot flashes by >2 per day. While this sub-study also supports a statistically significant improvement in severity of hot flushes, no indication of the clinical significance of this is

		・use of oral estrogen-, progestin-, androgen-, or SERM-containing drugs within 8 weeks before screening; vaginal hormone products within 4 weeks; or estrogen or progestin implants/injectables within 6 mo. ・estrogen-, progestin-, androgen-, or SERM-containing medications and treatments for vasomotor symptoms prohibited during study						evident. Furthermore, the study population is unlikely to reflect the population considered for this therapy. ・This sub-study is of insufficient duration to support the assessment of CE/BZA efficacy beyond 12 weeks or to assess the effect of discontinuation on severity of menopausal symptoms. Furthermore, the study population is unlikely to reflect the population considered for this therapy. ・This sub-study is of insufficient duration to assess or support the assessment of CE/BZA safety.
AC: active controlled, AEs: adverse events, CE/BZA: conjugated estrogens/bazedoxifene, DB: double blind, D/C: discontinuation, EE1: the subset of efficacy evaluable population who have moderate to severe vasomotor symptoms (see “Clinical Efficacy” section for definition); HF: hot flushes, LOCF: last observation carried forward, mITT: modified intent to treat (those who had taken ≥1 dose, ≥5 days of data at baseline, and ≥5 days of data for ≥1 on-therapy week), NA: not applicable, NR: not reported, MC: multicenter, PC: placebo controlled, PLA: placebo, RAL: raloxifene, RCT: randomized controlled trial, SAE: serious adverse event, TEAE: treatment-emergent adverse event, VMS: vasomotor symptom								

Prevention of Osteoporosis: [2, 14, 15]

Relevant Endpoints:
1) Vertebral, hip, or other fractures
2) Serious adverse reactions
4) Serious adverse reactions

Primary Study Endpoint:
1) Incidence of endometrial hyperplasia at 12 months (primary endpoint of the SMART 1 and SMART 5 main studies)
2) Mean percent change in BMD at the lumbar spine at 12 months and 24 months (as evaluated by the FDA) for SMART 5 and for SMART 1, respectively (endpoint of SMART 1 sub-studies, OP1 and OP2, and SMART 5 sub-study, OSS)

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results LOCF	ARR, NNT	Safety Results (CI, p-values)	ARR, NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. SMART 1 (Trial 303) supportive sub-studies Lindsay (2009) and FDA Med Review Phase 3, MC (94), DB, PC, AC, RCT Note: This study included 8 arms, 6 for CE/BZA, 1 for RAL, and 1 for PLA. Only the approved dose (CE 0.45 mg/BZA 20 mg) is addressed in this efficacy evaluation.	1. CE 0.45 mg/BZA 20 mg daily 2. RAL 60 mg daily 3. PLA daily Duration: 24 months	**Demographics:** CE/BZA, RAL, PLA, respectively, for OP1 sub-study (>5 y postmenopausal): · Age (mean): 58.4, 58.5, 58.3 · Ethnic origin (%) White: 79.7, 79.3, 71.7 Black: 19.2, 19.7, 26.6 Hispanic: 0.6, 0, 0.5 Other: 0.6, 1.1, 1.1 · BMI (mean): 25.7, 25.7, 26.1 · Years since last menstruation (mean): 11.3, 11, 11.4 · Age at last menstruation (mean): 47.6, 47.9, 47.5 · Baseline lumbar spine T-score (mean): –1.43, –1.48, –1.52 · Maternal history of fracture (%): 5.56%, 6.95%, 8.15% for OP2 sub-study (1 to 5 y postmenopausal): · Age (mean): 52.1, 52.3, 52.3	**mITT** **SA** OP1 1. 155 2. 157 3. 151 OP2 1. 95 2. 90 3. 95 Total trial randomization: N=3544 CE 0.625 mg/BZA 10 mg: 430 CE 0.625 mg/BZA 20 mg: 414 CE 0.625 mg/BZA 40 mg: 417 CE 0.45 mg/BZA 10 mg:	OP1 **LS mean % change in BMD at lumbar spine (p-value vs PLA); mean difference from PLA (CI) at 24 months:** 1. CE/BZA: 1.64 (p<0.001); 3.11 (2.29 to 3.93) 2. RAL: 0.75 (p<0.001); 2.22 (1.40 to 3.04) 3. PLA: –1.47 **LS mean % change in BMD at total hip; mean difference from PLA at 24 months** 1. CE/BZA: 1.07	NA	For the safety population (CE/BZA n=433, RAL n=423, PLA n=427): **Any SAE at month 24:** CE/BZA: 6% RAL: 7.6% PLA: 8% **Any TEAE at month 24:** CE/BZA: 92.6% RAL: 92.4% PLA: 91.8% **Endometrial hyperplasia/neoplasia:** CE/BZA: 0.68% RAL: 0% PLA: 0% **Venous thromboembolism at month 24:** CE/BZA: <1% RAL: <1% PLA: <1%	NA NA NA NA	**Quality rating:** Poor Selection: · The percentage of subjects within each treatment group with a maternal history of fracture varied across treatment groups. · The mean T-score for the OP2 group was within the normal range, with 45% of subjects having a T-score in the normal range Performance: · Blinding of researchers was described for the main study but not the sub-studies Detection: · These results are from two sub-studies of a main study investigating the incidence of endometrial hyperplasia. Therefore, secondary and sub-study endpoints were used.

		· Ethnic origin (%) White: 82, 77.6, 81.5 Black: 9.9, 15, 10.2 Hispanic: 7.2, 6.5, 8.3 Other: 1, 1, 0 · BMI (mean): 26, 26.2, 25.5 · Years since last menstruation (mean): 3, 3, 3 · Age at last menstruation (mean): 49.7, 50, 49.9 · Baseline lumbar spine T-score (mean±SD): –0.81±1.11, –0.81±1.1 –0.94±1.06 · Maternal history of fracture (%): 3.6%, 7.5%,6.5% **Inclusion Criteria:** · Same as SMART 1 "Treatment of Vasomotor Symptoms" Comparative Clinical Efficacy table plus the following: · for OP1: >5 years postmenopausal and BMD T-score between –1 and –2.5 and one additional risk factor for osteoporosis · for OP2: 1 to 5 years postmenopausal and one additional risk factor for osteoporosis **Exclusion Criteria:** · Same as SMART 1 "Treatment of Vasomotor Symptoms" Comparative Clinical Efficacy table plus the following: · for OP sub-studies: History of osteoporotic fracture; use of glucocorticoids, calcitonin, anabolic steroids, parathyroid hormones,	430 CE 0.45 mg/BZA 20 mg: 433 CE 0.45 mg/BZA 40 mg: 423 RAL 60 mg: 423 PLA: 427	(p<0.001); 1.73 (1.17 to 2.28) 2. RAL: 0.87 (p<0.001); 1.53 (0.97 to 2.08) 3. PLA: –0.65 OP2 **LS mean % change in BMD at lumbar spine; mean difference from PLA at 24 months:** 1. CE/BZA: 1.72 (p<0.001); 3.62 (2.64 to 4.6) 2. RAL: 0.13 (p<0.001); 2.03 (1.03 to 3.02) 3. PLA: –1.90 **LS mean % change in BMD at total hip; mean difference from PLA at 24 months:** 1. CE/BZA: 0.46 (p<0.001); 1.87 (1.19 to 2.54) 2. RAL: –0.27 (p=0.0011); 1.14 (0.45 to	NA NA	**Cardiovascular AEs at month 24:** CE/BZA: <1% RAL: <1% PLA: <1% **Discontinuation due to AEs:** CE/BZA: 10.6% RAL: 13.9% PLA: 14.3%	NA NA	Attrition: · The discontinuation rate was high across all 8 arms for the main study, ranging from 29.8% to 35.7%, and was 29.8% for CE 0.45 mg/BZA 20 mg, 35.7% for RAL, and 35.4% for PLA specifically. No discontinuation rate for the sub-study could be found. · A small number of patients were enrolled in the sub-studies **External Validity:** Recruitment: Patient Characteristics: · The study was limited to healthy postmenopausal women who had had uterine biopsy performed · Subjects were primarily 65 years of age or younger. Setting: · The average number patients per study center was very small. Therefore, any determinations about setting are likely not possible. Outcomes: · A surrogate endpoint was used · The sub-studies do not address the efficacy or effectiveness in improving fracture risk. ·The studies were of short duration compared with the length of use of drugs for bone loss.

		therapeutic fluoride, bisphosphonates, anticoagulants, or antihyperlipidemics without washout; diseases affecting bone metabolism; ≥2 abnormal lumbar vertebrae; baseline lumbar spine or total hip BMD T-score > 2.5 SD below the mean for healthy young women		1.82) 3. PLA: –1.41 **% responders lumbar spine BMD at 24 months:** 1. CE/BZA: 68% (p<0.001) 2. RAL: 59% (p<0.001) 3. PLA: 30%	NA 2.6 3.4			**Analysis:** · The results of the study support the indication, as CE/BZA significantly increases BMD at the lumbar spine and total hip. However, the study population was narrower in age than the intended population fo the indication. The study population, a generally healthy one, also is unlikely to reflect th general population considered for this treatment. · The duration of use is insufficient to make a determination regarding safety for long-term use.
2. SMART 5 Trial (3307) sub-study Pinkerton (2014) and FDA Med Review Phase 3, MC (166), DB, AC, PC, RCT	1. CE 0.45 mg/BZA 20 mg daily 2. BZA 20 mg daily 3. CE 0.45 mg/MPA 1.5mg daily 4. PLA daily Duration: 12 months	**Demographics:** CE/BZA, BZA, CE/MPA, PLA, respectively, for OSS population: · Age (mean; range): 53.1 (46 to 60), 53 (45 to 62), 52.8 (43 to 61), 53.1 (42 to 62) · Ethnic origin (%) White: 91.9, 94.5, 88.6, 91.8 Black: 5.9, 5.5, 8.6, 5.7 Other: 2.2, 2.9, 2.5, 1.9 · BMI (mean): 25.7, 26.5, 26.8, 25.5 · Years since last menstruation (mean): 2.42 (0.51 to 5.4), 2.43 (0.55 to 5.3), 2.49 (0.53 to 4.97), 2.63 (0.53	**mITT** 1. 119 2. 56 3. 59 4. 139	**LS mean % change in BMD at lumbar spine (p-value); mean difference from PLA (CI) at 12 months:** 1. CE/BZA: 0.24 (p<0.001); 1.51 (0.82 to 2.20) 2. BZA: 0.07 (p=0.0026); 1.34 (0.47 to 2.21) 3. CE/MPA:	 NA	For the safety population (CE/BZA n=445, BZA n=230, CE/MPA n=220, PLA n=474): **Any SAE at month 12:** 1. CE/BZA: 3.6% 2. BZA: 2.2% 3. CE/MPA: 5.9% 4. PLA: 3.8% **Any TEAE at month 12:** 1. CE/BZA: 84.3% 2. BZA: 84.3% 3. CE/MPA: 85% 4. PLA: 82.7%	 NA NA	**Quality rating:** Poor **Internal Validity:** <u>Selection:</u> · Mean years since menopause was 2.5 years. · Mean T-score was within the normal range. · Small patient numbers. <u>Attrition:</u> · High discontinuation rate and imbalance in discontinuation rate for the CE/MPA group (27.1%) and BZA 20 mg groups (24.7%) compared with CE/BZA

		to 20.87) ・T-score (mean±SD; range): –0.91±0.77 (–2.4 to 1.5) –0.82±0.75 (–2.2 to 0.8), –0.77±0.78 (–2.4 to 1.25), –0.95±0.91 (–2.6 to 2.65) ・FRAX major osteoporotic fracture score (mean±SD): 5.2±2.6, 4.6±1.8, 4.4±1.8, 5±1.8 ・FRAX hip fracture score (mean±SD): 0.38±0.38, 0.33±0.35, 0.29±0.34, 0.42±0.42 **Inclusion Criteria:** ・Healthy ・Intact uterus ・BMI ≤34 kg/m^2 ・Normal endometrial biopsy results ・≤5 y since their last menstruation ・2 evaluable BMD scans of the lumbar spine and hip at screening differing by <5% and <7.5%, respectively **Exclusion Criteria:** Similar to SMART 1 plus the following: ・Subjects w/ lumbar spine or total hip T-scores < –2.5 at screening or a current/history of osteoporosis or low-im- pact traumatic fracture		1.30 (p< 0.001); 2.57 (1.72 to 3.43) 4. PLA: –1.28 **LS mean % change in BMD at total hip; mean difference from PLA at 12 months:** 1. CE/BZA: 0.50 (p< 0.001); 1.21 (0.76 to 1.67) 2. BZA: 0.47 (p< 0.001); 1.19 (0.61 to 1.77) 3. CE/MPA: 0.71 (NR); 1.42 (0.85 to 1.99) 4. PLA: –0.72	NA	**Endometrial hyperplasia/neoplasm:** 1. CE/BZA: 0.3% (UL 1-sided CI: 1.41) 2. BZA: 0% (UL 1-sided CI: 1.76) 3. CE/MPA: 0% (UL 1-sided CI: 1.99) 4. PLA: 0.28% (UL 1-sided CI: 1.33) **Venous thromboembolism at month 12:** 1. CE/BZA: 0% 2. BZA: 0% 3. CE/MPA: 0.5% 4. PLA: 0% **Cardiovascular AEs at month 12:** 1. CE/BZA: 0.2% 2. BZA: 0% 3. CE/MPA: 0% 4. PLA: 0.4% **Breast cancer:** 1. CE/BZA: 0.4% 2. BZA: 0% 3. CE/MPA: 0.5% 4. PLA: 0.2% **Discontinuation due to AEs:** 1. CE/BZA: 7.6% 2. BZA: 7% 3. CE/MPA: 14.1% 4. PLA: 7%	NA NA NA NA NA	(19.3%) and PLA (18.4%) groups for the sub-study. **External Validity:** <u>Patient Characteristics:</u> ・The study does not address the efficacy and safety of CE/BZA in women older than 62 and more than 5.5 years postmenopausal. ・The study was limited to healthy postmenopausal women who had had uterine biopsy performed. <u>Setting:</u> ・The average number of patients per study center was very small. Therefore, any determinations about setting are likely not possible. <u>Outcomes:</u> ・A surrogate endpoints was used. ・The study was of short duration compared with the length of use of drugs for bone loss. <u>Analysis:</u> ・Same as SMART 1 sub-studies above.

AC: active controlled, AEs: adverse events, CE/BZA: conjugated estrogens/bazedoxifene, DB: double blind, D/C: discontinuation, LOCF: last observation carried forward, mITT: modified intent to treat (subjects who took ≥1 dose, had lumbar spine BMD values at baseline and ≥1 value on-therapy within 60 days of the last dose of study drug), LS: least square, MPA: medroxyprogesterone acetate, NA: not applicable, NR: not reported, MC: multicenter, OP1: osteoporosis prevention sub-study 1, OP2, osteoporosis prevention sub-study 2, OSS: osteoporosis sub-study, PC: placebo controlled, PLA: placebo, RAL: raloxifene, RCT: randomized controlled trial, SA: FDA sensitivity analysis (excludes 8.1% of patients with missing source documentation) SAE: serious adverse event, TEAE: treatment-emergent adverse event, UL: upper limit

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY [1]

Conjugated estrogens (CE) and bazedoxifene (BZA) bind to and activate estrogen receptors (ER). CE are agonists of ER-α and –β, while BZA is an estrogen agonist in some estrogen-sensitive tissues and an antagonist in others, such as the uterus. CE paired with BZA produces a composite effect specific to each target tissue. BZA reduces the risk of endometrial hyperplasia that can occur with the CE component.

PHARMACOKINETICS [1]

The following information is based on monotherapy studies:

Parameter	**CE Result**	BZA Result
Oral Bioavailability		6%
Protein Binding		98-99%
Elimination	Urine	biliary excretion, then feces (~85%), and < 1% urine*
Half-Life	17 hours	30 hours
Metabolism	Partially CYP3A4	Glucuronidation

*BZA is expected to undergo enterohepatic recycling

Note: In a single-dose, crossover study in 23 postmenopausal women given CE 0.625 mg/BZA 20 mg with a high fat/high calorie meal, food increased $AUC_{0-\infty}$ of BZA 25%. The C_{max} was unchanged.

DOSE & AVAILABILITY [1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Tablet with CE 0.45 mg/BZA 20 mg	oral	once daily	CE 0.45 mg/BZA 20 mg	Use in patients with renal impairment is not recommended. The pharmacokinetics have not been evaluated in patients with renal impairment.	Use is contraindicated in patients with hepatic impairment. The pharmacokinetics, safety, and efficacy have not been evaluated in patients with hepatic impairment.*	CE/BZA is not intended for nor has it been studied in this population.	Use in patients ≥75 years old is not recommended. CE/BZA has not been studied in this population.	• Swallow tablets whole • Add supplemental calcium and/or vitamin D if daily dietary intake is inadequate. Based on a PK model from four phase 1 studies, a 17% reduction in BZA exposure was predicted in women with BMI > 27 kg/m^2 vs those with BMI ≤ 27 kg/m^2. This could be associated with an increased risk for endometrial hyperplasia.

*In a pharmacokinetic studies of BZA 20 mg alone, the C_{max} increased 67%, 32%, 20% and the AUC increased 143%, 109%, 268% in women with mild, moderate, and severe hepatic impairment, respectively. No pharmacokinetic studies with CE were performed in women with hepatic impairment.

DRUG SAFETY [1]

Serious (REMS, Black Box Warnings, Contraindications):

Black box warning:

- Women taking CE/BZA should not take additional estrogens.
- Women who have a uterus and use estrogen-alone therapy (ET) are at increased risk of endometrial cancer.
- ET should not be used for preventing cardiovascular disease or dementia.
- The Women's Health Initiative (WHI) estrogen-alone sub-study reported increased risks of stroke and deep vein thrombosis (DVT).
- The WHI Memory Study reported an increased risk of probable dementia in postmenopausal (PM) women ≥65 years old.

Without comparable data for CE/BZA, these risks should be assumed to be similar for other CE doses and dosage forms. Estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with the patient's treatment goals and risks.

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Contraindication: CE/BZA use in women with hepatic impairment.

Warnings and Precautions:

Women taking CE/BZA should not take progestins, additional estrogens, or additional estrogen agonist/antagonists.

- Increased risk of cardiovascular disorders, including thromboembolism (TE), have been reported with ET and estrogen agonists/antagonists. CE/BZA should be discontinued if TE occurs or is suspected. Risk factors for arterial vascular disease or TE should be managed. If feasible, CE/BZA should be discontinued during periods of prolonged immobilization or at least 4 to 6 weeks before a surgery associated with an increased risk of TE.
- ET has been associated with an increased risk of endometrial cancer in women who have a uterus, with the greatest risk associated with prolonged ET use. BZA reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer and can occur with the CE component. Therefore, women taking CE/BZA should not take additional estrogens, as this may increase the risk of endometrial hyperplasia. The effect of CE/BZA on breast and ovarian cancer risk is unknown. However, ET has been associated with an increase in abnormal mammograms, but not with invasive breast cancer, and has been inconsistently associated with ovarian cancer.
- Estrogen use in postmenopausal (PM) women has been associated with an increased risk of gallbladder disease requiring surgery.
- Discontinue CE/BZA if papilledema or retinal vascular lesions occur. In a small number of case reports, increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In women with pre-existing hypertriglyceridemia, estrogens may be associated with plasma triglyceride elevations leading to pancreatitis. Consider discontinuing CE/BZA if pancreatitis occurs. Estrogens may be poorly metabolized in women with impaired liver function. On average, women with hepatic impairment treated with BZA alone, vs controls, have shown a 4.3-fold increase in overall exposures. Exercise caution for women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, and discontinue CE/BZA in the case of recurrence.
- Estrogen use increases thyroid-binding globulin levels. Therefore, women on thyroid hormone replacement who are using estrogens may require increased thyroid replacement.
- Estrogens may cause fluid retention. Because of this, patients who have conditions such as cardiac dysfunction or renal impairment warrant careful observation when using estrogens. CE/BZA use in patients with renal impairment is not recommended.
- Women with hypoparathyroidism should use estrogens cautiously as estrogen-induced hypocalcemia may occur.
- Estrogens exacerbate asthma, symptoms of angioedema, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- CE\BZA use is not recommended for premenopausal women.

Monitoring:

Monitoring is as follows for CE/BZA use: diagnostic measures to rule out malignancy in PM women with undiagnosed persistent or recurring abnormal genital bleeding; thyroid function tests in women on thyroid replacement therapy; yearly breast examinations by a healthcare provider; appropriately scheduled mammography; and monthly breast self-examinations.

Drug-Laboratory Test Interactions:

- accelerated prothrombin, partial thromboplastin, and platelet aggregation times;
- increased platelet count; fibrinogen and fibrinogen activity levels; plasminogen antigen and activity levels; and factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin;
- decreased antifactor Xa and antithrombin III and antithrombin III activity levels;
- increased thyroid-binding globulin and changes in related thyroid hormone levels;
- possibly decreased free hormone concentrations, such as testosterone and estradiol;
- possibly elevated binding proteins in serum (e.g., corticosteroid binding globulin and sex hormone-binding globulin and changes in related hormone levels) and plasma proteins (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin);
- increased plasma HDL and HDL2, reduced LDL, and increased triglyceride levels;
- impaired glucose tolerance.

Drug-Drug interactions:
In vitro and *in vivo* studies and clinical studies have been conducted only with the individual components of CE/BZA as follows:

- CYP3A4 inducers (e.g., St. John's Wort, phenobarbital, carbamazepine, and rifampin) may reduce CE plasma concentrations. CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice) may increase the exposure of CEs. Therefore, diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be taken to rule out malignancy in postmenopausal women who receive CYP3A4 inhibitors and CE/BZA concurrently for >30 days and have undiagnosed persistent or recurring abnormal genital bleeding.
- UGT inducers (e.g., rifampin, phenobarbital, carbamazepine, and phenytoin) may increase BZA metabolism. Therefore, diagnostic measures should be taken to rule out malignancy as described in the previous paragraph.

Food-Drug Interactions: Not reported

Allergy/Cross Reactive Substances: None reported

Pregnancy/lactation rating: Category X. Women who are or may become pregnant must not use CE/BZA. No animal studies have been conducted to evaluate the CE/BZA's effects on reproduction; however, rats given BZA ≥ 0.3 times the human AUC at the 20 mg dose had lower numbers of live fetuses and fetuses with reduced body weights but no observable developmental anomalies. The fetuses of treated pregnant rabbits experienced abortion and an increased incidence of heart and skeletal system anomalies at 2 times the human AUC at the 20 mg dose. CE/BZA should not be used by lactating women. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE alone, and estrogen decreases the quantity and quality of the milk in nursing mothers.

Carcinogenesis/Mutagenesis: Studies of carcinogenicity and mutagenicity with CE/BZA have not been conducted. In some animal species, long-term continuous administration of natural and synthetic estrogens increases the frequency of breast, uterus, cervix, vagina, testis, and liver carcinomas. Female transgenic mice receiving BZA 150 or 500 mg/kg/day for 6 months had a drug-related increased incidence of benign, ovarian granulosa-cell tumors. Female rats receiving 0.03% and 0.1% BZA concentrations for two years experienced a drug-related marked increased incidence of benign, ovarian granulosa-cell tumors. Systemic BZA AUC was 3 and 8 times that observed in postmenopausal women administered 20 mg/day. Male rats had drug-related renal tumors, in the presence of renal toxicity, at 0.06 to 5 times the clinical BZA AUC at a dose of 20 mg. BZA alone was not genotoxic or mutagenic in *in vitro* and *in vivo* bacterial and animal tests.

Impairment of Fertility: Studies of impairment of fertility studies have not been conducted with CE/BZA. BZA at 0.03 to 10 times the human AUC at the 20 mg dose adversely affects the fertility of female rats.

Dose Index (efficacy/toxic): No specific antidote exists for overdose, so treatment should be symptomatic.

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

NME Drug Name	Lexicomp	Clinical Judgment
LA/SA for conjugated estrogens/bazedoxifene	none	None
LA/SA for Duavee	none	Duovent

ADVERSE REACTIONS [1]

The most common adverse reactions (incidence ≥ 5%) more frequently reported in women treated with CE/BZA than placebo in clinical trials.

	DUAVEE (N=1224) n (%)	Placebo (N=1069) n (%)
Gastrointestinal disorders		
Nausea	100 (8)	58 (5)
Diarrhea	96 (8)	57 (5)
Dyspepsia	84 (7)	59 (6)
Abdominal pain upper	81 (7)	58 (5)
Musculoskeletal and connective tissue disorders		
Muscle spasms	110 (9)	63 (6)
Neck pain	62 (5)	46 (4)
Nervous system disorders		
Dizziness	65 (5)	37 (3)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	80 (7)	61 (6)

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Oregon Health Authority

Anaphylaxis Rescue: Abbreviated Class Review

Month/Year of Review: November 2014 **End date of literature search:** September 2014
Drugs Included: Epinephrine auto-injector (Adrenaclick®, Auvi-Q™, EpiPen®, EpiPen Jr®)

Current Management: Anaphylaxis rescue is not currently listed as a drug class on the Preferred Drug List (PDL).

Research Questions:

- What is the evidence for efficacy and safety of epinephrine for the treatment of anaphylaxis rescue?
- What is the comparative efficacy and safety evidence of different self-administered formulations of epinephrine?
- Are there subgroups of patients where one formulation may be more effective or safer?

Conclusions:

- There is insufficient evidence from randomized, double-blind, placebo-controlled clinical trials to define the benefits from administering epinephrine for anaphylaxis due to ethical concerns.[1–3]
- There is moderate evidence from one systematic review[1] that intramuscular injection is superior to subcutaneous route.
- There is insufficient evidence comparing the effectiveness of administering epinephrine via auto-injector versus other injectable formulations.[3]
- Epinephrine is recommended as first-line initial therapy for anaphylaxis in both children and adults.[4–6] In addition, the auto-injector is recommended as the preferred injectable formulation in the community.[4–6]

Recommendations:

- Add “Anaphylaxis Rescue”as a drug class to the PDL under “Allergy/Cold” to include epinephrine auto-injector as preferred.
- Evaluate comparative costs in the executive session for other PDL decisions.

Reason for Review:

Epinephrine, H_1-antihistamines, H_2-antihistamines, and systemic glucocorticosteroids are used for the initial treatment of anaphylaxis.[7] Epinephrine is the best studied medication in anaphylaxis[8]; however, it is not on the Preferred Drug List (PDL). This review will examine place in therapy for PDL placement and class inclusion.

Background:

Anaphylaxis is a serious allergic or hypersensitivity reaction that is rapid in onset and may cause death.[9,10] There are three recognized temporal patterns of anaphylaxis: uniphasic, biphasic, and protracted.[11] Uniphasic anaphylactic reactions are the most common type, accounting for an estimated 80 to 90 percent of all episodes. A uniphasic response usually peaks within 30 minutes to one hour after symptoms appear and resolves either spontaneously or with treatment within the next 30 minutes to one hour; a protracted anaphylactic reaction lasts hours to days without clearly resolving completely and biphasic reactions are characterized by a uniphasic response, followed by an asymptomatic period of an hour or more, and then a subsequent return of symptoms without further exposure to antigen.[11] In the United States, the lifetime prevalence of anaphylaxis is reported to be 1.6 percent, based on strict clinical diagnostic criteria.[12] The most common trigger factors include foods, insect venom, and medications.[4] In the health care setting, epinephrine, H_1-antihistamines, H_2-antihistamines, and systemic glucocorticosteroids are used for the initial treatment of anaphylaxis.[7] In anaphylaxis, no randomized controlled trials without methodological problems have been performed with above medications.[7] Epinephrine is the best studied medication in anaphylaxis. However, the evidence for its use comes from observational studies during anaphylaxis, randomized controlled clinical pharmacology studies at baseline, studies of anaphylaxis in animal models, and epidemiologic studies, including fatality studies. The evidence for use of H_1-antihistamines in anaphylaxis is extrapolated from their use in urticaria.[13,14] The evidence for the use of glucocorticosteroids in anaphylaxis is extrapolated from their use in acute asthma.[8]

Epinephrine is a α- and β- adrenergic agonist which results in relaxation of smooth muscle of the bronchials, cardiac stimulation (increasing myocardial oxygen consumption), and dilation of skeletal muscle vasculature.[7] It is frequently cited as first-line therapy and the single most important agent in the treatment of anaphylaxis.[4–6] Anaphylaxis often occurs in the community, in the absence of trained health care professionals; hence the development and popularity of self-injectable epinephrine that can be administered by patients or caregivers. In the United States, the generally recommended intramuscular (IM) epinephrine dose for adults is 0.3mg of a 1:1000 (1 mg/mL) solution or 0.01mg/kg (up to 0.3 mg) of a 1:1000 solution for children.[15] Self-injectable epinephrine is currently available in two auto-injector dosage formulations: 0.3mg/0.3 mL (typically for adults) and 0.15mg/0.15 mL (typically for children).[15]

Methods:

A MEDLINE Ovid search was conducted using the terms: anaphylaxis, anaphylaxis treatment, adrenaline or epinephrine. The search was limited to meta-analysis, systematic review, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Systematic Reviews and Meta-analyses: (See Appendix 1 for abstract)

The most recent systematic review by **Dahimi S et al**[1] in November 2013 evaluated the effectiveness of interventions for the acute and long-term management of anaphylaxis. The review searched for systematic reviews, randomized controlled trials (RTCs), quasi-randomized controlled trials, controlled clinical trials, controlled before-after studies and interrupted time series and, case series in relation to adrenaline investigating the effectiveness of interventions in managing anaphylaxis. Fifty - five studies were evaluated. Case fatality register studies have demonstrated the deaths can occur within minutes of the onset of an anaphylactic reaction. Therefore the consistent guidelines recommendation of prompt management with pharmacological interventions. The authors found some evidence investigating the role of epinephrine - the main drug advocated in guidelines; however the evidence was derived from case series, fatality registers and a limited number of trials in people not experiencing anaphylactic reactions. There were some evidence based on two RTCs that in both children and adults, maximum plasma concentration occurs quicker with the intramuscular than with subcutaneous route. The authors found no evidence from primary studies for other potential treatments such as glucocorticosteroids, antihistamines, methylxanthines and brochodilators.

Chipps BE (2013)[2]conducted a systematic review to update the pediatrician on the treatment of anaphylaxis in pediatrics. The author reviewed the literature published between 2007 and 2012. This review found food to be the most common trigger in children, but insect venom and drugs are other typical causes. Clinical diagnostic criteria include dermatological, respiratory, cardiovascular and gastrointestinal manifestation. Epinephrine is the drug of choice for acute reactions and is the only medication shown to be lifesaving properties when used promptly based on guidelines from World Allergy Organization. Auto-injector formulation provides unique advantage of prompt administration with proper training of caregivers.

A **Cochrane** review[3] from 2008 and last updated in 2010 assessed the effectiveness of epinephrine auto-injectors in relieving respiratory, cardiovascular and other symptoms during episodes of anaphylaxis that occur in the community. The authors found 1,328 studies relating to anaphylaxis and epinephrine auto-injector use but no randomized controlled trials on this subject. No new recommendations on the effectiveness of epinephrine auto-injectors for the treatment of anaphylaxis were made. Although randomized, double-blind, placebo-controlled clinical trials of high methodological quality are necessary to define the true extent of benefits from the administration of epinephrine in anaphylaxis via an auto-injector, such trials are unlikely to be performed in individuals experiencing anaphylaxis because of ethical and methodological concerns. There is, however, a need to consider trials in which, for example, auto-injectors of different doses of adrenaline and differing devices are compared in order to provide greater clarity on the dose and device of choice. Such trials would be practically challenging to conduct. In the absence of appropriate trials, the authors recommend that epinephrine administration by auto-injector should still be regarded as the most effective first-line treatment for the management of anaphylaxis in the community.

Treatment guidelines:

World Allergy Organization (WAO) Anaphylaxis Guidelines

In 2013 WAO published updated the guidelines with a focus on the epidemiology, risk factors, triggers, diagnosis and the management of anaphylaxis.[3] Epinephrine remains the first line initial treatment. Patients at risk for anaphylaxis in community settings should be equipped with epinephrine. Epinephrine auto-injectors are the preferred formulation;[16] ampules/syringes or prefilled syringes can be alternative formulations. H_1-antihistamines are not appropriate for initial anaphylaxis treatment due to lack of ability to relieve life-threatening respiratory symptoms or shock. Similarly, systemic glucocorticosteroids are not drug of choice in initial anaphylaxis treatment because of the relatively slower onset of action. However, glucocorticosteroids remain important options for anaphylaxis because they potentially prevent biphasic anaphylaxis.

Working Group of the Resuscitation Council of United Kingdom (UK) Emergency Treatment of Anaphylactic Reaction Guidelines

An updated guidance on the recognition, acute management and follow-up of adults with anaphylaxis was published by the Resuscitation Council (UK) in 2008.[5] The use of an airway, breathing, circulation, disability and exposure approach to recognize and treat anaphylaxis was emphasized in the guidelines. The guidelines has Grade C recommendation that designate epinephrine the most important drug for the treatment of anaphylaxis and it should be given to all patients with life-threatening features. All patients and caregivers should be given instructions on how to properly administer epinephrine auto-injector. (Grade C).

European Academy of Allergy and Clinical Immunology (EAACI) Task Force

Due to lack of specific guidelines for anaphylaxis in children, the EAACI task force released a position paper that outlined the epidemiology, clinical presentation and the management of anaphylactic reactions in children.[6] Intramuscular epinephrine is the acknowledged first-line therapy for anaphylaxis in the hospital and in the community as soon as the condition is recognized. There is no absolute contraindication to administering epineprhine in children. Additional therapies such as volume support, nebulized bronchodilators, antihistamines or glucocorticosteroids are supplementary to epinephrine.The prescription of epinephrine auto-injector is part of a larger, comprehensive approach to the management of anaphylaxis. Epinephrine auto-injector is mandatory for high risk children, especially in children with prior cardiorespiratory reactions.

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Appendix 1: Abstract of Selected Systemic Reviews and Meta-analyses

1. **Management of anaphylaxis: a systematic review.**
   Dhami S, Panesar SS, Roberts G, et al. *Allergy* 2014;69(2):168-175. doi:10.1111/all.12318.

   Abstract

   To establish the effectiveness of interventions for the acute and long-term management of anaphylaxis, seven databases were searched for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-after studies and interrupted time series and - only in relation to adrenaline - case series investigating the effectiveness of interventions in managing anaphylaxis. Fifty-five studies satisfied the inclusion criteria. We found no robust studies investigating the effectiveness of adrenaline (epinephrine), H1-antihistamines, systemic glucocorticosteroids or methylxanthines to manage anaphylaxis. There was evidence regarding the optimum route, site and dose of administration of adrenaline from trials studying people with a history of anaphylaxis. This suggested that administration of intramuscular adrenaline into the middle of vastus lateralis muscle is the optimum treatment. Furthermore, fatality register studies have suggested that a failure or delay in administration of adrenaline may increase the risk of death. The main long-term management interventions studied were anaphylaxis management plans and allergen-specific immunotherapy. Management plans may reduce the risk of further reactions, but these studies were at high risk of bias. Venom immunotherapy may reduce the incidence of systemic reactions in those with a history of venom-triggered anaphylaxis.

2. **Update in pediatric anaphylaxis: a systematic review.**
   Chipps BE. *Clin. Pediatr. (Phila.)* 2013; 52(5):451-461. doi:10.1177/0009922812474683.

   Abstract

   Anaphylaxis is common in children and has many differences across age groups. A systematic review of the literature from the past 5 years was conducted with the goal of updating the pediatrician. Food is the most common trigger in children, but insect venom and drugs are other typical causes. Clinical diagnostic criteria include dermatological, respiratory, cardiovascular, and gastrointestinal manifestations. A biphasic reaction is seen in some, with recurrence usually within 8 hours of the initial episode. Epinephrine is the drug of choice for acute reactions and the only medication shown to be lifesaving when administered promptly, but it is underutilized. Patients should have ready access to ≥2 doses of an epinephrine auto-injector, with thorough training regarding correct use of a given device and an emergency action plan. Management of anaphylaxis in schools presents distinct challenges. Pediatricians are in a unique position to assess and treat these patients chronically.

3. **Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community.**
   Sheikh A, Simons FER, Barbour V, Worth A. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2012.

   Abstract

Background: Anaphylaxis is a serious hypersensitivity reaction that is rapid in onset and may cause death. Adrenaline (epinephrine) auto-injectors are recommended as the initial, potentially life-saving treatment of choice for anaphylaxis in the community, but they are not universally available and have limitations in their use.

Objectives: To assess the effectiveness of adrenaline (epinephrine) auto-injectors in relieving respiratory, cardiovascular, and other symptoms during episodes of anaphylaxis that occur in the community.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 1), MEDLINE (Ovid SP) (1950 to January 2012), EMBASE (Ovid SP) (1980 to January 2012), CINAHL (EBSCO host) (1982 to January 2012), AMED (EBSCO host) (1985 to January 2012), LILACS, (BIREME) (1980 to January 2012), ISI Web of Science (1950 to January 2012). We adapted our search terms for other databases. We also searched websites listing on-going trials: the World Health Organization International Clinical Trials Registry Platform, the UK Clinical Research Network Study Portfolio, and the meta Register of Controlled Trials; and contacted pharmaceutical companies who manufacture adrenaline auto-injectors in an attempt to locate unpublished material.

Selection criteria: Randomized and quasi-randomized controlled trials comparing auto-injector administration of adrenaline with any control including no intervention, placebo, or other adrenergic agonists were eligible for inclusion.

Data collection and analysis: Two authors independently assessed articles for inclusion.

Main results: None of the 1328 studies that were identified satisfied the inclusion criteria.

Authors' conclusions: Based on this review, we cannot make any new recommendations on the effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis. Although randomized, double-blind, placebo-controlled clinical trials of high methodological quality are necessary to define the true extent of benefits from the administration of adrenaline in anaphylaxis via an auto-injector, such trials are unlikely to be performed in individuals experiencing anaphylaxis because of ethical concerns associated with randomization to placebo. There is, however, a need to consider trials in which, for example, auto-injectors of different doses of adrenaline and differing devices are compared in order to provide greater clarity on the dose and device of choice. Such trials would be practically challenging to conduct. In the absence of appropriate trials, we recommend that adrenaline administration by auto-injector should still be regarded as the most effective first-line treatment for the management of anaphylaxis in the community. In countries where auto-injectors are not commonly used, it may be possible to conduct trials to compare administration of adrenaline via auto-injector with adrenaline administered by syringe and ampoule, or comparing the effectiveness of two different types of auto-injector.

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Abbreviated Class Review: Long-Acting Injectable Antipsychotics

Month/Year of Review: November 2014 **End date of literature search:** September 2014
Current PDL Class: First Generation Antipsychotics and Second Generation Antipsychotics

Drugs Included in Review

Generic	Brand
Fluphenazine decanoate	Prolixin Decanoate®
Haloperidol decanoate	Haldol Decanoate®
Olanzapine pamoate	Zyprexa Relprevv®
Paliperidone palmitate	Invega Sustenna®
Risperidone LAI	Risperdal Consta®
Aripiprazole LAI	Abilify Maintena®

Research Questions:

- Are there differences in efficacy or safety between the LAI antipsychotic agents?
- Are there subpopulations that certain LAI antipsychotics are more effective or safer than others?
- Is there evidence that long-acting injectable antipsychotics are more efficacious or safer than oral antipsychotic agents?
- Is there evidence that long acting injectable (LAI) antipsychotics prevent relapse or improve adherence?

Conclusions:

- There is moderate quality evidence of no difference in relapse prevention between long-acting injectables (LAI) antipsychotics and oral antipsychotics in adults with schizophrenia (21 studies; RR = 0.93, 95% CI: 0.80-1.08; p=0.35).[1,2] There is low quality evidence that fluphenazine decanoate is superior to oral antipsychotics in preventing hospitalizations (4 studies, RR = 0.82, 95% CI: 0.67-0.99, p=0.04).[1] There is low quality evidence of no significant differences between LAI antipsychotics and placebo or oral antipsychotics with respect to death, overall number of treatment-adverse events, insomnia, or injection site pain.[2]
- There is insufficient evidence on the comparative efficacy between fluphenazine, olanzapine, risperidone and aripiprazole LAIs.
- There is low quality evidence of no difference in efficacy between paliperidone palmitate and haloperidol deconoate.[3]

- There is insufficient evidence data available for this class in regards to mortality and serious harms.
- There is low quality evidence of more weight gain with paliperidone palmitate compared to haloperidol decanoate (2.17 kg vs -0.96 kg) and more akathisia with haloperidol decanoate compared to paliperidone palmitate.[3]
- There is insufficient evidence to determine a meaningful difference in efficacy or harms between LAI antipsychotics in any subgroup population.
- Guidelines consistently include LAI antipsychotics as a treatment option for patients but are not consistent about stabilizing patients on oral medication before starting a LAI.[4–6]

Recommendations:

- Include LAI on the voluntary PDL; Review costs in executive session.
- Consistent with guidelines, consider limiting LAI antipsychotics to patients with recurrent relapses related to nonadherence and patients who prefer LAIs over oral medications.

Reason for Review:

Currently, all antidepressants are available without prior authorization for non-preferred placement. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs. First and second generation antipsychotics have been reviewed for clinical efficacy and safety and specific oral agents were chosen as clinically preferred; this eliminates a copayment. Oregon's Medicaid program does not currently charge a copayment for preferred PDL drugs.
The Oregon P&T Committee has reviewed both first and second generation oral antipsychotic medications (November 2013 and January 2014). Aripiprazole LAI was reviewed during the second generation class update in January 2014, but there has not been a review conducted comparing both generations of long-acting injectable antipsychotics for placement on the PDL.

Background:

Antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder and are divided into conventional, first generation antipsychotics and the second generation (or atypical) antipsychotics. There are currently ten second generation antipsychotics available in the US. Antipsychotics are available in many dosage forms (tablets, orally disintegrating tablets, and injectable), have an assortment of FDA-approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment of schizophrenia in adults), and are commonly used off-label for various psychiatric conditions. Side effect profiles between agents vary and are often an important factor in treatment selection. These side effects include extrapyramidal symptoms, autonomic effects, increased prolactin levels, metabolic effects, and cardiac risks including risk of ventricular arrhythmias.

Commonly used outcomes in clinical trials for assessing patients with schizophrenia include the Positive and Negative Syndrome Scale (PANSS) which is a validated 30-item rating scale used to assess the effects of drug treatment in schizophrenia, and the Clinical Global Impression Severity Scale (CGI-S) which measures the subject's current severity of illness. Data from the CATIE trial, a large, multicenter trial for patients with schizophrenia, suggests a minimal clinically important difference in the PANSS Scale is 15 points, but will vary according to a patient's baseline PANSS score.[7]

Long-acting injection (LAI) depot preparations of antipsychotics are widely used, especially for treating patients who show non-adherence or partial adherence to oral therapy. The proposed benefits of LAI's are their relapse-preventing properties, patient convenience, and improved compliance. Drug adherence is essential in improving clinical and social outcomes in schizophrenia. First generation antipsychotics LAIs (fluphenazine and haloperidol) have been available since the late 1960s, and more recently second generation antipsychotic LAI formulations have become available (olanzapine pamoate, paliperidone palmitate, risperidone LAI, and aripiprazole LAI). Data on the safety and efficacy of second generation antipsychotic LAI formulations is lacking, particularly head-to-head data.[8] There is some controversy over the most appropriate patient to select the LAI antipsychotics in, as some clinicians claim that depots would cause more adverse effects or patients would not accept injections.

The primary indication for using LAI antipsychotics is for patients with schizophrenia who have poor adherence to oral medication leading to relapse. They are commonly used in chronically ill patients with significant compliance issues. They are also used less frequently for patients how become symptomatic after stopping antipsychotics with behaviors leading to highly adverse consequences, when dose-related adverse events are experienced, or when patients are considered treatment resistant except for a question of medication nonadherence.[9]

The adverse effect profile of LAI antipsychotics is not yet fully understood. Olanzipine pamoate causes dose-dependent weight gain and adversely effects lipid and glucose metabolism, and may increase prolactin levels even in at low doses.[8] Postinjection syndrome, due to accidental intravascular injection of olanzapine pamoate, is characterized by delirium and/or excessive sedation (incidence 1.2%).[8] Hyperprolactinemia, extrapyramidal side effects, cardiovascular events (i.e. tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone LAI and paliperidone palmitate.[8] Risperidone LAI may also increase the risk of QT prolongation, although this may not be clinically significant.[8] The most common adverse event associated with paliperidone palmitate is worsening of psychotic symptoms (incidence between 3.5% and 16%).[8] There has only been one study of aripiprazole LAI; the most common adverse reactions were worsening of psychotic symptoms, extrapyramidal side effects, and weight gain.[8]

Methods:

A Medline literature search ending September 2014 for new systematic reviews, clinical guidelines, and head-to-head randomized controlled trials (RCTs) comparing LAI antipsychotic agents fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, risperidone or aripiprazole. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Kishimoto et al[1] conducted a systematic review to evaluate the efficacy of LAI antipsychotics and oral antipsychotics (OAPs). The review included 21 randomized controlled trials that lasted ≥6 months comparing LAIs and OAPs; 10 included first generation antipsychotics while 11 included second generation antipsychotics.

LAIs were similar to OAPs for relapse prevention at the longest time point (21 studies; RR = 0.93, 95% confidence interval (CI): 0.80-1.08; p=0.35). When restricting the analysis to outpatient studies lasting one year or longer, the finding was the same (12 studies, RR=0.93; 95% CI 0.71-1.07; p = 0.031). When comparing relapse rates at different time points (3, 6, 12, 18 and 24 months), pooled LAIs did not separate from OAPs. Neither individual LAI nor pooled LAIs separated from OAPs regarding all-cause discontinuation (21 studies, RR= 1.00; 95% CI: 0.89-1.13, p=0.99) or discontinuation due to adverse events (19 studies, RR = 1.10, 95% CI: 0.74-1.64, p=0.65). Among individual LAIs, only fluphenazine was superior to OAPs in drug efficacy (8 studies, RR = 0.78, 95% CI: 0.66-0.91, p=0.02). Among individual LAIs, only fluphenazine was superior to OAPs in preventing hospitalization (4 studies, RR = 0.82, 95% CI: 0.67-0.99, p=0.04). The authors concluded more studies in real-world settings are needed.

A systematic review and meta-analysis of second-generation LAIs in patients with schizophrenia was conducted.[2] Thirteen studies were included comparing second-generation LAIs to placebo and oral antipsychotics. LAI antipsychotics were associated with a statistically significant decrease in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end of the study period compared to placebo injections (Hedges's *g*=0.336, 95% CI 0.246–0.426, *Z*=7.325, *P*<0.001), but not significantly different from oral antipsychotics (Hedges's *g*=0.072, 95% CI -0.072 to 0.217, *Z*=0.983, *P*=0.326). No significant differences between LAI antipsychotics and placebo or OAPs were observed with respect to the number of deaths, overall number of treatment-adverse events, insomnia, or pain at the injection site. There was a greater risk of developing extrapyramidal symptoms (EPS) with LAI therapy than in both control groups (vs. placebo, RR=2.037, *P*<0.001; vs. OAPs, RR=1.451, *P*=0.048).

Guidelines:

American Psychiatric Association (APA) [4]

The APA guidelines were first released in 2004, and the 2009 updated literature search did not address LAI use specifically. The guidelines recommend using LAI antipsychotics in patients with recurrent relapses related to nonadherence and patients who prefer LAIs over oral medications. Patients may transition from an OAP to LAI; however, LAIs should not be initiated for acute psychotic episodes because LAIs can take months to reach stable steady state and are eliminated slowly, making it difficult to titrate the dose to control therapeutic effects and side effects.

Canadian Psychiatric Association [5,10]

Guidelines on LAI antipsychotics were released by the CPA in May 2013. The following were recommendations made based on medical evidence and consensus data solicited on LAI use in Canada:

- The overall evidence was not convincing of the superiority of LAIs compared with oral medications, suggesting equal effectiveness and some benefits of using LAIs in patients who are or who are likely to be nonadherent, irrespective of the phase of their illness.
- The use of LAIs may not prevent nonadherence but may allow for earlier recognition of nonadherence when a dose is missed and may help identify patients with poor or no response from those who are non- or partially adherent.
- For patients who are clearly adherent to OPAs, there may not be reason or evidence to switch to a LAI.
- In case of overt or impending nonadherence to medication, serious consideration should be given to using LAIs as one of the choices for addressing nonadherence.

- It is preferable to initiate treatment with an OAP, but not necessary to achieve stabilization with an OAP prior to initiating an LAI as long as the patient has been exposed to a test dose. This is particularly relevant for patients refusing to take oral medication or who are unlikely to take it during the acute phase of psychosis.

The National Institute for Health and Care Excellence (NICE): [6]

An update to NICE Psychosis and Schizophrenia in Adults evidence-based guidelines was released in February 2014. The recommendations for use of LAI antipsychotics are given:

- Consider offering depot/LAI antipsychotics to people with psychosis or schizophrenia who would prefer such treatment after an acute episode or to patients where avoiding covert nonadherence (either intentional or unintentional) is a clinical priority within the treatment plan.
- When initiating depot/LAI medication, take into account patient preference and attitudes, as well as risks and benefits of the drug regimen, and use a small initial test dose before injecting (not necessary to stabilize on oral medication).

Randomized Controlled Trials:

- In the ACLAIMS (A Comparison of Long-Acting Medications for Schizophrenia) trial, McEvoy et al[3] compared first-generation haloperidol decanoate to paliperidone palmitate in 311 adults with schizophrenia or schizoaffective disorder judged to be at risk for relapse for up to 24 months. The primary outcome was efficacy failure, which included psychiatric hospitalization; a need for crisis stabilization; a clinically meaningful increase in outpatient visits; a clinician's decision to discontinue the LAI antipsychotic agent due to inadequate benefit; or ongoing need for adjunctive OAP therapy. Approximately one-third of patients in both groups reported efficacy failure (defined as a psychiatric hospitalization, an increase in outpatient visits, or other clinical intervention). There was no difference between the two groups (adjusted hazard ratio, 0.98; 95% CI, 0.65-1.47). Side effect profiles between the two LAIs did differ. Patients experienced statistically significant more weight gain at 6 months in the paliperidone group (2.17 kg; 95% CI, 1.25-3.09) compared to those taking haloperidol (-0.96 kg; 95% CI, -1.88 to -0.04). This difference in weight change widened at 24 months between the two groups. Patients in the paliperidone group also experienced more moderate or severe adverse events than patients in the haloperidol decanoate group, including significantly higher serum prolactin levels among men and women; however, haloperidol decanoate was associated with more akathisia.

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Abbreviated Class Review: Prenatal Vitamins

Month/Year of Review: November 2014 **End date of literature search:** September 2014
PDL Class: None

Research Questions:

- Is there evidence to support and cover the use of specific products with good value?
- Are certain reformulations of prenatal vitamins more effective than safer than individual components or other formulations?
- Are there subpopulations that certain vitamins are more effective or safer than others?
- Is there evidence that supplementation improves clinical outcomes?

Conclusions:

- There is high quality evidence that folic acid supplementation (alone or in combination with other vitamins and minerals) is effective in preventing neural tube defects compared with placebo (RR 0.28; 95% CI 0.15 to 0.52).[1]
- There is moderate quality evidence that taking any vitamin supplements prior to pregnancy does not prevent women from experiencing miscarriages and there is insufficient evidence to evaluate differences in different combinations of vitamins.
- There is moderate quality evidence that prenatal supplementation with daily iron reduces the risk of low birthweight (RR 0.81; 95% CI 0.68 to 0.97) and prevents maternal anemia (RR 0.30; 95% CI 0.19 to 0.46) and iron deficiency (RR 0.43; 95% CI 0.27 to 0.66) during pregnancy.
- In settings of low calcium dietary intake, 1.5 to 2.0 g of elemental calcium per day is recommended in pregnant women.
- Well-nourished women may not need a multivitamin or prenatal vitamin and there is insufficient evidence of any benefit with universal supplementation. However, in the absence of a careful evaluation by a nutritionist, it is reasonable to recommend them. Often, the convenient way to get iron and folic acid is to take a daily multivitamin containing adequate amounts of both.
- There is no evidence of any difference between formulations of prenatal vitamins. An adequate prenatal vitamin should include 400 to 800 micrograms of folic acid and 30 mg of iron.

Recommendations:

- Evaluate comparative costs in executive session to list specific agents as preferred and non-preferred.
- Include formulations with adequate amounts of folic acid, iron, and calcium.

Reason for Review:
The multivitamins, antioxidant multivitamins, and electrolytes were reviewed for clinical efficacy/effectiveness and safety. Prior authorization was proposed for multivitamins and antioxidant multivitamin supplements to approve for documented nutritional deficiency or diagnosis associated with nutritional deficiency. For mono vitamin supplements and electrolytes, including calcium, vitamin D, folic acid, vitamin B, the ferrous salt formulations, potassium, magnesium, and phosphate, specific agents were listed as preferred and non-preferred based on cost comparisons when no clinical advantage was identified. The additional minerals, electrolytes, and vitamins will be reviewed similarly.

Background:
Complementary and alternative medicine refers to preventive and therapeutic modalities not considered to be part of conventional medicine.[2] This includes dietary supplements and has increased dramatically in North America recently in general populations, as well as CVD populations. Evidence of both benefits and harms of adding supplements to medical treatments has been reported, and there remains debate concerning the efficacy and safety of dietary supplements [3] Safety concerns include the potential adverse effects, contamination of preparations, and mislabeling. Dietary supplements are regulated with much less rigor than prescription medications.[4] While randomized controlled trials are the gold standard for evidence based medicine, data on the efficacy and safety of dietary supplements is lacking, insufficient, or inconsistent. There is also a paucity of standardized guidelines for the use of these products. Even if there is guidance and/or evidence that a particular vitamin or dietary supplement may benefit patients, the question of which manufacturer or product to recommend is also raised. There are quality assessment programs available to ensure the quality of these products. This includes consumerlab.com, NSF International, and US pharmacopeia. Currently there are no specific vitamin policies under the Oregon Health Plan. A multivitamin with folic acid is included in the prevention table for pregnant patients.

Nutrient deficiencies are a public health concern in many countries in the world. RCTs in children in developing nations have shown that vitamin A supplementation decreases morbidity and all-cause mortality. However, the benefit of these supplements in nonpregnant adults in the US and other Western nations is less clear.[5] Malnutrition is both a cause and effect of poor health.[6] Factors contributing to disease related malnutrition include impaired intake (confusion, medication, poor appetite), impaired digestion and/or absorption (medical and surgical problems effecting the stomach, intestine, pancreas, and liver), altered requirements (increased metabolic demands), excess losses (vomiting, diarrhea, fistulae, stomas, burns). The National Institute for Health and Clinical Excellence recommends that all patients who have malnutrition due to one of the above reasons, in addition to sufficient calories, protein, and fluids, receive adequate electrolytes, minerals, micronutrients, and fiber if appropriate. [6] However, their evidence review found no data to support the routine use of vitamin and mineral supplements in either acute hospitalized patients or older residents in nursing homes. They recommend that if there is a concern about adequate micronutrient intake, a complete oral multivitamin and mineral supplement providing the reference nutrient intake should be considered by healthcare professionals.

Prenatal vitamins generally contain a variety of vitamins and minerals and are often similar to multivitamins used outside of pregnancy, with some differences. Prenatal vitamins typically contain more folic acid and iron than do standard adult multivitamins. Some vitamins come from strong evidence, including folic acid. Periconceptional folic acid supplementation is recommended since there is strong evidence that it reduces the risk of neural tube defects. Approximately 41.8% of pregnant women worldwide are anemic.[7] Iron has been shown to support the baby's growth and development and supplementation with iron is recommended in the United States. But for most vitamins, data are limited and there is insufficient evidence supporting preventive supplementation with vitamin and mineral supplements outside of folic acid.[8] Multivitamin supplements are recommended for pregnant women who cannot meet the recommended intake through food intake and are especially beneficial for women in developing countries.[9]

Methods:
A Medline literature search ending September 2014 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) for prenatal vitamins and nutrition during pregnancy 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. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A Cochrane Collaboration systematic review evaluated the effectiveness and safety of any vitamin supplementation on the risk of spontaneous miscarriage, maternal adverse outcomes and fetal and infant adverse outcomes.[10] A total of 28 trials were included in the analysis. Studies included vitamin A, alone or with iron, folic acid, zinc or multivitamins. Overall, no significant differences were observed between women taking vitamins compared to control for total fetal loss (RR 1.04; 95% CI 0.95 to 1.14), early or late miscarriage (RR 1.09; 95% CI 0.95 to 1.25) or stillbirth (RR 0.86; 95% CI 0.65 to 1.13). Women on vitamins were more likely to have a multiple pregnancy (RR 1.38; 95% CI 1.12 to 1.70). The authors concluded that taking any vitamin supplements prior to pregnancy does not prevent women from experiencing miscarriages and there is insufficient evidence to evaluate differences in different combinations of vitamins.

The Cochrane Collaboration reviewed the effects of periconceptional supplementation with folic acid to reduce neural tube defects.[1] A total of 5 randomized controlled trials (n=6105) were included in the systematic review. In all trials, supplementation started before pregnancy and discontinued after 12 weeks of pregnancy. However, the doses varied from less than 360 mcg to 4000 mcg daily. Of the 6105 women, 1949 had a history of neural tube defects and 4156 did not. All of the studies were published before 2001 and had an unclear or low risk of bias. Overall, the results are consistent in showing a protective effect of daily folic acid supplementation (alone or in combination with other vitamins and minerals) in preventing neural tube defects compared with placebo (RR 0.28; 95% CI 0.15 to 0.52). Four trials included women with a history of neural tube defects and folic acid supplementation reduced the recurrence of a pregnancy affected by another defect (RR 0.32; 95% CI 0.17 to 0.60). Four of the trials included folic acid with other micronutrients compared with micronutrients without folic acid and also showed a significant difference in favor of those receiving folic acid supplementation (RR 0.29; 95% CI 0.15 to 0.56). There was no statistically significant difference in any effects on prevention of other birth defects, including cleft palate, cleft lip, congenital cardiovascular defects, and miscarriages.

A third systematic review from the Cochrane Collaboration evaluated multiple-micronutrient supplementation (MMS) for women in developing countries during pregnancy.[11] Results from 21 trials demonstrated that compared with iron and folate supplementation, no supplementation, or placebo MMS resulted in a statistically significant decrease in the number of low birth weight babies (RR 0.89; 95% CI 0.83 to 0.94) and small for gestational age (SGA) babies (RR 0.87; 95% CI 0.81 to 0.95). No differences were seen in preterm births, miscarriage, maternal mortality, perinatal mortality, stillbirths and neonatal mortality. There was insufficient data to assess neural tube defects, neurodevelopmental delay, cost of supplementation, side-effects of supplements, maternal well-being or nutritional status of children. The authors concluded that although a benefit in low birthweight outcomes was seen, more evidence is needed to replace the recommendation of routine iron and folate supplementation with multiple micronutrients.

A high quality systematic review from the Cochrane Collaboration assessed daily oral iron supplementation during pregnancy.[12] Forty three studies were

included in the meta-analysis, and the daily dose of elemental iron ranged from 9-90 mg in trials. Overall, moderate quality evidence showed that women taking oral supplementation were less likely to have low birthweight newborns compared with no iron (RR 0.81; 95% CI 0.68 to 0.97; based on 11 trials). Iron supplementation reduces the risk of maternal anemia at term (RR 0.30; 95% CI 0.19 to 0.46) and iron deficiency (RR 0.43; 95% CI 0.27 to 0.66). Women on iron supplements experienced a non-statistical significant increase in side effects (RR 2.36; 95% CI 0.96 to 5.83), especially at doses greater than 60mg of elemental iron. Women on iron supplementation also experienced more adverse events, including constipation and other gastrointestinal side effects.

Clinical Guidelines:

The CDC and IOM recommend a multivitamin for pregnant women who did not consume an adequate diet. At minimum, the daily supplement should contain iron, calcium (at least 250 mg) and folate. The U.S. Preventive Services Task Force and Centers for Disease Prevention and Control recommend that all women of childbearing age take a daily vitamin supplement containing 400 to 800 mcg of folic acid from at least one month before conception through the first three months of pregnancy.[13,14] Patients who previously had a pregnancy affected by a neural tube defect should have 4 mg daily.

The World Health Organization (WHO) recommends daily oral iron and folic acid supplementation as part of the antenatal care to reduce the risk of low birth weight, maternal anemia and iron deficiency (strong recommendation).[7] In all settings, 30-60mg of elemental iron and 400 mcg of folic acid is recommended throughout pregnancy and started as early as possible. In addition, supplements to include other vitamin and minerals may be used to overcome other possible maternal micronutrient deficiencies. In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of pre-eclampsia in pregnant women, particularly amont those at higher risk of developing hypertension (Strong recommendation), in doses of 1.5-2.0 g elemental calcium/day from 20 weeks' gestation until the end of pregnancy.

The Institute for Clinical Symptoms Improvement (ICSI) states that there is no clinical evidence that universal supplementation with a multivitamin or prenatal vitamin in the preconception period or during pregnancy is beneficial.[13]

The following recommendations for multivitamins are provided from the Department of Veterans Affairs[15]:

- Multivitamin supplements should be taken one month preconceptually and should be continued through the first trimester (Strength of evidence C)
- Pregnant women taking supplements for a medical condition should continue that supplementation throughout pregnancy.
- Pregnant women on restrictive diets should have nutrition consultation to customize vitamin supplementation regimen.
- Folate supplements should be taken one month preconceptually, continued through the first trimester and should be administered as part of the multivitamin supplementation (Strength of recommendation A)
- Women who have delivered a child with an open neural tube defect should supplement their diets with 4 mg folate daily for at least one month prior to conception.
- Calcium supplementation may be considered to reduce the risk or preeclampsia in high risk women and those with baseline calcium intake (Strength of recommendation A).
- There is insufficient evidence to support the use of Omega 3 supplements in the prevention of preterm birth, preeclampsia, and low birth rate.
- Other dietary supplements should be used with caution and only after discussion with the provider.

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Drug Use Research & Management Program
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Month/Year of Review: November 2014 **Date of Last Review:** August 2013
PDL Classes: Antiemetics, Newer **Source Document:** DERP

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

Previous Conclusions and Recommendation:
- In patients with post-operative nausea and vomiting (PONV) and chemotherapy induced nausea and vomiting (CINV):
  - Dolasetron, granisetron and ondansetron are equally effective in preventing nausea or vomiting.
  - There is evidence that palonsetron may be superior to other 5HT3 antagonists in the treatment of chemotherapy induced nausea and vomiting for moderately emetogenic chemotherapy and that ondansetron, dolasetron, and granisetron are equally effective.
- In patients with radiotherapy-induced nausea and vomiting (RINV):
  - Granisetron and ondansetron showed no difference in efficacy.
- In pregnant patients:
  - Ondansetron was not superior to promethazine for effectiveness, but was less sedating.
  - Long term studies show no difference in number of live births, proportion of infant deformities, and birth weight between ondansetron and the active control groups.
- Ondansetron is superior to granisetron for complete response rates in subpopulations based on a predisposition to nausea/vomiting such as motion sickness or previous treatment with emetogenic chemotherapy.
- There is low quality evidence that the combination of doxylamine/pyridoxine led to significantly greater improvement in nausea vomiting symptoms as compared with placebo (-4.8 PUQE score vs. -3.9; p=0.006) but insufficient comparative evidence compared to other available agents.

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

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

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

References:

1. Peterson, Kim. Drug Effectiveness Review Project: Drug Class Review on Newer Antiemtics. Preliminary Scan Report, May 2014.

Appendix 1

Antiemetics, New

Goal(s):

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

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

Requires PA:

- Non-preferred drugs.

Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/

Check the Reason for PA:

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

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

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the drug requested preferred?	**Yes:** Go to #4	**No**: Go to #3
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA for <4 days/week. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class and dose limits. If dose > limits, continue to #4.	**No:** Go to #4

4. Is client currently diagnosed with cancer AND receiving chemotherapy or radiation therapy more frequently than every 7 days?	**Yes:** Approve for 3 days past length of therapy (Chemo regimen more frequently than weekly)	**No:** Go to #5
5. Does client have refractory nausea that would require hospitalization or ER visits?	**Yes:** Go to #6	**No:** go to #8
6. Has client tried and failed two conventional antiemetics, listed below? Generic Name / Brand Name Metoclopramide / Reglan Prochlorperazine / Compazine Promethazine / Phenergan	**Yes:** Approve up to 6 months.	**No:** Go to #7
7. Does client have contraindications to conventional antiemetics, e.g. Allergy; or cannot tolerate?	**Yes:** Document reason and approve up to 6 months. (Contraindications to required alternative medications)	**No:** Pass to RPH; Go to #8
8. RPH only: All other indications need to be evaluated as to whether they are above the line or below the line. • Above: Deny, (Medical Appropriateness) • Below: Deny, (Not Covered by the OHP)		

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

Drug Class Review
On
Newer Antiemetics

Preliminary Scan Report

May 2014

Last Report: Update #1 January 2009

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

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OBJECTIVE

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

Date of Last Update Report

Update #1 Final Report: January 2009 (searches through October 2008)

Date of Last Preliminary Update Scan Report

The last preliminary update scan was conducted in April 2013.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?

2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?

3. Are there subgroups of patients based on demographics (age, race, and gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adults or children at risk for or with nausea, vomiting (including retching), or both related to the following therapies and conditions:

- Chemotherapy of various emetogenicity
- Radiation therapy
- Surgical procedure
- Pregnancy

In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999(1, 2) to clarify the level of emetogenicity of the chemotherapeutic regimen with which the cancer population of the study is being treated. This scale rates the emetic potential of the chemotherapeutic agent (or combination of agents) given to a cancer patient as if the patient would not be receiving any antiemetic drugs; that is, it classifies the chemotherapeutic agents by the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as "1" on this scale have a low emetic potential, while agents rated as "5" are considered to be severely emetic (a >90% chance of emesis in patients).

Interventions

Included interventions are listed in Table 1.

Table 1. Included interventions

Drug	Trade name	Formulations
Aprepitant/fosaprepitant	Emend®	injectable, oral
Doxylamine Succinate; Pyridoxine Hydrochloride	Diclegis	Tablet, oral, delayed release
Dolasetron	Anzemet®	injectable, oral
Granisetron	Generics, Sancuso®	injectable, oral, transdermal patch
Ondansetron	Zofran®, generics Zuplenz®	injectable, oral, orally disintegrating tablet, oral film
Palonosetron[a]	Aloxi®	injectable

Shading = new since last full report update

Effectiveness outcomes

Treatment of established postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient
    - Early: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Early: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in the postoperative period
    - Acute: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the postoperative period
    - Acute: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of nausea and/or vomiting related to chemotherapy

- Success: Absence of vomiting and/or retching
    - Acute: During the first 24 hours of chemotherapy administration
        - Vomiting and/or retching induced by highly emetic chemotherapy
        - Vomiting and/or retching induced by moderately emetic chemotherapy
    - Late: After the first 24 hours of chemotherapy administration
        - Vomiting and/or retching induced by highly emetic chemotherapy
        - Vomiting and/or retching induced by moderately emetic chemotherapy
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Acute: During the first 24 hours of chemotherapy administration
        - Emetic event induced by highly emetic chemotherapy
        - Emetic event induced by moderately emetic chemotherapy
    - Late: After the first 24 hours of chemotherapy administration
        - Emetic event induced by highly emetic chemotherapy
        - Emetic event induced by moderately emetic chemotherapy
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention of radiation-induced nausea and/or vomiting

- Success: Absence of vomiting and/or retching
    - Acute: During the first 24 hours of onset of radiation therapy
    - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Acute: During the first 24 hours of onset of radiation therapy
    - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, or need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Treatment of nausea and/or vomiting associated with pregnancy (including hyperemesis gravidarum)

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman
- Success: Absence of any emetic event (nausea, vomiting, retching)
- Change in Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes per period of time, need for rescue medications, serious emetic sequelae, number of emesis-free days, number of episodes and duration of hospitalization

  Wherever possible, data on effective dose range, dose response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.ert text

Harms

- Overall adverse events
- Specific adverse events (headache, constipation, dizziness, sedation, etc)
- Withdrawals due to adverse events
- Serious adverse events reported

Study designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews.
- For safety, controlled clinical trials and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE from January 2013 to May 2014. We used terms for included drugs and limits for humans, English and controlled clinical trials. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm). We also

searched FDA websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

Study Selection

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

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

No new drugs were identified.

New drugs identified in previous Preliminary Update Scan(s)

Doxylamine succinate/pyridoxine hydrochloride (Diclegis®) – FDA-approved April 2013 for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.
Granisetron transdermal patch (Sancuso®) – FDA-approved on 9/12/2008
Ondansetron oral film (Zuplenz®) – FDA-approved on 7/2/2010

New Indications

Identified in this Preliminary Update Scan
No new indications were identified.

Identified in previous Preliminary Update Scan(s)
None.

New Safety Alerts

Identified in this Preliminary Update Scan

No new safety alerts were identified.

Identified in previous Preliminary Update Scan(s)

On 12/17/2010, FDA notified healthcare professionals that the injection form of dolasetron should no longer be used to prevent nausea and vomiting associated with chemotherapy in pediatric and adult patients, due to risk of developing torsade de pointes, which in some cases can be fatal (Appendix A).

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

No new comparative effectiveness reviews were identified.

Reviews identified in previous Preliminary Update Scan(s)

On 12/4/2012 the FDA notified health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm (Appendix A).

In September of 2011 the FDA approved a safety labeling change warning for Anzemet (dolasetron mesylate) tablet and injection indicating that it has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients for which it should be used with caution certain patients (Appendix A).

An updated practice guideline for antiemetics in Oncology was published by the American Society of Clinical Oncology in November 2011. Abstract is included in Appendix B. A rapid response review on Ondansetron for the management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients was produced by CADTH in February 2013. See appendix B for the research questions on this topic.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches conducted for this scan resulted in 73 citations. Of those, there were 13 potentially relevant new trials, including 5 head-to-head trials and 8 placebo-controlled trials (see Appendix C for abstracts). We found no new trials of the fixed dose combination product doxylamine succinate and pyridoxine hydrochloride.

Including the 18 head-to-head trials and 13 placebo-controlled trials identified in the previous scans from April 2013, March 2011 and December 2009 (Appendix D), there are now cumulative totals of 23 head-to-head trials and 21 placebo-controlled trials. Characteristics of the head to head trials are shown in Table 2, below. Shading indicates trials identified in this scan; others were identified in previous scans. Placebo controlled trials are listed in Table 3. There are two placebo controlled trials on the new fixed dose combination product doxylamine succinate and pyridoxine hydrochloride.

Table 2. New head-to-head trials

Trial	Drugs	Indication
Habib 2011	Ondansetron vs aprepitant	PONV in adults
Grover 2009	Ondansetron orally disintegrating tablet vs IV ondansetron	PONV in adults
Kim 2004	Dolasetron vs ondansetron	Chemotherapy in adults

Mandanas 2005	Dolasetron vs ondansetron	Chemotherapy in adults
Maru 2013	Fosaprepitant vs aprepitant	Chemotherapy in adults
Boccia 2011	Granisetron transdermal vs Granisetron oral	Chemotherapy in adults
Metaxari 2011	Granisetron vs ondansetron	PONV in adults
Siddique 2011	Granisetron vs ondansetron	Chemotherapy in children
Dabbous 2010	Granisetron vs ondansetron	PONV in adults
Jain 2009	Granisetron vs ondansetron	PONV in adults
Tan 2010	Granisetron vs ondansetron	PONV in adults
Basu 2011	Palonosetron vs ondansetron vs granisetron	PONV in adults
Moon 2012	Palonosetron vs ondansetron	PONV in adults
Park 2011	Palonosetron vs ondansetron	PONV in adults
Kim 2013	Palonosetron vs ondansetron	PONV in adults
Kim 2013	Palonosetron vs ondansetron	PONV in adults
Laha 2013	Palonosetron vs ondansetron	PONV in adults
Kaushal 2010	Palonosetron vs ondansetron	Chemotherapy in adults
Mattiuzzi 2010	Palonosetron vs ondansetron	Chemotherapy in adults
Wenzell 2013	Palonosetron vs ondansetron	Chemotherapy in adults
Saito 2009	Palonosetron vs granisetron	Chemotherapy in adults
Tian 2011	Palonosetron vs granisetron	Chemotherapy in Chinese adults
Yu 2009	Palonosetron vs granisetron	Chemotherapy in adults

*Shading indicates trials identified in this scan; others were identified in previous scans.

Table 3. Placebo-Controlled Trials

Placebo-controlled trials of 5-HT3 antagonists		
Albany 2012	Aprepitant	PONV in adults
Jung 2013	Aprepitant	PONV in adults
Lim 2013	Aprepitant	PONV in adults
Sinha 2014	Aprepitant	PONV in adults
Tanioka 2013	Aprepitant	Chemotherapy in adults
Saito 2013	Fosaprepitant	Chemotherapy in adults
Barrett 2011	Ondansetron	PONV in adults
de Orange 2012	Ondansetron	PONV in children
Ebrahim Soltani, 2011	Ondansetron	PONV in adults
Zhang 2013	Ondansetron	PONV in adults
Chun 2014	Palonosetron	PONV in adults
Hesketh, 2012	Palonosetron	PONV in adults
Wagner 2007	Ondansetron orally disintegrating tablet	PONV in children
Vallejo 2012	aprepitant	PONV in adults
Trials of Aprepitant triple-therapy (aprepitant + 5-HT3 antagonist + corticosteroid) vs 5-HT3		

antagonist + corticosteroid		
Hu 2014	Granisetron	Chemotherapy in Chinese adults
Takahashi 2010	Granisetron	Chemotherapy in Japanese adults
Gore 2009	Ondansetron	Chemotherapy in adolescents
Rapoport 2010	Ondansetron	Chemotherapy in adults
Yeo 2009	Ondansetron	Chemotherapy in Chinese adults
Other		
Koren, 2010	Doxylamine succinate and pyridoxine hydrochloride	PONV in pregnancy
Reeve, 2005	Doxylamine succinate and pyridoxine hydrochloride	PONV in women undergoing laparoscopic tubal ligation

*Shading indicates trials identified in this scan; others were identified in previous scans.

PONV=post-operative nausea and vomiting, 5-HT3 Antagonists = ondansetron, granisetron, dolasetron and palonosetron

1. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. Journal of Clinical Oncology. [C]. 1997;15(1):103-9.
2. Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice. Oncologist. 1999;4(3):191-6.

APPENDIX A. NEW FDA WARNINGS AND PRECAUTIONS

Ondansetron (Zofran) 32 mg, Single Intravenous (IV) Dose: Updated Safety Communication – Product Removal due to Potential For Serious Cardiac Risks
[Posted: 12/4/2012]
ISSUE: FDA is notifying health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of the potential for serious cardiac risks.
BACKGROUND: The 32 mg, single IV dose of Zofran had been used to prevent chemotherapy-induced nausea and vomiting. A previous Drug Safety Communication (DSC), issued on June 29, 2012, communicated that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm. These drugs are sold pre-mixed in solutions of either dextrose or sodium chloride in plastic containers.
FDA anticipates these products will be removed from the market through early 2013. FDA does not anticipate that removal of the 32 mg intravenous dose of ondansetron currently sold as pre-mixed injections will contribute to a drug shortage of IV ondansetron, as the 32 mg dose makes up a very small percentage of the current market
RECOMMENDATION: FDA continues to recommend the intravenous regimen of 0.15 mg/kg administered every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. Oral dosing of Ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting. At this time, there is not enough information available for FDA to recommend an alternative single IV dose regimen.
Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

Anzemet (dolasetron mesylate) tablet and injection-labeling revision
September 2011
Anzemet prolongs the QT interval in a dose dependent fashion. Torsade de Pointes has been reported during post-marketing experience. Avoid Anzemet in patients with congenital long QT syndrome, hypomagnesemia, or hypokalemia. Hypokalemia and hypomagnesemia must be corrected prior to Anzemet administration. Monitor these electrolytes after administration as clinically indicated. Use ECG monitoring in patients with congestive heart failure, bradycardia, renal impairment, and elderly patients.
PR and QRS Interval Prolongation
Anzemet has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients. At particular risk are patients with underlying structural heart disease and preexisting conduction system abnormalities, elderly, patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia or patients receiving drugs known to prolong the PR interval (such as verapamil) and QRS interval (e.g., flecainide or quinidine). Anzemet should be used with caution and with ECG monitoring in these patients. Anzemet should be avoided in patients with complete heart block or at risk for complete heart block, unless they have an implanted pacemaker.

Anzemet (dolasetron mesylate): Drug Safety Communication - Reports of Abnormal Heart Rhythms
[Posted 12/17/2010]
AUDIENCE: Oncology, Cardiology

ISSUE: FDA notified healthcare professionals that a contraindication is being added to the prescribing information advising that the injection form of Anzemet (dolasetron mesylate) should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric and adult patients. New data demonstrate that Anzemet injection can increase the risk of developing torsade de pointes, an abnormal heart rhythm, which in some cases can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Anzemet causes a dose-dependant prolongation in the QT, PR, and QRS intervals on an electrocardiogram.

BACKGROUND: FDA previously noted cardiovascular safety concerns which suggested Anzemet could cause QT prolongation. However, limitations of the previous data did not clearly establish the degree to which Anzemet may cause QT prolongation. FDA recommended that the drug sponsor conduct a thorough QT study in adults in order to determine the degree of the prolongation. A pediatric study was not recommended due to the wide variability in heart rate and, thus, QTc interval in the pediatric population. See the Data Summary section of the Drug Safety Communication (DSC) for information that supports this change in the prescribing information.

RECOMMENDATION: Anzemet should not be used in patients with congenital long-QT syndrome. Hypokalemia and hypomagnesemia should be corrected before administering Anzemet. These electrolytes should be monitored after administration as clinically indicated. Use electrocardiogram monitoring in patients with congestive heart failure, patients with bradycardia, patients with underlying heart disease, the elderly and in patients who are renally impaired who are taking Anzemet. Anzemet injection may still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used are less likely to affect the electrical activity of the heart and result in abnormal heart rhythms.

Anzemet tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this drug is less than that seen with the injection form. However, a stronger warning about this potential risk is being added to the Warnings and Precautions sections of the Anzemet tablet label.

See the DSC for additional recommendations for healthcare professionals and for patients.

APPENDIX B. NEW COMPARATIVE EFFECTIVENESS REVIEWS AND GUIDELINES

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

Purpose
To update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology.
Methods
A systematic review of the medical literature was completed to inform this update. MEDLINE, the Cochrane Collaboration Library, and meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer were all searched. Primary outcomes of interest were complete response and rates of any vomiting or nausea.
Results
Thirty-seven trials met prespecified inclusion and exclusion criteria for this systematic review. Two systematic reviews from the Cochrane Collaboration were identified; one surveyed the pediatric literature. The other compared the relative efficacy of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists.
Recommendations
Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5. The Update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.

J Clin Oncol 29:4189-4198.

Ondansetron for the Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients: A Review of the Clinical Effectiveness, Safety and Guidelines
http://www.cadth.ca/media/pdf/htis/apr-2013/RC0424-Ondansetron-Final.pdf

RESEARCH QUESTIONS

1. What is the clinical effectiveness of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients?

2. What is the clinical evidence on the safety and harms of ondansetron for the management of CINV in pediatric patients?

3. What are the evidence-based guidelines regarding the use of ondansetron for the management of CINV in pediatric patients?

Appendix C. Abstracts of new randomized controlled trials from current scan

Head-to-head trials

Kim, S.-H., J.-Y. Hong, et al. (2013). "Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a prospective, randomized, double-blinded study." Korean Journal of Anesthesiology **64**(6): 517-523.

BACKGROUND: Postoperative nausea and vomiting (PONV) continues to be a major problem, because PONV is associated with delayed recovery and prolonged hospital stay. Although the PONV guidelines recommended the use of 5-hydroxy-tryptamine (5-HT3) receptor antagonists as the first-line prophylactic agents in patients categorized as high-risk, there are few studies comparing the efficacies of ondansetron, ramosetron, and palonosetron. The aim of present study was to compare the prophylactic antiemetic efficacies of three 5HT3 receptor antagonists in high-risk patients after laparoscopic surgery.

METHODS: In this prospective, randomized, double-blinded trial, 109 female nonsmokers scheduled for elective laparoscopic surgery were randomized to receive intravenous 4 mg ondansetron (n = 35), 0.3 mg ramosetron (n = 38), or 75 g palonosetron (n = 36) before anesthesia. Fentanyl-based intravenous patient-controlled analgesia was administered for 48 h after surgery. Primary antiemetic efficacy variables were the incidence and severity of nausea, the frequency of emetic episodes during the first 48 h after surgery, and the need to use a rescue antiemetic medication.

RESULTS: The overall incidence of nausea/retching/vomiting was lower in the palonosetron (22.2%/11.1%/5.6%) than in the ondansetron (77.1%/48.6%/28.6%) and ramosetron (60.5%/28.9%/18.4%) groups. The rescue antiemetic therapy was required less frequently in the palonosetron group than the other groups ($P < 0.001$). Kaplan-Meier analysis showed that the order of prophylactic efficacy in delaying the interval to use of a rescue emetic was palonosetron, ramosetron, and ondansetron.

CONCLUSIONS: Single-dose palonosetron is the prophylactic antiemetics of choice in high-risk patients undergoing laparoscopic surgery.

Kim, Y. Y., S. Y. Moon, et al. (2013). "Comparison of palonosetron with ondansetron in prevention of postoperative nausea and vomiting in patients receiving intravenous patient-controlled analgesia after gynecological laparoscopic surgery." Korean Journal of Anesthesiology **64**(2): 122-126.

BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after anesthesia and surgery. This study was designed to compare the effects of palonosetron and ondansetron in preventing PONV in high-risk patients receiving intravenous opioid-based patient-controlled analgesia (IV-PCA) after gynecological laparoscopic surgery.

METHODS: One hundred non-smoking female patients scheduled for gynecological laparoscopic surgery were randomly assigned into the palonosetron group (n = 50) or the ondansetron group (n = 50). Palonosetron 0.075 mg was injected as a bolus in the palonosetron group. Ondansetron 8 mg was injected as a bolus and 16 mg was added to

the IV-PCA in the ondansetron group. The incidences of nausea, vomiting and side effects was recorded at 2 h, 24 h, 48 h and 72 h, postoperatively.

RESULTS: There were no significant differences between the groups in the incidence of PONV during 72 h after operation. However, the incidence of vomiting was lower in the palonosetron group than in the ondansetron group (18% vs. 4%, P = 0.025). No differences were observed in use of antiemetics and the side effects between the groups.

CONCLUSIONS: The effects of palonosetron and ondansetron in preventing PONV were similar in high-risk patients undergoing gynecological laparoscopic surgery and receiving opioid-based IV-PCA.

Laha, B., A. Hazra, et al. (2013). "Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: a randomized controlled trial." Indian Journal of Pharmacology **45**(1): 24-29.

OBJECTIVES: Incidence of postoperative nausea and vomiting (PONV), without active intervention, following laparoscopic cholecystectomy is unacceptably high. We evaluated the effectiveness of intravenous (IV) palonosetron in counteracting PONV during the first 24 hrs following laparoscopic cholecystectomy, using ondansetron as the comparator drug.

MATERIALS AND METHODS: In a randomized, controlled, single blind, parallel group trial, single pre-induction IV doses of palonosetron (75 mcg) or ondansetron (4 mg) were administered to adult patients of either sex undergoing elective laparoscopic cholecystectomy. There were 49 subjects per group. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary effectiveness measure was total number of PONV episodes in the 24 hrs period following end of surgery. The frequencies of individual nausea, retching and vomiting episodes, visual analog scale (VAS) score for nausea at 2, 6 and 24 hrs, use of rescue antiemetic (metoclopramide), number of complete responders (no PONV or use of rescue in 24 hrs) and adverse events were secondary measures.

RESULTS: There was no statistically significant difference between the groups in primary outcome. Similarly, the frequencies of nausea, retching and vomiting episodes, when considered individually, did not show significant difference. Nausea score was comparable at all time points. With palonosetron, 14 subjects (28.6%) required rescue medication while 13 (26.5%) did so with ondansetron. The number of complete responders was 14 (28.6%) and 16 (32.7%), respectively. Adverse events were few and mild. QTc prolongation was not encountered.

CONCLUSION: Palonosetron is comparable to ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.

Maru, A., V. P. Gangadharan, et al. (2013). "A Phase 3, randomized, double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting: Results of an Indian population subanalysis." Indian Journal of Cancer **50**(4): 285-291.

Context: Currently, there is limited data on the prevention of chemotherapy-induced nausea and vomiting (CINV) in Indian patients. Aims: This post hoc study assessed the efficacy and safety of fosaprepitant compared with aprepitant for prevention of CINV in the Indian population. A subgroup analysis was performed from data collected in a phase 3 study of intravenous (IV) fosaprepitant or oral aprepitant, plus the 5-HT 3 antagonist ondansetron and the

corticosteroid dexamethasone, in cisplatin-nave patients with solid malignancies. Materials and Methods: Patients scheduled to receive cisplatin (>70 mg/m 2) were administered a single IV dose of fosaprepitant dimeglumine (150 mg) on day 1 or a 3-day dosing regimen of oral aprepitant (day 1:125 mg, days 2 and 3:80 mg) with standard doses of ondansetron and dexamethasone. Patients recorded nausea and/or vomiting episodes and their use of rescue medication and were monitored for adverse events (AEs) and tolerability. Statistical Analysis Used: Differences in response rates between fosaprepitant and aprepitant were calculated using the Miettinen and Nurminen method. Results: In the Indian subpopulation (n = 372), efficacy was similar for patients in both the fosaprepitant or aprepitant groups; complete response in the overall, acute, and delayed phases and no vomiting in all phases were approximately 4 percentage points higher in the fosaprepitant group compared with the aprepitant group. Fosaprepitant was generally well-tolerated; common AEs were similar to oral aprepitant. Conclusions: IV fosaprepitant is as safe and effective as oral aprepitant in the Indian subpopulation and offers an alternative to the oral formulation.

Wenzell, C. M., M. J. Berger, et al. (2013). "Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy." Supportive Care in Cancer **21**(10): 2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

Placebo-controlled trials

Chun, H. R., I. S. Jeon, et al. (2014). "Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial." British Journal of Anaesthesia **112**(3): 485-490.

BACKGROUND: The aim of this study was to evaluate the efficacy of palonosetron, the latest 5-HT3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) during the first 72 h after operation.

METHODS: In this randomized, double-blinded, placebo-controlled study, 204 healthy inpatients who were undergoing elective surgery with general anaesthesia were enrolled. Patients were divided into two groups: the palonosetron group (palonosetron 0.075 mg i.v.; n=102) and the placebo group (normal saline i.v.; n=102). The treatments were given after the induction of anaesthesia. The incidence of nausea, vomiting, severity of nausea, and the use of rescue anti-emetics during the first 72 h after surgery were evaluated.
RESULTS: The incidence of PONV was lower in the palonosetron group compared with the placebo group during the 0-24 h (33% vs 47%) and 0-72 h period (33% vs 52%) ($P<0.05$), but not during the 24-72 h postoperative period (6% vs 11%). The incidence of nausea was also significantly lower in the palonosetron group than in the placebo group during the 0-24 and 0-72 h period ($P<0.05$), but not during the 24-72 h postoperative period. However, there were no significant differences in the incidence of vomiting, and the use of rescue anti-emetics between the groups.
CONCLUSIONS: Palonosetron 0.075 mg i.v. effectively reduced the incidence of PONV during the first 72 h after operation, with most of the reduction occurring in the first 24 h.

Hu, Z., Y. Cheng, et al. (2014). "Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial." Supportive Care in Cancer **22**(4): 979-987.
PURPOSE: Aprepitant, an oral neurokinin-1 receptor antagonist, has demonstrated improved control of chemotherapy-induced nausea and vomiting (CINV) in previous studies. This is the first phase III study to evaluate the efficacy and tolerability of aprepitant in patients receiving highly emetogenic chemotherapy (HEC) in Asian countries.
METHODS: This multicenter, double-blind, placebo-controlled trial assessed the prevention of CINV during the acute phase (AP), delayed phase (DP), and overall phase (OP). Patients receiving HEC were randomized to either an aprepitant group (day 1, aprepitant 125 mg; days 2-3, aprepitant 80 mg) or a standard therapy group (days 1-3, placebo). Both groups received intravenous granisetron and oral dexamethasone. The primary end point was complete response (CR; no emesis and no use of rescue therapy) during the OP.
RESULTS: Of the 421 randomized patients, 411 (98%) were assessable for efficacy; 69.6% (142/204) and 57.0% (118/207) of patients reported CR during the OP in the aprepitant and standard therapy groups, respectively ($P = 0.007$). CR rates in the aprepitant group were higher during the DP (74.0% vs. 59.4%, $P = 0.001$) but were similar during the AP (79.4% vs. 79.3%, $P = 0.942$). Toxicity and adverse events were comparable in both groups.
CONCLUSIONS: The addition of aprepitant to standard antiemetic treatment regimens for Chinese patients undergoing HEC provided superior CINV prevention and was well tolerated.

Jung, W. S., Y. B. Kim, et al. (2013). "Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy." Journal of Anesthesia **27**(3): 396-401.
PURPOSE: The use of opioids following surgery is associated with a high incidence of postoperative nausea and vomiting (PONV). We conducted a prospective, randomized, double-blind, placebo-controlled study to investigate the effect of orally administered

aprepitant, a neurokinin-1 receptor antagonist, for reducing PONV in patients with fentanyl-based, patient-controlled analgesia (PCA) given intravenously after gynecological laparoscopy.

METHODS: One hundred and twenty female patients (ages 21-60) undergoing laparoscopic hysterectomy were randomly allocated to receive 80 mg (A80 group, n = 40) or 125 mg aprepitant (A125 group, n = 40) or placebo (control group, n = 40) orally 2 h before anesthesia induction. Anesthesia was maintained with isoflurane and remifentanil, and PCA IV using fentanyl and ketorolac were provided for 48 h after surgery. Incidences of nausea, vomiting/retching, and use of rescue antiemetics were recorded at 2, 24, and 48 h after surgery. Complete response was defined as no PONV and no need for rescue treatment.

RESULTS: The incidence of complete response was significantly lower in the A80 and A125 groups than in controls, 56 % and 63 %, vs. 28 %, respectively, P = 0.007 and P = 0.003, respectively, during the first 48 h, and 65 % and 65 % vs. 38 %, respectively, both P = 0.025, during the first 2 h. However, there were no statistically significant differences between A80 and A125 groups in the incidences of complete response and PONV during the study period.

CONCLUSIONS: Aprepitant 80 mg orally was effective in lowering the incidence of PONV in the first 48 h after anesthesia in patients receiving fentanyl-based PCA after gynecological laparoscopy.

Lim, C. S., Y.-K. Ko, et al. (2013). "Efficacy of the oral neurokinin-1 receptor antagonist aprepitant administered with ondansetron for the prevention of postoperative nausea and vomiting." Korean Journal of Anesthesiology **64**(3): 212-217.

BACKGROUND: 5-HT3 receptor antagonist, dexamethasone and droperidol were used for the prevention of postoperative nausea and vomiting (PONV). Recently, neurokinin-1 (NK1) antagonist has been used for PONV. We evaluated the effect of oral aprepitant premedication in addition to ondansetron.

METHODS: A total 90 patients scheduled for elective rhinolaryngological surgery were allocated to three groups (Control, Ap80, Ap125), each of 30 at random. Ondansetron 4 mg was injected intravenously to all patients just before the end of surgery. On the morning of surgery, 80 mg and 125 mg aprepitant were additionally administered into the Ap80 group and Ap125 group, respectively. The rhodes index of nausea, vomiting and retching (RINVR) was checked at 6 hr and 24 hr after surgery.

RESULTS: Twelve patients who used steroids unexpectedly were excluded. Finally 78 patients (control : Ap80 : Ap125 = 24 : 28 : 26) were enrolled. Overall PONV occurrence rate of Ap125 group (1/26, 3.9%) was lower (P = 0.015) than the control group (7/24, 29.2%) at 6 hr after surgery. The nausea distress score of Ap125 group (0.04 + 0.20) was lower (P = 0.032) than the control group (0.67 + 1.24) at 6 hr after surgery. No evident side effect of aprepitant was observed.

CONCLUSIONS: Oral aprepitant 125 mg can be used as combination therapy for the prevention of PONV.

Saito, H., H. Yoshizawa, et al. (2013). "Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose

cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial." Annals of Oncology **24**(4): 1067-1073.

BACKGROUND: We evaluated the efficacy and safety of single-dose fosaprepitant in combination with intravenous granisetron and dexamethasone.

PATIENTS AND METHODS: Patients receiving chemotherapy including cisplatin (>70 mg/m(2)) were eligible. A total of 347 patients (21% had received cisplatin with vomiting) were enrolled in this trial to receive the fosaprepitant regimen (fosaprepitant 150 mg, intravenous, on day 1 in combination with granisetron, 40 mug/kg, intravenous, on day 1 and dexamethasone, intravenous, on days 1-3) or the control regimen (placebo plus intravenous granisetron and dexamethasone). The primary end point was the percentage of patients who had a complete response (no emesis and no rescue therapy) over the entire treatment course (0-120 h).

RESULTS: The percentage of patients with a complete response was significantly higher in the fosaprepitant group than in the control group (64% versus 47%, P = 0.0015). The fosaprepitant regimen was more effective than the control regimen in both the acute (0-24 h postchemotherapy) phase (94% versus 81%, P = 0.0006) and the delayed (24-120 h postchemotherapy) phase (65% versus 49%, P = 0.0025).

CONCLUSIONS: Single-dose fosaprepitant used in combination with granisetron and dexamethasone was well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Sinha, A. C., P. M. Singh, et al. (2014). "Aprepitant's prophylactic efficacy in decreasing postoperative nausea and vomiting in morbidly obese patients undergoing bariatric surgery." Obesity Surgery **24**(2): 225-231.

BACKGROUND: Postoperative nausea and vomiting is a major cause of patient dissatisfaction towards surgery. For bariatric surgery, increased vomiting/retching is detrimental to surgical anastomosis. The present study evaluated the efficacy of aprepitant (neurokinin-1 inhibitor) as a prophylactic antiemetic in morbidly obese patients for laparoscopic bariatric surgery.

METHODS: After institutional review board approval, 125 morbidly obese patients were recruited into this double-blind placebo-controlled trial. On random division, the patients received a tablet of aprepitant (80 mg) in group A, or a similar-appearing placebo in group P, an hour prior to surgery. All patients received intravenous ondansetron (4 mg) intraoperatively. Postoperatively, the patients were evaluated for nausea and vomiting by a blinded evaluator at 30 min, 1, 2, 6, 24, 48, and 72 h.

RESULTS: Both groups were evenly distributed for age, body mass index, type, and length of surgery. Cumulative incidence of vomiting at 72 h was significantly lower in group A (3%) compared to group P (15%; p=0.021). Odds ratio for vomiting in group P compared to group A was 5.47 times. On Kaplan-Meier plot, time to first vomiting was also significantly delayed in group A (p=0.019). A higher number of patients showed complete absence of nausea or vomiting in group A compared to group P (42.18 vs. 36.67%). On the other hand, nausea scores were unaffected by aprepitant, and no significant difference between groups was found at any of the measured time points.

CONCLUSIONS: In morbidly obese patients undergoing laparoscopic bariatric surgery, addition of aprepitant to ondansetron can significantly delay vomiting episodes simultaneously lowering the incidence of postoperative vomiting.

Tanioka, M., A. Kitao, et al. (2013). "A randomised, placebo-controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy." British Journal of Cancer **109**(4): 859-865.

BACKGROUND: We evaluated the efficacy of aprepitant plus granisetron and an increased dose of dexamethasone in selected patients undergoing moderately emetogenic chemotherapy (MEC).

METHODS: Nondrinking women <70 years undergoing MEC were randomly assigned to aprepitant (day 1, 125 mg; days 2 and 3, 80 mg) or placebo. Dexamethasone on days 1-3 was 12, 4, and 4 mg with aprepitant and 20, 8, and 8 mg with placebo. The primary end point was complete response (CR; no emesis or rescue therapy) during 120 h of the first cycle. Logistic regression analysis was performed to identify predictors of overall CR.

RESULTS: Of the 94 patients enrolled, 91 were assessable. Most received carboplatin-based chemotherapy. In the aprepitant (n=45) and placebo (n=46) groups, the overall, acute (day 1), and delayed (days 2-5) CR rates were 62% and 52%, 98% and 96%, and 62% and 52%, respectively. Although not statistically significant, the overall CR rate was 10% higher in the aprepitant group. Both regimens were well tolerated. On multivariate analysis, advanced ovarian cancer (OR, 0.26 (0.10-0.72)) was independently associated with a lower CR.

CONCLUSION: Even with an increased dose of dexamethasone, aprepitant seemed more effective than placebo in these selected patients undergoing MEC; however, delayed phase management remains a significant problem.

Zhang, D., Z. Shen, et al. (2013). "Effect of ondansetron in preventing postoperative nausea and vomiting under different conditions of general anesthesia: a preliminary, randomized, controlled study." Upsala Journal of Medical Sciences **118**(2): 87-90.

METHODS: Two hundred and forty patients were randomly allocated into six groups: Group I, anesthesia was maintained with sevoflurane; Group II, anesthesia was maintained with sevoflurane and 8 mg of ondansetron; Group III, anesthesia was maintained with propofol; Group IV, anesthesia was maintained with propofol and 8 mg of ondansetron; Group V, anesthesia was maintained with sevoflurane and propofol; Group VI, anesthesia was maintained with sevoflurane combined with propofol and 8 mg of ondansetron.

RESULTS: We found that the incidence of vomiting was lower in group II (17.5%), group IV (7.5%), and group VI (10%) compared with group I (55%), group III (27.5%), and group V (30%), respectively ($P < 0.05$). The incidence of vomiting was also lower in group III (27.5%) and group V (30%) when compared with group I (55%) ($P < 0.05$). The incidence of nausea was 55% in group I, 42.5% in group II, 30% in group III, 27.5% in group IV, 30% in group V, and 30% in group VI. Groups III and V had a lower incidence of nausea than group I ($P < 0.05$).

CONCLUSIONS: We conclude that compared with sevoflurane anesthesia alone, anesthesia with either propofol alone or propofol combined with sevoflurane resulted in a reduced incidence of vomiting and nausea during the first 24 h after surgery. Administration of

ondansetron effectively reduced the incidence of vomiting but not that of nausea for all three types of general anesthesia.

Wenzell, C. M., M. J. Berger, et al. (2013). "Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy." Supportive Care in Cancer **21**(10): 2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

APPENDIX D. ABSTRACTS OF POTENTIALLY RELEVANT TRIALS FOUND IN PREVIOUS SCANS

Head to head trials

Basu, A., D. Saha, et al. (2011). "Comparison of palanosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery." Journal of the Indian Medical Association 109(5): 327-329.

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

Boccia, R. V., L. N. Gordan, et al. (2011). "Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study." Supportive Care in Cancer 19(10): 1609-1617.

PURPOSE: A novel transdermal formulation of granisetron (the granisetron transdermal delivery system (GTDS)) has been developed to deliver granisetron continuously over 7 days. This double-blind, phase III, non-inferiority study compared the efficacy and tolerability of the GTDS to daily oral granisetron for the control of chemotherapy-induced nausea and vomiting (CINV).

PATIENTS AND METHODS: Six hundred forty-one patients were randomized to oral (2 mg/day, 3-5 days) or transdermal granisetron (one GTDS patch, 7 days), before receiving multi-day chemotherapy. The primary endpoint was complete control of CINV (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final administration. The prespecified non-inferiority margin was 15%.

RESULTS: Five hundred eighty-two patients were included in the per protocol analysis. The GTDS displayed non-inferiority to oral granisetron: complete control was achieved by 60% of patients in the GTDS group, and 65% in the oral granisetron group (treatment

difference, -5%; 95% confidence interval, -13-3). Both treatments were well tolerated, the most common adverse event being constipation.

CONCLUSIONS: The GTDS provides effective, well-tolerated control of CINV associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron.

Dabbous, A. S., S. I. Jabbour-Khoury, et al. (2010). "Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery." Middle East Journal of Anesthesiology **20**(4): 565-70.

In a prospective randomized double-blind study, we compared the effectiveness of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery. Hundred ASA I and II patients scheduled for laparoscopic surgery were enrolled in the study and 84 patients completed it. Following induction of anesthesia, group I (n=42) received granisetron 1 mg and dexamethasone 8 mg, group II (n=42) received ondansetron 4 mg and dexamethasone 8 mg. Nausea and vomiting episodes, pain scores as well as side effects were recorded during the first hour and subsequently during the first 6 and 24 hours postoperatively. Satisfaction scores were obtained at discharge. There was no statistically significant difference between the 2 groups during the 1st 24 hours following surgery in regards to pain scores, satisfaction and side effects manifestations. At 0-1 hour interval, 100% of patients in group I and 97.6% in group II had no vomiting. Total response (no moderate or severe nausea and no rescue antiemetics) was 83.3% in group I and 80.95% in group II, and metoclopramide was used in 7.1% of patients in both groups. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II. At 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. In conclusion, the combination of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg following induction of anesthesia in patients undergoing laparoscopic surgery showed no statistically significant difference in antiemetic efficacy with minimal side effects and excellent patient satisfaction.

Grover, V. K., P. J. Mathew, et al. (2009). "Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study." Anaesthesia **64**(6): 595-600.

Peri-operative prophylactic anti-emetics are commonly used parenterally. Orally disintegrating ondansetron is efficacious during chemotherapy. Therefore, we aimed to study the efficacy of orally disintegrating ondansetron for postoperative nausea and vomiting. In a randomised, double-blind, placebo controlled trial on 109 patients scheduled for laparoscopic cholecystectomy, oral ondansetron was compared to intravenous ondansetron and placebo. The anaesthetic technique was standardised. Mean time (SD) to tolerating oral intake was delayed in the placebo group to 366.1 (77.6) min compared to oral 322.9 (63.7) min and intravenous 322.4 (65.2) min groups. This is corroborated by a higher incidence of nausea and vomiting in the control group during the first 6 h

postoperatively (control 44.4%, oral 17.7%, intravenous 18.2%). There was no significant difference between oral and intravenous groups. In conclusion, orally disintegrating ondansetron was as efficacious as intravenous ondansetron in the peri-operative phase and may be a viable option for prophylaxis of emesis in day care surgery

Habib, A. S., J. C. Keifer, et al. (2011). "A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy." Anesthesia & Analgesia 112(4): 813-818.

BACKGROUND: Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 hours. In addition to causing patient discomfort, the physical act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery, aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 hours postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia.

METHODS: Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 hours after surgery. Statistical analysis was performed using Wilcoxon's ranked sum test and (2) test. $P < 0.05$ was considered statistically significant.

RESULTS: One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($P = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% vs. 21%, $P = 0.0419$) and 24 hours (14% vs. 36%, $P = 0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs. 60%), nausea scores, need for rescue antiemetics (65% vs. 60%), complete response (no PONV and no rescue, 22% vs. 36%), or patient satisfaction with the management of PONV.

CONCLUSION: The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

Jain, V., J. K. Mitra, et al. (2009). "A randomized, double-blinded comparison of ondansetron, granisetron, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy." Journal of Neurosurgical Anesthesiology **21**(3): 226-30.

Postoperative nausea and vomiting (PONV) are frequent and distressing complications after neurosurgical procedures. We evaluated the efficacy of ondansetron and granisetron to prevent PONV after supratentorial craniotomy. In a randomized double-blind, placebo controlled trial, 90 adult American Society of Anesthesiologists I, II patients were included in the study. A standard anesthesia technique was followed. Patients were divided into 3 groups to receive either placebo (saline), ondansetron 4 mg, or granisetron 1 mg intravenously at the time of dural closure. After extubation, episodes of nausea and vomiting were noted for 24 hours postoperatively. Statistical analysis was performed using chi2 test and 1-way analysis of variance. Demographic data, duration of surgery, intraoperative fluids and analgesic requirement, and postoperative pain (visual analog scale) scores were comparable in all 3 groups. It was observed that the incidence of vomiting in 24 hours, severe emetic episodes, and requirement of rescue antiemetics were less in ondansetron and granisetron groups as compared with placebo ($P<0.001$). Both the study drugs had comparable effect on vomiting. However, the incidence of nausea was comparable in all 3 groups ($P=0.46$). A favorable influence on the patient satisfaction scores, and number needed to prevent emesis was seen in the 2 drug groups. No significant correlation was found between neurosurgical factors (presence of midline shift, mass effect, pathologic diagnosis of tumor, site of tumor) and the occurrence of PONV. We conclude that ondansetron 4 mg and granisetron 1 mg are comparably effective at preventing emesis after supratentorial craniotomy. However, neither drugs prevented nausea effectively.

Kaushal, J., M. C. Gupta, et al. (2010). "Clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer." Singapore Medical Journal **51**(11): 871-5.

INTRODUCTION: Palonosetron and ondansetron are two selective 5-hydroxytryptamine (5-HT3) receptor antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of moderately emetic anticancer chemotherapy. Their efficacy is enhanced by the concurrent administration of dexamethasone. In the present study, we aimed to compare the antiemetic efficacy of a palonosetron plus dexamethasone (PD) schedule versus an ondansetron plus dexamethasone (OD) schedule. METHODS: A randomised, crossover trial was conducted in 30 patients with head and neck cancer who were receiving moderately emetogenic chemotherapy. The patients were divided into two groups. In the first cycle, one group was given a PD schedule and the other, an OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases. RESULTS: Complete response in the acute phase was observed in 83.3 percent of the patients on the PD schedule and in 80 percent of those on the OD schedule. In the delayed phase, complete response was observed in 76.7 percent and 66.7 percent of the patients on the PD schedule and OD schedule, respectively. The overall rate of complete response was 66.7 percent in the PD group and 46.7 percent in the OD group. In the PD group, there were 73.3 percent of nausea-free patients as opposed to 66.7 percent in the OD group.

CONCLUSION: The results suggest that the PD schedule was superior to the OD schedule in controlling emesis in cancer chemotherapy, although this difference was not statistically significant.

Kim, J.-S., J. Y. Baek, et al. (2004). "Open-label, randomized comparison of the efficacy of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed cisplatin-induced emesis in cancer patients." Cancer Research & Treatment **36**(6): 372-6.

PURPOSE: The aim of this study is to compare the antiemetic efficacy and tolerability of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed emesis. MATERIAL AND METHODS: From April 2002 through October 2002, a total of 112 patients receiving cisplatin- based combination chemotherapy were randomized to receive a single i.v. dose of dolasetron 100 mg or ondansetron 8 mg, 30 minutes before the initiation of chemotherapy. In the ondansetron group, two additional doses of ondansetron 8 mg were given at intervals of 2 to 4 hours. To prevent delayed emesis, dolasetron 200 mg p.o. daily or ondansetron 8 mg p.o. bid was administered from the 2(nd) days to a maximum of 5 days. The primary end point was the proportion of patients that experienced no emetic episodes and required no rescue medication (complete response, CR) during the 24 hours (acute period) and during Day 2 to Day 5+/-2 days (delayed period), after chemotherapy. The secondary end points included the incidence and severity of emesis. RESULTS: 105 patients were evaluable for efficacy. CR rates during the acute period were 36.0% for a single dose of dolasetron 100 mg, and 43.6% for three doses of ondansetron 8 mg. CR rates during the delayed period were 8.0% and 10.9%, respectively. There was no significant difference in the efficacy between the two groups. Adverse effects were mostly mild to moderate and not related to study medication. CONCLUSIONS: A single i.v. dose of dolasetron 100 mg is as effective as three i.v. doses of ondansetron 8 mg in preventing acute and delayed emesis after cisplatin-based chemotherapy, with a comparable safety profile.

Mandanas, R. A., R. Beveridge, et al. (2005). "A randomized, multicenter, open-label comparison of the antiemetic efficacy of dolasetron versus ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy." Supportive Cancer Therapy **2**(2): 114-21.

This study assessed the efficacy and safety of dolasetron compared with ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy followed by peripheral blood stem cell support. Twenty centers randomized 197 patients to receive dolasetron 100 mg intravenously (I.V.) followed 8-12 hours later by a single oral dose of dolasetron 100 mg or ondansetron 32 mg I.V., followed 8-12 hours later by a single oral dose of ondansetron 8 mg during high-dose chemotherapy (HDC) regimens for breast cancer (n = 96; 48.7%), non-Hodgkin's lymphoma (n = 83; 42.1%), or Hodgkin's disease (n = 18; 9.1%). All patients received a daily I.V. bolus of dexamethasone 10 mg with study antiemetic agents and a continuous infusion of diphenhydramine, lorazepam, and dexamethasone (ie, BAD pump) throughout the course of the study, with patient-controlled on-demand bolus doses as needed. After completing a daily diary of emetic episodes and rescue medication use, 164 of 197 patients were evaluable. Total plus complete responses (no emesis, no nausea, no rescue) over the entire study period were achieved in 45.7% and 46.9% of patients on the dolasetron and

ondansetron arms, respectively. Dolasetron and ondansetron were well-tolerated. This study demonstrates that dolasetron and ondansetron are equally safe and effective in the prevention of nausea and vomiting associated with HDC (P = 0.955).

Mattiuzzi, G. N., J. E. Cortes, et al. (2010). "Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia." Cancer **116**(24): 5659-66.

BACKGROUND: Nausea and vomiting in patients with acute myelogenous leukemia (AML) can be from various causes, including the use of high-dose cytarabine.
METHODS: The authors compared 2 schedules of palonosetron versus ondansetron in the treatment of chemotherapy-induced nausea and vomiting (CINV) in patients with AML receiving high-dose cytarabine. Patients were randomized to: 1) ondansetron, 8 mg intravenously (IV), followed by 24 mg continuous infusion 30 minutes before high-dose cytarabine and until 12 hours after the high-dose cytarabine infusion ended; 2) palonosetron, 0.25 mg IV 30 minutes before chemotherapy, daily from Day 1 of high-dose cytarabine up to Day 5; or 3) palonosetron, 0.25 mg IV 30 minutes before high-dose cytarabine on Days 1, 3, and 5. RESULTS: Forty-seven patients on ondansetron and 48 patients on each of the palonosetron arms were evaluable for efficacy. Patients in the palonosetron arms achieved higher complete response rates (no emetic episodes plus no rescue medication), but the difference was not statistically significant (ondansetron, 21%; palonosetron on Days 1-5, 31%; palonosetron on Days 1, 3, and 5, 35%; P = .32). Greater than 77% of patients in each arm were free of nausea on Day 1; however, on Days 2 through 5, the proportion of patients without nausea declined similarly in all 3 groups. On Days 6 and 7, significantly more patients receiving palonosetron on Days 1 to 5 were free of nausea (P = .001 and P = .0247, respectively). CONCLUSIONS: The daily assessments of emesis did not show significant differences between the study arms. Patients receiving palonosetron on Days 1 to 5 had significantly less severe nausea and experienced significantly less impact of CINV on daily activities on Days 6 and 7. Cancer 2010. Copyright 2010 American Cancer Society.

Metaxari, M., A. Papaioannou, et al. (2011). "Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents." Journal of Anesthesia 25(3): 356-362.

PURPOSE: The aim of this double-blind randomized study was to compare the antiemetic efficacy of three 5-hydroxytryptamine type 3 antagonists in terms of the incidence and intensity of postoperative nausea and vomiting (PONV) in a homogenous group of female patients undergoing thyroidectomy.
METHODS: The study cohort consisted of 203 American Society of Anesthesiologists PS I-II female patients randomized into four groups to receive at induction of anesthesia an intravenous (IV) bolus of 5 ml solution of one of the following: normal saline (placebo), granisetron 3 mg, ondansetron 4 mg, or tropisetron 5 mg. Nausea and vomiting were evaluated at five time points: during the first hour in the postanesthesia care unit (PACU) and 6, 12, 18, and 24 h postoperatively. Nausea intensity was measured using a visual analogue scale score (0-10).
RESULTS: Patients in the placebo group displayed a high incidence of nausea in the PACU and at 6, 12, and 18 h postoperatively (44, 60, 50, and 34%, respectively) and of

vomiting (26, 42, 30 and 10%). The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 h (26, 18, and 2%, respectively) and vomiting at 6 and 12 h (10 and 6%, respectively). Ondansetron reduced significantly the incidence of nausea and vomiting only at 6 h postoperatively (28 and 12%, respectively). The administration of tropisetron did not affect the incidence of PONV compared to placebo. CONCLUSION: Among the female patients of this study undergoing thyroid surgery, granisetron 3 mg provided the best prophylaxis from PONV. Ondansetron 4 mg was equally effective, but its action lasted only 6 h, whereas tropisetron 5 mg was found ineffective.

Moon, Y. E., J. Joo, et al. (2012). "Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study.[Erratum appears in Br J Anaesth. 2012 Jun;108(6):1047-8]." British Journal of Anaesthesia 108(3): 417-422.

BACKGROUND: Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking. This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy.
METHODS: A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue anti-emetics, and adverse effects were evaluated during 0-2 and 2-24 h.
RESULTS: The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, P=0.045). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2-24 h. The only difference in the use of rescue anti-emetics was at 2-24 h (10% with palonosetron compared with 28% with ondansetron, P=0.02).
CONCLUSIONS: Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2-24 h after surgery.

Park, S. K. and E. J. Cho (2011). "A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery." Journal of International Medical Research 39(2): 399-407.

This randomized, double-blind study evaluated the relative efficacy of palonosetron (a new, selective 5-hydroxytryptamine type 3 [5-HT(3)] receptor antagonist) and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 45) or ondansetron 8 mg (n = 45), intravenously, immediately before induction of general anaesthesia. The occurrence of nausea and vomiting and the severity of nausea according to a visual analogue scale were monitored immediately after the end of surgery and during the following 24 h. The incidence of PONV was significantly

lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale for nausea. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.

Saito, M., K. Aogi, et al. (2009). "Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial.[see comment]." Lancet Oncology **10**(2): 115-24.

BACKGROUND: Palonosetron is a second-generation 5-hydroxytryptamine 3 (5-HT(3))-receptor antagonist that has shown better efficacy than ondansetron and dolasetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy, and similar efficacy to ondansetron in preventing CINV in patients receiving highly emetogenic chemotherapy. In this phase III, multicentre, randomised, double-blind, double-dummy, stratified, parallel-group, active-comparator trial, we assessed the efficacy and safety of palonosetron versus granisetron for chemotherapy-induced nausea and vomiting, both of which were administered with dexamethasone in patients receiving highly emetogenic chemotherapy. METHODS: Between July 5, 2006, and May 31, 2007, 1143 patients with cancer who were receiving highly emetogenic chemotherapy (ie, cisplatin, or an anthracycline and cyclophosphamide combination [AC/EC]) were recruited from 75 institutions in Japan, and randomly assigned to either single-dose palonosetron (0.75 mg), or granisetron (40 microg/kg) 30 min before chemotherapy on day 1, both with dexamethasone (16 mg intravenously) on day 1 followed by additional doses (8 mg intravenously for patients receiving cisplatin or 4 mg orally for patients receiving AC/EC) on days 2 and 3. A non-deterministic minimisation method with a stochastic-biased coin was applied to the randomisation of patients. Covariates known to effect emetic risk, such as sex, age, and type of highly emetogenic chemotherapy, were used as stratification factors of minimisation to ensure balance between the treatment groups. Primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute phase (0-24 h postchemotherapy; non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24-120 h postchemotherapy; superiority comparison with granisetron). The non-inferiority margin was predefined in the study protocol as a 10% difference between groups in the proportion of patients with complete response. The palonosetron dose of 0.75 mg was chosen on the basis of two dose-determining trials in Japanese patients. All patients who received study treatment and highly emetogenic chemotherapy were included in the efficacy analyses (modified intention to treat). This trial is registered with ClinicalTrials.gov, number NCT00359567. FINDINGS: 1114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. 418 of 555 patients (75.3%) in the palonosetron group had complete response during the acute phase compared with 410 of 559 patients (73.3%) in the granisetron group (mean difference 2.9% [95% CI -2.70 to 7.27]). During the delayed phase, 315 of 555 patients (56.8%) had complete response in the palonosetron group compared with 249 of 559 patients (44.5%) in the granisetron group ($p<0.0001$). The main treatment-related adverse events were constipation (97 of 557

patients [17.4%] in the palonosetron group vs 88 of 562 [15.7%] in the granisetron group) and raised concentrations of serum aminotransferases (aspartate aminotransferase: 24 of 557 [4.3%] vs 34 of 562 [6.0%]; alanine aminotransferase: 16 of 557 [2.9%] vs 33 of 562 [5.9%]); no grade 4 main treatment-related adverse events were reported. INTERPRETATION: When administered with dexamethasone before highly emetogenic chemotherapy, palonosetron exerts efficacy against chemotherapy-induced nausea and vomiting which is non-inferior to that of granisetron in the acute phase and better than that of granisetron in the delayed phase, with a comparable safety profile for the two treatments. FUNDING: Taiho Pharmaceutical (Tokyo, Japan).

Siddique, R., M. G. Hafiz, et al. (2011). "Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia." Mymensingh Medical Journal: MMJ 20(4): 680-688.

Effect of ondansetron and granisetron were evaluated in sixty (60) children (age 4-11 years) irrespective of sex, diagnosed case of acute lymphoblastic leukemia (ALL) who received high dose methotrexate and did not receive any antiemetic 24 hours prior to HDMTX. This was a prospective, randomized, double-blind, single center study. Of 60 children, 30 received oral ondansetron (4mg) and rest 30 granisetron (1mg) half an hour before therapy. Drugs were randomly allocated with appropriate code. The patients were followed up from day 1 to day 5 of therapy. Episodes of nausea and vomiting were recorded and scorings was done every 24 hours following chemotherapy. No significant difference was found between two groups according to acute emesis (Day-1) ($p=0.053$). In day two and day three it was significant ($p<0.05$). In day four it was significant ($p=0.002$). Early chemotherapy induced nausea and vomiting (CINV) were controlled 90% in children who received granisetron and 70% in children who received ondansetron. Delayed (Day 2-4) CINV were controlled in 80% of children who received granisetron and 43.4% who received ondansetron ($p<0.05$). Granisetron group required additional doses only 3.3% cases and ondanseton group 30% cases on the second day ($p<0.05$). Result was significant between two groups. About 36.7% patients had episodes of nausea on day four of chemotherapy in ondansetron group and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself ($p=0.001$). Maximum episodes of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% ($p=0.003$). Though adverse effects like headache, constipation, abdominal pain and loose motion were common in both group of children but their number was much less in children who received granisetron. On second day of therapy score of nausea and vomiting was maximum in ondansetron and minimum in granisetron treated on day 4 and the result was significant. So, to prevent acute and delayed CINV in children with ALL, oral graniseteron can be considered as more effective and well tolerated with minimum adverse effects compared with ondansetrons.

Tan, T., R. Ojo, et al. (2010). "Reduction of severity of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine: a randomised comparison of prophylactic granisetron and ondansetron." International Journal of Obstetric Anesthesia **19**(1): 56-60.

BACKGROUND: The incidence of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine may be 60-100%, and is a common cause of maternal dissatisfaction. Ondansetron has been shown to reduce pruritus but the effect is

short-lived. The objective of this randomized double-blind trial was to evaluate the anti-pruritic efficacy of granisetron compared with ondansetron. METHODS: Eighty ASA I or II women undergoing elective caesarean section received spinal anaesthesia with 0.5% hyperbaric bupivacaine 10 mg, fentanyl 25 microg and preservative-free morphine 150 microg. After delivery of the baby and clamping of the umbilical cord, they were randomised to receive granisetron 3mg i.v. (group G) or ondansetron 8 mg i.v. (group O). RESULTS: The two groups were similar for age, gestational age, height and weight. According to visual analogue pruritus scores, patients in group G experienced less pruritus at 8h (P=0.003) and 24h (P=0.01). Fewer patients in group G (n=8) than group O (n=18) required rescue anti-pruritic medication (P=0.03). Satisfaction scores were also higher in group G than in group O (P=0.03). There was no difference in overall incidence of pruritus, nausea and vomiting, and visual analogue pain scores between the two groups. CONCLUSIONS: Administration of granisetron 3mg i.v. reduces the severity of pruritus and the use of rescue anti-pruritic medication, and improves satisfaction but does not reduce the overall incidence of pruritus in women who have received subarachnoid morphine 150 microg compared to ondansetron 8 mg i.v. Copyright 2009 Elsevier Ltd. All rights reserved.

Tian, W., Z. Wang, et al. (2011). "Randomized, double-blind, crossover study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population." Medical Oncology **28**(1): 71-8.

The objective of this study was to compare the efficacy and tolerability of palonosetron and granisetron in a Chinese population receiving highly emetogenic cisplatin-based chemotherapy or moderately emetogenic chemotherapy. Patients were stratified by chemotherapy with cisplatin (yes/no) and then randomly assigned to receive either palonosetron (0.25mg i.v.) in the first cycle followed by granisetron (3mg i.v.) in the second cycle or vice versa. The primary efficacy endpoint was the proportion of patients with complete response 0-24h post-chemotherapy administration. The proportions of patients with complete response 24-120 and 0-120h following chemotherapy were also compared. Of the 144 patients randomized, 36 (25%) received 60-80mg/m(2) cisplatin; 66 of 72 patients in the palonosetron to granisetron group and 56 of 72 patients in the granisetron to palonosetron group completed treatment with both antiemetics. The efficacy and safety analyses included 128 palonosetron treatments and 138 granisetron treatments. Palonosetron consistently produced numerically higher complete response rates than granisetron in the acute phase (0-24h, 71.09 vs. 65.22%), the delayed phase (24-120h, 60.16 vs. 55.80%), and overall (0-120h, 53.13 vs. 50.00%) though the differences were not significant. Both palonosetron and granisetron were well tolerated. Palonosetron was well tolerated and effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in a Chinese population. When used as monotherapy, 0.25-mg palonosetron was not inferior to 3-mg granisetron for preventing vomiting following highly or moderately emetogenic chemotherapy.

Yu, Z., W. Liu, et al. (2009). "The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicenter, randomized, double-blind, parallel, comparative clinical trial." Supportive Care in Cancer **17**(1): 99-102.

PURPOSE: This clinical trial was conducted to evaluate the efficacy and safety of Palonosetron in preventing chemotherapy-induced vomiting (CIV) among the Chinese cancer patients. PATIENTS AND METHODS: Two hundred and forty patients were scheduled to be enrolled and randomized to receive a single intravenous dose of palonosetron 0.25 mg, or granisetron 3 mg, 30 min before receiving highly emetogenic chemotherapy. The primary efficacy endpoint was the complete response (CR) rate for acute CIV (during the 0-24-h interval after chemotherapy). Secondary endpoints included the CR rates for delayed CIV (more than 24 h after chemotherapy). RESULTS: Two hundred and eight patients were accrued and received study medication. CR rates for acute CIV were 82.69% for palonosetron and 72.12% for granisetron, which demonstrated that palonosetron was not inferior to granisetron in preventing acute CIV. Comparisons of CR rates for delayed CIV yielded no statistical difference between palonosetron and granisetron groups and did not reveal non-inferiority of palonosetron to granisetron. Adverse events were mostly mild to moderate, with quite low rates among the two groups. CONCLUSIONS: A single dose (0.25 mg) of palonosetron is not inferior to a single dose (3 mg) of granisetron in preventing CIV and possesses an acceptable safety profile in the Chinese population.

Placebo-controlled trials

Albany, C., M. J. Brames, et al. (2012). "Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study." Journal of Clinical Oncology 30(32): 3998-4003.

PURPOSE: Aprepitant, a 5-HT3 receptor antagonist (5HT3-RA), and dexamethasone are standard antiemetic therapy for prevention of single-day, cisplatin-induced nausea and vomiting. We conducted a double-blind, placebo-controlled phase III cross-over study that compared aprepitant to placebo combined with standard antiemetic prophylaxis (a 5HT3-RA and dexamethasone) in patients receiving 5 days of cisplatin combination chemotherapy for testicular cancer.

PATIENTS AND METHODS: Patients receiving two consecutive identical courses of a 5-day cisplatin-based chemotherapy were randomly assigned to aprepitant 125 mg on day 3 and 80 mg per day on days 4 through 7 or to placebo with the initial course and crossover to the opposite treatment with the second course. The primary objective was complete response (CR). Secondary end points were emetic episodes (acute and delayed), nausea measurement based on a visual analog scale (VAS), and patient-stated preference after the second study cycle.

RESULTS: In all, 71 patients were screened for the study and 69 were evaluable. Thirty-five patients were randomly assigned to receive aprepitant and 34 to receive placebo for the first course. Forty-two percent achieved CR with aprepitant compared with 13% with placebo ($P < .001$). Eleven patients (16.2%) had at least one emetic episode during the aprepitant cycle versus 32 patients (47.1%) with placebo. Thirty-eight patients preferred the aprepitant cycle whereas 11 preferred placebo ($P < .001$). There was no statistical difference in VAS for nausea, but it was numerically superior with aprepitant. There was no toxicity with aprepitant compared with placebo.

CONCLUSION: There was a significant improvement in CR rate with aprepitant combined with a 5HT3-RA and dexamethasone. Patient preference strongly favored the aprepitant cycle.

Barrett, T. W., D. M. DiPersio, et al. (2011). "A randomized, placebo-controlled trial of ondansetron, metoclopramide, and promethazine in adults." American Journal of Emergency Medicine 29(3): 247-255.

OBJECTIVES: The objective of the study was to assess whether ondansetron has superior nausea reduction compared with metoclopramide, promethazine, or saline placebo in emergency department (ED) adults.

METHODS: This randomized, placebo-controlled, double-blinded superiority trial was intended to enroll a convenience sample of 600 patients. Nausea was evaluated on a 100-mm visual analog scale (VAS) at baseline and 30 minutes after treatment. Patients with a minimum preenrollment VAS of 40 mm were randomized to intravenous ondansetron 4 mg, metoclopramide 10 mg, promethazine 12.5 mg, or saline placebo. A 12-mm VAS improvement in nausea severity was deemed clinically important. We measured potential drug adverse effects at baseline and 30 minutes. Patients received approximately 500 mL of saline hydration during the initial 30 minutes.

RESULTS: Of 180 subjects who consented, 163 completed the study. The median age was 32 years (interquartile range, 23-47), and 68% were female. The median 30-minute VAS reductions (95% confidence intervals) and saline volume given for ondansetron, metoclopramide, promethazine, and saline were -22 (-32 to -15), -30 (-38 to -25.5), -29 (-40 to -21), and -16 (-25 to -3), and 500, 500, 500, and 450, respectively. The median 30-minute VAS differences (95% confidence intervals) between ondansetron and metoclopramide, promethazine, and saline were -8 (-18.5 to 3), -7 (-21 to -5.5), and 6 (-7 to 20), respectively. We compared the antiemetic efficacy across all treatments with the Kruskal-Wallis test (P = .16).
CONCLUSIONS: Our study shows no evidence that ondansetron is superior to metoclopramide and promethazine in reducing nausea in ED adults. Early study termination may have limited detection of ondansetron's superior nausea reduction over saline.

de Orange, F. A., J. Marques, et al. (2012). "Dexamethasone versus ondansetron in combination with dexamethasone for the prophylaxis of postoperative vomiting in pediatric outpatients: a double-blind, randomized, placebo-controlled clinical trial." Paediatric Anaesthesia 22(9): 890-896.

OBJECTIVES: To determine the frequency of postoperative vomiting (POV) in children submitted to outpatient surgery and to compare the efficacy of antiemetic drugs in preventing this complication.
BACKGROUND: Nausea and vomiting are common in the immediate postoperative period following anesthetic and surgical procedures. Compared to adults, pediatric patients are more likely to develop postoperative nausea and vomiting, the incidence of which ranges from 8.9% to 42%.
METHODS: This double-blind, randomized, placebo-controlled clinical trial included 129 children. The participants were randomized into three prophylactic treatment groups: dexamethasone (n = 43), ondansetron in combination with dexamethasone (n = 44), and placebo (n = 42). The variables studied were the frequency of POV and the incidence of vomiting after the patient had been discharged from hospital, the need for antiemetic rescue therapy in the postanesthesia care unit (PACU), need for hospitalization, and the time the patient remained in the PACU. A significance level of 5% was adopted.
RESULTS: Postoperative vomiting occurred in 12.4% of the children, with no statistically significant difference between the groups: 6.8% in the group receiving ondansetron combined with dexamethasone, 14.3% in the placebo group, and 14% in the group that received dexamethasone alone (P = 0.47). Furthermore, no significant difference was found between the groups with respect to the time the children remained in the PACU, and only five patients reported having vomited following discharge from hospital.
CONCLUSIONS: The prophylactic use of antiemetic drugs failed to reduce the incidence of POV in pediatric outpatient surgery with a low emetic potential; therefore, routine prophylaxis may be unnecessary.

Ebrahim Soltani, A. R., H. Mohammadinasab, et al. (2011). "Comparing the efficacy of prophylactic p6 acupressure, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery." Acta Medica Iranica 49(4): 208-212.

To compare the efficacy of acupressure wrist bands, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery. Two hundred patients, ASA physical status I or II, aged between 10 and 60 years, undergoing strabismus surgery in Farabi Hospital in 2007-2008 years, were included in this randomized, prospective, double-blind and placebo-controlled study. Group I was the Control, group II received metoclopramide 0.2 mg/kg, group III received ondansetron 0.15 mg/kg iv just before induction, in Group IV acupressure wristbands were applied at the P6 points. Acupressure wrist bands were placed inappropriately in Groups I, II and III. The acupressure wrist bands were applied 30 min prior to the induction of anesthesia and removed six hours after surgery. Postoperative nausea and vomiting (PONV) was evaluated within 0-2 hours and 2-24 hours after surgery by a blinded observer. Results were analyzed by X(2) test. A P value of < 0.05 was taken as significant. The incidence of PONV was not significantly different in acupressure, metoclopramide and ondansetron during the 24 hours. Acupressure at P6 causes a significant reduction in the incidence of PONV 24 hours after strabismus surgery as well as metoclopramide 0.2 mg/kg and ondansetron 0.15 mg/kg iv for patients aged 10 or more.

Gore, L., S. Chawla, et al. (2009). "Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability." Pediatric Blood & Cancer **52**(2): 242-7.

BACKGROUND: The neurokinin-1 receptor antagonist aprepitant, plus a 5HT3 antagonist and corticosteroid is well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in adults but has not been formally assessed in adolescents. PROCEDURE: Patients age 11-19 years old receiving emetogenic chemotherapy were randomized 2:1 to aprepitant triple therapy (aprepitant [A] 125 mg p.o., dexamethasone [D] 8 mg p.o., and ondansetron [O] 0.15 mg/kg i.v. t.i.d. day 1; A 80 mg, D 4 mg, and O 0.15 mg/kg t.i.d. day 2; A 80 mg and D 4 mg day 3; and D 4 mg day 4) or a control regimen (D 16 mg and O 0.15 mg/kg t.i.d. day 1; D 8 mg and O 0.15 mg/kg t.i.d. day 2; and D 8 mg days 3 and 4). The primary endpoint was the difference in drug-related adverse events during and for 14 days following treatment. Efficacy and aprepitant pharmacokinetics were assessed. RESULTS: Baseline characteristics were similar between aprepitant (N = 28) and control (N = 18) groups. Febrile neutropenia was more frequent in the aprepitant group (25% vs. 11.1%). Complete response (CR) rates were 35.7% for aprepitant triple therapy versus 5.6% for the control group. Mean plasma aprepitant AUC(0-24 hr) and C(max) on day 1 and mean trough concentrations on days 2 and 3 were consistently lower compared to historical data obtained from healthy adults; however, the differences were not clinically significant. CONCLUSION: Aprepitant triple therapy was generally well tolerated; CR were greater with aprepitant, although not statistically significant. Pharmacokinetics suggest that the adult dosing regimen is appropriate for adolescents. (c) 2008 Wiley-Liss, Inc.

Hesketh, P. J., G. Morrow, et al. (2012). "Efficacy and safety of palonosetron as salvage treatment in the prevention of chemotherapy-induced nausea and vomiting in patients receiving low emetogenic chemotherapy (LEC)." Supportive Care in Cancer **20**(10): 2633-2637.

PURPOSE: The purpose of this study is to evaluate the efficacy and safety of intravenous (IV) palonosetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients with cancer who had incomplete control of CINV during their previous cycle of low emetogenic chemotherapy (LEC).

METHODS: Patients with histologically or cytologically confirmed cancer, >=18 years of age, with a Karnofsky Performance Scale score of >=50% who had received LEC that induced vomiting and/or at least moderate nausea during their previous treatment cycle received palonosetron 0.25 mg IV 30 min before chemotherapy. Outcomes were recorded in patient diaries over 120 h and at an end-of-study visit on days 6, 7, or 8 after LEC administration. The primary efficacy variable was the complete response rate, defined as no emetic episodes and no rescue medication at 0-24 h (acute post-chemotherapy phase), 24-120 h (delayed phase), and 0-120 h (overall).

RESULTS: Complete responses among the intent-to-treat study population (n = 34) were recorded for 88.2 % of patients in the acute phase, 67.6% in the delayed phase, and 67.6% overall. No emetic episodes occurred in 91.2 and 79.4% of patients during the acute and delayed phases, respectively, and no nausea in 73.5 and 52.9%, respectively. Palonosetron was well tolerated; only two patients experienced treatment-related adverse events.

CONCLUSIONS: Among the patients with cancer who had a history of CINV with LEC, palonosetron was effective in preventing CINV in both the acute and delayed post-chemotherapy phases, and was well tolerated. Randomized comparative studies in larger populations of patients receiving LEC are needed to confirm these findings.

Koren, G., S. Clark, et al. (2010). "Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial." American Journal of Obstetrics & Gynecology 203(6): 571.e571-577.

OBJECTIVE: To evaluate the effectiveness of Diclectin (doxylamine succinate 10 mg-pyridoxine hydrochloride 10 mg, delayed-release preparation) as compared with placebo for nausea and vomiting of pregnancy.

STUDY DESIGN: A randomized, double-blind, multicenter placebo controlled trial studying pregnant women suffering from nausea and vomiting of pregnancy, analyzed by intention to treat. Women received Diclectin (n = 131) or placebo (n = 125) for 14 days. Nausea and vomiting of pregnancy symptoms were evaluated daily using the pregnancy unique quantification of emesis scale.

RESULTS: Diclectin use resulted in a significantly larger improvement in symptoms of nausea and vomiting of pregnancy compared with placebo based on both the pregnancy unique quantification of emesis score (-4.8 +/- 2.7 vs -3.9 +/- 2.6; P = .006) and quality of life. After the trial, 64 (48.9%) women receiving Diclectin asked to continue compassionate use of their medication, as compared with 41 (32.8%) of placebo-treated women (P = .009).

CONCLUSION: Diclectin delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating nausea and vomiting of pregnancy.

Rapoport, B. L., K. Jordan, et al. (2010). "Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study." Supportive Care in Cancer **18**(4): 423-31.

PURPOSE: Aprepitant was shown previously to be effective for prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately emetogenic chemotherapy (MEC) in breast cancer patients receiving an anthracycline and cyclophosphamide (AC)-based regimen. This study assessed aprepitant in patients receiving a broad range of MEC regimens with a variety of tumor types. METHODS: This phase III, randomized, gender-stratified, double-blind trial enrolled patients with confirmed malignancies, naive to MEC or highly emetogenic chemotherapy, who were scheduled to receive a single dose of at least one MEC agent. Patients received an aprepitant triple-therapy regimen (aprepitant, ondansetron, and dexamethasone) or a control regimen (ondansetron and dexamethasone) administered orally. Primary and key secondary efficacy endpoints were proportions of patients with no vomiting and complete response (no vomiting and no rescue medication), respectively, during the 120 h post-chemotherapy. RESULTS: Of 848 randomized patients, 77% were female, and 52% received non-AC-based antineoplastic regimens. Significantly, more patients in the aprepitant group achieved no vomiting and complete response, regardless of whether they received AC or non-AC regimens, in the 120 h after chemotherapy. Overall, the incidences of adverse events were generally similar in the aprepitant (62.8%) and control groups (67.2%). CONCLUSIONS: The aprepitant regimen provided superior efficacy in the treatment of CINV in a broad range of patients receiving MEC (non-AC or AC) in both no vomiting and complete response endpoints. Aprepitant was generally well tolerated. These results show the benefit of including aprepitant as part of the standard antiemetic regimen for cancer patients receiving MEC.

Reeve, B. K., D. J. Cook, et al. (2005). "Prophylactic Diclectin reduces the incidence of postoperative vomiting." Canadian Journal of Anaesthesia 52(1): 55-61.

BACKGROUND: Diclectin(R) (DCL) is an effective antiemetic used for relief of nausea and vomiting in pregnancy. It is unknown whether DCL is effective in the prevention of postoperative nausea and vomiting (PONV).

METHODS: We conducted a randomized, stratified, double-blind placebo-controlled trial to examine the incidence of PONV in women undergoing elective laparoscopic tubal ligation in the day surgery setting. DCL (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) was administered orally the night before surgery, the morning of surgery, and upon hospital discharge.

RESULTS: We enrolled 146 women in the trial, 127 of whom were included in the effectiveness analysis and 102 of whom were included in the efficacy analysis. We did not detect a difference in the incidence of nausea and vomiting in the first six hours postoperatively after adjusting for additional antiemetics administered. Patients receiving DCL as compared with placebo were significantly less likely to experience vomiting six to 24 hr

postoperatively [5/59 (8.5%) vs 14/55 (25.4%), P < 0.017]. Treated patients tended to return to work earlier than those who received placebo (1.74 vs 3.7 days P = NS). CONCLUSION: Perioperative oral DCL reduces the incidence of postoperative vomiting in women undergoing elective laparoscopic tubal ligation, and may accelerate return to work.

Takahashi, T., E. Hoshi, et al. (2010). "Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin." Cancer Science **101**(11): 2455-61.

Aprepitant is a new neurokinin-1 (NK(1)) receptor antagonist developed as a treatment for chemotherapy-induced nausea and vomiting (CINV). To evaluate the efficacy and safety of aprepitant used in combination with standard therapy (granisetron and dexamethasone), we conducted a multicenter, phase II, placebo-controlled, double-blind, randomized study in Japanese cancer patients who received cancer chemotherapy including cisplatin (>=70mg/m(2)). Aprepitant was administered for 5days. A total of 453 patients were enrolled. In the three study groups, (i) standard therapy, (ii) aprepitant 40/25mg (40mg on day 1 and 25mg on days 2-5) and (iii) aprepitant 125/80mg (125mg on day 1 and 80mg on days 2-5), the percentage of patients with complete response (no emesis and no rescue therapy) was 50.3% (75/149 subjects), 66.4% (95/143 subjects) and 70.5% (103/146 subjects), respectively. This shows that efficacy was significantly higher in the aprepitant 40/25mg and 125/80mg groups than in the standard therapy group ((2) test [closed testing procedure]: P=0.0053 and P=0.0004, respectively) and highest in the aprepitant 125/80mg group. The delayed phase efficacy (days 2-5) was similar to the overall phase efficacy (days 1-5), indicating that aprepitant is effective in the delayed phase when standard therapy is not very effective. In terms of safety, aprepitant was generally well tolerated in Japanese cancer patients. (ClinicalTrials.gov number, NCT00212602.) Copyright 2010 Japanese Cancer Association.

Vallejo, M. C., A. L. Phelps, et al. (2012). "Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery." Plastic & Reconstructive Surgery 129(2): 519-526.

BACKGROUND: Postoperative nausea and vomiting is a major challenge in the perioperative setting. The incidence can be as high as 80 percent, and the majority of the symptoms among outpatients occur after discharge. This study evaluated the efficacy of a neurokinin-1 receptor antagonist (aprepitant) in reducing postoperative symptoms for up to 48 hours in patients undergoing outpatient plastic surgery.
METHODS: A prospective, double-blinded, randomized, two-arm evaluation of 150 ambulatory plastic surgery patients receiving a standardized general anesthetic, including postoperative nausea and vomiting prophylaxis with ondansetron and either aprepitant or placebo, was performed. The main outcome measures were the occurrence of vomiting and the severity of nausea for up to 48 hours postoperatively.
RESULTS: Overall, 9.3 percent of patients who received aprepitant versus 29.7 percent in group B had vomiting, with the majority of vomiting episodes occurring after hospital discharge. The Kaplan-Meier plot of the hazards of vomiting revealed an increased incidence of emesis in patients receiving ondansetron alone compared with the combination of ondansetron and aprepitant (p = 0.006). The incidence of nausea was not significantly different in the two groups. Severity of nausea, however, was significantly higher in those receiving ondansetron alone compared with those receiving ondansetron

and aprepitant, as measured by a peak nausea score (p = 0.014) and by multivariate analysis of variance results comparing repeated verbal rating scale scores over 48 hours after surgery (p = 0.024).
CONCLUSION: In patients undergoing plastic surgery, the addition of aprepitant to ondansetron significantly decreases postoperative vomiting rates and nausea severity for up to 48 hours postoperatively.
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Wagner, D. S., V. Gauger, et al. (2007). "Ondansetron oral disintegrating tablets for the prevention of postoperative vomiting in children undergoing strabismus surgery." Therapeutics & Clinical Risk Management **3**(4): 691-4.

Strabismus surgery in pediatric patients is associated with a high incidence of postoperative nausea and vomiting (PONV). Ondansetron disintegrating tablets (ODT), an oral freeze-dried formulation of the 5-HT(3) antagonist, are well-tolerated and have been shown to reduce chemotherapy-induced vomiting. The purpose of this study was to assess the efficacy of the ODT in preventing postoperative vomiting (POV) in children undergoing strabismus repair. Healthy children aged 4-12 years of age were administered a 4 mg ODT 30 minutes prior to the induction of general anesthesia. Induction and maintenance of anesthesia were standardized; each child received acetaminophen and ketorolac pre-emptively for analgesia. This study group was compared with a historical control group who received a placebo in previously conducted identical trials of POV. The 35 children included in this study were compared with 31 controls. The incidence and severity of POV and use of rescue antiemetics were significantly lower in children who received ODT compared with placebo (p </= 0.001). The acute complete response (ie, no emesis and no rescue antiemetics in 24 hours) was 76% in the ODT group compared with 16% in the controls (p </= 0.001). Results suggest that ODT given preoperatively reduces the incidence and severity of POV in children undergoing strabismus surgery.

Yeo, W., F. K. F. Mo, et al. (2009). "A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy." Breast Cancer Research & Treatment **113**(3): 529-35.

OBJECTIVES: This is a single center, randomized, double-blind placebo-controlled study to evaluate the NK(1)-receptor antagonist, aprepitant, in Chinese breast cancer patients. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy. The secondary objective was to compare the patient-reported quality of life in these two groups of patients. PATIENTS AND METHODS: Eligible breast cancer patients were chemotherapy-naive and treated with adjuvant AC chemotherapy (i.e. doxorubicin 60 mg/m(2) and cyclophosphamide 600 mg/m(2)). Patients were randomly assigned to either an aprepitant-based regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, aprepitant 80 qd) or a control arm which consisted of standard regimen (day 1, ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and

ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary, patients quality of life were assessed by self-administered Functional Living Index-Emesis (FLIE). RESULTS: Of 127 patients randomized, 124 were assessable. For CINV in Cycle 1 AC, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea'. The requirement of rescue medication appears to be lesser in patients treated with the aprepitant-based regimen compared to those with the standard regimen (11% vs. 20%; P = 0.06). Assessment of FLIE revealed that while there was no difference in the nausea domain and the total score between the two groups; however, patients receiving standard antiemetic regimen had significantly worse quality of life in the vomiting domain (mean score [SD] = 23.99 [30.79]) when compared with those who received the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) (P = 0.0002). Both treatments were generally well tolerated. Patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (53.2% vs. 35.5%, P = 0.0468), grade >or= 3 neutropenia (21.0% vs. 45.2, P = 0.0042) and delay in subsequent cycle of chemotherapy (8.1% vs. 27.4%, P = 0.0048). CONCLUSION: The aprepitant regimen appears to reduce the requirement of rescue medication when compared with the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide, and is associated with a better quality of life during adjuvant AC chemotherapy.

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Month/Year of Review: November 2014 **Date of Last Review:** August 2013
PDL Classes: Skeletal Muscle Relaxants **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: BACLOFEN, CYCLOBENZAPRINE HCL, TIZANDINE HCL
- Non-Preferred Agents: CHLORZOXAZONE, METAXALONE, METHOCARBAMOL, DANTROLENE SODIUM, ORPHENADRINE CITRATE, CARISOPRODOL , CYCLOBENZARPINE ER (AMRIX®)

Previous Conclusions and Recommendation:

- The evidence does not support any conclusions about the comparative effectiveness between baclofen, tizanidine, or dantrolene for spasticity. All are effective and equivalent to diazepam. Dantrolene is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions for the comparative efficacy or safety between skeletal muscle relaxants for musculoskeletal conditions.
- Cyclobenzaprine had the largest body of evidence to support its efficacy compared to placebo.
- Chlorzoxazone is associated with rare serious dose-related hepatotoxicity.
- The evidence does not support any conclusions about the comparative efficacy or adverse effects for different subpopulations of patients such as race, gender, or age.

PA Criteria: Prior authorization is in place to support preferred PDL skeletal muscle relaxants and to cover for OHP above the line diagnoses only. A quantity limit restricts carisoprodol products to less than 56 tablets within 90 days unless the patient has a terminal illness. (Appendix 1).

Conclusions and Recommendations:

- There is limited new evidence since the last review on skeletal muscle relaxants; no further review or research needed.
- Evaluate comparative costs in executive session.

Methods:

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

References:

1. Holzhammer, B. Drug Effectiveness Review Project: Drug Class Review on Skeletal Muscle Relaxants. Preliminary Scan Report #6. May 2014.

Appendix 1: PA Criteria

Skeletal Muscle Relaxants

Goal(s):

- Cover non-preferred drugs only for above the line diagnoses.
- Restrict carisoprodol to short-term use per medical evidence.
    a. There are no long-term studies of efficacy or safety for carisoprodol.
    b. Case reports suggest it is often abused and can be fatal when used in association with opioids, benzodiazepeines, alcohol, or illicit drugs.
    c. Carisoprodol is metabolized to meprobamate.

Length of Authorization: Up to 6 months

Requires PA:

- Non-preferred NSAIDs

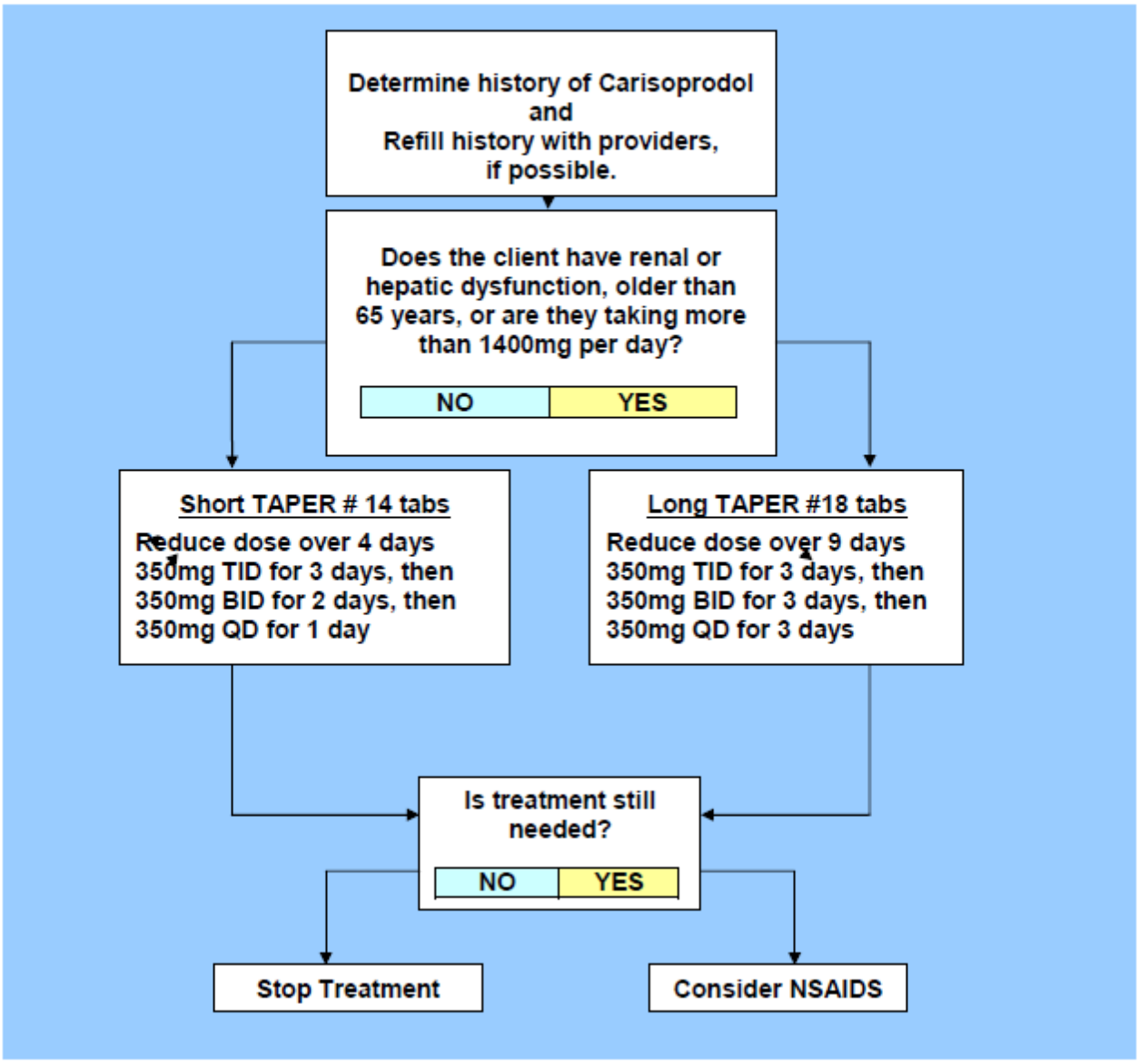
Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/
Cyclobenzaprine has the largest body of evidence supporting long-term use and is the preferred product in the muscle relaxant class. For patients that have contraindications to TCAs, NSAIDs, benzodiazepeines or opioids are other alternatives. OHP does not cover pain clinic treatment.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is diagnosis covered by the Oregon Health Plan?	Yes: Go to #3.	No: Pass to RPH; Deny, (Not Covered by the OHP)
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC).	Yes: Inform provider of covered alternatives in class	No. Go to #4
4. Is drug requested carisoprodol (Soma®)?	Yes: Go to #5	No. Approve for up to 6 months

5. Does total quantity of carisoprodol (Soma®) products exceed 56 tablets within 90 days? From claims, document product, dose, directions, and amount used during last 90 days:	Yes: Go to #6	No: Approve for up to 6 months
6. Does patient have a terminal illness (e.g. metastatic CA, end stage HIV, ALS)?	Yes: Approve for 6 months.	No: Pass to RPH. Go to #7

7. Pharmacist's Statement:
 	
• Carisoprodol cannot be approved for long term usage.
• Patients are limited to 56 tablets in a 90 day period.
• It is recommended that the patient undergo a "taper" of the Soma (Carisoprodol) product of which a supply may be authorized for this to occur.
• The amount and length of taper depends upon the patient's condition. Does the patient meet one or more of the following?:
  ○ >65 years old
  ○ Renal Failure
  ○ Hepatic failure
 	
Take > 1400mg per day (>3.5 tablets)
	Yes: Document reason and approve long taper:
	
	• Authorize 18 tablets
	• Reduce dose over 9 days
	• 350mg TID X 3 days, then
	• 350mg BID X 3 days, then
	• 350mg QD x 3 days then evaluate
		No: Approve short taper:
		
		• Authorize 10 tablets
		• Reduce dose over 4 days
		• 350 mg tid x 1 day, then
		• 350 mg bid x 2 days, then
		• 350 mg QD x 1 day, then evaluate

Tapering Carisoprodol



Drug Class Review
on
Skeletal Muscle Relaxants

Preliminary Scan Report #6

May 2014

Last Report: Update 2 (May 2005)

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

Scan conducted by:
Brittany Holzhammer, MPH

Drug Effectiveness Review Project
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Oregon Health & Science University

OBJECTIVE

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

Date of Last Update Report

Original Report: September 2003
Update #1: January 2004
Update#2: May 2005 (searches through November 2004)

Date of Last Preliminary Update Scan Report

Update #3 Preliminary Scan #1: February 2007
Update #3 Preliminary Scan #2: March 2008
Update #3 Preliminary Scan #3: June 2009
Update #3 Preliminary Scan #4: September 2010
Update #3 Preliminary Scan #5: May 2013 (searches through April Week 3 2013)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

- Adult or pediatric patients with spasticity or a musculoskeletal condition. We defined spasticity as muscle spasms associated with an upper motor neuron syndrome. Musculoskeletal conditions were defined as peripheral conditions resulting in muscle or soft tissue pain or spasms.
- We included patients with nocturnal leg cramps however, excluded patients with restless legs syndrome or nocturnal myoclonus.
- Obstetric and dialysis patients were also excluded.

Interventions

Table 1. Included interventions*

Active Ingredient	Brand name	Forms
Baclofen	Generic	Oral tablet
Carisoprodol	Soma®	Oral tablet
Chlorzoxazone	Parafon Forte® DSC	Oral tablet
Cyclobenzaprine hydrochloride	Amrix®	Extended release oral capsule
Cyclobenzaprine hydrochloride	Generic	Oral tablet
Dantrolene	Dantrium®	Oral capsule
Metaxalone	Skelaxin®	Oral tablet
Methocarbamol	Robaxin®, Robaxin-750	Oral tablet
Orphenadrine	Generic	Extended release oral tablet
Tizanidine	Zanaflex®	Oral tablet and oral capsule

Study designs

- Controlled clinical trials/randomized controlled trials
- Comparative effectiveness reviews

Comparators: Effectiveness and harms of individual skeletal muscle relaxants

- Benzodiazepines were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with any of the skeletal muscle relaxants listed above.
- Other medications used for spasticity but considered to be in another drug class, such as gabapentin (a neuroleptic) and clonidine (an antihypertensive), were also only reviewed when they were directly compared to an included skeletal muscle relaxant.
- Quinine was only included if it was compared to a skeletal muscle relaxant.

Effectiveness outcomes

- Relief of muscle spasms or pain, functional status, quality of life
- Non-clinical outcomes such as electromyogram measurements or spring tension measurements were excluded.

Harms outcomes

- Somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction
- Withdrawal rates and adverse events
- We also paid special attention to reports of serious hepatic injury.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2013 through May 14, 2014 using terms for included drugs and limited to humans, English language, controlled clinical trials and randomized clinical trials. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm).

Study Selection

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

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan
None

New drugs identified in previous Preliminary Update Scan(s)
Amrix® (cyclobenzaprine hydrochloride, 15 mg and 30 mg extended-release oral tablet): indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions in adult patients (02/11/2007).

Soma® (carisoprodol, 250 mg oral capsule): indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults (9/13/2007).

New Indications

New indications identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
None

New Safety Alerts

Identified in this Preliminary Update Scan
None

Identified in previous Preliminary Update Scan(s)
Dantrium (dantrolene sodium) Oral Capsule: July 2012

BOXED WARNING

- Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving Dantrium. However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
None

Reviews identified in previous Preliminary Update Scan(s)
None

Randomized Controlled Trials

Trials identified since the most recent scan
Medline searches resulted in 10 citations, none of which were relevant to the key questions and populations of interest in this scan. Table 2 includes all placebo-controlled trials that were identified in previous preliminary update scans. Appendix A includes the abstracts for each relevant trial identified in previous preliminary update scans.

Table 2. Previously identified potentially relevant trials

Author Year	Drugs/Comparisons	Focus
Placebo-Controlled Trials		
Malanga, 2009	Cyclobenzaprine ER vs. placebo (report of two trials)	Low back and neck pain
Serfer, 2010	Carisoprodol vs. placebo	Low back spasm
Mathew 2005	Diazepam vs. placebo	Motor function in children with cerebral palsy

Ketenci 2005	Thiocolchicoside vs. Tizanidine vs. placebo	Low back pain associated with muscle spasm

Summary

There is no new evidence on skeletal muscle relaxants since the last preliminary update scan. No new head-to-head trials, placebo controlled trials, or comparative effectiveness reviews pertaining to existing drugs were identified in this preliminary update scan.

Appendix A. Abstracts of relevant trials and systematic reviews of skeletal muscle relaxants identified in previous scans (N=5)

Placebo-Controlled Trials (N=4)

Ketenci, A., E. Ozcan, et al. (2005). "Assessment of efficacy and psychomotor performances of thiocolchicoside and tizanidine in patients with acute low back pain." International Journal of Clinical Practice 59(7): 764-70.

> Objectives of this study were to assess efficacy and effects on psychomotor performances of thiocolchicoside (TCC) and tizanidine (TZ) compared to placebo. Patients complaining of acute low back pain (LBP) associated with muscle spasm were enrolled in this randomised, double-blind clinical trial, comparing the effects of oral TCC, TZ and placebo on psychomotor performances assessed by a visual analogue scale of tiredness, drowsiness, dizziness and alertness and by psychometric tests after 2 and 5-7 days of treatment. The efficacy assessments, both TCC and TZ, were more effective than placebo in improving pain at rest, hand-to-floor distance, Schober test and decreased paracetamol consumption. There were significant differences among the treatment groups in favour of TCC compared to TZ in visual analog scale-parameters. TZ-induced reduction of psychomotor performances of the patients was confirmed by psychometric tests, which showed significant differences among groups. This study showed that TCC is at least as effective as TZ in the treatment of acute LBP, while it appears devoid of any sedative effect in contrast to TZ.

Malanga, G.A., G. E. Ruoff, et al. (2009). “Cyclobenzaprine ER for muscle spasm associated with low back and neck pain: two randomized, double-blind, placebo-controlled studies of identical design.” Current Medical Research & Opinion **25**(5): 1179-96.

> OBJECTIVE: To evaluate efficacy and tolerability of once-daily cyclobenzaprine extended release (CER) 15- and 30-mg capsules in patients with muscle spasm associated with acute, painful musculoskeletal conditions. METHODS: Two identically designed, randomized, double-blind, placebo- and active-controlled, parallel-group studies in patients aged 18-75 years with muscle spasm associated with neck or back pain. Patients received CER 15 or 30 mg once daily, cyclobenzaprine immediate release (CIR) 10 mg three times daily, or placebo for 14 days. Primary efficacy measures were patient's rating of medication helpfulness and physician's clinical global assessment of response to therapy at day 4. Secondary measures were patient's rating of medication helpfulness and physician's clinical global assessment of response (days 8 and 14), relief from local pain, global impression of change, restriction in activities of daily living, restriction of movement, daytime drowsiness, quality of nighttime sleep (days 4, 8, and 14), and quality of life (days 8 and 14). RESULTS: A total of 156/254 randomized patients in study 1 and 174/250 in study 2 completed 14 days of treatment. Significant improvements in patient's rating of medication helpfulness were reported with CER versus placebo (CER 30 mg, study 1, p = 0.007; CER 15 mg, study 2, p = 0.018) at day 4. Significant improvements with CER 30 mg versus placebo were also seen at day 4 in study 1 for patient-rated global impression of change (p = 0.008), relief of local pain (p =

0.004), and restriction of movement (p = 0.002). Neither study reported differences between study groups on the physician's clinical global assessment. Improvements with CER were comparable to that of CIR. In both studies, daytime drowsiness was reported more frequently in active treatment groups than in the placebo group; however, reports of drowsiness decreased over time in all groups. In general, daytime drowsiness was reported more frequently in CIR groups than in CER groups. More adverse events were reported in the active treatment groups versus placebo and were similar in the CER and CIR groups, except somnolence, which occurred more frequently with CIR. CONCLUSIONS: Once-daily CER 15 mg (study 2) and CER 30 mg (study 1) were effective in treating muscle spasm associated with painful musculoskeletal conditions after 4 days of treatment. Differences between CER and placebo groups did not reach statistical significance on all efficacy measures, and the protocols were not powered to detect differences between active treatment arms. CER was generally safe and well tolerated, with low rates of somnolence.

Mathew, A., M. C. Mathew, et al. (2005). "The efficacy of diazepam in enhancing motor function in children with spastic cerebral palsy." Journal of Tropical Pediatrics 51(2): 109-13.

Muscle spasm and hypertonia limit mobility in children with spastic cerebral palsy. This double-blind, placebo-controlled, randomized controlled clinical trial studies the clinical efficacy of a low dose of diazepam in enhancing movement in children with spastic cerebral palsy. One hundred and eighty children fulfilled the criteria and were randomly allocated to receive one of two doses of diazepam or placebo at bedtime; 173 completed the study. There was a significant reduction of hypertonia, improvement in the range of passive movement, and an increase in spontaneous movement in the children who received diazepam. There was no report of daytime drowsiness. In developing countries, where cost factors often determine choice of drug, diazepam is a cheap and effective way of relieving spasm and stiffness, optimizing physical therapy and facilitating movement in children with spasticity.

Serfer, G.T., W. J. Wheeler, et al. (2010). “Randomized, double-blind trials of carisoprodol 250 mg compared with placebo and carisoprodol 350 mg for the treatment of low back spasm.” Current Medical Research & Opinion 26(1): 91-9.

BACKGROUND: Carisoprodol, a centrally active skeletal muscle relaxant, is widely used for the treatment of acute, painful musculoskeletal disorders. When administered at a dose of 350 mg four times daily, carisoprodol demonstrated significant clinical benefit in its early clinical development trials; however, some unfavorable side effects, such as drowsiness and dizziness, were reported. Recently, research was conducted to determine if a lower dose of carisoprodol would retain efficacy but improve tolerability compared to the higher 350-mg dose. OBJECTIVE: The purpose of this multicenter study was to compare the efficacy and safety of carisoprodol 250-mg tablets four times daily to 350-mg tablets four times daily and to placebo in patients with acute, painful musculoskeletal spasm of the lower back. RESEARCH DESIGN AND METHODS: In this 1-week double-blind, placebo-controlled, parallel-group multicenter trial, patients 18 to 65 years of age with moderate to severe back spasm were randomly assigned to treatment with

carisoprodol 250-mg tablets (n = 264), 350-mg tablets (n = 273), or matching placebo tablets (n = 269) three times daily and at bedtime. RESULTS: The carisoprodol 250-mg regimen was significantly more effective than placebo as assessed by both patient-rated relief from starting backache (p = 0.0001) and patient-rated global impression of change (p = 0.0046). There were no significant differences between the 250-mg and 350-mg dosages for the coprimary efficacy endpoints, and patients improved with or without sedation. Fewer than 1% of patients in the carisoprodol 250-mg group discontinued prematurely because of treatment-emergent adverse events, and no patient discontinued because of drowsiness. CONCLUSIONS: When administered three times daily and at bedtime, carisoprodol 250 mg was as effective as 350 mg three times daily and at bedtime with a lower incidence of adverse events and fewer discontinuations of therapy due to adverse events. Patients improved whether or not they reported sedation as an adverse event.

Systematic Reviews (N=1)

Taricco, M., M. C. Pagliacci, et al. (2006). "Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review." Europa Medicophysica 42(1): 5-15.

The aim of this paper was to assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in spinal cord injury (SCI) patients, as well as the effectiveness and safety of different routes of administration of baclofen. A systematic review of randomised controlled trials (RCTs), within the Cochrane Collaboration Injuries Group, was carried out. The Cochrane Injuries Group Specialised Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE and CINAHL were searched up to July 2006 without language restriction. Drug companies and experts active in the area were also contacted to find other relevant studies. Two investigators independently identified relevant studies, extracted data and assessed methodological quality of studies resolving disagreement by consensus. Nine out of 55 studies met the inclusion criteria. The heterogeneity among studies did not allow quantitative combination of RESULTS: Study designs were: 8 crossover, 1 parallel-group trial. Two studies (14 SCI patients) showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth score and activities of daily living [ADL] performances), compared to placebo, without any adverse effect. The study comparing tizanidine to placebo (118 SCI patients) showed a significant effect of tizanidine in improving Ashworth score but not in ADL performances. The tizanidine group reported significant rates of adverse effects (drowsiness, xerostomia). For the other drugs (gabapentine, clonidine, diazepam, amytal and oral baclofen) the results do not provide evidence for a clinical significant effectiveness. This systematic review indicates that there is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care. [References: 66]

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Month/Year of Review: November 2014 **Date of Last Review:** August 2013
PDL Classes: Nonsteroidal Anti-inflammatory Drugs (NSAIDS) **Source Document:** DERP

Current Status of PDL Class:

- Preferred Agents: DICLOFENAC POTASSIUM, DICLOFENAC SODIUM DR, ETODOLAC TABLET, FLURBIPROFEN, IBUPROFEN CAPSULE/DROPS/ORAL SUSP/CHEWABLE/TABLET, INDOMETHASONE CAPSULE, KETOPROFEN, MELOXICAM, NABUMETONE, NAPROXEN TABLET, NAPROXEN DR, NAPROXEN SODIUM, OXAPROZIN, SALSALATE, SULINDAC
- Non-Preferred Agents: CELECOXIB (CELEBREX®), DICLOFENAC TAB ER 24H, DIFLUNISAL, ETODOLAC CAPSULE, ETODOLAC TABLET ER 24H, FENOPROFEN, INDOMETHASONE ORAL SUSPENSION/CAPSULE ER, KETOPROFEN CAPSULE 24H, KETOROLAC TALET, KETOROLAC NASAL SPRAY (SPRIX®), MECLOFENAMATE SODIUM, MEFENAMIC ACID, NAPROXEN CAPSULE, PIROXICAM ,TOLMETIN SODIUM, NAPROXEN AND ESOMEPRAZOLE (VIMOVO®)

Previous Conclusions and Recommendation:

- For pain relief, no significant short-term (< 6 months) differences were found among oral NSAIDs.
- For serious harms, celecoxib did not appear to be associated with higher risk of cardiovascular (CV) events and is gastroprotective in the short term compared with nonselective NSAIDs.
- Findings vary by subgroup, depending on age, recent history of gastrointestinal bleeding, and concomitant use of antiulcer medication.
- Nonselective NSAIDs were associated with similar increased risks of serious GI events, and all but naproxen were associated with similar increased risk of serious CV events, but eh partially selective NSAID nabumetone was gastroprotective compared with nonselective NSAIDs.
- A meta-analysis of randomized controlled trials showed diclofenac to be associated with an increased incidence of major vascular events (driven by coronary events) and death due to vascular causes, similar to those seen with selective COX-2 inhibitors, such as celecoxib. Naproxen was shown to confer less cardiovascular (CV) risk.
- A meta-analyses of observational data showed diclofenac to have a higher risk of acute myocardial infarction (MI) than other commonly used NSAIDS.2
- Gastrointestinal (GI) risks were similar for diclofenac compared to other NSAIDS.
- Overall, there is limited evidence on safety data associated with diclofenac therapy and the inherent risks associated with all NSAIDs.

PA Criteria: Prior authorization is in place to ensure that non-preferred NSAIDs are used for above the line conditions and to restrict ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning (Appendix 1).

Methods:

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

Conclusions and Recommendations:

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

References:

1. Peterson, Kim. Drug Effectiveness Review Project: Drug Class Review Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Preliminary Scan Report #2, May 2014.

Appendix 1: PA Criteria

Analgesics, Non-Steroidal Anti-Inflammatory Drugs

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred NSAIDs are used for an above the line condition and restrict ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning.

WARNING - Ketorolac is indicated for the short-term (up to 5 days) management of moderately severe acute pain that requires analgesia at the opioid level. It is not indicated for minor or chronic painful conditions. Ketorolac is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac is indicated, especially when the drug is used inappropriately. Increasing the dose beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Length of Authorization: Up to 12 months

Requires PA:

- Non-preferred NSAIDs
- Ketorolac: Maximum of one claim per 60 days. That claim can be a maximum of 20tablets/5 days, i.e. there is a 5 day maximum per 60 days.

Preferred Alternatives: Preferred alternatives listed at: http://www.orpdl.org/

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis covered by the Oregon Health Plan? All indications need to be evaluated as to whether they are above the line or below the line.	**Yes:** Go to #3	**No**: Pass to RPH; Deny, (Not covered by the OPH)
3. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	**Yes:** Document prior therapy in PA record. Go to #4	**No**: Go to #5
4. Is request for ketorolac greater than a 5 day supply within 60 days (200mg total over 5 days for tablets, 630mg total over 5 days for the nasal spray)?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness). Review FDA warnings	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message:	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.

• Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.		

P&T/DUR Action: 2/23/12 (TW). 9/24/09 (DO/KK), 2/23/06
Revision(s): 5/14/12, 1/1/10
Initiated: ?

Drug Class Review

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Preliminary Scan Report #2

May 2014

Last Report: Update #4 (November 2010)
Last Preliminary Scan: July 2013

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

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)

Date of Last Preliminary Update Scan Report

July 2013

Scope and Key Questions

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
2. Are there clinically important differences in short-term harms (< 6 months) between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
3. Are there clinically important differences in long-term harms (≥ 6 months) between NSAIDs, with or without antiulcer medication, when used chronically in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one

medication is more effective or associated with fewer harms?

Inclusion Criteria

Populations

Adults with:

- Chronic pain from osteoarthritis
- Rheumatoid arthritis
- Soft-tissue pain
- Back pain
- Ankylosing spondylitis

Interventions

- Oral drugs: celecoxib, diclofenac potassium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketoprofen extended release, ketoprofen sustained release, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen delayed release, naproxen sustained release, naproxen sodium, oxaprozin, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid, and tolmetin
- Topical drugs: diclofenac epolamine 1.3% topical patch, diclofenac sodium 1% topical gel, diclofenac sodium 1.5% topical solution, diclofenac sodium 3% topical gel, and topical diclofenac diethylamine 1.16%.

Comparisons

Celecoxib compared with NSAIDs
NSAIDs compared with NSAIDs

Outcomes

Effectiveness outcomes

- Pain
- Functional status
- Discontinuations due to lack of effectiveness.

Harms

- Serious gastrointestinal events (gastrointestinal bleeding, symptomatic ulcer disease, perforation of the gastrointestinal tract, and death)
- Serious cardiovascular events (myocardial infarction, angina, stroke, transient ischemic

attack, cardiovascular death, hypertension, congestive heart failure, and related measures)
- Tolerability and adverse event (discontinuation due to any adverse event; any serious adverse event; the overall rate of adverse events; the rate of gastrointestinal adverse events; the combined rate of adverse events related to renal and cardiovascular function, including increased creatinine, edema, hypertension, or congestive heart failure; and the frequency of, and discontinuations due to, abnormal laboratory tests—primarily elevated transaminases).

Timing

Inclusion of randomized controlled trials were limited to only those of at least 4 weeks' duration

Study Designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews
- For harms, controlled clinical trials, good-quality systematic reviews and observational studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2013 through May 13, 2014 using terms for included drugs and conditions. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm).

Study Selection

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

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

Pennsaid (diclofenac sodium 2% topical). Approved on 1/16/14 for the treatment of osteoarthritis of the knee.

New drugs identified in previous Preliminary Update Scan

Vimovo (naproxen and esomeprazole magnesium fixed-dose combination tablet): Approved on 4/30/10 to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis

New Indications

New indications identified in this Preliminary Update Scan

None.

New indications identified in previous Preliminary Update Scan

None.

New Safety Alerts

New Safety Alerts Identified in this Preliminary Update Scan

None.

New Safety Alerts Identified in previous Preliminary Update Scan

None.

Comparative Effectiveness Reviews

We identified two new comparative effectiveness reviews. The abstracts of these reviews are attached in Appendix A, and links to the full reports are listed below.

Reviews identified in this Preliminary Update Scan

From CADTH:

Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Safety. August 2013. http://www.cadth.ca/en/publication/3919

Reviews identified in previous Preliminary Update Scans

Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm
.

Randomized Controlled Trials Identified since the most recent Full Report

Medline searches for this scan resulted in 96 citations. Of those, there was only one new companion publication (shaded row in Table 1).

From the previous scan, there were six potentially relevant new randomized controlled trials and one new companion publication (Table 1).

Among the new randomized controlled trials, five involved head-to-head comparisons and one was placebo-controlled. Among the head-to-head trials, two involved the new naproxen/esomeprazole magnesium fixed-dose combination product, which has not been included in any previous full update DERP report.

The two companion publications pertained to the CONDOR trial (Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis), which we included in our DERP Update #4 report from November 2010.

Abstracts of all of these trials are attached in Appendix B.

Table 1. New potentially relevant randomized controlled trials

Author Year	Comparison	Focus
Head-to-head trials		
Cryer 2013 (GI-REASONS)	Celecoxib vs NSAIDs	Osteoarthritis
Essex 2012	Celecoxib vs naproxen	Knee osteoarthritis

Kellner 2012 *(companion to CONDOR, Chan 2010)*	Celecoxib vs diclofenac plus omeprazole	Subgroup analysis of elderly patients
Kellner 2013 *(companion to CONDOR, Chan 2010)*	Celecoxib vs diclofenac plus omeprazole	Improvement in arthritic signs and symptoms
Schmitt 1999	Diclofenac sodium dual release capsule vs standard release	Activated osteoarthritis
Cryer 2011/Hochberg 2011	Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib	Knee osteoarthritis
Goldstein 2010	Naproxen/esomeprazole magnesium fixed-dose combination tablet vs celecoxib vs naproxen alone	Patients with a history of ulcer
Placebo-controlled trials		
Baraf 2010	Diclofenac sodium topical gel 1% vs placebo	Knee osteoarthritis

Appendix A. Abstracts of potentially relevant new comparative effectiveness reviews of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

CADTH: Non-steroidal Anti-inflammatory Drugs for Pain: A Review of Saftey

Context
Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in pain management for clinical conditions such as headaches, menstrual disorders, post-operative pain, spinal and soft tissue pain, rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Technology
NSAIDs reduce pain by blocking cyclooxygenase (COX) enzymes needed to produce prostaglandin. There are two forms of the enzyme: COX-1 and COX-2. Traditional NSAIDs, called "non-selective NSAIDs," block both forms. NSAIDs that target only the COX-2 form are called "COX-2 selective NSAIDs" or "COX-2 inhibitors."

Celecoxib (Celebrex) is the only COX-2 inhibitor currently available in Canada.

Issue
Based on their mechanism of action, COX-2 inhibitors are thought to be safer than non-selective NSAIDs in terms of gastrointestinal (GI) bleeding. However, COX-2 inhibitors are associated with an increased risk of major cardiovascular events such as heart attacks and strokes. The COX-2 inhibitor rofecoxib (Vioxx) was removed from the Canadian market in 2004 for this reason. Generic versions of celecoxib will soon be available in Canada.

A review of the comparative safety of NSAIDs will help inform decisions on their use for the management of pain.

Methods
A limited literature search was conducted of key resources, and titles and abstracts of the retrieved publications were reviewed. Full-text publications were evaluated for final article selection according to predetermined selection criteria (population, intervention, comparator, outcomes, and study designs).

Key Messages

- The COX-2 inhibitor, celecoxib, appears to be associated with:
  - a cardiovascular risk similar to diclofenac and ibuprofen, and a higher risk than naproxen
  - a GI bleeding risk similar to diclofenac, and a lower risk than ibuprofen and naproxen.
- Among non-selective NSAIDs:
  - diclofenac may be associated with a higher cardiovascular risk than ibuprofen or naproxen

  - naproxen may be associated with a lower cardiovascular risk than diclofenac, ibuprofen, or indomethacin.
- Interpret these results with caution as:
  - study durations were short (generally less than three months)
  - studies used different NSAID doses.

Results
The literature search identified 275 citations, with an additional 8 articles identified from other sources. Of these, 13 were deemed potentially relevant and 6 met the criteria for inclusion in this review — 5 systematic reviews and 1 health technology assessment.

Abstracts for comparative reviews from previous update:

Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Comparative Effectiveness Review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ Publication No. 11(12)-EHC076-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Structured Abstract

Objectives:
To update a previous report on the comparative benefits and harms of oral non-steroidal anti-inflammatory drugs (NSAIDs) , acetaminophen, over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Data Sources:
Ovid MEDLINE (1996–January 2011), the Cochrane database (through fourth quarter 2010), and reference lists.

Review Methods:
We included randomized trials, cohort studies, case-control studies, and systematic reviews that met predefined inclusion criteria. For each study, investigators abstracted details about the study population, study design, data analysis, followup, and results, and they assessed quality using predefined criteria. We assessed the overall strength of each body of evidence using predefined criteria, which included the type and number of studies; risk of bias; consistency; and precision of estimates. Meta-analyses were not performed, though pooled estimates from previously published studies were reported.

Results:
A total of 273 studies were included. Overall, we found no clear differences in efficacy for pain relief associated with different NSAIDs. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI 0.07 to 0.76) compared to nonselective NSAIDs. Coprescribing of proton pump inhibitors, misoprostol, and H2-antagonists reduce the risk of endoscopically detected gastroduodenal ulcers compared to placebo in persons prescribed NSAIDs. Celecoxib

and most nonselective, nonaspirin NSAIDs appeared to be associated with an increased risk of serious cardiovascular (CV) harms. There was no clear association between longer duration of NSAID use or higher doses and increased risk of serious CV harms. There were no clear differences between glucosamine or chondroitin and oral NSAIDs for pain or function, though evidence from a systematic review of higher-quality trials suggests that glucosamine had some very small benefits over placebo for pain. Head-to-head trials showed no difference between topical and oral NSAIDs for efficacy in patients with localized osteoarthritis, lower risk of gastrointestinal (GI) adverse events, and higher risk of dermatological adverse events, but serious GI and CV harms were not evaluated. No head-to-head trials compared topical salicylates or capsaicin to oral NSAIDs.

Conclusions:
Each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. Choosing the optimal analgesic for an individual with osteoarthritis requires careful consideration and thorough discussion of the relevant tradeoffs.

Appendix B. Abstracts of potentially relevant new randomized controlled trials of Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Head-to-Head Trials

Cryer, B., C. Li, et al. (2013). "GI-REASONS: a novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial." American Journal of Gastroenterology **108**(3): 392-400.

OBJECTIVES: Because of the limitations of randomized controlled trials (RCTs) and observational studies, a prospective, randomized, open-label, blinded endpoint (PROBE) study may be an appropriate alternative, as the design allows the assessment of clinical outcomes in clinical practice settings. The Gastrointestinal (GI) Randomized Event and Safety Open-Label Nonsteroidal Anti-inflammatory Drug (NSAID) Study (GI-REASONS) was designed to reflect standard clinical practice while including endpoints rigorously evaluated by a blinded adjudication committee. The objective of this study was to assess if celecoxib is associated with a lower incidence of clinically significant upper and/or lower GI events than nonselective NSAIDs (nsNSAIDs) in standard clinical practice.

METHODS: This was a PROBE study carried out at 783 centers in the United States, where a total of 8,067 individuals aged >= 55 years, requiring daily NSAIDs to treat osteoarthritis, participated. The participants were randomized to celecoxib or nsNSAIDs (1:1) for 6 months and stratified by Helicobacter pylori status. Treatment doses could be adjusted as per the United States prescribing information; patients randomized to nsNSAIDs could switch between nsNSAIDs; crossover between treatment arms was not allowed, and patients requiring aspirin at baseline were excluded. The primary outcome was the incidence of clinically significant upper and/or lower GI events.

RESULTS: Significantly more nsNSAID users met the primary endpoint (2.4% (98/4,032) nsNSAID patients and 1.3% (54/4,035) celecoxib patients; odds ratio, 1.82 (95% confidence interval, 1.31-2.55); P = 0.0003). Moderate to severe abdominal symptoms were experienced by 94 (2.3%) celecoxib and 138 (3.4%) nsNSAID patients (P=0.0035). Other non-GI adverse events were similar between treatment groups. One limitation is the open-label design, which presents the possibility of interpretive bias.

CONCLUSIONS: Celecoxib was associated with a lower risk of clinically significant upper and/or lower GI events than nsNSAIDs. Furthermore, this trial represents a successful execution of a PROBE study, where therapeutic options and management strategies available in clinical practice were incorporated into the rigor of a prospective RCT.

Essex, M. N., P. Bhadra, et al. (2012). "Efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis of the knee: a randomized, double-blind, double-dummy trial." Journal of International Medical Research **40**(4): 1357-70.

OBJECTIVE: To assess the efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis (OA) of the knee.

METHODS: This 6-month, randomized, double-blind, double-dummy trial was conducted at 47 centres in the USA. Patients with OA of the knee were randomized to receive 200 mg

celecoxib orally once daily or 500 mg naproxen orally twice daily. The primary endpoint was defined as a 20% improvement from baseline to 6 months in Western Ontario and McMaster Universities (WOMAC) OA total score.

RESULTS: A total of 586 out of 589 randomized patients received at least one dose of celecoxib (n=294) or naproxen (n=292). The primary endpoint (6-month response rate) was achieved by 52.7% and 49.7% of patients in the celecoxib and naproxen treatment groups, respectively. Significantly fewer discontinuations due to gastrointestinal adverse events occurred in patients receiving celecoxib than in those receiving naproxen (4.1% versus 15.1%, respectively).

CONCLUSIONS: Over the 6month study period, celecoxib provided similar improvements in OA symptoms to naproxen. In addition, celecoxib provided better upper gastrointestinal tolerability than naproxen.

Kellner, H. L., C. Li, et al. (2012). "Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial." Current Medical Research & Opinion **28**(9): 1537-45.

OBJECTIVE: To compare the safety and efficacy of celecoxib versus diclofenac slow release (SR) plus omeprazole in elderly arthritis patients.

RESEARCH DESIGN AND METHODS: Patients aged>=65 years, with osteoarthritis and/or rheumatoid arthritis, at high gastrointestinal (GI) risk who participated in the CONDOR trial (Celecoxib vs. Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) were included in this subanalysis. CONDOR was a 6-month prospective, double-blind, randomized, parallel-group, multicenter, international study comparing treatment with celecoxib 200mg twice daily (BID) versus diclofenac SR 75mg BID plus omeprazole 20mg daily.

MAIN OUTCOME MEASURES: The primary end point was a composite of Clinically Significant Upper and Lower GI Events adjudicated by an independent blinded expert committee. Efficacy was determined by the Patient's Global Assessment of Arthritis.

RESULTS: A total of 2446 patients aged>=65 years were included in the intent-to-treat (ITT) population (n=1219 celecoxib; n=1227 diclofenac). Eight patients in the celecoxib group and 52 in the diclofenac group were adjudicated as having Clinically Significant Upper and Lower GI events (adjusted odds ratio: 6.27; p<0.0001). Clinically significant reductions in hemoglobin (>=2g/dL) and/or hematocrit (>=10%) were observed in 23 patients in the celecoxib group and in 76 in the diclofenac group (relative risk: 3.22 [95% confidence interval: 2.04-5.07]; p<0.0001). Incidence of moderate-to-severe abdominal symptoms and discontinuation of treatment due to GI adverse events (AEs) were lower in the celecoxib group. The Patient's Global Assessment of Arthritis score least squares mean change from baseline to final visit and percentage of patients rating treatment efficacy as good/very good at baseline and final visit were similar in both groups.

LIMITATIONS: The dose of celecoxib used is consistent with the European label for the management of osteoarthritis and may not reflect what is commonly prescribed in current clinical practice in the United States. The data were obtained in a clinical trial setting where patients were enrolled based on specific inclusion and exclusion criteria;

as such, the patients may not be broadly representative of the patient population in a general practice setting.

CONCLUSIONS: Efficacy was comparable in the two treatment groups. There were fewer endpoints as well as fewer GI AEs reported in patients treated with celecoxib compared with diclofenac. These data may help physicians in their treatment decisions for elderly patients with arthritis.

Kellner, H. L., C. Li, et al. (2013). "Celecoxib and Diclofenac Plus Omeprazole are Similarly Effective in the Treatment of Arthritis in Patients at High GI Risk in the CONDOR Trial." The open rheumatology journal **7**: 96-100.

OBJECTIVE: Compare effectiveness of celecoxib versus diclofenac plus omeprazole in improving arthritis signs and symptoms in patients at high gastrointestinal (GI) risk who were enrolled in the CONDOR (Celecoxib vs Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) trial.

METHODS: CONDOR was a 6-month, prospective, double-blind, triple-dummy, parallel-group, randomized, multicenter trial comparing celecoxib 200 mg twice daily versus diclofenac slow release (SR) 75 mg twice daily plus omeprazole 20 mg daily. Patients were Helicobacter pylori negative, had osteoarthritis (OA) or rheumatoid arthritis (RA), were aged >60 years, were with or without a history of gastroduodenal ulceration, or were >18 years with previous gastroduodenal ulceration. Patients' Global Assessment of Arthritis was determined at each study visit.

RESULTS: A total of 4484 patients were randomized to treatment (2238 celecoxib, 2246 diclofenac SR) and included in the intention-to-treat analyses. Least squares mean (LSM) (standard error [SE]) for Patients' Global Assessment of Arthritis was 3.219 (0.017) and 3.221 (0.017) at baseline for celecoxib and diclofenac SR (p=0.90). Improvement in both groups was similar in months 2, 4, and 6; at month 1 the LSM (SE) was 2.647 (0.017) and 2.586 (0.017) for celecoxib and diclofenac (p=0.0025). LSM difference (SE) from baseline to final visit demonstrated an improvement of 0.75 (0.02) in celecoxib-treated patients and 0.77 (0.02) in diclofenac SR-treated patients (p=0.42).

CONCLUSIONS: Celecoxib and diclofenac plus omeprazole were shown to have similar efficacy in patients with OA and/or RA at increased GI risk who were enrolled in the CONDOR trial.

TRIAL REGISTRY: Trial was registered under ClinicalTrials.gov identifier NCT00141102.

Schmitt, W., K. Walter, et al. (1999). "Clinical trial on the efficacy and safety of different diclofenac formulations: multiple-unit formulations compared to enteric coated tablets in patients with activated osteoarthritis." Inflammopharmacology **7**(4): 363-75.

This double-blind, randomised, multicentre study investigated the efficacy and safety of two different dosages of a diclofenac sodium dual release capsule (150 mg or 75 mg once daily) in comparison to a standard treatment with enteric coated tablets (50 mg t.i.d.) and placebo in patients with activated osteoarthritis. Pain relief as the main efficacy variable was measured through 24 hours by means of a Visual Analogue Scale at baseline and on five assessment days during the 12 weeks of treatment. Efficacy was

observed in all treatment groups with a statistically significant difference between the verum groups and placebo. The overall safety and tolerability of the active treatments was good. For the 75 mg group, a lower incidence of liver and biliary system-related side effects was reported. Considering efficacy, safety, and compliance aspects, the once daily administration of diclofenac sodium 75 mg dual release capsule is the appropriate dosage regimen for mid- and long-term treatment of osteoarthritis.

Cryer, B. L., M. B. Sostek, et al. (2011). "A fixed-dose combination of naproxen and esomeprazole magnesium has comparable upper gastrointestinal tolerability to celecoxib in patients with osteoarthritis of the knee: results from two randomized, parallel-group, placebo-controlled trials." Annals of Medicine **43**(8): 594-605.

BACKGROUND. Non-steroidal anti-inflammatory drugs are associated with poor upper gastrointestinal (UGI) tolerability and increased ulcer risk, but patient adherence to gastroprotective co-therapy is frequently inadequate. A fixed-dose combination of enteric-coated naproxen 500 mg and immediate-release esomeprazole magnesium 20 mg was evaluated: efficacy is reported by Hochberg et al. (Curr Med Res Opin 2011;27:1243-53); tolerability findings are reported here. PATIENTS AND METHODS. In two 12-week double-blind, placebo-controlled, multicenter, phase III studies (PN400-307 and PN400-309), patients aged >= 50 years with symptomatic knee osteoarthritis randomly (2:2:1) received naproxen/esomeprazole magnesium BID, celecoxib 200 mg QD, or placebo. Tolerability end-points included: modified Severity of Dyspepsia Assessment (mSODA); heartburn severity; and UGI adverse events (AEs). RESULTS. Overall, 619 (PN400-307) and 615 (PN400-309) patients were randomized; mSODA scores improved (baseline to week 12) in each group, with no significant treatment differences between naproxen/esomeprazole magnesium and celecoxib (95% CIs: PN400-307: -0.4, 1.9; PN400-309: -1.8, 0.6). Naproxen/esomeprazole magnesium-treated patients reported significantly more heartburn-free days versus celecoxib (95% CIs: PN400-307: 2.1, 12.7; PN400-309: 2.5, 13.4). UGI AE incidence (PN400-307: 17.3%; PN400-309: 20.3%) was similar between treatment groups. UGI AEs resulted in few discontinuations (< 4%, either study). CONCLUSIONS. Naproxen/esomeprazole magnesium has comparable UGI tolerability to celecoxib in patients with osteoarthritis.

Hochberg, M. C., J. G. Fort, et al. (2011). "Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials." Current Medical Research & Opinion **27**(6): 1243-53.

OBJECTIVE: To demonstrate that a fixed-dose combination of enteric-coated naproxen 500mg and immediate-release esomeprazole magnesium 20mg has comparable efficacy to celecoxib for knee osteoarthritis.

RESEARCH DESIGN AND METHODS: Two randomized, double-blind, parallel-group, placebo-controlled, multicenter phase III studies (PN400-307 and PN400-309) enrolled patients aged >=50 years with symptomatic knee osteoarthritis. Following an osteoarthritis flare, patients received naproxen/esomeprazole magnesium twice daily, celecoxib 200mg once daily, or placebo for 12 weeks.

CLINICAL TRIAL REGISTRATION: NCT00664560 and NCT00665431.

MAIN OUTCOME MEASURES: Three co-primary efficacy endpoints were mean change from baseline to week 12 in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain and function subscales, and Patient Global Assessment of osteoarthritis using a visual analog scale (PGA-VAS).

RESULTS: In Study 307, 619 patients were randomized and 614 treated. In Study 309, 615 patients were randomized and 610 treated. Both naproxen/esomeprazole magnesium and celecoxib were associated with improvements (least squares mean change from baseline to week 12) in WOMAC pain (Study 307: -42.0 and -41.8, respectively; Study 309: -44.2 and -42.9, respectively), WOMAC function (Study 307: -36.4 and -36.3, respectively; Study 309: -38.9 and -36.8, respectively), and PGA-VAS (Study 307: 21.2 and 21.6, respectively; Study 309: 29.0 and 25.6, respectively). A prespecified non-inferiority margin of 10mm between naproxen/esomeprazole magnesium and celecoxib was satisfied for each co-primary endpoint at week 12 in both studies. Significant improvements were observed with naproxen/esomeprazole magnesium versus placebo in both studies ($p<0.05$). Celecoxib was significantly different from placebo in Study 307 ($p<0.05$); however, the improvements were not significant in Study 309. Acetaminophen use and patient expectation of receiving active treatment (80% probability) may have contributed to a high placebo response observed.

CONCLUSIONS: Naproxen/esomeprazole magnesium has comparable efficacy to celecoxib for the management of pain associated with osteoarthritis of the knee over 12 weeks.

Goldstein, J. L., M. C. Hochberg, et al. (2010). "Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone." Alimentary Pharmacology & Therapeutics **32**(3): 401-13.

BACKGROUND: Gastroprotective co-therapy may reduce the risk of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, but adherence is suboptimal.

AIM: To compare the incidence of gastric ulcers with PN 400 [enteric-coated (EC) naproxen 500 mg and immediate-release esomeprazole 20 mg], or EC naproxen.

METHODS: Two randomized, double-blind, multicentre studies (PN400-301, PN400-302). Patients [stratified by low-dose aspirin (< or =325 mg) use] aged > or =50 years or 18-49 years with a history of ulcer, received PN 400 BID (301, n = 218; 302, n = 210) or EC naproxen 500 mg BID (301, n = 216; 302, n = 210) for 6 months. The primary endpoint was the cumulative incidence of endoscopic gastric ulcers.

RESULTS: The cumulative incidence of gastric ulcers was significantly lower with PN 400 vs. EC naproxen (301: 4.1% vs. 23.1%, $P < 0.001$; 302: 7.1% vs. 24.3%, $P < 0.001$). PN 400 was associated with a lower combined incidence of gastric ulcers vs. EC naproxen in low-dose aspirin users (n = 201) (3.0% vs. 28.4%, $P < 0.001$) and non-users (n = 653) (6.4% vs. 22.2%, $P < 0.001$). The incidence of, and discontinuations due to, upper gastrointestinal (UGI) AEs was significantly lower with PN 400 relative to EC naproxen ($P < 0.01$, both studies).

CONCLUSIONS: PN 400 significantly reduces the incidence of gastric ulcers, regardless of low-dose aspirin use, in at-risk patients, and is associated with improved UGI tolerability relative to EC naproxen (ClinicalTrials.gov, NCT00527782).

Placebo-Controlled Trials

Baraf, H. S., M. S. Gold, et al. (2010). "Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial." Physician & Sportsmedicine **38**(2): 19-28.

Background Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may provide an alternative to oral NSAIDs to relieve pain from osteoarthritis (OA), reducing systemic exposure. This 12-week, randomized, double-blind, parallel-group, multicenter trial examined the efficacy and safety of topical diclofenac sodium 1% gel (DSG) for symptomatic knee OA. Methods Eligible patients were aged >/= 35 years with symptomatic Kellgren-Lawrence grade (KLG) 1 to 3 OA in 1 or both knees for >/= 6 months. Patients meeting entry criteria applied DSG 4 g or vehicle 4 times daily to the symptomatic knee(s). Primary endpoints were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and global rating of benefit at week 12. Pain on movement at week 4 was an additional primary endpoint for European regulatory purposes. Secondary endpoints included primary outcomes at weeks 1, 4, and 8; WOMAC stiffness subscale; spontaneous pain; global rating of disease; and global evaluation of treatment. Subanalyses were performed according to KLG, the number of knees treated, and age. Results Four hundred twenty patients were randomly assigned to DSG (n = 208) or vehicle (n = 212). At week 12, DSG provided significantly greater reductions in WOMAC pain (52.6% vs 43.1%; P = 0.008) and physical function (49.7% vs 39.4%; P = 0.004) versus vehicle and provided significant improvements in most secondary endpoints. Treatment-related adverse events (AEs) were infrequent (DSG, 7.7%; vehicle, 4.2%), with application site dermatitis being the most common AE (DSG, 4.8%; vehicle, 0%). No treatment-related gastrointestinal or serious AEs occurred with DSG. Conclusion Topical DSG treatment provided effective pain relief and functional improvement of OA in 1 or both knees and was well tolerated, irrespective of disease severity or patient age.

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Month/Year of Review: November 2014
PDL Classes: Anti-anginals, Cardiovascular

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

Table 1. Current Status of PDL Class.[1]

Current Preferred Agents	Current Non-Preferred Agents
Nitrates	
Isosorbide dinitrate capsule (*Dilatrate-SR®*) Isosorbide dinitrate tablet (*generic*, Isordil Titradose®) Isosorbide mononitrate tablet (*generic*) Nitroglycerin capsule, extended release (*generic*, Nitro-Time®) Nitroglycerin patch, 24-hour transdermal (*generic*, Minitran®, Nitro-Dur®) Nitroglycerin tablet, sublingual (Nitrostat®)	Amyl nitrate solution, nasal inhalation (*generic*) Isosorbide dinitrate capsule, extended release (Dilatrate-SR®) Isosorbide dinitrate tablet, extended release (*generic*, IsoDitrate®) Isosorbide mononitrate tablet, extended release (*generic*, Imdur®) Nitroglycerin solution, translingual (*generic*, Nitrolingual®, NitroMist®) Nitroglycerin ointment, transdermal (Nitro-Bid®)
Cardiovascular Agent, Miscellaneous	
	Ranolazine ER tablet (*Ranexa®*)

Previous Conclusions:

- Most studies of short-acting nitrate treatment in unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI) have been small and uncontrolled. The rationale for NTG in UA/NSTEMI is extrapolated from pathophysiological principles and extensive, although uncontrolled, clinical observations. Recommendations from American College of Cardiology Foundation/American Heart Association (ACCF/AHA) in this setting have Class I recommendation as first line treatment, yet they only have evidence level C grading.
- The role for long acting nitrates is for patients with stable angina who cannot tolerate or are contraindicated to a beta-blocker or calcium channel blocker.
- The efficacy of isosorbide dinitrate and hydralazine is further recognized in clinical practice guidelines for the management of congestive heart failure.
- Available formulations differ in both onset and duration of action. There is insufficient evidence demonstrating differences in formulations.
- Headache, dizziness and hypotension are common side effects associated with nitrate use. Nitrate tolerance is a limitation of long term use and is dose and duration-dependent.

Previous Recommendations:

- Add nitrates to PDL
- Include a short acting nitrate for angina prevention and treatment. There is no clinical advantage of nitroglycerin spray over NTG sublingual.
- Include a long-acting nitrate for angina prophylaxis and treatment of angina and include isosorbide dinitrate ER for the management of heart failure.

- Further evaluate costs of various formulations for preference.

Conclusions and Recommendations:

- There is high quality evidence sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with stable ischemic heart disease.[3]
- There is high quality evidence long-acting nitrates are recommended for relief of symptoms when first-line therapy (i.e., beta-blockers or calcium channel blockers) is contraindicated or causes unacceptable side effects. Long-acting nitrates may also be used in combination with beta-blockers for symptom relief when initial treatment with beta-blockers is unsuccessful.[3,4]
- There is low quality evidence that ranolazine reduces weekly angina frequency compared to placebo (mean difference -0.687 episodes per week; 95% CI, -0.973 to -0.402).[2]
- There is insufficient evidence comparing ranolazine to nitrates at reducing angina frequency.[2]
- Available formulations for nitrate products differ in both onset and duration of action. There is insufficient evidence demonstrating clinical differences between formulations.
- Headache, dizziness and hypotension are common side effects associated with nitrate use. Nitrate tolerance is a limitation of continuous, around-the-clock use.
- No new evidence requires changes to the PDL at this time. Evaluate comparative costs in executive session.
- No further review or research needed.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) from 2012 through September 2014 assessing clinically meaningful outcomes (e.g., symptom relief, morbidity and mortality) of anti-anginal or nitrate therapy to active controls was performed. Placebo-controlled RCTs were excluded because anti-anginal or nitrate therapy are well established in medical literature and clinical practice. The search was limited to evaluation of patients with angina or heart failure and was conducted with limits to randomized controlled trials and for English. Studies evaluating intravenous nitrate therapy were excluded. Search terms included: angina; angina pectoris; stable angina; unstable angina; heart failure; nitroglycerin; nitrate; isosorbide dinitrate; isosorbide mononitrate; ranolazine. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs Drug Class Reviews, 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.

<u>New Systematic Reviews:</u>

A systematic review and meta-analysis was conducted to assess the effects of ranolazine on symptoms, electrocardiographic signs of ischemia and hemodynamic changes in patients with stable coronary artery disease.[2] Only trials randomly allocating patients prospectively to ranolazine or a control (placebo or active) were included in the analysis. However, only data evaluating symptom management is reviewed here. The study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Two independent reviewers screened articles for eligibility. Methodological quality of trials was assessed by Detsky method, scoring for method of randomization, blindness, adequate description of outcome and outcome assessment, inclusion/exclusion criteria, number of patients excluded and reasons, description of therapy in treatment and control groups and appropriateness of statistical analysis. The assumption of statistical homogeneity was tested by Q statistic and further quantified by I^2 statistics. Six trials enrolling 9223 patients with a median follow-up of 9 weeks were eligible for inclusion.

Prepared by Andrew Gibler, Pharm.D. Date: November 2014

All 6 trials were placebo-controlled and only 3 trials assessed weekly nitroglycerin consumption and weekly angina frequency.

Ranolazine reduced weekly angina frequency compared to placebo by a mean difference of -0.687 episodes per week (95% CI, -0.973 to -0.402; heterogeneity p=0.337; I^2=11.2%). In addition, ranolazine reduced weekly nitroglycerin consumption by a mean difference of -0.534 doses per week (95% CI, -0.789 to -0.280; heterogeneity p=0.186; I^2=37.7%). No important heterogeneity was identified between the 3 trials evaluating these outcomes.[2]

New Treatment Guidelines:

2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: Executive Summary: A Report from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (2012)[3]

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effects. Level A evidence is from data derived from multiple randomized, controlled trials or meta-analyses; Level B evidence is from data derived from a single randomized trial or nonrandomized studies; Level C evidence consists of consensus opinion, case studies or standard of care.

Beta-blockers are the initial anti-ischemic medications recommended for relief of angina symptoms in patients with stable ischemic heart disease (SIHD). Long-acting nitrates are indicated for relief of symptoms when beta-blockers are contraindicated or cause unacceptable side effects. In addition, long-acting nitrates are indicated in combination with beta-blockers for symptom relief when the initial treatment with beta-blockers is unsuccessful (*Class I Recommendation, Level of Evidence B*).

Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (*Class I Recommendation, Level of Evidence B*).

Ranolazine should only be considered as a substitute for beta-blockers for relief of symptoms in patients with SIHD if initial treatment with beta-blockers is contraindicated (*Class IIa Recommendation, Level of Evidence B*). Ranolazine in combination with beta-blockers should only be considered for relief of symptoms when initial treatment with beta-blockers is not successful (*Class IIa Recommendation Level of Evidence A*).

National Institute for Health and Care Excellence (NICE) Clinical Guideline for Management of Stable Angina (2012)[4]

NICE clinical guidelines are systematically-developed recommendations on how healthcare and other professionals should care for people with specific conditions in the national health system of England and Wales. Guidelines are developed by the National Clinical Guideline Center for Acute and Chronic Conditions and represent best available evidence. The recommendations in this guideline relate only to people with a diagnosis of stable angina.

Either a beta-blocker or a calcium channel blocker is recommended as first-line therapy of stable angina. Decision of which drug class to use is based on patient comorbidities, contraindications and patient preference. If the patient cannot tolerate agents from one drug class, it is recommended to switch to the other drug class. In addition, if patient symptoms persist, consider switching to the other drug class or using a combination of the two. It is not recommended

to offer other anti-anginal drugs other than from these two drug classes as first-line therapy in patients with stable angina.

If a patient cannot tolerate beta-blockers and calcium channel blockers, or both are contraindicated, monotherapy with either a long-acting nitrate or ranolazine is recommended. Alternatively, if patient symptoms persist on beta-blocker or calcium channel blocker monotherapy and the other option (calcium channel blocker or beta-blocker) is contraindicated or not tolerated, monotherapy with either a long-acting nitrate or ranolazine is recommended. Clinical decisions on which drug to use are based on patient comorbidities, contraindications and patient preference.

A third anti-anginal drug should only be considered in patients with persistent angina symptoms despite two anti-anginal drugs and the person is waiting for revascularization, or revascularization is not considered appropriate or acceptable.

Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines for the Management of Patients with Refractory Angina (2012)[5]

Refractory angina is a persistent, painful condition characterized by the presence of angina caused by coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty/percutaneous interventions, and coronary bypass surgery. This guideline included only systematic reviews, randomized controlled trials and quasi-experimental and pre-pose studies. Observational, retrospective and case studies did not meet inclusion criteria and are not considered in this guideline. Specific outcomes included chest pain, nitrate use, morbidity, quality-of-life, exercise tolerance and mortality.

Specific nitrates were not assessed in the guideline since one outcome evaluated in the guideline was the decreased use of nitrates. Ranolazine was evaluated, though it is not approved for refractory angina specifically. Robust RCTs focused on refractory angina are needed before ranolazine can be recommended as an anti-anginal agent in this population. Ranolazine may have benefit at reducing angina symptoms, particularly in patients who cannot tolerate standard anti-anginal agents that may suppress heart rate and blood pressure (*Weak Recommendation, Moderate-Quality Evidence*).

Allopurinol, another medication studied for angina, requires more robust RCTs focused on refractory angina (*Strong Recommendation, Low-Quality Evidence*).

New drugs:
None.

New Formulations/Indications:
None.

New FDA safety alerts:
None.

New Trials:

A total of 54 citations resulted from the initial Medline search. All citations were excluded because of either inappropriate study design or because clinically meaningful outcomes were not assessed as described previously in the methodology.

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Month/Year of Review: November 2014
PDL Classes: Diuretics, Cardiovascular

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

Table 1. Current Status of PDL Class.

Current Preferred Agents[1]	**Current Non-Preferred Agents**
Thiazide/Thiazide-like Diuretics	
Bendroflumethiazide tablet (*unavailable*)[2] Hydrochlorothiazide tablet, capsule or solution (*generic*, Microzide®) Indapamide tablet (*generic*)	Chlorothiazide (*generic*, Diuril®) Chlorthalidone (*generic*) Metolazone (*generic*, Zaroxolyn®)
Loop Diuretics	
Bumetanide tablet (*generic*) Furosemide tablet or solution (*generic*, Lasix®) Torsemide tablet (*generic*, Demadex®)	Ethacrynic Acid (Edecrin®)
Potassium-sparing Diuretics	
Amiloride/HCTZ tablet (*generic*) Spironolactone tablet (*generic*, Aldactone®) Spironolactone/HCTZ tablet (*generic*, Aldactizide®) Triamterene capsule (Dyrenium®) Triamterene/HCTZ capsule (*generic*, Maxzide®, Dyazide®)	Amiloride (*generic*) Eplerenone (*generic*, Inspra®)

Previous Recommendations and Conclusions:[3]

- Thiazide diuretics are recommended as first-line blood pressure lowering agents because they have shown to improve mortality and stroke.
- There is insufficient evidence demonstrating efficacy and safety differences among different thiazide diuretics.
- Loop diuretics lower blood pressure modestly but play a role in heart failure patients with reduced left ventricular ejection fraction (LVEF) who are symptomatic with fluid retention.
- There is insufficient evidence comparing efficacy and safety of different loop diuretics.
- Potassium sparing diuretics, specifically aldosterone antagonists, reduce heart failure hospitalization and decrease mortality in patients with LVEF less than 35%.
- There is insufficient evidence comparing efficacy and safety of spironolactone and eplerenone.
- Add loop, thiazide/thiazide-like and potassium sparing diuretics to PDL.
- Include aldosterone antagonists in PDL due to mortality benefit in select patients with heart failure.

Conclusions and Recommendations:

- High quality evidence suggests thiazide diuretics should continue to be recommended as a first-line option for hypertension due to benefit at reducing mortality and stroke.[6,7]
- Thiazide diuretics with high quality data include hydrochlorothiazide, chlorthalidone and indapamide.[4]

- There is insufficient evidence demonstrating efficacy and safety differences among different thiazide diuretics. Hydrochlorothiazide is the only thiazide diuretic with evidence of dose-dependent lowering of blood pressure.[4]
- There is high quality evidence loop diuretics provide short-term relief of fluid retention in symptomatic patients heart failure patients with preserved or reduced LVEF.[8,9] However, there is insufficient evidence to confirm long-term benefits of diuretics in patients with heart failure.[5]
- There is insufficient evidence comparing efficacy and safety differences among different loop diuretics.
- There is high quality evidence that aldosterone receptor antagonists (spironolactone or eplerenone), unless contraindicated, reduce morbidity and mortality when added to evidence-based heart failure therapy in patients with systolic heart failure and reduced LVEF.[8,9] There is insufficient evidence comparing spironolactone with eplerenone.
- There is moderate quality evidence that adding spironolactone to patients with systolic heart failure and preserved LVEF reduces hospitalizations; however, spironolactone does not yield any additional morbidity or mortality benefit.[9,10]
- Remove bendroflumethiazide from the PDL due to market unavailability[2] and limited data versus other thiazide diuretics.[4]
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) from 2012 through September 2014 comparing diuretics or diuretic combination therapy to placebo or active controls was performed. The search was limited to evaluation of patients with hypertension or heart failure and was conducted with limits to randomized controlled trials and for English. Search terms included: hypertension; heart failure; bendroflumethiazide; hydrochlorothiazide; indapamide; chlorothiazide; chlorthalidone; metolazone; bumetanide; furosemide; torsemide; ethacrynic acid; amiloride; spironolactone; triamterene; and eplerenone. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews for Hypertension:

No systematic reviews have been recently published assessing cardiovascular morbidity and mortality outcomes with diuretics.

A 2014 *Cochrane Review* assessed the dose-related effect on blood pressure with thiazide diuretics compared to placebo in patients with primary hypertension.[4] This review did not assess different thiazides in reducing mortality or cardiovascular morbidity. Double-blind, randomized, controlled trials comparing a fixed-dosed, 3- to 12-week regimen of thiazide diuretic monotherapy with placebo were included. Sixty trials assessing six different thiazide diuretics in 11,282 patients with a mean duration of 8 weeks were included in the review. The mean age was 55 years and mean baseline blood pressure was 158/99 mmHg. Adequate data were available for hydrochlorothiazide, chlorthalidone and indapamide. There was no evidence of dose-dependent lowering of blood pressure of any of the thiazide diuretics other than hydrochlorothiazide, which demonstrated moderate to high quality evidence. Overall, maximum lower of blood pressure was similar between thiazide diuretics, with a mean lowering of 9 mmHg/4 mmHg (95% CI, 9-10 mmHg/3-4 mmHg) versus placebo. Thiazide diuretics have demonstrated a greater effect on lowering systolic blood pressure compared to diastolic blood pressure, and lowers pulse pressure by 4 to 6 mmHg.

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Table 2. Comparative Mean Blood Pressure Lowering of Thiazide Diuretics.[4]

Hydrochlorothiazide Daily Dose *(33 trials)*	Mean SBP Lowering vs. Placebo	Mean DBP Lowering vs. Placebo
	Baseline Mean 150-100 mmHg	
6.25 mg	4 mmHg (95% CI, 2-6 mmHg)	2 mmHg (95% CI, 1-4 mmHg)
12.5 mg	6 mmHg (95% CI, 5-7 mmHg)	3 mmHg (95% CI, 3-4 mmHg)
25 mg	8 mmHg (95% CI, 7-9 mmHg)*	3 mmHg (95% CI, 3-4 mmHg)*
50 mg	11 mmHg (95% CI, 6-15 mmHg)**	5 mmHg (95% CI, 3-7 mmHg)**

Chlorthalidone Daily Dose *(7 trials)*	Mean SBP Lowering vs. Placebo	Mean DBP Lowering vs. Placebo
	Baseline Mean 163/88 mmHg	
12.5 – 75 mg	12 mmHg (95% CI, 10-14 mmHg)**	4 mmHg (95% CI, 3-5 mmHg)**

Indapamide Daily Dose *(10 trials)*	Mean SBP Lowering vs. Placebo	Mean DBP Lowering vs. Placebo
1 – 5 mg	9 mmHg (95% CI, 7-10 mmHg)**	4 mmHg (95% CI, 3-5 mmHg)**

*Judged to be high-quality evidence; **Judged to be low-quality evidence
Key: SBP = systolic blood pressure; DBP = diastolic blood pressure

The authors concluded that hydrochlorothiazide has a dose-related blood pressure-lowing effect. However, trials were short term and important clinical cardiovascular outcomes were not evaluated.

New Systematic Reviews for Heart Failure:

A 2012 *Cochrane Review* assessed the risks and benefits of diuretics for chronic heart failure.[5] Double-blind, randomized, controlled trials comparing one diuretic with placebo, or one diuretic with another active agent in patients with chronic heart failure were included in the review. Fourteen small trials lasting from 4 to 24 weeks were identified for inclusion (525 participants); half were placebo-controlled and half the trials actively compared a diuretic to another agent, such as an angiotensin converting enzyme inhibitor (ACE-I) or digoxin. Analysis of mortality was limited to three trials (202 participants), which was lower if patients received a diuretic versus placebo, with an odds ratio (OR) of 0.24; 95% confidence interval (CI), 0.07 – 0.83; p=0.02. According to the review, about 80 deaths may be avoided for every 1000 people treated with diuretics. Analysis of hospital admission for worsening heart failure was limited to two trials (169 participants), which was lower if patients received a diuretic versus placebo, OR 0.07; 95% CI 0.01 – 0.52; p=0.01. Diuretics also improved exercise capacity by 28% - 33% compared to active controls, difference in means WMD 0.72; 95% CI, 0.40 – 1.04; p<0.0001.

Evidence for diuretics in heart failure is limited to a few small trials of short duration for a chronic health condition. The methodological quality of the fourteen trials was found to be inconsistent as diuretic use was not standardized across the studies. According to the investigators, more research is needed to confirm long-term benefits of diuretics in patients with heart failure.[5]

New Hypertension Treatment Guidelines:

The Eighth Report of the Joint National Committee (JNC 8) (2014)[6]

Earlier this year, guidelines for the management of high blood pressure in adults were reported from the JNC8 panel. Quality of evidence was rated as High, Moderate or Low, depending on the limitations of the evidence. For example, a well designed randomized controlled trial or meta-analysis would be high quality evidence, but randomized controlled trials with major limitations or observational studies would be low quality evidence. Strength of the recommendation

was graded A (strong), B (moderate), C (weak), D (against recommending), E (opinion) or N (insufficient evidence for recommendation).

The JNC 8 retains thiazide-type diuretics as a first-line treatment option in all hypertensive adult patients *without* chronic kidney disease. Specifically for nonblack patients, first-line options include a thiazide-type diuretic, an ACE-I, an angiotensin receptor-blocker (ARB) or calcium channel blocker (CCB), alone or in combination (*Moderate Recommendation, Grade B*); for black patients, ACE-Is and ARBs are not first-line options (*Weak Recommendation, Grade C*). In all hypertensive adult patients *with* chronic kidney disease, regardless of race, an ACE-I or ARB, alone or in combination with other drug classes, is recommended as the first-line option (*Moderate Recommendation, Grade B*).

The guidelines reminds readers that drug selection, dose and titration schedule of the first-line therapy options are flexible in order to quickly achieve a goal blood pressure in any individual patient.

American Heart Association/American Stroke Association Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2014)[7]

Recommendations follow the American Heart Association (AHA) and the American College of Cardiology (ACC) methods of classifying the level of certainty of the treatment effect and the class of evidence. Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effects. Level A evidence is from data derived from multiple randomized, controlled trials or meta-analyses; Level B evidence is from data derived from a single randomized trial or nonrandomized studies; Level C evidence consists of consensus opinion, case studies or standard of care.

Diuretics, or diuretics in combination with an ACE-I, are the only specific regimens recommended in this guideline for secondary prevention of stroke or transient ischemic attack based on clinical evidence for efficacy in this population (*Class I Recommendation, Level of Evidence A*). However, the choice of specific drugs utilized should be individualized based on drug pharmacology and specific patient characteristics and indications (e.g., renal impairment, cardiac disease, diabetes mellitus, etc.).

New Heart Failure Treatment Guidelines:

2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation and the American Heart Association Task Force on Practice Guidelines (2013)[8]

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. Grading of evidence is the same as AHA/ASA guideline detailed previously.

Oral diuretics are recommended for patients with heart failure with either preserved or reduced ejection fraction and evidence of fluid retention to improve symptoms (*Class I Recommendation, Level of Evidence C*). Oral diuretics recommended for use in the treatment of symptomatic chronic heart failure are illustrated in the table extracted from the guidelines below.

Table 3. Recommended Doses of Oral Diuretics for Symptomatic Heart Failure.[8]

Drug	Initial Daily Dose	Maximum Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5 to 1 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 mg once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-sparing diuretics*			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg	1 to 3 hours
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential nephron blockade			
Metolazone	2.5 to 10 mg once with loop diuretic	N/A	N/A
Hydrochlorothiazide	25 to 100 mg once or twice with loop diuretic	N/A	N/A

*Eplerenone is a potassium-sparing diuretic but is primarily used for its aldosterone receptor antagonist properties in chronic heart failure without symptoms.

Though not technically diuretics, spironolactone and eplerenone block receptors that bind aldosterone, and are more appropriately described as mineralocorticoid receptor antagonists (MRAs). Both of these agents are recommended to decrease morbidity and mortality in patients with NYHA class II-IV heart failure who have a LVEF of 35% or less. Patients with NYHA class II heart failure should have a history of prior cardiovascular hospitalization or elevated brain natriuretic peptide (BNP) levels to be considered for this therapy. These agents should not be initiated in patients with an estimated glomerular filtration rate of 30 mL/min or less, nor should they be initiated in patients with serum potassium higher than 5.0 mEq/L due to risk of hyperkalemia (*Class I Recommendation, Level of Evidence A*).

The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute on Chronic Heart Failure (2013)[9]

The Canadian Cardiovascular Society recommendations follow the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The GRADE system classifies the quality of evidence as High (further research very unlikely to change confidence in the estimate of effect), Moderate (further research likely to have an important impact on confidence in the estimate of effect and may change the estimate), Low (further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate), and Very Low (estimate of effect very uncertain). The GRADE system offers 2 grades of recommendation: “Strong” (desirable effects clearly outweigh undesirable effect or clearly do not) and “Weak”.

Diuretics are recommended to control symptoms from pulmonary congestion and peripheral edema (*Strong Recommendation, High-Quality Evidence*). A loop diuretic is particularly recommended for patients with symptomatic heart failure and the guideline recommends reducing the dose of the diuretic to the lowest dose effective at stabilizing signs and symptoms of the disease (*Strong Recommendation, Low-Quality Evidence*). A second diuretic, such as a thiazide or metolazone, is recommended for patients with persistent volume overload despite optimal medical therapy and increasing doses of the loop diuretic, as long as it is possible to monitor morning weight, renal function and serum potassium (*Weak Recommendation, Moderate-Quality Evidence*).

Eplerenone is recommended in addition to standard heart failure therapy for patients older than 55 years with mild to moderate heart failure and reduced LVEF of 30% or less and recent cardiovascular hospitalization (within 6 months) or elevated BNP (*Strong Recommendation, High-Quality Evidence*).

Spironolactone is recommended in addition to standard heart failure therapy in patients with severe heart failure (NYHA class IIIb-IV) and reduced LVEF below 30% (*Strong Recommendation, High-Quality Evidence*).

European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2012)[10]

The level of evidence and the strength of recommendation set by the European Society of Cardiology is weighed and graded according to pre-defined scales. The COR is an estimate of the size of the treatment effect, with consideration given to risks versus benefits. The LOE is an estimate of the certainty or precision of the treatment effects. Level A evidence is from data derived from multiple randomized, controlled trials or meta-analyses; Level B evidence is from data derived from a single randomized trial or nonrandomized studies; Level C evidence consists of consensus opinion, case studies or standard of care.

The guideline does not differentiate between spironolactone and eplerenone in its recommendations, as any subtle differences between the populations studied or pharmacology with each agent are not considered clinically significant. The guideline therefore recommends an MRA for all patients with persistent heart failure symptoms (NYHA class II-IV) and an LVEF of 35% or less, despite treatment with an ACE-I or ARB and a beta-blocker to reduce the risk of heart failure hospitalization and the risk of premature death in these patients (*Class I Recommendation, Level of Evidence A*).

Data from the Randomized Aldactone Evaluation Study (RALES)[11] published in 1999 and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[12] trial published in 2011 largely drove this recommendation. In RALES (n=1663), spironolactone decreased both mortality and heart failure hospitalizations in patients with NYHA class III heart failure and reduced LVEF. In EMPHASIS-HF (n=2737), eplerenone had similar results in patients with NYHA class II heart failure and reduced LVEF.

New drugs:
None.

New Formulations/Indications:
None.

New FDA safety alerts:
None.

New Trials:

A total of 178 citations resulted from the initial Medline search. The majority of articles were excluded due to the inappropriate study design (observational, retrospective) or if clinically meaningful outcomes such as cardiovascular morbidity or mortality were not assessed. The remaining 2 RCTs evaluating morbidity or mortality outcomes are briefly described below.

Pitt, et al.[13] conducted a randomized, multi-centered, double-blind, placebo-controlled trial that evaluated spironolactone using a composite endpoint of death from cardiovascular causes, aborted cardiac arrest or hospitalization for the management of heart failure in 3445 participants with heart failure with preserved ejection fraction. The study was supported by a grant from the National Heart, Lung, and Blood Institute, National Institutes of

Health. Eligible patients were at least 50 years of age with at least one symptom of heart failure, preserved LVEF, with controlled systolic blood pressure and normal serum potassium levels. In addition, eligible patients had to have been hospitalized in the last 12 months secondary to heart failure or had to have an elevated BNP level at least 100 pg/mL or greater or an N-terminal pro-BNP level at least 360 pg/mL or greater in the 60 days before randomization. Randomization occurred with the use of permuted blocks and was stratified according to whether the patient met the criterion for previous hospitalization or elevated BNP. Spironolactone was initiated at 15 mg daily and increased to a maximum of 45 mg daily. Participants continued to receive treatment for heart failure and other coexisting illnesses throughout the trial. Baseline characteristics were similar between the spironolactone and placebo group but information regarding concurrent treatment for cardiovascular conditions, including heart failure, was missing. Mean follow-up was 3.3 years in each group and attrition rates were similar. The primary outcome occurred in 320 patients (18.6%) in the spironolactone group and 351 patients (20.4%) in the placebo group, with a hazard ratio (HR) of 0.89 (95% CI, 0.77 to 1.04; p=0.14). Of the components making up the composite outcome, only hospitalization for heart failure was statistically improved for spironolactone (12.0% vs. 14.2%, HR 0.83; 95% CI, 0.69 to 0.99; p=0.04). In addition, treatment with spironolactone was associated with increased serum creatinine levels and double the rate of hyperkalemia compared to the placebo group (18.7% vs. 9.1%). The investigators concluded that adding spironolactone to existing therapy in patients with heart failure and preserved ejection fraction does not significantly reduce the incidence of the primary outcome studied.

Vizzardi, et al.[14] conducted a small randomized, single-blind, placebo-controlled, single-centered trial evaluating the effect of spironolactone in patients with heart failure and mild to no symptoms (NYHA functional classes I-II) on cardiovascular mortality and hospitalizations. Eligible patients had heart failure with a LVEF less than 40% and no history of acute decompensation (NYHA class III or IV) in the previous year and were treated with an ACE-I or ARB, and a beta-blocker, unless contraindicated. Notable exclusion criteria included a estimated glomerular filtration rate (eGFR) less than 30 mL/min per $1.73m^2$; serum potassium greater than 5 mEq/L; and recent unstable angina, acute myocardial infarction or coronary revascularization procedure. After a 4-week run-in phase, participants were randomized to spironolactone 25 mg once daily or placebo. Spironolactone was titrated to 50 mg once daily at 4 weeks if serum potassium was not greater than 5 mEq/L and eGFR was at least 50 mL/min per 1.73^2. Mean duration of follow-up was 44 months in a total of 130 participants (65 in the spironolactone group and 65 in the placebo group). The primary composite outcome of cardiovascular death or cardiovascular hospitalization occurred in 13.5% of patients receiving spironolactone and 43% of patients receiving placebo, with a HR of 0.37 (95% CI, 0.1856 to 0.7184; p=0.0035). However, there was not a significant difference in cardiovascular death as the composite outcome results were influenced by cardiovascular hospitalizations, which occurred in 9.2% of patients receiving spironolactone and 36.9% of patients receiving placebo, with a HR of 0.29 (95% CI, 0.1385 to 0.6147; p=0.0012). In addition, all-cause mortality was equal between the groups (12.3% in each arm). Six patients had a serum potassium greater than 5.5 mEq/L in the spironolactone group (9.2%) and 1 patient (1.5%) in the placebo group.

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