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, March 23, 2017 1:00 - 5:00 PM
Barbara Roberts Human Services Building, HSB 137 A-D
500 Summer St. NE
Salem, OR 97301

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	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	B. Origer (Chair)
	D. Department Update	D. Weston (OHA)
1:10 PM	II. Health Evidence Review Commission (HERC) Update	D. Coffman (HERC)
1:30 PM	III. DUR ACTIVITIES	
	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (HPE)
	C. RetroDUR Report	R. Citron (OSU)
	D. Oregon State Drug Reviews	K. Sentena (OSU)
	1. Guideline and Policy Updates for Use of Opioids for Non-Cancer Pain and Opioid Use Disorder	
	2. Treatment of Gout	
	IV. PREFERRED DRUG LIST NEW BUSINESS	
1:50 PM	A. Hepatitis B Class Update	M. Smith (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

2:05 PM	B. Non-analgesics for Pain Review 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:20 PM	C. Skeletal Muscle Relaxants Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Vo (OSU)
2:30 PM	D. Tramadol Drug Review 1. Evidence Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2: 45 PM	E. Sedatives Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid(OSU)
3:00 PM	BREAK	
3:10 PM	F. Ophthalmic VEGF Inhibitor Class Update 1. Class Update/Prior Authorization 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:25 PM	G. Tetracycline Antibiotics Class Update 1. Class Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
3:35 PM	H. Abbreviated Drug Reviews 1. Cholbam® (cholic acid) 2. Exondys 51™ (etiplirsen) 3. Spinraza™ (nusinersen) 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	S. Servid (OSU) D. Moretz (OSU)
4:00 PM	V. DUR NEW BUSINESS	
	A. Pediatric Antipsychotic Metabolic Monitoring 1. Policy Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)

4:10 PM VI. EXECUTIVE SESSION

4:40 PM VII. RECONVENE for PUBLIC RECOMMENDATIONS

5:00 PM VIII. ADJOURN

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

Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2019
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 26, 2017, 1:00-5:00 PM
Human Services Building
Salem, OR 97301

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: Bill Origer, MD; Rich Clark, MD, MPH; Walter Hardin, D.O., MBA; Phil Levine, PhD; Caryn Mickelson, PharmD

Members Present by Phone: Tracy Klein, PhD, FNP; Dave Pass, MD; Kelly Burnett, DO; Stacy Ramirez, PharmD

Staff Present: Andrew Gibler, PharmD; Kathy Sentena PharmD; Richard Holsapple, RPh; Roger Citron, RPh; Dee Weston; Sarah Servid, PharmD; Kim Wentz, MD; Deanna Moretz, PharmD, BCPS; Lindsay Newton;

Staff Present by Phone:

Audience: *Deb Profant/Alkermes; Joe Schreck/Allergan; *Martin Klos/MD; *Curtis Sianchuk/Intercept; *Rajesh Patel/Intercept; Georjette Dawilewski/Indivior; *Harish Thiagaraj/Rph; KJ Jackson/Trividia Health; *Margaret Olmon/AbbVie; *Tim Murphy/Bridgeway Recovery Services; *Eric Geisler MD/Serenity Lane Treatment Center; Lisa Boyle/ WVP Health Authority; Melissa Smith/OSU; Jennifer Srec/Medimpact; Dean Hayley/OSU; Jeana Colabianchi/Sunovion; Kerry Kostman Bonilla; *Alex Cuyler/Lane County

(*) Provided verbal testimony

Written testimony provided:

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:01 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.

C. Election of chair and vice chair for 2017. Bill Origer was nominated as chair and Tracy Klein was nominated as vice chair.

ACTION: Motion to approve proposal, 2nd. All in favor. Approved.

D. Approval of agenda and November minutes presented by Mr. Citron. (pages 5 - 9)

ACTION: Motion to approve, 2nd, All in Favor.

E. Department updates for OHA presented by Ms. Weston.

II. DUR ACTIVITIES

A. Buprenorphine and Vivitrol Drug Policies (pages 10-14) – presented by Dr. Gibler
   1. Remove PA for Suboxone (buprenorphine/naloxone) sublingual tablets unless average daily dosage exceeds 24 mg of buprenorphine
   2. Remove pharmacy lock-in requirement since prescribers are asked to routinely check the Oregon Prescription Drug Monitoring Program (PDMP)
   3. Remove PA for Vivitrol ® (naltrexone ER injection) and add the agent to the PDL

ACTION: Motion to approve proposal, 2nd. 8 in favor, 1 opposed. Approved.

B. Oral Multiple Sclerosis Drug Policy (pages 15-17) – presented by Dr. Gibler
   1. Deny use of an oral MS agent if no form of relapsing multiple sclerosis is present.

ACTION: Motion to approve proposal, 2nd. All in favor. Approved.

III. PREFERRED DRUG LIST NEW BUSINESS

A. Gout Drugs Class Update (pages 18 - 32)
Dr. Sentena presented the class update and following recommendation:

   1. Continue preferred status for allopurinol on the PDL.
   2. Approve clinical PA criteria for non-preferred drugs as presented with the addition of question 8 added back in.

ACTION: Motion to approve, 2nd. All in favor. Approved.

B. Conventional Antiemetics Class Review (pages 33 - 61)
Dr. Moretz presented the class update and the following recommendation:

   1. Add conventional antiemetics to the OHP FFS PMPDP.

2. Designate scopolamine, dimenhydrinate, and meclizine as non-preferred since these drugs are primarily prescribed for nonfunded conditions.
3. Consolidate the current clinical PA criteria for newer antiemetics and dronabinol into one policy which requires approval by the Committee. Move question #11 to the #2 spot. Non-preferred conventional anitemetics will also be subject to this PA.

ACTION: Motion to approve, 2nd. All in favor. Approved.

C. Hormone Replacement Therapy Class Update (pages 62 - 97)
Dr. Servid presented the scan and following recommendation:

1. Combine progestin agents into one PDL class and designate at least one preferred product for FDA-approved indications funded by the OHP (i.e., endometriosis, endometrial cancer, endometrial hyperplasia, abnormal bleeding disorders, and prevention of preterm birth) based utilization and comparative drug costs in the executive session.
2. Restrict non-funded use of ospemifene by PA.
3. Update clinical PA criteria for hydroxyprogesterone caproate that will apply to both branded and generic products and apply to pharmacy and physician-administered claims.

ACTION: Motion to approve, 2nd. All in favor. Approved.

D. Antidiarrheals Class Review (pages 98 - 110)
Dr. Moretz presented the class update and the following recommendations:

1. Add antidiarrheal medication class to the OHP FFS PMPDP and designate all drugs except Loperamide as non-preferred to restrict use to only funded conditions.
2. Add quantity limits to loperamide, diphenoxylate/atropine, and crofelemer to insure safe and appropriate use:
    a. Loperamide=maximum 16 mg per 24 hours
    b. Diphenoxylate/atropine=maximum 20 mg/0.2 mg per 24 hours
    c. Crofelemer=maximum 500 mg per 24 hours

ACTION: Motion to approve, 2nd. All in favor. Approved.

E. Vitamin D Analogs Class Review (pages 111-125)
Dr. Sentena presented the following class update and recommendations:

1. Add Vitamin D analogs to the OHP FFS PMPDP.
2. Continue to keep calcitriol as the only preferred vitamin D analog and designate paricalcitol, doxercalciferol and calcifediol non-preferred.

ACTION: Motion to approve, 2nd. All in favor. Approved.

F. Ocaliva® (obeticholic acid) New Drug Evaluation (pages 126-139)

Dr. Servid presented the class update along with the following recommendations:

1. Incorporate STC 05 Bile Therapy drugs (obeticholic acid, ursodiol, cholic acid) into one PDL class.
2. Designate ursodiol as a preferred agent and obeticholic acid as a non-preferred agent. No other recommendations for other bile therapy medications will be made at this time.
3. Approve proposed clinical PA criteria as amended below* for all non-preferred drugs which restricts use of obeticholic acid to populations that may benefit from this from this therapy without undue harm.

*In the PA for obeticholic acid, re-phrase wording for #4 to ask if patient has no evidence of complications from cirrhosis or hepatic decompensation; re-phrase wording for #5 to ask if the total bilirubin level is less than 2-times the upper limit of normal. Deny claim if either criteria is not met.

ACTION: Motion to approve as amended, 2nd. All in favor. Approved.

G. Adlyxin® (lixisenatide) New Drug Evaluation (pages 152-163)
Dr. Sentena presented the class update along with the following recommendation:

1. Designate lixisenatide non-preferred and subject to current prior authorization (PA) criteria for GLP-1 receptor agonists.

ACTION: Motion to approve, 2nd. All in favor. Approved.

H. Zinbryta™ (daclizumab) New Drug Evaluation (pages 164-179)
Dr. Moretz presented the class update along with the following recommendations:

1. Designate daclizumab as non-preferred and approve proposed clinical PA criteria which limit use to:
    a. Adult patients with relapsing MS; and
    b. Without hepatic disease; and
    c. Higher degree of ambulatory ability (EDSS≤5); and
    d. History of inadequate response to at least 2 disease modifying agents approved for MS; and
    e. Prescribed by a neurologist.

ACTION: Motion to approve, 2nd. All in favor. Approved.

I. Nuplazid™ (pimavanserin) New Drug Evaluation (pages 180-191)
Dr. Servid presented the class update along with the following recommendation:

1. Approve proposed safety edit to restrict use of the drug to populations that may benefit without undue harm.

ACTION: Motion to approve, 2nd. All in favor. Approved.

J. Xiidra™ (lifitegrast) New Drug Evaluation (pages 192-202)

Dr. Sentena presented the class update along with the following recommendation:

1. Restrict non-funded use of lifitegrast ophthalmic solution by PA.

ACTION: Motion to approve, 2nd. All in favor. Approved.

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Gout Drugs Class Update (pages 18 - 32)
*__ACTION:__ No changes to the PDL.
Motion, 2nd, All in Favor. Approved.

B. Conventional Antiemetics Class Review (pages 33 - 61)
*__ACTION:__ Make dronabinol and nabilone non-preferred, subject to approved clinical PA criteria. Make metoclopramide rapid dissolving tablets non-preferred. Make trimethobenzamide non-preferred. Make promethazine and prochlorperazine tablets, syrups and rectal suppositories, metoclopramide tablets and oral solutions and phosphoric acid/ dextrose/fructose preferred on the PDL.
Motion, 2nd, All in Favor. Approved

C. Hormone Replacement Therapy Class Update (pages 62 - 97)
*__ACTION:__ No PDL changes to the estrogen classes recommended. Make medroxyprogesterone acetate tablets, micronized progesterone capsules, norethindrone acetate tablets, and Depo-Provera injection preferred on the PDL. Keep Makena (hydroxyporgesterone caproate) preferred andmake all other progestins non-preferred.
Motion, 2nd, All in Favor. Approved

VII. ADJOURN

Drug Use Research & Management Program
DHS - Health Systems Division
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Pharmacy Utilization Summary Report: July 2015 - June 2016

Eligibility	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Total Members (FFS & Encounter)	1,030,099	1,053,977	1,051,180	1,055,600	1,018,999	1,033,098	1,045,449	1,066,593	1,076,454	1,058,671	1,045,530	1,034,285	1,047,495
FFS Members	135,197	145,013	138,135	143,529	146,793	125,393	132,175	136,513	132,588	150,635	144,444	140,048	139,205
OHP Basic with Medicare	30,262	30,466	30,646	30,825	30,889	30,968	31,349	31,408	31,594	31,864	32,133	32,393	31,233
OHP Basic without Medicare	15,354	14,992	14,714	14,234	14,190	13,045	13,175	12,913	13,091	13,272	13,285	13,242	13,792
ACA	89,581	99,555	92,775	98,470	101,714	81,380	87,651	92,192	87,903	105,499	99,026	94,413	94,180
Encounter Members	894,902	908,964	913,045	912,071	872,206	907,705	913,274	930,080	943,866	908,036	901,086	894,237	908,289
OHP Basic with Medicare	39,574	39,754	39,815	40,037	39,946	39,951	39,907	40,356	40,276	39,984	39,968	40,100	39,972
OHP Basic without Medicare	92,850	90,593	85,877	84,019	73,277	73,440	72,813	72,503	71,622	70,953	70,303	69,870	77,343
ACA	762,478	778,617	787,353	788,015	758,983	794,314	800,554	817,221	831,968	797,099	790,815	784,267	790,974

Gross Cost Figures for Drugs	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	YTD Sum
Total Amount Paid (FFS & Encounter)	$66,100,962	$65,000,405	$65,498,852	$66,447,679	$63,711,667	$69,368,732	$68,631,424	$70,170,364	$75,736,236	$68,959,844	$68,893,955	$70,023,390	$818,543,510
Mental Health Carve-Out Drugs	$10,821,027	$10,677,035	$10,763,436	$10,911,014	$10,466,317	$11,529,032	$11,124,100	$11,457,685	$10,391,160	$8,266,844	$8,416,470	$8,375,169	$123,199,289
OHP Basic with Medicare	$11,082	$8,812	$3,611	$1,048	$778	$1,762	$1,137	$427	$367	$639	$737	$407	$30,807
OHP Basic without Medicare	$5,067,438	$4,866,542	$4,830,935	$4,857,822	$4,678,572	$5,196,184	$4,792,656	$4,967,194	$4,383,889	$3,409,644	$3,476,587	$3,510,152	$54,037,614
ACA	$5,723,225	$5,779,473	$5,899,623	$6,013,231	$5,729,953	$6,265,953	$6,256,596	$6,416,324	$5,943,452	$4,804,311	$4,880,108	$4,809,173	$68,521,422
FFS Physical Health Drugs	$3,479,545	$3,033,957	$3,217,262	$3,299,096	$3,258,164	$3,004,259	$3,188,808	$3,394,439	$3,605,620	$3,527,006	$3,302,539	$3,559,628	$39,870,323
OHP Basic with Medicare	$263,038	$225,706	$218,199	$212,525	$207,563	$211,099	$217,533	$219,605	$231,120	$195,139	$210,329	$210,609	$2,622,465
OHP Basic without Medicare	$991,645	$989,033	$953,819	$1,045,522	$996,771	$900,139	$960,220	$991,151	$1,032,108	$961,941	$959,894	$998,914	$11,781,155
ACA	$2,163,064	$1,757,647	$1,966,526	$1,949,300	$1,976,591	$1,797,537	$1,911,995	$2,068,293	$2,238,121	$2,292,129	$2,047,950	$2,252,999	$24,422,153
FFS Physician Administered Drugs	$1,599,208	$1,584,890	$1,470,317	$1,477,271	$1,299,907	$1,325,372	$1,367,090	$1,339,305	$1,436,903	$1,417,227	$1,556,176	$1,789,652	$17,663,318
OHP Basic with Medicare	$282,746	$273,243	$276,877	$270,912	$243,594	$316,105	$304,997	$327,671	$385,681	$386,316	$277,965	$358,485	$3,704,591
OHP Basic without Medicare	$244,257	$312,171	$280,485	$240,283	$216,877	$286,929	$261,443	$299,668	$302,578	$203,165	$314,216	$251,491	$3,213,562
ACA	$865,415	$776,570	$699,925	$771,655	$579,491	$526,759	$557,447	$484,693	$528,809	$619,263	$751,403	$886,322	$8,047,753
Encounter Physical Health Drugs	$42,238,192	$42,169,417	$42,600,239	$43,728,089	$41,861,448	$45,949,060	$44,629,754	$45,727,123	$50,860,909	$47,572,513	$47,223,411	$48,030,363	$542,590,518
OHP Basic with Medicare	$202,208	$212,016	$145,132	$152,195	$141,102	$138,151	$124,557	$130,781	$135,730	$133,874	$131,517	$126,542	$1,773,804
OHP Basic without Medicare	$12,298,160	$12,032,897	$11,814,537	$12,091,542	$11,381,465	$12,435,204	$12,054,810	$12,203,335	$13,579,444	$12,646,136	$12,432,887	$12,604,017	$147,574,436
ACA	$29,602,270	$29,790,616	$30,477,074	$31,278,075	$30,055,920	$33,051,458	$32,062,127	$33,016,919	$36,694,114	$34,340,590	$34,191,509	$34,836,452	$389,397,125
Encounter Physician Administered Drugs	$7,962,990	$7,535,107	$7,447,597	$7,032,209	$6,825,831	$7,561,009	$8,321,672	$8,251,812	$9,441,645	$8,176,253	$8,395,360	$8,268,577	$95,220,062
OHP Basic with Medicare	$162,748	$124,937	$169,114	$121,616	$90,054	$138,295	$232,707	$214,283	$186,811	$177,808	$220,985	$197,120	$2,036,476
OHP Basic without Medicare	$2,349,169	$1,972,732	$1,870,932	$1,868,250	$1,857,513	$1,907,602	$1,894,497	$2,149,814	$2,297,988	$1,856,165	$1,945,303	$1,966,537	$23,936,502
ACA	$5,321,143	$5,358,223	$5,312,919	$4,952,467	$4,753,805	$5,418,430	$6,000,044	$5,722,146	$6,779,683	$5,941,810	$6,102,411	$5,987,261	$67,650,342

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last Updated: January 18, 2017

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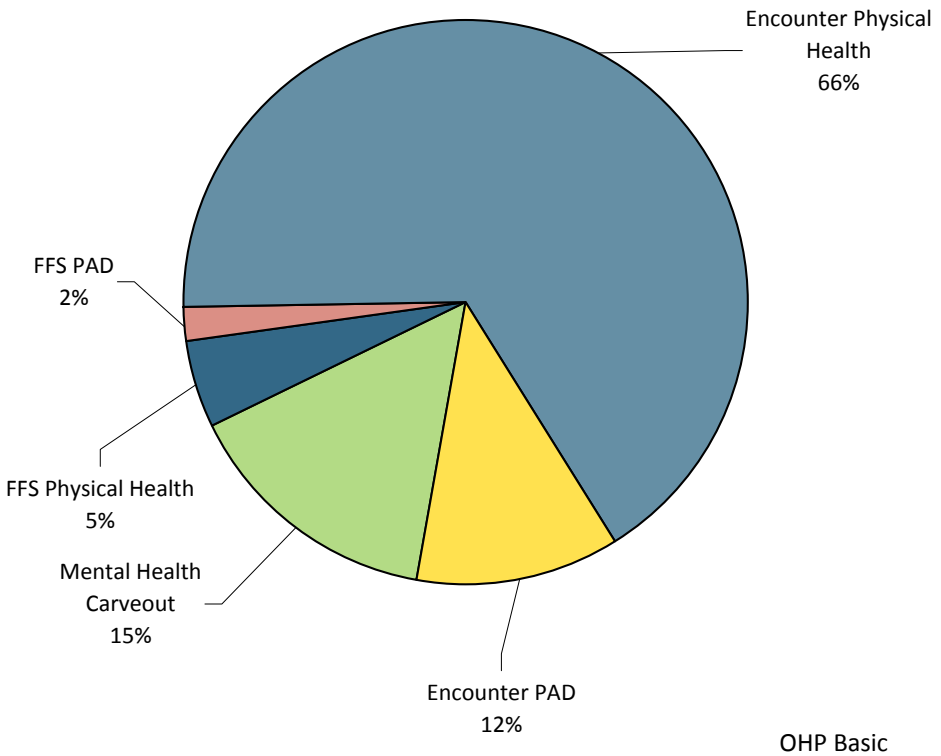
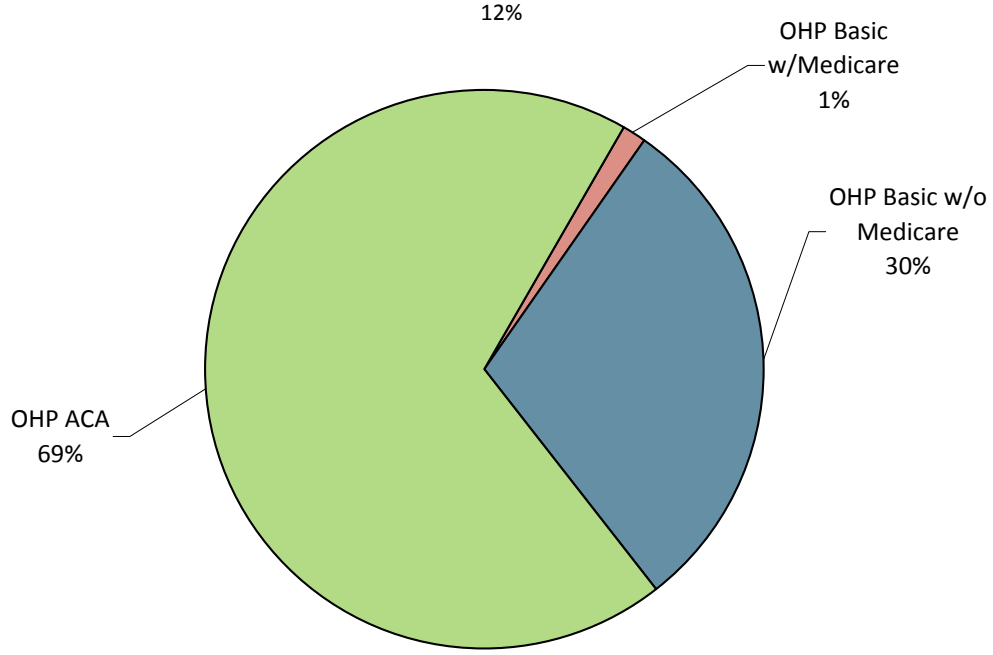
Pharmacy Utilization Summary Report: July 2015 - June 2016

YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last Updated: January 18, 2017

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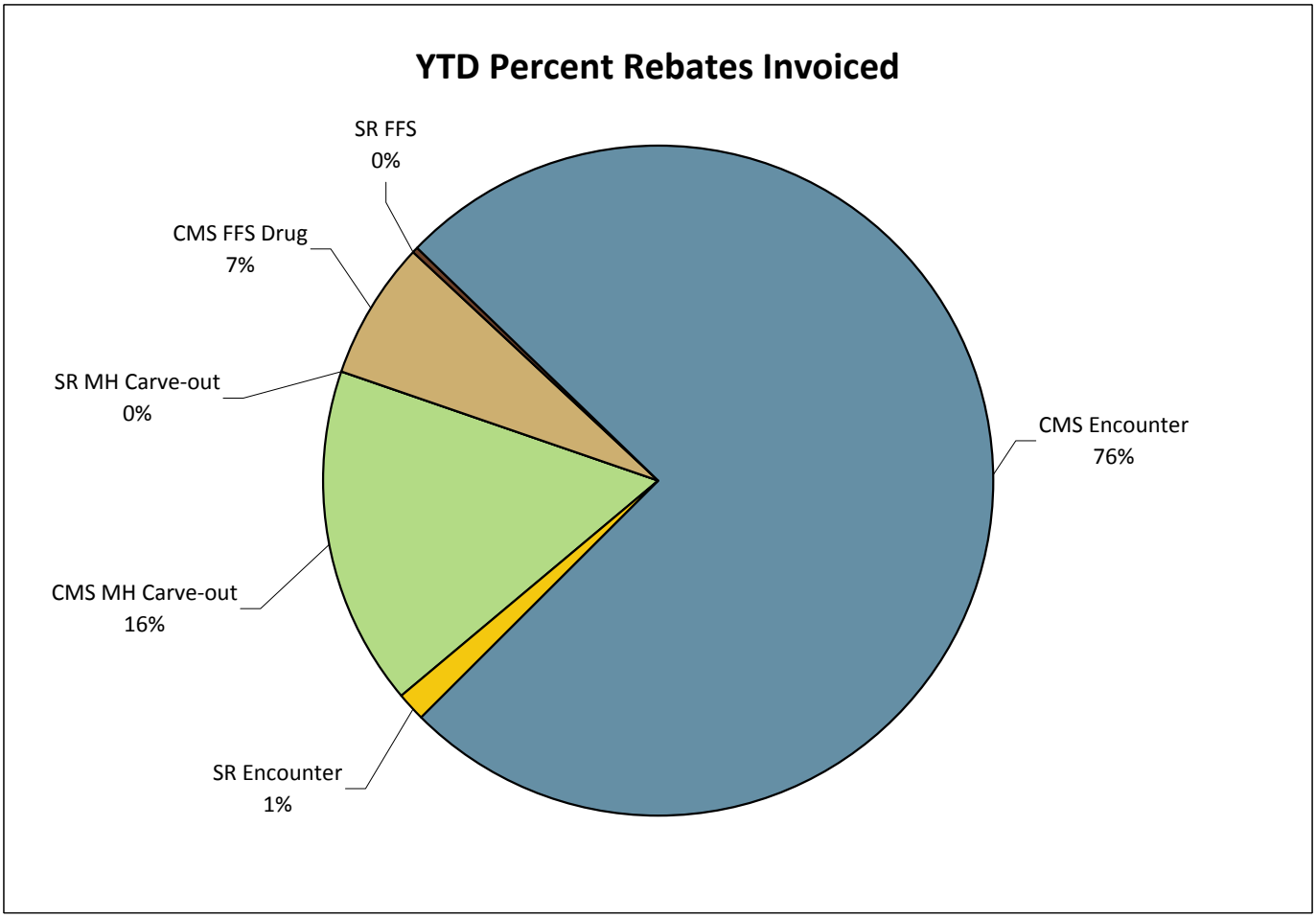
Pharmacy Utilization Summary Report: July 2015 - June 2016

Quarterly Rebates Invoiced	2015-Q3	2015-Q4	2016-Q1	2016-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$93,552,958	$96,235,037	$107,969,610	$101,908,972	$399,666,577
CMS MH Carve-out	$17,375,190	$18,188,211	$19,026,455	$11,119,142	$65,708,998
SR MH Carve-out					$0
CMS FFS Drug	$6,157,546	$5,856,800	$7,279,240	$6,821,399	$26,114,985
SR FFS	$250,196	$334,651	$262,343	$296,724	$1,143,914
CMS Encounter	$68,012,508	$70,477,233	$80,817,700	$82,098,761	$301,406,202
SR Encounter	$1,757,518	$1,378,142	$583,872	$1,572,947	$5,292,478

Quaterly Net Drug Costs	2015-Q3	2015-Q4	2016-Q1	2016-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$103,047,261	$103,293,041	$106,568,413	$105,968,217	$418,876,932
Mental Health Carve-Out Drugs	$14,886,308	$14,718,152	$13,946,490	$13,939,341	$57,490,291
FFS Phys Health + PAD	$7,977,438	$7,472,618	$6,790,581	$8,034,106	$30,274,742
Encounter Phys Health + PAD	$80,183,515	$81,102,272	$85,831,343	$83,994,770	$331,111,900



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

Last Updated: January 18, 2017

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Pharmacy Utilization Summary Report: July 2015 - June 2016

PMPM Drug Costs (Rebates not Included)	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$64.17	$61.67	$62.31	$62.95	$62.52	$67.15	$65.65	$65.79	$70.36	$65.14	$65.89	$67.70	$65.11
Mental Health Carve-Out Drugs	$10.50	$10.13	$10.24	$10.34	$10.27	$11.16	$10.64	$10.74	$9.65	$7.81	$8.05	$8.10	$9.80
FFS Physical Health Drugs	$25.74	$20.92	$23.29	$22.99	$22.20	$23.96	$24.13	$24.87	$27.19	$23.41	$22.86	$25.42	$23.91
FFS Physician Administered Drugs	$11.83	$10.93	$10.64	$10.29	$8.86	$10.57	$10.34	$9.81	$10.84	$9.41	$10.77	$12.78	$10.59
Encounter Physical Health Drugs	$47.20	$46.39	$46.66	$47.94	$47.99	$50.62	$48.87	$49.16	$53.89	$52.39	$52.41	$53.71	$49.77
Encounter Physician Administered Drugs	$8.90	$8.29	$8.16	$7.71	$7.83	$8.33	$9.11	$8.87	$10.00	$9.00	$9.32	$9.25	$8.73

Claim Counts	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Total Claim Count (FFS & Encounter)	1,015,449	1,003,237	1,015,858	1,037,867	977,187	1,031,827	1,029,265	1,042,203	1,131,552	1,042,265	1,045,160	1,028,403	1,033,356
Mental Health Carve-Out Drugs	152,180	150,978	151,853	153,828	146,402	157,690	152,946	153,457	164,670	153,114	154,659	154,926	153,892
FFS Physical Health Drugs	73,666	67,651	69,915	72,180	70,902	67,797	68,179	70,655	74,603	71,715	70,851	68,665	70,565
FFS Physician Administered Drugs	15,582	14,583	14,617	13,335	11,850	12,083	11,878	11,800	12,621	13,166	13,417	14,012	13,245
Encounter Physical Health Drugs	692,850	690,397	700,265	718,215	673,982	721,607	709,535	720,857	787,103	717,516	719,851	700,674	712,738
Encounter Physician Administered Drugs	81,171	79,628	79,208	80,309	74,051	72,650	86,727	85,434	92,555	86,754	86,382	90,126	82,916

Amount Paid per Claim (Rebates not Included)	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$65.10	$64.79	$64.48	$64.02	$65.20	$67.23	$66.68	$67.33	$66.93	$66.16	$65.92	$68.09	$65.99
Mental Health Carve-Out Drugs	$71.11	$70.72	$70.88	$70.93	$71.49	$73.11	$72.73	$74.66	$63.10	$53.99	$54.42	$54.06	$66.77
FFS Physical Health Drugs	$47.23	$44.85	$46.02	$45.71	$45.95	$44.31	$46.77	$48.04	$48.33	$49.18	$46.61	$51.84	$47.07
FFS Physician Administered Drugs	$102.63	$108.68	$100.59	$110.78	$109.70	$109.69	$115.09	$113.50	$113.85	$107.64	$115.99	$127.72	$111.32
Encounter Physical Health Drugs	$60.96	$61.08	$60.83	$60.88	$62.11	$63.68	$62.90	$63.43	$64.62	$66.30	$65.60	$68.55	$63.41
Encounter Physician Administered Drugs	$98.10	$94.63	$94.03	$87.56	$92.18	$104.07	$95.95	$96.59	$102.01	$94.25	$97.19	$91.74	$95.69

Amount Paid per Claim - Multi Source Drugs (Rebates not Included)	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$27.85	$27.59	$27.72	$27.59	$27.40	$27.38	$28.88	$29.18	$27.27	$25.71	$25.50	$25.47	$27.29
Mental Health Carve-Out Drugs	$51.87	$51.26	$50.98	$50.72	$51.07	$51.29	$55.62	$56.00	$43.95	$34.43	$33.76	$32.97	$46.99
FFS Physical Health Drugs	$22.13	$21.41	$21.74	$22.54	$21.26	$21.07	$22.67	$22.50	$23.41	$23.00	$22.52	$22.12	$22.20
Encounter Physical Health Drugs	$23.01	$22.84	$23.07	$22.93	$22.72	$22.58	$23.50	$23.92	$24.03	$24.06	$23.96	$24.08	$23.39

Amount Paid per Claim - Single Source Drugs (Rebates not Included)	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$530.56	$524.35	$484.53	$476.63	$515.55	$551.73	$580.86	$587.19	$600.40	$615.36	$609.38	$643.04	$559.97
Mental Health Carve-Out Drugs	$510.14	$514.25	$522.36	$518.39	$521.50	$547.36	$553.71	$580.65	$586.27	$579.33	$588.89	$602.98	$552.15
FFS Physical Health Drugs	$375.40	$353.06	$354.74	$325.34	$359.08	$354.23	$377.13	$394.80	$389.64	$410.94	$375.48	$452.23	$376.84
Encounter Physical Health Drugs	$549.43	$541.70	$491.96	$486.11	$530.33	$569.51	$603.41	$607.02	$621.96	$639.47	$634.84	$666.44	$578.51

Multi-Source Drug Use Percentage	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Multi-Source Drug Use Percentage	93.3%	93.2%	92.6%	92.5%	92.8%	93.0%	93.8%	93.7%	93.7%	93.7%	93.7%	93.6%	93.3%
Mental Health Carve-Out Drugs	95.8%	95.8%	95.8%	95.7%	95.7%	95.6%	96.6%	96.4%	96.5%	96.4%	96.3%	96.3%	96.1%
FFS Physical Health Drugs	92.9%	92.9%	92.7%	92.3%	92.7%	93.0%	93.2%	93.1%	93.2%	93.3%	93.2%	93.1%	93.0%
Encounter Physical Health Drugs	92.8%	92.6%	91.9%	91.8%	92.2%	92.5%	93.2%	93.2%	93.2%	93.1%	93.2%	93.1%	92.7%

Preferred Drug Use Percentage	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Avg Monthly
Preferred Drug Use Percentage	86.33%	86.45%	86.45%	86.80%	86.84%	86.74%	86.64%	86.86%	87.01%	86.56%	86.30%	85.99%	86.6%
Mental Health Carve-Out Drugs	76.24%	76.38%	76.26%	76.12%	76.10%	76.20%	76.25%	75.91%	77.59%	76.14%	75.51%	75.28%	76.2%
FFS Physical Health Drugs	95.23%	95.40%	95.42%	95.17%	95.84%	95.57%	95.45%	95.36%	95.37%	95.22%	95.25%	95.15%	95.4%
Encounter Physical Health Drugs	87.54%	87.71%	87.72%	88.19%	88.15%	88.12%	87.97%	88.29%	88.14%	87.85%	87.71%	87.41%	87.9%

Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last Updated: January 18, 2017

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2016

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$3,864,151	10.6%	3,792	$1,019	Y
2	STRATTERA	ADHD Drugs	$1,931,100	5.3%	4,613	$419	Y
3	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,390,932	3.8%	867	$1,604	V
4	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,153,246	3.2%	1,830	$630	V
5	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$937,033	2.6%	12,099	$77	V
6	ABILIFY MAINTENA	Antipsychotics, Parenteral	$622,113	1.7%	385	$1,616	Y
7	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$608,503	1.7%	1,202	$506	V
8	FLUOXETINE HCL	Antidepressants	$592,253	1.6%	29,999	$20	Y
9	HARVONI	Hepatitis C, Direct-Acting Antivirals	$588,856	1.6%	21	$28,041	Y
10	QUETIAPINE FUMARATE ER	Antipsychotics, 2nd Gen	$576,390	1.6%	1,008	$572	V
11	SAPHRIS	Antipsychotics, 2nd Gen	$546,427	1.5%	918	$595	Y
12	Ipilimumab Injection	Physican Administered Drug	$522,810	1.4%	5	$104,562	
13	DULOXETINE HCL	Antidepressants	$522,472	1.4%	25,558	$20	V
14	PRISTIQ	Antidepressants	$481,663	1.3%	1,590	$303	V
15	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$463,410	1.3%	1,441	$322	V
16	SERTRALINE HCL	Antidepressants	$434,432	1.2%	37,199	$12	Y
17	RISPERDAL CONSTA	Antipsychotics, Parenteral	$398,195	1.1%	508	$784	Y
18	TRAZODONE HCL	Antidepressants	$384,531	1.1%	35,768	$11	
19	BUPROPION XL	Antidepressants	$323,268	0.9%	17,394	$19	V
20	VENLAFAXINE HCL ER	Antidepressants	$320,048	0.9%	1,916	$167	V
21	LANTUS	Diabetes, Insulins	$294,323	0.8%	867	$339	Y
22	INVEGA TRINZA	Antipsychotics, Parenteral	$293,693	0.8%	58	$5,064	V
23	VIIBRYD	Antidepressants	$286,840	0.8%	1,314	$218	V
24	VRAYLAR	Antipsychotics, 2nd Gen	$283,077	0.8%	282	$1,004	V
25	AMITRIPTYLINE HCL	Antidepressants	$270,540	0.7%	15,968	$17	Y
26	Factor Viii Recombinant Nos	Physican Administered Drug	$269,861	0.7%	7	$38,552	
27	LAMOTRIGINE	Antiepileptics (oral & rectal)	$266,675	0.7%	20,363	$13	Y
28	REXULTI	Antipsychotics, 2nd Gen	$262,835	0.7%	277	$949	V
29	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$260,749	0.7%	4,040	$65	Y
30	CITALOPRAM HBR	Antidepressants	$255,289	0.7%	26,517	$10	Y
31	Infliximab Not Biosimil 10mg	Physican Administered Drug	$248,955	0.7%	114	$2,184	
32	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$240,547	0.7%	2,214	$109	
33	TRINTELLIX	Antidepressants	$232,342	0.6%	722	$322	V
34	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$230,926	0.6%	3,964	$58	Y
35	ESCITALOPRAM OXALATE	Antidepressants	$229,268	0.6%	19,089	$12	Y
36	ENBREL	Biologics for Autoimmune Conditions	$226,901	0.6%	59	$3,846	Y
37	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$223,704	0.6%	13,762	$16	
38	VENLAFAXINE HCL ER	Antidepressants	$210,154	0.6%	13,772	$15	Y
39	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$194,263	0.5%	545	$356	V
40	EPCLUSA	Hepatitis C, Direct-Acting Antivirals	$192,444	0.5%	8	$24,055	N
		Top 40 Aggregate:	**$21,635,218**		**302,055**	**$5,463**	
		All FFS Drugs Totals:	**$36,531,296**		**666,723**	**$488**	

Notes
- FFS Drug Costs only, rebates excluded
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last updated: January 18, 2017

ProDUR Report for October through December 2016

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	18	7	0	11	0.01%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,542	331	0	1,210	1.43%
DD (Drug/Drug Interaction)	Set alert/Pay claim	234	59	0	175	0.17%
ER (Early Refill)	Set alert/Deny claim	72,440	13,958	101	58,365	69.43%
ID (Ingredient Duplication)	Set alert/Pay claim	20,280	5,444	13	14,800	19.40%
LD (Low Dose)	Set alert/Pay claim	875	175	0	700	0.80%
LR (Late Refill/Underutilization)	Set alert/Pay claim	11	6	0	5	0.01%
MC (Drug/Disease Interaction)	Set alert/Pay claim	874	230	0	644	0.80%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,216	351	4	857	1.10%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	113	66	0	47	0.09%
TD (Therapeutic Duplication)	Set alert/Pay claim	6,641	1,999	2	4,636	6.33%
	Totals	**104,244**	**22,626**	**120**	**81,450**	**99.57%**

ProDUR Report for October through December 2016

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)	7	15	39	0	73	0
	Hydrocodone/APAP	0	1	26	0	17	0
	Oxycodone	4	0	47	0	33	0
	Lorazepam	6	3	57	0	104	0
	Alprazolam	7	12	34	0	58	0
	Lamictal (Lamotrigine)	33	39	168	2	234	0
	Abilify (Aripiprazole)	13	17	70	0	191	0
	Seroquel (Quetiapine)	23	36	123	0	235	0
	Risperdal (Risperidone)	9	15	85	0	198	0
	Wellbutrin (Bupropion)	21	44	90	0	201	0
	Zoloft (Sertraline)	26	56	271	0	331	0
	Prozac (Fluoxetine)	23	42	127	0	229	0
	Celexa (Citalopram)	25	23	84	2	164	0
	Trazodone	20	42	205	1	376	0
	Cymbalta (Duloxetine)	29	38	123	0	233	0
	TOTALS =	**246**	**383**	**1,549**	**5**	**2,677**	**0**

		Nov and Dec 2016	Nov and Dec 2016	Nov and Dec 2016		Jan and Feb 2017	Jan and Feb 2017	Jan and Feb 2017
HICL Sequence Number	**Generic Drug Name**	**# ER Alerts**	**# Overridden**	**Percent Overridden**		**# ER Alerts**	**# Overridden**	**Percent Overridden**
6438	FENTANYL	4	1	25.00%		8	4	50.00%
1730	HYDROCODONE/ACETAMINOPHEN	106	38	35.85%		105	51	48.57%
1695	HYDROMORPHONE HCL	15	3	20.00%		10	6	60.00%
1745	METHADONE HCL	0	0	0.00%		2	1	50.00%
1694	MORPHINE SULFATE	16	7	43.75%		25	6	24.00%
1742	OXYCODONE HCL	125	43	34.40%		135	52	38.52%
1741	OXYCODONE HCL/ACETAMINOPHEN	41	16	39.02%		47	19	40.43%
8317	TRAMADOL HCL	50	5	10.00%		40	10	25.00%
	ALL OPIOIDS =	**357**	**113**	**31.65%**		**372**	**149**	**40.05%**

Opioid daily morphine equivalent quantity limits were reduced from 120 MEQ to 90 MEQ on 1/1/2017

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	50	17		
		Total Faxes Successfully Sent	37	6		
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	10			
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	2			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$9,907			

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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	21			
		Profiles Sent	5			
		Responses Received	0			
		Response Rate	0%			
		Information Useful or Will Change Practice	0			
		Patient Not With Office	0			
		Already Scheduled	0			
		Will Not Schedule	0			
		Requested No Future Notifications	0			
	Antipsychotic Metabolic Monitoring	Members Identified	658			
		Profiles Sent	649			
		Members With Response	0			
		Response Rate	0%			
		Newly Scheduled	0			
		Provider Contacted	247			
		Provider Agreed with Recommendation	0			
		Patient Not With Office	0			

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	1			
		Disqualified - No Provider Info	1			
		Faxes Sent	5	1		
		Fax Sent - SABA	1			
		Fax Sent - Controller	1			
		No Subsequent Pulmonary Claims	3	1		

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Guideline and Policy Updates for Use of Opioids for Non-cancer Pain and Opioid Use Disorder

By Andrew Gibler, PharmD, OSU College of Pharmacy Drug Utilization Research and Management

Assessment and treatment of chronic pain is challenging because of its associated clinical, psychological and social consequences. Pain can limit the ability to perform certain activities, and can result in decreased work productivity, reduced quality of life, and stigma. Certain patient populations can also be at increased risk for inadequate pain treatment, such as the elderly, racial and ethnic minority groups, persons with cognitive impairment, and patients with cancer or at the end of life.[1] Furthermore, all patients will build tolerance with regular use of opioids which can result in the practice of prescribing higher and higher doses at the expense of higher risk for serious adverse events such as respiratory suppression and death.

About 20% of patients who present to clinicians with non-cancer pain symptoms or pain-related diagnoses (acute or chronic) receive an opioid prescription.[1] Opioid analgesics are now the most commonly prescribed class of medications in the U.S.[2] Although they have been used for decades to manage pain, there are serious harms associated with opioid use. Opioids can produce feelings of euphoria, tranquility and sedation that have resulted in an epidemic of misuse and abuse. From 2007 to 2014, the number of private insurance claims with an opioid dependence diagnosis increased 3,203%, with most of the claims for persons between 19-35 years of age.[3] With the dramatic increase in misuse and abuse of prescription opioids and ease of accessibility to illicit opioids such as heroin and potent synthetic fentanyl analogs, it is imperative that clinicians understand how to manage pain carefully; and, if necessary, navigate treatment strategies of opioid use disorder with their patients.

CDC Recommendations for Management of Chronic Non-cancer Pain

To address some of these issues, the U.S. Centers for Disease Control and Prevention (CDC) issued guidance this year for prescribing opioids for chronic non-cancer pain.[1] Final recommendations were based on a systematic review of controlled clinical trials and observational studies over the past 20 years, expert clinical opinion, and review from key stakeholders.[1] The 12 recommendations focus on 1) determining when to initiate or continue an opioid for chronic pain; 2) opioid selection, dosage, duration, follow-up and discontinuation; and 3) assessing risk and addressing harms of opioid use.[1] A summary of the 12 CDC recommendations for opioid prescribing in non-cancer pain are provided in Table 1. It is recommended the reader review the CDC guideline for more information.[1]

Table 1. Summary CDC Recommendations.[1]

Recommendation	Supporting Evidence
When to Initiate or Continue Opioids for Chronic Pain.	
1. Try non-pharmacological therapy and/or non-opioid analgesics first.	Physical therapy, psychological therapies (e.g., CBT), exercise and weight loss have shown to ameliorate many types of chronic pain without the harm associated with opioids. Acetaminophen, NSAIDs, and some antidepressants and anticonvulsants can also effectively treat many types of pain.
2. Establish realistic treatment goals for pain and function first. Develop a plan for discontinuation of the opioid if goals are not met.	There is insufficient evidence to determine long-term benefits of opioid therapy for chronic pain; however, some patients who can tolerate opioids may experience clinically meaningful pain relief.
3. Regularly discuss patient and clinician responsibilities for managing therapy; also reassess risks and benefits of opioid therapy regularly.	Many patients lack information about opioids. Given the substantial gaps in evidence for opioids, uncertain benefits of long-term use and potential for serious harms, patient education and discussion of treatment expectations can mitigate harms.
Opioid Selection, Dose, Duration, Follow-up and Discontinuation.	
4. Prescribe an intermittent SAO instead of a LAO when starting opioid therapy for chronic pain.	Continuous, regularly-scheduled use of a LAO is not more effective than intermittent use of a SAO but is associated with higher risk for accidental overdose. There is also insufficient evidence to determine the safety of a SAO for breakthrough pain in patients already on a LAO for chronic non-cancer pain. This practice is associated with dose escalation over time.
5. Use caution when increasing the dose of a LAO ≥ 50 MME/day. Daily doses ≥ 90 MME should be avoided.	Data show increasing the dose of an opioid beyond 50 MME/day does not provide further pain or functional benefit. Doses ≥90 MME/day significantly increase risk for motor vehicle accidents, opioid use disorder, and overdose by nearly 5-fold compared to doses < 20 MME/day.
6. Most acute pain can be managed sufficiently with 3 days or less of a SAO. Rarely is 7 days of SAO needed. Avoid LAOs for acute pain.	Use of a SAO for acute pain is associated with long-term opioid use. Greater initial exposure is associated with greater risk for long-term use. Limiting days of opioid exposure also minimizes the need to taper and prevents withdrawal symptoms.
7. Evaluate benefits and harms of opioid therapy within 1 to 4 weeks of initiation or dose escalation. Follow-up should occur routinely at least every 3 months with chronic opioid use. Discontinue or reduce the opioid dose if harms outweigh the benefit.*	Patients who do not experience benefit with an opioid in the first month are unlikely to experience benefit at 6 months. Because there is substantial risk for opioid use disorder with continuing an opioid beyond 3 months, it is imperative that both benefits (decreased pain, improved function and quality of life*) and harms (tolerance, dependence, addiction or overdose risk, and adverse CNS/GI effects) are routinely and frequently re-evaluated, even in chronic opioid users. *Pain control, quality of life, and function can be quickly assessed in the primary care setting using the 3-item PEG scale.[4,5]
Assessing Risk and Addressing Harms of Opioid Use.	
8. Develop strategies to mitigate opioid-related harms in patients at risk for opioid overdose. Routinely reassess risk factors which can evolve over time.	Patients at risk for overdose include patients with: 1) history of substance overdose; 2) history of substance use disorder; 3) higher opioid dosages (≥50 MME/day); or 4) concurrent benzodiazepine use. Mitigation management strategies for these patients include offering naloxone and referral to a pain and/or behavioral health specialist. Other important populations at risk include: 1) patients with sleep disorders (e.g., sleep apnea); 2) pregnant women; 3) patients with hepatic or renal impairment; 4) patients ≥65 years of age; and 5) patients with mental health conditions.
9. Enroll and routinely review the state PDMP when initiating an opioid and at least once every 3 months for patients on chronic opioid therapy.	Most fatal overdoses are associated with patients who receive opioids from multiple prescribers and/or patients who on high total daily doses of opioids. Implementation of the PDMP has been associated with a reduction in opioid-related deaths.[6]
10. Perform a UDS before starting an opioid and at least once annually for chronic opioid users.	Concurrent use of prescription opioids with other opioids, benzodiazepines, or heroin increase risk for overdose and death. Routine use, rather than random use, of UDS testing can result in less stigmatization to patients

	but still provide important information to clinicians. Note that some immunoassays do not detect synthetic opioids such as fentanyl and methadone.
11. Avoid prescribing an opioid with a benzodiazepine.	The combined use of an opioid with a benzodiazepine or other drugs that suppress the CNS have resulted in numerous cases of respiratory depression and death.[7]
12. Treat opioid use disorder.	Buprenorphine/naloxone and methadone are equally effective for maintenance therapy of opioid use disorder when offered with psychosocial interventions as part of a supportive treatment program.
Abbreviations: CBT = cognitive behavior therapy; CNS = central nervous system; GI = gastrointestinal; LAO = long-acting opioid; MME = morphine milligram equivalent; PDMP = prescription drug monitoring program (www.orpdmp.com); SAO = short-acting opioid; UDS = urine drug screen.	

The Oregon Health Plan (OHP) has adopted policies based on the CDC recommendations.[8] Patients on chronic opioids for non-cancer pain or not on palliative care must taper their opioid dosage down to less than an equivalent of 90 mg of morphine per day (e.g., oxycodone <60 mg/day). Prescribers will also be asked to routinely assess prescription data of controlled substances in the Oregon Prescription Drug Monitoring Program. Pain associated with fibromyalgia and chronic headache will continue to not be covered under the OHP.

In addition, the Health Evidence Review Commission (HERC) has implemented strict opioid use policies for back pain. Patients prescribed opioids for back pain, for which there is insufficient evidence for meaningful effectiveness,[9] will be limited to 7 days of a short-acting opioid only after an initial trial of a non-opioid analgesic has failed. Spinal manipulation, physical therapy, yoga, and acupuncture therapies are encouraged and will be covered under the OHP to manage chronic back pain. Implementation of these policies will be a long and arduous process since thousands of patients will be initially affected. The Oregon Health Authority understands the substantial burden this will place on clinicians and this newsletter is only one part of a coordinated outreach to prescribers to inform them of these upcoming changes. Details of what is covered for pain associated with back and spine conditions are outlined in Guideline Note 60 (*Opioids for Conditions of the Back and Spine*) of the Prioritized List of Health Services published by the HERC.[10] Beginning January 1, 2017, the OHP will require an individualized taper plan for each patient on a chronic opioid for back pain. The taper must include an end-date of no later than December 31, 2017. Taper plans must include non-pharmacological treatment strategies based on the HERC Guideline Note 56 (*Non-Interventional Treatments for Conditions of the Back and Spine*) of the Prioritized List of Health Services.[10] As always, prescribers can appeal these policies for individual patients who benefit from their current opioid dose without signs of adverse effects or aberrant behaviors.

Tapering Off Opioids

Long-term use of opioids results in physical and psychological dependence which makes tapering down opioid doses especially challenging. Opioid dose reduction can cause anxiety in patients on established doses and may unmask opioid use disorder. However, all patients on high doses of opioids should be offered the opportunity to re-evaluate their continued use of opioids in light of the evidence for increased harms.[1] Taper protocols that reduce opioid dosage by 10% per week of the original dose is recommended, but slower tapers (e.g., 10% per month) may be needed to minimize signs and symptoms of withdrawal in patients who have been on chronic opioids for years.[1] Tapers should be considered successful as long as the patient is making progress; however, a taper should not be reversed. Clinicians should remain alert to signs of anxiety, depression, and opioid use disorder that might be unmasked by the taper.[1] Tapers can always be slowed or temporarily paused to manage withdrawal symptoms. Several helpful tools and guidance documents are available free to clinicians from the Washington State Agency Medical Directors' Group at www.agencymeddirectors.wa.gov.

Management of Opioid Use Disorder

State and Federal agencies have responded to expand resources to treat opioid overdose and manage patients struggling with opioid use disorder. In July 2016, the Comprehensive Addiction and Recovery Act was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs and expand the availability of naloxone to first responders.[11] The Substance Abuse and Mental Health Services Administration (SAMHSA) oversees accreditation of opioid treatment programs and requests that providers adhere to recognized clinical practice guidelines when treating patients with opioid use disorder (Table 2).[12]

Table 2. Clinical Practice Guidelines for Opioid Use Disorder

American Society of Addiction Medicine National Practice Guidelines for the Use of Medications in the Treatment of Addiction Involving Opioid Use www.asam.org
SAMHSA Treatment Improvement Protocol 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction https://store.samhsa.gov
World Health Organization Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence www.who.int/substance_abuse/publications/
Department of Veterans Affairs /Department of Defense Clinical Practice Guideline on Management of Substance Use Disorder www.healthquality.va.gov/guidelines/
Federation of State Medical Boards' Model Policy on the Drug Addiction Treatment Act of 2000 and Treatment of Opioid Addiction in the Medical Office www.fsmb.org

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Treatment of Gout

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Gout is the most common inflammatory arthritis with an incidence of approximately 4% in U.S. adults.[1] The annual estimated cost of treating gout in the U.S. is $1 billion.[1] Pharmacological therapies are key to both symptom management and treatment of the underlying pathophysiology of gout. The purpose of this article is to discuss treatment recommendations provided by updated guidelines from the American College of Physicians (ACP) and the European League Against Rheumatism (EULAR).[1,2] In addition, the evidence for lesinurad (Zurampic®), the new uricosuric agent for chronic gout, will be reviewed.[3]

Review of Gout

The etiology of gout stems from high serum urate levels that exceed the saturation point in the blood leading to crystals that deposit in cartilage, bones, tendons and other sites. Guidelines recommend that serum urate levels be lowered to less than 6 mg/dL for most patients with gout when hypouricemic therapy is needed.[2,4,5] Gout attacks usually begins with acute flares and over the years can become chronic in nature. Typical presentation of acute gout is pain in a single joint usually in the lower extremity and is characterized by attacks of pain and inflammation lasting 7-14 days which are self-limiting.[1] Chronic gout develops after multiple acute attacks, and results in chronic persistent inflammation, multiple joint involvement, and the development of tophi and bone damage.[1] Asymptomatic hyperuricemia is very common; however, there is no evidence to support urate-lowering treatment as a preventative strategy for progression to symptomatic gout.[6]

Treatment of Gout

The goal of treating acute gout is to minimize inflammation and the goal of treating chronic gout is to lower serum uric acid and dissolve the crystals that have formed.[1,7,8] Treatment for acute gout should be started as soon as possible after an attack has started (within 24 hours of onset).[4] Monotherapy with an oral NSAID, a systemic corticosteroid, or colchicine is recommended for an acute gout flare of mild to moderate severity. Comparative evidence has found similar efficacy for therapies used for acute gout flares. Treatment selection should be based on patient tolerability and comorbidities. Gastrointestinal (GI) adverse events (nausea, vomiting, diarrhea and cramping) have been a limiting factor in the utilization of colchicine. NSAIDS may cause dyspepsia, GI ulcers and bleeding. Corticosteroids are associated with mood disorders, immune suppression and blood glucose elevations.[1] Severe acute gout attacks (consisting of severe pain or polyarticular involvement) can be treated with combination therapy, which could include 1) an NSAID and colchicine; 2) an oral corticosteroid and colchicine; or 3) intra-articular steroid injections and one of the oral treatment options.[4] Although acute gout tends to resolve in 5-7 days, frequently much more prolonged therapy up to several weeks may be needed.[2]

Chronic gout is treated with urate lowering therapy (ULT) with the intent of reducing serum uric acid concentrations. Lowering the serum urate level to less than 5-6 mg/dl allows the urate crystals already formed in tissues to dissolve. Patients who have had only one attack, or have very infrequent attacks, may not need ULT. However, ULT should be started in patients who have more than 2 attacks per year, polyarticular attacks, or have begun developing tophi.[7] Xanthine oxidase inhibitors (XOI), allopurinol or febuxostat, are recommended as first-line options to lower urate levels.[1,2,7] Secondary options include the uricosurics probenecid or lesinurad. However, probenecid is recommended over lesinurad due to limited evidence for efficacy of lesinurad and concerning renal adverse effects, such as reversible and non-reversible elevations in serum creatinine and acute renal failure.[3] If XOI monotherapy fails to lower serum urate levels to target, combination therapy with a XOI and probenecid can be used.[7] With any of these options, clinical benefit requires that the serum urate level drops to 5-6 mg/dl. There are no "standard" dose for these drugs, and the dose may require adjustment to achieve this uric acid level. Serum urate levels should be checked every 2-5 weeks during the dose titration phase and every 6 months once a maintenance dose is determined.[1] There is no evidence-based recommendation on duration of ULT therapy; however, common practice is to continue ULT indefinitely to prevent gout attack reoccurrence.

The patient may have more frequent episodes of gout in the 6-12 months after starting ULT. To prevent these flares, prophylactic anti-inflammatory therapy should be started along with ULT. Due to increased risk of flares when initiating ULT, low dose colchicine is recommended first-line for prophylaxis of acute gout flares and a low dose NSAID is recommended as an alternative. Low dose prednisone or prednisolone are also suggested as alternatives to first-line agents in some patients but should be limited due to their long-term adverse effects.[5] Acute gout prophylaxis is recommended for at least the first 6 months of ULT. Historically, it was recommended that ULT be started 2 weeks after an acute flare subsided, because ULT was thought to increase the risk of acute gout flares upon initiation. However, there is limited evidence that such a delay is necessary.[7]

Guideline Recommendations

American College of Physicians Management of Gout Guidelines

In 2016, the ACP published a new guideline on the management of acute and recurrent gout.[1] Four main recommendations were issued based on moderate to high-quality evidence:

- *Evidence supports the use of corticosteroids, NSAIDs or colchicine for treatment of inflammation of acute gout;*
- *If colchicine is used, then low-dose colchicine as opposed to high dose colchicine, is recommended for acute gout flare treatment;*
- *Long-term ULT is not recommended for most patients after the first gout attack or for those with infrequent attacks; and*
- *Patients should be made aware of the benefits, harms and costs, and individual preferences should be discussed before initiating ULT, including concomitant prophylaxis for acute gout flares*

EULAR 2016 Guideline on the Management of Gout

Updated EULAR guidelines recommend treatment strategies based upon acute versus chronic treatment.[2] First-line recommendations for acute gout flares are as follows:

- colchicine (within 12 hours of symptom onset); and/or
- NSAID; or
- Oral corticosteroid; or
- Articular aspiration and injection of corticosteroids

Prophylaxis with colchicine (0.5-1 mg/day in patients with normal renal function) against an acute gout flare is recommended in the first 6 months of ULT.[2] NSAIDs can also be used as an alternative option. If ULT is indicated, allopurinol 100 mg/day, titrating every 2-4 weeks to a maximum dose of 300 mg/day if needed (in patients with normal renal function) is recommended first line. If serum urate targets are not met after appropriate dose titration of allopurinol, then patients should be switched to febuxostat or a uricosuric (probenecid or lesinurad) with or without allopurinol.[2] Dose adjustments for patients with renal impairment are required for colchicine, NSAIDs and allopurinol.

Lesinurad

Lesinurad is a new uricosuric agent which increases excretion of uric acid in a mechanism similar to probenecid.[3] Lesinurad was approved for use in combination with a XOI when a XOI alone fails to lower serum urate levels to target. Approval for lesinurad was based on three phase 3, double-blind, randomized, placebo-controlled clinical trials lasting 12 months.[9–11] The primary

endpoint was the proportion of subjects who had a serum uric acid level less than 5.0 mg/dL or 6.0 mg/dL. An additional study was initiated to investigate the efficacy and safety of lesinurad monotherapy, but this study was prematurely discontinued by the sponsor for concerns of renal-associated adverse events.[10]

Efficacy

All three studies were conducted in adults between 22-82 years of age with hyperuricemia and gout diagnosis on a stable dose of a XOI. Patients had to have at least 2 gout flares in one year or less to be included. Patients with a creatinine clearance of less than 30 mL/minute were excluded and the majority of patients had normal renal function. All patients had the option to receive routine colchicine or NSAID of unknown doses with or without a proton pump inhibitor through month 5 for prevention of gout flares.[9–11] Patients with significant cardiac disease or hepatic disease were excluded. The majority of patients enrolled in these trials were white males.

In one of the trials (n= 603 patients), individuals were randomized to daily allopurinol (≥300 mg or 200 mg for moderate renal dysfunction) plus one of the following: placebo, lesinurad 200 mg daily, or lesinurad 400 mg daily.[9,11] In the lesinurad 200 mg arm, 54% of patients obtained the target serum urate level of less than 6 mg/dL compared to 28% in the placebo arm (relative risk [RR] 0.26; 95% CI 0.17 to 0.36; p<0.0001).[9,11] In the lesinurad 400 mg arm, 59% of patients obtained a serum urate level less than 6 mg/dL (RR 0.31 vs. placebo; 95% CI 0.22 to 0.41; p<0.0001).[9,11] However, the addition of lesinurad to allopurinol did not reduce gout flares versus allopurinol alone.

In a second study, 610 patients were randomized into similar arms as in the previous study.[10,11] Serum urate levels were reduced to less than 6 mg/dL in 55% of patients in the lesinurad 200 mg arm, 67% of patients in the lesinurad 400 mg arm, and 23% of patients in the placebo arm (RR 0.32; 95% CI 0.23 to 0.41; p<0.0001 and RR 0.43; 95% CI 0.34 to 0.52; p<0.001 vs. placebo, respectively).[10,11] Again, the addition of lesinurad to allopurinol did not reduce gout flares versus allopurinol alone.

In a small 12-month trial (n=324), lesinurad was combined with febuxostat 80 mg daily in patients with tophaceous gout.[11] Patients were randomized to lesinurad 200 mg daily plus febuxostat, lesinurad 400 mg daily plus febuxostat or placebo plus febuxostat. At month 6, 57% of patients in the lesinurad 200 mg arm, 76% of patients in the lesinurad 400 mg arm and 47% of patients in the placebo arm achieved a serum urate level of less than 5 mg/dL (all used in combination with fubuxostat). The number of patients obtaining goal uric acid levels reached statistical significance in the 400 mg lesinurad group compared to placebo with an absolute risk reduction of 29% and a number needed to treat of 4.

Safety

Adverse events associated with lesinurad were dose-related and most commonly upper respiratory tract infections, hypertension, headache and influenza. Overall, adverse events leading to discontinuation occurred in 9.4%, 6.3%, and 5.4% in the lesinurad 400 mg, lesinurad 200 mg, and placebo groups, respectively.[11]

More serious adverse events were identified in a safety review.[12] Lesinurad was found to have higher rates of death, major adverse cardiac events (MACE), serious adverse events, and rates of serious and non-serious renal adverse events.[11] Exposure-adjusted combined incidence of death for lesinurad arms were higher than placebo (0 for placebo; 5 [<1%] for lesinurad). The incidence of MACE were comparably low in the lesinurad 200 mg arm and placebo arm, but almost doubled in the lesinurad 400 mg arm with the majority of increased events attributed to nonfatal myocardial infarction.[11] Blood pressure, cholesterol, and ECG findings appeared to be unaffected by lesinurad. The increased risk of adverse renal events was highest with lesinurad 400 mg daily but lesinurad 200 mg daily was similar to placebo. Increased serum creatinine was the most common adverse event leading to discontinuation in 1.8%, 0.8%, and 0.8% of the lesinurad 400 mg, lesinurad 200 mg, and placebo arms, respectively.[11] A FDA boxed warning identifies risk of acute renal failure with lesinurad, which is more common when used as monotherapy. Therefore, it is recommended that lesinurad only be used with a XOI.[3] Thestudieswere not designed to assess long-term safety data or to specifically identify the risk of MACE with lesinurad.

Conclusion

Appropriate and timely management of gout is paramount due to the highly symptomatic nature of the disease. In the last decade new therapies have expanded the serum urate lowering options but have failed to show superiority to previously available agents. Updated guidelines reinforce previous recommendations of traditional gout therapies. Due to low quality evidence, lesinurad is recommended as an option only after other urate lowering therapies have failed to reduce serum urate levels and control gout flares. Based on a review of the evidence, the Oregon Health Plan (OHP) fee-for-service program supports use of NSAIDs as first-line treatment of acute gout flares and for prophylaxis of gout flare when initiating ULT.[12] Allopurinol is recommended first-line for urate lowering therapy when indicated for chronic gout.

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Class Update: Antivirals for Hepatitis B

Date of Review: March 2017 **Date of Last Review:** March 2014

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

Purpose for Class Update: To identify and evaluate new comparative evidence for the safety and efficacy of medications used in the treatment of Hepatitis B virus (HBV) and review updated guidelines since the last class review was published.

Research Questions:
1. Is there new evidence demonstrating differences in efficacy or effectiveness between antivirals for the treatment of HBV?
2. Is there new evidence demonstrating differences in the safety of antivirals for the treatment of HBV?
3. Are there specific populations (e.g. pregnancy) in which one antiviral may be more effective or safer for the treatment of HBV?

Conclusions:
- There is limited, low-quality evidence suggesting greater efficacy of entecavir over lamivudine and adefovir.
- There is no difference in terms of efficacy or safety between entecavir and tenofovir. Both antiviral agents are recommended as first-line treatments by consensus guidelines.
- There is no difference in efficacy between tenofovir, lamivudine, and telbivudine in reducing perinatal transmission during pregnancy. According to consensus guidelines, safety evidence for tenofovir and lamivudine is demonstrated through outcomes in Antiretroviral Pregnancy Registry.
- One randomized trial showed tenofovir had favorable outcomes in treatment of HBV in known-lamivudine resistant patients. Switching to tenofovir is recommended by guidelines in cases of known resistance to other antiviral agents.
- There is insufficient evidence of improved efficacy or effectiveness or safety of tenofovir alafenamide compared to other antivirals for the treatment of HBV.

Recommendations:
- Maintain at least one of the guideline-recommended first line treatments, tenofovir and entecavir, as preferred agents on the PDL. Compare costs in executive session for cost comparison.
- Add tenofovir alafenamide to Preferred Drug List as a non-preferred antiviral.
- Revise prior authorization criteria as follows:
    - Add pediatric indication for telbivudine
    - Update recommendations for undetectable HBV DNA as defined by consensus guidelines below 10 IU/ml

Previous Conclusions and Recommendations:

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

Background:

Hepatitis B infection caused by the hepatitis B virus (HBV), can be defined as either acute or chronic disease.[1] It is estimated approximately 850,000 persons have chronic hepatitis B (CHB) in the United States, and may be up to 2.2 million including foreign-born persons.[2,3] HBV is transmitted through percutaneous or mucosal exposure to blood or bodily fluids of an infected person. Once a person is infected, HBV infection can be either asymptomatic or symptomatic and can progress into a chronic disease.[4] The risk of developing CHB depends on the age at which the individual becomes infected, with the majority of chronic infection developing in those initially infected in infancy and childhood.[4] Approximately 90% of infants infected with HBV in the perinatal period will develop CHB, whereas only 5% of adults acutely infected develop CHB.[1] The early identification of infected individuals, prevention through vaccination, and treatment of those infected with HBV can reduce morbidity and mortality of CHB.[5]

The diagnosis of hepatitis B is based on clinical examination and serologic testing. Hepatitis B surface antigen (HBsAg) in the blood gives a diagnosis of hepatitis B infection. Routine assessment of additional serologic markers, such as HBV DNA, hepatitis B "e-antigen" (HBeAg), and alanine aminotransferase (ALT) levels, should be performed in order to guide the management of hepatitis B. Additional testing to determine the advancement of liver fibrosis through non-invasive tests such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) or FibroTest is also recommended.[1]

Chronic hepatitis B is defined as having detectable levels of HBsAg in the blood for greater than 6 months.[1] Due to the dynamic nature of CHB, there have been different phases of disease described in literature. The phases are of variable duration and are not sequential. Not every person infected can be described in a specific phase and treatment will not always correlate to a specific phase.[1, 5] The phases are described in **Table 1**.

Table 1. Phases of Chronic Hepatitis B[5]

Phase	HBV DNA	ALT	HBeAg status
Immune-tolerant phase	Elevated, typically >1 million IU/mL	Normal	Positive
HBeAg-positive immune-active phase	Elevated, ≥20,000 IU/mL	Elevated[†]	Positive
Inactive CHB phase	Low or undetectable, <2,000 IU/mL	Normal	Negative
HBeAg-negative immune reactivation phase	Elevated, ≥2,000 IU/mL	Elevated[†]	Negative

[†]Elevated ALT defined at >2 times upper limit of normal (ULN) (normal ALT 30 U/L for males, 10 U/L for females)

Although most patients with CHB will not develop liver-related complications, the 5-year incidence of cirrhosis is approximately 8-20%, with relatively few of these cases developing hepatocellular carcinoma (HCC) (2-5%).[5] Deaths from cirrhosis and HCC were estimated to be 310,000 and 340,000 per year, worldwide.[5] Additional risk factors for developing cirrhosis and HCC in patients with CHB, include high serum HBV DNA (>2,000 IU/mL), elevated ALT levels, prolonged time to HBeAg seroconversion and development of HBeAg-negative CHB.[5]

Current antiviral therapy for CHB does not eradicate the virus, but can produce an immunological cure, defined as loss of HBsAg from the serum and sustained HBV DNA suppression. The goal of therapy is to reduce the incidence of liver-related complications including cirrhosis and hepatocellular carcinoma in patients with CHB.[6] The available treatment options for CHB include pegylated interferon or nucleoside/nucleotide analogs (NAs).[5] The American Association for the Study of Liver Diseases (AASLD) guidelines recommend the use of pegylated interferon, entecavir, or tenofovir as first line treatment, however for the purpose of this class review, only evidence relating to NAs will be evaluated. The available NAs are described in **Table 2.** Lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate require dose adjustment for creatinine clearance less than 50 mL/min.

Table 2. Nucleoside/Nucleotide Analogs (NAs) Approved for Treatment of Hepatitis B[5–7]

Drug	Adult Dose	Pediatric Dose	Severe adverse effects	Resistance Patterns
Lamivudine	100 milligram (mg) daily	Age ≥2 years: 3 mg/kilogram (kg) daily up to max 100 mg/day	Pancreatitis, lactic acidosis	Lamivudine resistance occurs in 16-32% in first year, up to 60-70% after 5 years of treatment
Adefovir dipivoxil	10 mg daily	Age ≥12 years: 10 mg daily	Acute renal failure, Fanconi syndrome, lactic acidosis	Occurs in 20-29% after 5 years of treatment
Telbivudine	600 mg daily	Age ≥16 years: 600 mg daily	Myopathy, peripheral neuropathy, lactic acidosis	Lower rate of resistance compared to lamivudine; mutations are cross-resistant with lamivudine
Entecavir	0.5 mg daily; 1 mg daily in lamivudine/ telbivudine-experienced patients or decompensated cirrhosis	Age ≥2 years: weight based dosing from 10-30 kg; >30 kg 0.5 mg daily	Lactic acidosis	Very low resistance pattern (<1% at one year, 1.2% at 5 years)
Tenofovir	300 mg daily (tenofovir disoproxil fumarate) 25 mg daily (tenofovir alafenamide)	Age ≥12 years: 300 mg daily (tenofovir disoproxil fumarate) Not approved in pediatrics (tenofovir alafenamide)	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis	No resistance detected through 96 weeks of treatment

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and

Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

One new systematic review and meta-analysis was identified comparing antiviral therapy and interferon therapy for the treatment of CHB. A total of 73 studies were included, with 59 studies (15 RCTs and 44 observational studies) reporting clinical outcomes.[8] Evaluation using the assessment of multiple systematic reviews (AMSTAR) tool determined this was a high quality systematic review. The Cochrane Risk of Bias assessment tool, for RCTs, and the modified Newcastle-Ottawa Scale, for observational studies, were used to assess the risk of bias.[8] The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8] For the purpose of this class review, only outcomes relating to NAs will be discussed. Only one observational study in patients with compensated cirrhosis measured all-cause mortality and demonstrated a reduction in all-cause mortality with entecavir compared to lamivudine (RR=0.4, 95% Confidence Interval (CI) 0.3-0.6), which was determined to be very low-quality evidence given the high risk of bias associated with the design of the study.[8] In decompensated cirrhosis, one RCT showed reduced risk of HCC with entecavir compared to adefovir (RR=0.4, 95% CI 0.2-0.8, moderate-quality evidence) and entecavir significantly reduced all-cause mortality versus lamivudine in one observational study with very low-quality evidence (RR=0.4, 95% CI 0.3-0.7).[8] Low-quality evidence from two observational studies suggested increased risk of viral relapse in those who stopped antiviral therapy compared to those who continued therapy following HBeAg seroconversion (RR=94.4, 95% CI 13.3-670.0, I^2=0%).[8] The overall conclusion of this systematic review was entecavir and tenofovir are preferred NAs given their potent antiviral activity and low risk of resistance in those with immune-active CHB, based on low-moderate quality evidence from observational studies.[8] There was little outcomes data in patients with advanced disease and limited evidence in regards to duration of therapy. No significant difference in safety profiles of entecavir and tenofovir was found.[8]

Another systematic review compared the safety and efficacy of tenofovir and entecavir in CHB.[9] A total of 2 RCTs, 4 cohort studies, and 1 case-cohort study were included (n=844).[9] The systematic review was determined to be high quality using the AMSTAR tool. Methodological quality of the RCTs was assessed using the Quality of Reporting of Meta-Analyses (QUOROM) guidelines and the JADAD scale.[9] The included non-RCTs were case matched, had well-defined inclusion and exclusion criteria, and a clear definition of treatment response.[9] No significant difference was found between tenofovir and entecavir in terms of HBV DNA suppression (6 studies included) and ALT normalization (4 studies included) at 48 weeks.[9] Tenofovir had an HBV DNA suppression rate of 80% at 48 weeks, compared to 76% for entecavir (RR=1.07, 95% CI 0.99-1.17).[9] ALT normalization occurred in 74% of the tenofovir group compared to 81% in the entecavir group (RR=0.91, 95% CI 0.83-1.01).[9] HBeAg seroconversion rates at 48 weeks were compared in 4 studies and found no difference between tenofovir (16%) and entecavir (10%) (RR=1.09, 95% CI=0.57-2.11).[9] There was no difference in terms of adverse effects related to the two agents.[9] Entecavir and tenofovir were found to be comparable in terms of efficacy and safety, however, there was a limited number of studies (7 included) comparing the two agents, with the majority being non-RCTs (5 of 7 studies), and analysis was underpowered for some indicators.[9] Therefore, more long term studies with larger sample size are needed to confirm the results of this meta-analysis.

A systematic review and meta-analysis sought to determine efficacy and safety of antiviral therapy in pregnancy.[10] It included 10 RCTs and 16 non-randomized studies in 3622 pregnant women with CHB.[10] The Cochrane Risk of Bias assessment tool and Newcastle-Ottawa Scale were used to assess the risk of bias and the

quality of evidence was evaluated using the GRADE approach.[10] Five of the RCTs were determined to have high risk of bias due to unclear/unreported method of randomization, allocation concealment, blinding, or incomplete data reporting, while the other 5 RCTs had low risk of bias.[10] Oral antiviral therapy was compared to no therapy in HBeAg-positive women with high viral load (200,000 IU/mL) in regards to infant HBsAg seropositivity (8 RCTs) and infant HBV DNA positivity (5 RCTs).[10] Low to moderate-quality evidence showed antiviral therapy reduced infant HBsAg seropositivity (RR=0.3, 95% CI 0.2-0.4) and infant HBV DNA positivity (RR=0.3, 95% CI 0.2-0.5) at 6-12 months.[10] No difference was seen in infant HBsAg seropositivity at 6-12 months when comparing lamivudine versus telbivudine (RR=1, 95% CI 0.7-1.5) or tenofovir (RR=2.93, 95% CI 0.12-70.08).[10] Maternal outcomes evidence was very low-quality due to lack of evidence and imprecision. One cohort showed pregnant women treated with telbivudine, compared to lamivudine, had greater HBV DNA suppression at delivery (RR=1.8, 95% CI 1.3-2.6).[10] The benefit of antiviral therapy in immune-tolerant women is still unproven.[10]

New Guidelines:

Guidelines from the World Health Organization (WHO) [1]

The WHO published their guidelines focused on the prevention, care, and treatment of persons with chronic hepatitis B in March 2015.[1] The guidelines were developed in response to a lack of guidance for treating persons with CHB in low- and middle-income countries (LMICs), however the recommendations are also relevant to high-income countries.[1] The WHO guidelines address who to treat, recommendations for first and second-line therapies, when to stop treatment, and management of CHB in special populations.[1]

The guidelines recommend that:

- All persons with CHB and evidence of compensated or decompensated cirrhosis, should be treated as a priority (regardless of ALT level, HBeAg status, or HBV DNA level) (Strong recommendation, moderate quality of evidence).[1]
- Adults age >30 years old without evidence of cirrhosis, if they have persistently abnormal ALT levels and elevated HBV DNA >20,000 IU/mL should be treated (Strong recommendation, moderate quality of evidence).[1]
- Tenofovir or entecavir are first-line therapy in adults, due to the high barrier of drug resistance, with entecavir being recommended in children aged 2 to 11 years (Strong recommendation, moderate quality of evidence).[1]
- Therapy should be switched to tenofovir if antiviral resistance to lamivudine, entecavir, adefovir, or telbivudine is confirmed or suspected (Strong recommendation, low quality of evidence).[1]
- All persons with cirrhosis continue antiviral therapy lifelong, due to the risk of HBV reactivation causing liver complications (Strong recommendation, low quality of evidence).[1]
- NA therapy discontinuation can be considered in persons who meet the following criteria: no evidence of cirrhosis, can be followed long term for reactivation, evidence of HBeAg loss and conversion to anti-HBe with an additional one year of treatment, persistently normal ALT levels, and undetectable HBV DNA levels (Conditional recommendation, low quality of evidence).[1]
- The guidelines do recommend retreatment with antiviral therapy in cases of reactivation (HBsAg or HBeAg become positive, increase in ALT levels, or detectable HBV DNA) (Strong recommendation, low quality of evidence).[1]

The recommendations on when to treat pregnant women are the same as for other adults.[1] The preferred antiviral therapy is tenofovir based on safety data in HBV-infected pregnant women from the Antiretroviral Pregnancy Registry.[1]

Guidelines from the American Association for the Study of Liver Diseases (AASLD) [5]

The AASLD issued practice guidelines for the treatment of chronic hepatitis B in August 2015.[5] The guideline committee evaluated the evidence using the GRADE approach and summarized the quality of the evidence. Recommendations were based on quality of evidence, benefits and harms, patients' preferences, and clinical context.[5] The guideline recommendations are summarized in **Table 3**.

Table 3. Summary of AASLD Guideline Recommendations[5]

Recommendation	Quality of Evidence	Strength of Recommendation
Treatment of Persons with Immune-Active CHB		
Treat with antiviral therapy, regardless of HBeAg status	Moderate	Strong
Pegylated interferon (Peg-IFN), entecavir, or tenofovir as preferred initial therapy	Low	Strong
Treatment of Persons with Immune-Tolerant CHB		
No treatment recommended for most	Moderate	Strong
Consider treatment if >40 years old, HBV DNA ≥1,000,000 IU/mL, and liver biopsy showing fibrosis	Very Low	Conditional
Treatment of CHB in Pregnancy		
Treatment is recommended in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL	Low	Conditional
No treatment in pregnant women with HBV DNA ≤200,000 IU/mL	Low	Strong

Immune-active CHB is defined as ALT elevation of >2 times the ULN in addition to elevated HBV DNA >2,000 IU/mL in HBeAg negative or >20,000 IU/mL in HBeAg positive.[5] Therapy is recommended by the AASLD guidelines for all persons with immune-active CHB.[5] Additionally, therapy is recommended for all persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level. Additional factors that may be considered increased risk are age 40 years and older, family history of HCC, and presence of extrahepatic manifestations.[5] Antiviral therapies are similar in reducing the risk of liver-related complications with head-to-head comparisons failing to show superiority of one agent over another.[5] Peg-IFN, tenofovir, and entecavir are considered the preferred therapies largely due to lack of resistance with long-term use.[5] Length of NA therapy is variable, in some cases indefinite therapy is warranted. Factors to consider in determining duration of therapy include HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis/decompensation.[5]

The AASLD guidelines recommend against antiviral therapy in those with immune-tolerant CHB, defined as ALT ≤30 U/L for men and ≤19 U/L for women.[5] The guidelines do suggest therapy in adults >40 years of age, HBV DNA ≥1,000,000 IU/mL, and liver biopsy showing significant necroinflammation or fibrosis.[5] Those with immune-tolerant CHB should have ALT levels tested at least every 6 months to monitor for potential transition to immune-active or immune-inactive CHB (Quality of evidence: Very low, Strength of recommendation: Conditional).[5]

In HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on therapy, AASLD guidelines suggest discontinuing NA therapy after a period of treatment consolidation.[5] The period of consolidation includes continuing treatment for at least 12 months with persistently normal ALT levels and

undetectable HBV DNA.[5] However, an alternative approach would be to treat until serum HBsAg loss.[5] Indefinite antiviral therapy is recommended in all HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on NA therapy, due to concerns for decompensation and potential death.[5] Indefinite antiviral therapy is recommended in adults with HBeAg-negative immune-active CHB (Quality of evidence: Low, Strength of recommendation: Conditional).[5]

AASLD recommends treatment to reduce the risk of perinatal transmission in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL.[5] Tenofovir, lamivudine, and telbivudine are the only antivirals that have been studied in pregnancy, however the guidelines do not recommend one agent over another.[5]

New Safety Alerts:
None

New Formulations or Indications:
Vemlidy® (tenofovir alafenamide) was FDA approved for treatment of CHB infection in November 2016.[11] It is a nucleotide analog reverse transcriptase inhibitor and prodrug of tenofovir, similar to that of tenofovir disoproxil fumarate.[11] Tenofovir alafenamide has shown greater plasma stability compared to tenofovir disoproxil fumarate which allow for lower doses of tenofovir alafenamide to be efficacious.[12] The efficacy and safety of tenofovir alafenamide was studied in two randomized, double-blind, active-controlled, Phase 3 clinical trials, Study 108 and Study 110.[11] Tenofovir alafenamide 25 mg daily was compared to tenofovir disoproxil fumarate 300 mg daily in HBeAg-negative subjects in Study 108 (n=425) and in HBeAg-positive subjects in Study 110 (n=873).[11] They included both treatment-naïve and treatment-experienced subjects with compensated liver disease.[11] The efficacy endpoint in both trials was the proportion of subjects with plasma HBV DNA levels < 29 IU/mL at Week 48.[11] At week 48, both studies showed tenofovir alafenamide was statistically non-inferior to tenofovir disoproxil fumarate, with treatment difference of 1.8% (95% CI -3.6%-7.2%) in Study 108 and -3.6% (95% CI -9.8%-2.6%) in Study 110.[11] There was no significant difference in discontinuations due to adverse reactions between the two groups, in either of the studies.[11] In a combined analysis of Study 108 and Study 110, there was a statistically significant difference in change from baseline estimated glomerular filtration rate using Cockcroft-Gault ($eGFR_{CG}$) with tenofovir disoproxil fumarate at week 72 compared to tenofovir alafenamide (-4.2 mL/min vs. -0.6 mL/min, P<0.001).[12] A smaller decrease in bone mineral density in the hip (-2.43% vs -0.29%) and spine (-2.52% vs. -0.6%) at week 72 was also observed (P<0.001).[12]

Vemlidy is dosed at 25 mg once daily and is recommended to be taken with food.[11] Tenofovir alafenamide does not require dosage adjustment in patients with creatinine clearance (CrCl) 15-50 mL/min, compared to tenofovir disoproxil fumarate which requires dose adjustment with CrCl < 50 mL/min.[12] It is not recommended for use in patients with creatinine clearance less than 15 mL/min or those with severe hepatic impairment.[11] Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp), which effects bioavailability of the drug, therefore drugs that strongly effect P-gp will alter absorption of tenofovir alafenamide.[11] Common adverse reactions are similar to tenofovir disoproxil fumarate, which includes headache, fatigue, abdominal pain, cough, and back pain.[11]

Randomized Controlled Trials:
A total of 20 citations were manually reviewed from the literature search. After manual review, 19 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in **Table 4**. Full abstracts are included in

Table 4: Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Fung, et al.[13] DB, MC	TDF 300 mg once daily vs. FTC/TDF 200/300 mg once daily x 240 weeks	CHB (positive HBsAg test for ≥6 months) with HBV DNA ≥3000 IU/mL and confirmed LAM resistance (n=280)	Suppressed plasma HBV DNA (<69 IU/mL) at 96 weeks	89.4% in TDF group (n=141) vs. 86.3% in FTC/TDF group (n=139) (P=0.43) *HBeAg positive*: 84.6% in TDF group vs. 82.4% in FTC/TDF group (P=0.73) *HBeAg negative*: 93.4% in TDF group vs. 90% in FTC/TDF group (P=0.53)

Abbreviations: DB=Double blind; MC = Multi-center; TDF= tenofovir; FTC/TDF= emtricitabine + tenofovir; CHB= chronic hepatitis B; HBsAg= hepatitis B surface antigen; HBV= hepatitis B virus; LAM= lamivudine

References:

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13. Fung S, Kwan P, Fabri M, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2014;146(4):980-988. doi:10.1053/j.gastro.2013.12.028.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SOLUTION	EPIVIR HBV	LAMIVUDINE	Y
ORAL	TABLET	EPIVIR HBV	LAMIVUDINE	Y
ORAL	TABLET	LAMIVUDINE	LAMIVUDINE	Y
ORAL	TABLET	LAMIVUDINE HBV	LAMIVUDINE	Y
ORAL	TABLET	VIREAD	TENOFOVIR DISOPROXIL FUMARATE	Y
ORAL	POWDER	VIREAD	TENOFOVIR DISOPROXIL FUMARATE	N
ORAL	SOLUTION	BARACLUDE	ENTECAVIR	N
ORAL	TABLET	ADEFOVIR DIPIVOXIL	ADEFOVIR DIPIVOXIL	N
ORAL	TABLET	BARACLUDE	ENTECAVIR	N
ORAL	TABLET	ENTECAVIR	ENTECAVIR	N
ORAL	TABLET	HEPSERA	ADEFOVIR DIPIVOXIL	N
ORAL	TABLET	TYZEKA	TELBIVUDINE	N
ORAL	TABLET	VEMLIDY	TENOFOVIR ALAFENAMIDE	N

Appendix 2: Abstracts of Clinical Trials

1. Fung S, Kwan P, Fabri M, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2014;146(4):980-988.

Background & Aims: Tenofovir disoproxil fumarate (TDF) is active against lamivudine-resistant hepatitis B virus (HBV) infection, but data to support its clinical efficacy in this setting are limited.
Methods: In a prospective, double-blind, 96-week trial, patients were randomly assigned (1:1) to groups given TDF (300 mg, n = 141) or a combination of emtricitabine (FTC, 200 mg; n = 139) and TDF (300 mg, FTC/TDF). Patients were hepatitis B e antigen (HBeAg)−positive or HBeAg-negative, with levels of HBV DNA ≥3 log10 IU/mL and lamivudine resistance mutations (HBV polymerase or reverse transcriptase amino acid substitutions rtM204I/V ± rtL180M by INNO-LiPA Multi-DR v3; Innogenetics, Inc, Alpharetta, GA). The primary end point was proportion with HBV DNA <69 IU/mL (Roche COBAS Taqman assay; Roche Molecular Systems, Inc, Pleasanton, CA).
Results: Patient groups were well matched for demographic and disease characteristics, including region (60% from Europe), HBV genotype (45% genotype D), HBeAg status (47% HBeAg-positive), and duration of lamivudine treatment (mean, 3.8 years). At week 96 of treatment, 89.4% of patients in the TDF group and 86.3% in the FTC/TDF group had levels of HBV DNA <69 IU/mL (P = .43). HBeAg loss and seroconversion did not differ between groups; only 1 patient (0.7%) in the FTC/TDF group lost hepatitis B surface antigen. Treatment was well tolerated; confirmed renal events (creatinine increase of ≥0.5 mg/dL [>44 umol/L], creatinine clearance <50 mL/min, or level of PO4 <2 mg/dL [<0.65 mmol/L]) were generally mild and infrequent (<1%). Small reductions (<2%) in mean bone mineral density of hip and spine were detected by dual-energy x-ray absorptiometry in both groups. No TDF resistance developed through 96 weeks of treatment.
Conclusions: TDF alone is safe and effective for treatment of patients with lamivudine-resistant, chronic HBV infection.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2017

1 exp Hepatitis B/dt, th [Drug Therapy, Therapy] 8517
2 exp Lamivudine/ 5752
3 exp Tenofovir/ 2791
4 adefovir.mp. 2031
5 entecavir.mp. 1533
6 telbivudine.mp. 524
7 2 or 3 or 4 or 5 or 6 9837
8 1 and 7 4043
9 limit 8 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 174

Appendix 4: Prior Authorization Criteria

Hepatitis B Antivirals

Goal(s):

- Approve treatment supported by medical evidence and consensus guidelines
- Cover preferred products when feasible for covered diagnosis

Length of Authorization:

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

Requires PA:

- All Hepatitis B antivirals

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Pediatric Age Restrictions:

- lamivudine (Epivir HBV) – 2-17 years
- adefovir dipivoxil (Hepsera) – 12 years and up
- entecavir (Baraclude) – 2 years and up
- telbivudine (Tyzeka) –16 years and up
- tenofovir disoproxil fumarate (Viread) – 12 years and up
- tenofovir alafenamide (Vemlidy) – safety and effectiveness not established in pediatrics

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the request for an antiviral for the treatment of HIV/AIDS?	**Yes:** Approve for up to 12 months	**No:** Go to #4

Approval Criteria		
4. Is the request for treatment of chronic Hepatitis B?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is this a continuation of current therapy previously approved by the FFS program (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin."***	**Yes:** Go to Renewal Criteria	**No:** Go to #6
6. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	**Yes:** Document intolerance or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30-day supply.	**No:** Go to #7
7. Will the prescriber consider a change to a preferred product?	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve requested treatment for 6 months with monthly quantity limit of 30-day supply
Renewal Criteria		
1. Is the patient adherent with the requested treatment (see refill history)?	**Yes:** Go to #2	
2. Is HBV DNA undetectable (below 10 IU/mL by real time PCR) or the patient has evidence of cirrhosis? Note: Antiviral treatment is indicated irrespective of HBV DNA level in patients with cirrhosis to prevent reactivation.	**Yes:** Approve for up to 1 year with monthly quantity limit of 30-day supply	

P&T Review: *3/17; 3/12*
Implementation: *5/29/14; 1/13*

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Drug Class Update: Non-analgesics for Pain

Date of Review: March 2017 **Date of Last Review:** June 2011 (DERP)

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

Purpose for Class Update:
Evaluate recent evidence for alternatives to opiate medications such as antiepileptics, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine in managing chronic and neuropathic pain.

Research Questions:
1. What is the comparative effectiveness of antiepileptics, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine for chronic non-cancer pain or neuropathic pain?
2. What are the comparative harms of antiepileptics, tricyclic antidepressants, SNRIs, and topical lidocaine for neuropathic pain or chronic pain?
3. Are there differences in effectiveness or harms of antiepileptics, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

Conclusions:
Efficacy
- Recent comparative trials do not reveal a clear preference for one class of medications over another for management of neuropathic pain.[1]
- Moderate quality evidence exists to support the use of pregabalin to manage central neuropathic pain.[2]
- Moderate quality evidence shows that duloxetine is an effective agent to manage chronic LBP.[3]
- Low quality evidence supports the safety and efficacy of desipramine and amitriptyline in management of DPN or post herpetic neuropathy (PHN).[4,5]
- Low quality evidence supports the efficacy of carbamazepine in trigeminal neuralgia, DPN, and post-stroke pain.[6]
- Moderate quality evidence shows no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in treatment of diabetic peripheral neuropathy (DPN).[7]
- Moderate quality evidence indicates little or no effect for lamotrigine, oxcarbazepine and topiramate for treatment of neuropathic pain.[1, 3, 4] There is insufficient evidence to demonstrate the efficacy of valproic acid, lacosamide, levetiracetam, and phenytoin in management of neuropathic pain.[2]
- There is insufficient evidence to evaluate the effect of antiepileptics to manage acute nonradicular low back pain (LBP).[3]
- There is insufficient evidence to support the use of topical lidocaine in mixed peripheral neuropathic pain.[10]
- There is insufficient evidence to support the use of milnacipran for management of neuropathic pain.[11]

Safety

- There is insufficient comparative evidence in patients with neuropathic pain or chronic pain to assess comparative safety.
- Moderate quality evidence revealed approximately 80% of participants experienced an adverse event with an antiepileptic, but about 70% of participants receiving placebo did as well. Withdrawals due to adverse events were much higher with antiepileptics than placebo.[2]
- Moderate quality evidence showed that adverse events experienced with gabapentin were significantly higher than with placebo (RR 1.25; 95% CI 1.2 to 1.3). Adverse events noted with gabapentin included somnolence, dizziness, peripheral edema and gait disturbances.[12]
- Low quality evidence showed that 65% of participants experienced at least one adverse event with carbamazepine, and 27% with placebo. For every 5 participants treated, 2 experienced an adverse event who would not have done so with placebo.[6]
- Almost 10% of participants in one low quality lamotrigine trial reported a skin rash (RR 1.4; 95% CI 1.01 -2.0; NNH 27; 95% CI 16-89).[9]
- Low quality evidence demonstrated that participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.[4]

Specific Populations

- There is insufficient evidence to identify differences in effectiveness or harms of antiepileptics, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain.

Recommendations:

- Revise prior authorization (PA) criteria as outlined in **Appendix 6** to restrict use to funded pain conditions and include separate PA criteria for the following medications:
    - Pregabalin
    - Milnacipran
    - Lidocaine Patch
    - Topiramate Extended Release (non-preferred products)
- Add quantity limit of 3 patches/24 hours for topical lidocaine patches which is the maximum approved daily dose to insure safe use.

Previous Conclusions:

- Overall, there is low to moderate evidence comparing benefits and harms of available drugs for neuropathic pain.
- The majority of available direct comparative evidence is in patients with either diabetic neuropathy or postherpetic neuralgia and included comparisons between amitriptyline or nortriptyline and gabapentin, pregabalin, or lamotrigine.
- There is insufficient comparative effectiveness evidence in patients with other types of neuropathic pain to assess comparative safety. Conclusions for efficacy were largely based from placebo-controlled trials and indirect analyses.
- In patients with diabetic neuropathy and postherpetic neuralgia, there is moderate evidence that there is not a statistically significant difference in response or withdrawal due to adverse events with gabapentin, pregabalin, and lamotrigine compared to tricyclic antidepressants and low strength evidence that there is no difference between oral pregabalin and the lidocaine patch.
- Low strength evidence based on indirect comparisons demonstrates that duloxetine, pregabalin, and gabapentin are superior to lacosamide and lamotrigine and there are no differences between pregabalin, duloxetine, and gabapentin or comparisons of lidocaine and amitriptyline or gabapentin.

Previous Recommendations:

- Include topical analgesics into current neuropathic pain PA criteria including Lidoderm patch and capsaicin 8% patch to restrict use to patients with postherpetic neuralgia who have failed or cannot tolerate oral therapy with gabapentin and TCA's.
- Designate gabapentin ER as a line extension of currently available gabapentin and as a non-preferred agent due no management demonstrated in evidence-based guidelines and alternative therapy with available comparative effectiveness evidence showing efficacy in neuropathic pain.

Background:

Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain that typically last greater than 3 months or past the time of normal tissue healing.[14] A Medical Expenditure Panel survey completed in 2008 estimated that approximately 100 million adults in the United States (U.S.) were affected by chronic pain.[15] The costs of medical care for patients with a primary diagnosis of pain including headache, abdominal pain, chest pain and back pain ranged from $261 to $300 billion.[15] The IASP defines neuropathic pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system.[16] Neuropathic pain can be caused by injury, medical interventions (e.g., chemotherapy, surgery), or different diseases (e.g., diabetes, herpes zoster, or human immunodeficiency virus).[17] Opiates are frequently used to treat patients with persistent non-cancer pain despite minimal evidence to support their use. Multiple studies have been published that describe the harms of long-term opiate therapy in patients with chronic, non-cancer pain.[18] A recent retrospective study of Tennessee Medicaid patients compared the risk of death among chronic non-cancer patients taking long-acting opiates with patients taking an antiepileptic or low dose antidepressant for their analgesic effect.[19] The long-acting opioid group was followed up for a mean 176 days and had 185 deaths while the alternative treatment group was followed up for a mean 128 days and had 87 deaths.[19] The hazard ratio (HR) for mortality in the opioid cohort was 1.64 (95% CI, 1.26-2.12) with a risk difference of 68.5 excess deaths (95% CI, 28.2-120.7) per 10,000 person-years.[19] Given the adverse impact of prolonged long term opiate therapy, there is increased interest in alternative therapies to manage chronic non-cancer pain. The focus of this review will be on the comparative safety and effectiveness of non-analgesics used in practice to manage neuropathic and other forms of chronic pain, such as antidepressants, antiepileptics and topical lidocaine. **Appendix 2** lists the specific medications that were included in this review and identifies their status on the Oregon Health Plan (OHP) preferred drug list (PDL). **Table 1** in **Appendix 5** outlines pain conditions that are funded under the OHP. Skeletal muscle relaxants used to manage low back pain (LBP) will be reviewed separately.

Tricyclic antidepressants (TCAs), which include amitriptyline, imipramine, nortriptyline and desipramine, have been shown to be effective in treating a variety of painful neuropathic conditions like DPN, PHN, polyneuropathy, and post-stroke pain.[20] The analgesic effect of TCAs occurs at a lower dose than doses used to treat depression and with more rapid onset.[21] Studies have shown that the analgesic effects are independent of the presence of any changes in depression or mood state.[21] The primary mechanism of TCA action is through reuptake inhibition of norepinephrine and serotonin, which increases the activation of descending inhibitory pathways in the midbrain and spinal cord and contributes to their analgesic effect.[17] Of the TCAs, secondary amines, including nortriptyline and desipramine, are preferred because they provide pain relief that is comparable to amitriptyline while causing fewer side effects.[17] Serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, have also shown efficacy in treating peripheral neuropathic pain and other chronic pain conditions.[17] Duloxetine has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of painful DPN, fibromyalgia, and chronic musculoskeletal pain.[22] Venlafaxine has approval for the treatment of depression, anxiety disorder, and panic disorder but does not have FDA approval for pain management.[23] Milnacipran, another SNRI, is approved for the treatment of fibromyalgia, but not for depression or other neuropathic pain conditions.[24] Of note, fibromyalgia is not an OHP-funded condition, so prior authorization (PA) criteria have been developed to restrict use of milnacipran for funded conditions.

The first antiepileptic used in clinical trials to treat a neuropathic pain disorder was carbamazepine. Prior to approval for seizures, carbamazepine was approved by the FDA for trigeminal neuralgia.[25] Carbamazepine acts to stabilize the inactivated state of voltage-gated sodium channels thereby decreasing the excitability of frequency-dependent neuronal activity of A-delta and C-fibers, thus suppressing spontaneous activity.[14] Carbamazepine and its derivative oxcarbazepine have continued to be used for the treatment of trigeminal neuralgia, but have not been shown to be as effective in treating other neuropathic pain disorders.[17] Gabapentin and pregabalin are structural analogs of the neurotransmitter gamma-aminobutyric acid (GABA). However, they do not inhibit GABA receptors; they inhibit calcium influx and consequently decrease the release of excitatory neurotransmitters which modulate pain.[26] Gabapentin and pregabalin have both been shown to be effective when compared with placebo in treating painful DPN, PHN, polyneuropathy, neuropathic cancer pain, central post-stroke pain, and spinal cord injury pain.[17] Other antiepileptic drugs such as topiramate, valproic acid, levetiracetam, zonisamide, tiagabine and lamotrigine have been studied for various neuropathic pain disorders; however, evidence of their effectiveness is lacking.[17] A 2007 systematic review of lamotrigine for acute and chronic pain concluded it does not have a place in the treatment of pain, given other more effective therapies.[15]

Lidocaine is a local anesthetic that blocks abnormal activity in sodium channels located on peripheral neurons in painful regions.[27] Topical lidocaine products are available as a cream, ointment or patch. Only 1-5% of the topical lidocaine dose is absorbed which produces an analgesic effect, but does not cause a complete sensory block.[27] The lidocaine patch is approved for relief of pain associated with PHN.[27] The FDA approval was based on one unpublished trial in a single dose study in 35 PHN patients whose pain intensity was monitored over 12 hours.[27] After reviewing the initial study, the FDA requested more data. Therefore, an additional open label, multiple dose, 2-week treatment trial was conducted in 32 subjects who had responded in the previous study. Statistically significant differences favoring the lidocaine patch over observation were noted in terms of time to exit from the trial (14 versus 3.8 days; $p < 0.001$).[27] A 2014 Cochrane review found insufficient evidence to support the use of topical lidocaine formulations (patch, cream, gel or spray) in mixed peripheral neuropathic pain.[10] This Cochrane review was included in the topical analgesic scan discussed at the January 2016 P and T committee meeting.[28]

A summary of recent head to head trials is included in **Table 2**. The head-to-head trials were primarily of amitriptyline, duloxetine, gabapentin, and pregabalin in patients with painful DPN. The comparative trials do not reveal a clear preference for one class of medications over another. Effectiveness outcomes utilized in these trials included patient pain response, use of rescue analgesics, speed and duration of response, relapse, and functional capacity. Both duloxetine and amitriptyline demonstrated efficacy in DPN.[29] Another study concluded was no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in treating diabetic patients with DPN.[7] Amitriptyline and nortriptyline were shown to be equivalent for overall adverse effects and discontinuation rates in patients with DPN.[30] Another study showed the efficacy of venlafaxine, pregabalin, and carbamazepine in pain reduction in patients with diabetic neuropathy, and although pregabalin was shown to be superior to carbamazepine and venlafaxine in relieving pain, no significant superiority was shown between carbamazepine and venlafaxine.[31] In patients with DPN inadequately treated with gabapentin, switching to duloxetine instead of pregabalin may have provided better pain reduction.[32]

Dosing recommendations for non-opiate medications used in chronic pain management are outlined in **Appendix 3, Table 1**. Precautions and warnings for these medications are included in **Appendix 3, Table 2**. A summary of evidence supporting the use of these therapies in different pain conditions is described in **Appendix 3, Table 3**.

The interpretation of chronic pain trials is difficult due to a number of potential biases. Most of the trials are of short duration and include a small number of subjects.[33] The use of the "last observation carried forward" imputation method can bias results, often generating statistical significance when adverse event withdrawals are high.[33] Furthermore, the use of average pain scores can be misleading compared with responder analysis in which withdrawal is regarded as

non-response.[33] In addition to evaluating the risk of potential biases, it is difficult to compare studies because randomized controlled trials (RCTs) differ substantially in research design. Many older RCTs of TCAs are crossover trials, while newer medications have been assessed using a parallel group research design.[17] Also, recent trials have often used a run-in period and have required pain of at least moderate baseline severity.[17] The outcomes measured have also varied; newer RCTs have used measures such as daily numeric ratings of pain intensity and measures of health-related quality of life that were not collected in many older RCTs.[17] In general, most trials of effective treatments have found that less than 50% of patients achieve satisfactory pain relief.[17]

Utilization of the non-analgesics from July 1, 2016 through September 30, 2016 is described in **Appendix 5**. Because this information is based on claims data, it is not clear which diagnosis is associated with each claim. The antiepileptics and antidepressants may be prescribed for other reasons besides pain. The most commonly prescribed non-analgesic drug that might be used for pain was duloxetine, followed by gabapentin, amitriptyline, and venlafaxine. The requests for lidocaine patch were substantially less than the other 4 agents. In addition to total claims data, the reasons why fee for service clients may not have received medications are also described. Some patients lost eligibility while others may have received insurance coverage from another provider.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews

Overview of Antiepileptics for Neuropathic Pain

A 2013 Cochrane overview assessed the evidence for antiepileptics in treatment of neuropathic pain.[2] Ten Cochrane reviews were included in this assessment. Ninety-one studies including 17,955 subjects were included.[2] Antiepileptics studied for management of neuropathic pain included carbamazepine (n= 15 studies), gabapentin (n=29), lacosamide (n=6), lamotrigine (n=11), oxcarbazepine (n =4), pregabalin (n= 19), topiramate (n= 4), and valproic acid (n=3). Most of the studies were conducted over short durations (i.e., 6 weeks) with small sample sizes. All of the trials were randomized and double-blinded. The efficacy data for each painful condition was analyzed in 3 tiers, according to outcome and freedom from known sources of bias.[2] The first tier met current best standards; at least 50% pain intensity reduction over baseline was assessed as an outcome, the use of last observation carried forward (LOCF) for dropouts was not used, an intention-to-treat (ITT) analysis was completed, and parallel group studies had at least 200 participants lasting 8 weeks or more.[2] The second tier used data from at least 200 participants where one or more of the above conditions were not met.[2] The third tier of evidence related to data from fewer than 200 participants, or with several important methodological problems that limited interpretation.[2] This tier analysis was employed by the other authors in subsequent systematic reviews evaluating the efficacy of pharmacologic agents in neuropathic pain management.

No studies in the Cochrane overview reported top tier results. Second tier (moderate) evidence was available to assess gabapentin and pregabalin for efficacy in DPN and PHN.[2] Trials for gabapentin versus placebo in DPN utilized a wide range of doses from 600 to 3600 mg per day to reduce pain intensity by 50% from baseline (Risk Ratio (RR)1.8; 95% CI 1.4-2.2).[3] The calculated NNT was 5.8 (95% CI 4.3-9.0) based on data pooled from 4 studies with a total of 829 participants.[2] Similar results were noted when pregabalin 600 mg per day was compared to placebo for 50% pain reduction (RR 1.5; 95% CI 1.3-1.8) in 1005 subjects from 4 pooled trials.[2] There was less of an impact on 50% pain reduction observed when pregabalin 300 mg per day was compared to placebo (RR 1.3; 95% CI 1.1-1.6; NNT = 11; 95% CI 6.1-54) than was noted with gabapentin or pregabalin 600 mg.[2]

Relief of PHN with gabapentin required higher daily doses (1800-3600 mg) for at least a 50% reduction in pain intensity compared to placebo (RR = 1.7; 95% CI 1.3-2.2) with a NNT of 8 (95% CI 6-14) in 3 studies comprised of 892 subjects.[2] Pregabalin 300 mg and 600 mg once daily gave similar results relative to placebo in reducing pain intensity by 50% from baseline (RR 2.7; 95% CI 1.9-4.0 and RR 2.8; 95% CI 2.0-3.9, respectively). Estimated NNT for pregabalin 300 mg per day was 6 (95% 4-9) and 4 (95% CI 4-6) for the 600 mg daily dose.[2] There were data from approximately 500 patients pooled for the pregabalin PHN analysis. For relief of central neuropathic pain, the only data available was with pregabalin 600 mg once daily. In 2 studies with a total of 176 patients, pregabalin compared to placebo showed a 50% pain reduction with a RR of 3.6 (95% CI 1.5-8.4) and NNT of 6 (95% CI 4-14).[2]
No second tier evidence was found to evaluate antiepileptics in treatment of trigeminal neuralgia or HIV-related neuropathic pain. For other antiepileptic drugs, there was very little evidence to evaluate efficacy (valproic acid) or low quality evidence subject to a number of biases that overestimated efficacy (carbamazepine).[2] Moderate quality evidence indicated little or no effect for lamotrigine, oxcarbazepine and topiramate in treatment of neuropathic pain.[2] There was insufficient evidence of efficacy for valproic acid, lacosamide, levetiracetam, and phenytoin in treatment of neuropathic pain.[2] Evidence for lacosamide was too unreliable to make any conclusions.[2] There were no effective trials that evaluated levetiracetam or phenytoin in management of neuropathic pain.

Withdrawals due to adverse events were much higher with antiepileptics than placebo except for carbamazepine, where studies were of short duration, and for the low dose of 150 mg daily of pregabalin.[2] Numbers needed to harm (NNH) decreased as doses increased for pregabalin and locasamide. About 80% of participants experienced an adverse event with an antiepileptic, but about 70% of participants receiving placebo did as well.[2]

Carbamazepine for Neuropathic Pain
A 2014 Cochrane systematic review updated a 2011 report which evaluated carbamazepine for acute and chronic pain in adults.[6] The update used higher standards of evidence than the earlier review, which resulted in the exclusion of five studies that were previously included.[6] However, no additional studies were identified for inclusion. Ten studies evaluated trigeminal neuralgia, DPN, and post-stroke pain in 480 subjects.[6] Nine studies used a cross-over design, and one trial used a parallel group design. Most of the studies were of short duration, lasting 4 weeks or less. The studies were graded as low quality due to relatively short trial periods, poorly defined outcomes, incomplete reporting, and small sample size.[6] The evidence for this review was compiled by the same authors as the 2013 Cochrane review of antiepileptic drugs in neuropathic pain. Consequently, the same 3 tiers of evidence were used to evaluate outcomes as previously described. No study provided first or second tier evidence for an efficacy outcome. Third tier (low quality) evidence from 4 trials showed carbamazepine generally provided better pain relief than placebo in trigeminal neuralgia, DPN, and post stroke patients with pain. At least 50% pain reduction from baseline for carbamazepine 100 mg to 2400 mg daily compared to placebo resulted in a RR of 6.5 (95% CI 3.4 -12) with a NNT of 2 (95% CI 2-3).[6] In the 4 studies, 65% of participants experienced at least one adverse event with carbamazepine, and 27% with placebo. Reported adverse events included blood dyscrasias, rash, life threatening cutaneous reactions, and impaired mental and motor function.[6] For every 5 participants treated, 2 experienced an adverse event who would not

have done so with placebo.[6] This systematic review provides low quality evidence to support the use of carbamazepine in treatment of trigeminal neuralgia, DPN, and post-stroke pain.

Oxcarbazepine for Neuropathic Pain

A 2013 Cochrane review focused on the safety and efficacy of oxcarbazepine in treatment of neuropathic pain.[8] Four multi-centered, randomized, placebo-controlled, double-blind trials with a total of 779 participants were eligible for inclusion.[8] All 4 studies were funded by the manufacturer. Three of them investigated oxcarbazepine in people with painful DPN (n=634) and one was a trial of oxcarbazepine for neuropathic pain due to radiculopathy (n=145).[8] The authors graded the evidence as moderate quality due to the large amount of incomplete outcome data leading to possible attrition bias, although they acknowledged the studies were well designed due to adequate blinding and randomization.[8] Results for painful DPN showed that compared to baseline, the proportion of participants who reported a 50% or 30% reduction of pain scores after 16 weeks of treatment was significantly higher in the oxcarbazepine group than the placebo group [50% pain reduction: RR 1.91 ; 95% CI 1.08 - 3.39; NNT 6; 95% CI 4 to 41 and 30% reduction: RR 1.57; 95% CI 1.01 to 2.44 ; NNT 7; 95% CI 4 to 114].[8] However, both results were based on data from a single positive trial (n=146) since the 2 negative trials did not provide data that could be included in a meta-analysis.[8] For participants with neuropathic pain due to radiculopathy, the trial demonstrated no significant efficacy for oxcarbazepine.[8] Although trial reports stated that most adverse effects were mild to moderate in severity, the proportion of events leading to withdrawals was statistically higher in the oxcarbazepine group than in the placebo group both for painful diabetic neuropathy (RR 3.86; 95% CI 2.29 - 6.40) and radiculopathy (RR 2.84; 95% CI 1.55 - 5.23).[8] There was insufficient evidence to determine the efficacy or safety of oxcarbazepine for other kinds of neuropathic pain. The authors concluded more well designed RCTs are needed.[8]

Lamotrigine for Neuropathic Pain

A 2013 Cochrane review updated a previous 2007 report that evaluated lamotrigine for acute and chronic pain.[9] This updated review did not identify any new additional studies but used higher standards of evidence than previous reports.[9] Twelve studies were included involving 1,511 participants with chronic neuropathic pain: central post-stroke pain (n= 1 trial), chemotherapy-induced neuropathic pain (n=1), diabetic neuropathy (n=4), HIV-related neuropathy (n=2), mixed neuropathic pain (n=2), spinal cord injury-related pain (n=1), and trigeminal neuralgia (n=1).[9] Study duration was 2 weeks in one study and at least 6 weeks in the remainder; 8 trials were of 8-week duration or longer.[9] The authors used 3 tiers to evaluate the quality of evidence as previously described. No study provided first-tier evidence for an efficacy outcome. The included studies were rated as second (moderate quality) to third (low quality) tier evidence because of LOCF imputation and small study size.[9] There was no convincing evidence that lamotrigine is effective in treating DPN at doses of 200 mg to 400 mg daily as the relative risk for 50% pain reduction was not significant (RR = 1.1; 95% CI 0.82 to 1.4).[9] Almost 10% of participants in the lamotrigine arm reported a skin rash (RR 1.4; 95% CI 1.01 -2.0; NNH 27; 95% CI 16-89).[9] The authors concluded that given the availability of more effective treatments including antiepileptics and antidepressant medicines, lamotrigine does not have a significant place in therapy based on the available evidence.[9] The adverse effect profile of lamotrigine is also of concern.[9]

Gabapentin for Neuropathic Pain

A 2015 Canadian Agency for Drugs and Technologies in Health (CADTH) report evaluated the clinical efficacy and safety of gabapentin compared with placebo in adults with neuropathic pain.[34] Seven publications including 6 systematic reviews and 1 RCT met criteria for inclusion in the CADTH report. Most of the patients included in the trials had either PHN or DPN while a small proportion (11%) had mixed neuropathic pain or nerve injury pain. For PHN, 1,816 patients were included in placebo controlled trials with gabapentin. Thirty-four percent of patients treated with gabapentin showed substantial benefit (defined as > 50% pain

intensity reduction) compared to 21% of patients that received placebo (RR 1.6; 95% CI 1.3 to 1.9) with an NNT of 8 (95% CI 6 to 12). [34] For DPN, 1,277 patients were included in the placebo controlled gabapentin trials. Thirty-eight percent of patients treated with gabapentin showed substantial benefit compared to 21% of placebo treated patients (RR 1.9; 95% CI 1.5 to 2.3) with an NNT of 6 (95% CI 5 to 9).[34] Withdrawals due to adverse events (AEs) were significantly higher and withdrawals due to lack of efficacy significantly lower with gabapentin compared to placebo for the various conditions considered together (RR 1.4; 95% CI 1.1 to 1.7 for withdrawal due to AEs and RR 0.5 95% CI 0.3 to 0.8 for withdrawal due to lack of efficacy).[34] Also, considering the various conditions together, the adverse events experienced with gabapentin were significantly higher than with placebo (RR 1.25; 95% CI 1.2 to 1.3).[34] Adverse events included somnolence, dizziness, peripheral edema and gait disturbances.

Milnacipran for Neuropathic Pain

A 2015 Cochrane review updated an earlier 2012 report that assessed the analgesic efficacy and associated adverse events of milnacipran for chronic neuropathic pain in adults.[11] Twenty-seven studies were identified, but only 1 short-term, low quality study of 40 participants met inclusion criteria for the updated review.[11] The subjects had a history of LBP with pain radiating to the legs or buttocks. The study was rated low quality due to inadequate details describing randomization, concealment of allocation, and blinding. The study found no difference in pain scores between milnacipran 100 mg to 200 mg daily or placebo after 6 weeks.[11] Adverse event rates were similar between treatments in this trial. There is insufficient evidence to support the use of milnacipran in managing neuropathic pain.

Desipramine for Neuropathic Pain

A 2014 Cochrane review examined 5 studies that treated 177 participants with DPN or PHN.[4] Four studies used a cross-over design, and one used a parallel group design.[4] Desimpramine doses ranged from 100 mg to 150 mg once daily following titration. Comparators were placebo in 3 studies, fluoxetine, clomipramine (one study each), and amitriptyline (2 studies), and treatment ranged from 2 to 6 weeks.[4] All studies had one or more source of potential bias. The review used the same methods to evaluate the quality of evidence as previous systematic reviews evaluating management of neuropathic pain. No study provided first or second tier evidence for any outcome. No data were available on the proportion of people with at least 50% or 30% reduction in pain, so pooling of data was not possible.[4] Third tier (low quality) evidence in individual studies indicated some improvement in pain relief with desipramine compared with placebo.[4] These data were derived primarily from group mean data and completer analyses in small, short duration studies so major bias was possible. There were too few participants in comparisons of desipramine with another active treatment to draw any conclusions.[4] All studies reported some information about adverse events, but reporting was inconsistent and fragmented. Very low quality evidence demonstrated that participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.[4] Reported adverse effects included syncope, jitteriness, hypotension, tremor, confusion, and sedation. This review found little evidence to support the use of desipramine to treat neuropathic pain. There was very low quality evidence of benefit and harm, but this came from studies that were methodologically flawed and potentially subject to major bias.[4]

Amitriptyline for Neuropathic Pain

The most recent Cochrane review evaluating the safety and efficacy of amitriptyline in neuropathic pain was published in 2015.[35] The review included 15 studies from a previous 2012 review and 2 new studies. Types of neuropathy included painful DPN (n = 5 studies), PHN (n=5), spinal cord injury (n =2), cancer-related pain (n=2), mixed neuropathic pain (n =1), HIV neuropathy (n=1), and post-stroke pain (n=1).[35] Eight cross-over studies with 302 participants had a median of 36 participants, and 9 parallel group studies with 1,040 participants had a median of 84 participants.[35] Study quality analysis was completed using a 3 tier rating as previously described. Most studies were at high risk of bias due to small sample size.[35] There was no first-tier or second-tier evidence for amitriptyline in

treatment for any neuropathic pain condition. Only third-tier (low quality) evidence was available. Combining results from the DPN, PHN and mixed neuropathic pain trials (n=382, 4 trials), benefit for amitriptyline was found compared with placebo (RR 2.0; 95% CI 1.5 to 2.8), with an NNT of 6 (95% CI 4 to 10).[35] More participants who received amitriptyline experienced at least one adverse event compared to placebo (55% vs. 36%, respectively; RR 1.5; 95% CI 1.3 to 1.8).[35] The NNH for one additional harmful outcome was 5.2 (95% CI 3.6 to 9.1).[35] Serious adverse events were rare. Adverse events and early study withdrawal rates were not different, but were rarely reported.[35] This systematic review was unable to find high or moderate quality evidence to support the use of amitriptyline in management of neuropathic pain. Low quality evidence supports the efficacy of amitriptyline in management of DPN, PHN and mixed neuropathic pain.

Duloxetine for Treating Painful Neuropathy or Chronic Pain

A 2014 Cochrane review updated a 2010 assessment of the benefits and harms of duloxetine in treating painful neuropathy and chronic pain.[36] The reviewers identified 18 trials which included 6,407 subjects. The different types of pain included DPN (n=8 studies), fibromyalgia (n=6), depression with painful physical symptoms (n=3) and central neuropathic pain (n=1). The reviewers graded the evidence as moderate quality, although significant attrition and imputation methods increased risk of bias. In addition, nearly every study was sponsored by the drug manufacturer.[36] Duloxetine 60 mg once daily was shown to be effective compared to placebo in treatment of painful DPN, with a RR for ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08).[36] The estimated NNT was 5 (95% CI 4 to 7).[36] Duloxetine 60 mg once daily was also effective when compared to placebo for 50% pain reduction from baseline in patients with painful conditions and depression (RR 1.37, 95% CI 1.19 to 1.59; NNT 8, 95% CI 5 to 14).[36] When compared to placebo in 48 patients with central neuropathic pain, duloxetine showed no effect in improving pain over 12 weeks as measured on a 1-10 VAS (Mean Difference = -1.0, 95% CI -2.05 to 0.05).[36] In all conditions, adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect.[36] The most common adverse effects included nausea, headache, dry mouth, constipation, sedation or dizziness. Most adverse effects were minor, but 16% of participants stopped the drug due to adverse effects.[36] Serious adverse events were rare. Moderate quality evidence supports the use of duloxetine 60 mg once daily in management of DPN.

Noninvasive Treatments for Low Back Pain

A 2016 AHRQ report of noninvasive treatments for LBP evaluated systematic reviews of pharmacologic treatments for nonradicular or radicular LBP.[3] Most of the trials enrolled patients with pain symptoms of at least moderate intensity (> 5 on a 0-10 numeric rating scale for pain).[3] Pain intensity was the most commonly reported outcome, followed by back-specific function. Pharmacological treatments included nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opiates, muscle relaxants, antiepileptics, and antidepressants.[3] For LBP, one systematic review found no differences in pain between TCAs and placebo (4 trials; Standardized Mean Difference (SMD) = -0.10; 95% CI -0.51 to 0.31; I^2 = 32%).[3] Moderate quality evidence showed antidepressants were associated with high risk of adverse events compared with placebo, although there was no difference in the risk of serious adverse effects.[3] Three placebo-controlled trials of moderate quality evaluated duloxetine in management of chronic LBP and found duloxetine was associated with lower pain intensity (differences: 0.58 to 0.74 on a 0-10 scale) and better function (differences 0.58 to 0.74 on the Brief Pain Inventory-Interference on a 0 -10 scale) than placebo.[3] No studies compared TCAs with duloxetine. There was insufficient evidence to evaluate the effect of antiepileptics on controlling acute nonradicular LBP.[3]

New Guidelines

International Association for the Study of Pain

In 2015 IASP funded a neuropathic pain guideline update supported by evidence compiled through a systematic review and meta-analysis.[37] Evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification.[38] The target population included patients of any age with neuropathic pain associated with diabetes, herpes, surgery, amputation, stroke, spinal cord injury, HIV, or multiple sclerosis. Low back pain and trigeminal neuralgia were not assessed in this publication. The primary effect measurements were 30% or 50% pain reduction from baseline. A total of 229 reports published from January 1966 through April 2013 met inclusion criteria developed by the 5 reviewers. Approximately half of the trials were conducted in patients with DPN or PHN. The NNT for most of the positive trials ranged from 4 to 10 patients, which reinforces the modest effect in pain reduction observed with these drugs.[37] Previous IASP recommendations supported the use of TCAs, pregabalin, gabapentin and lidocaine patches as first line agents.[20] This recent update now includes duloxetine as a first line agent and no longer recommends lidocaine patches as first line therapy due the weak quality of evidence.[37] **Table 1** summarizes the recent IASP recommendations.

Table 1. IASP recommendations of drugs that can be used to manage neuropathic pain[37]

	Total Daily Dose	**Recommendations**	**Quality of Evidence**
Strong Recommendations for Use			
Gabapentin	1200-3600 mg in 3 divided doses	First line	High
Pregabalin	300- 600 mg in 2 divided doses	First line	High
Duloxetine	60 -120mg once daily	First line	High
Venlafaxine	150-225mg once daily	First line	High
Tricyclic Antidepressants*	25-150mg once daily or in 2 divided doses	First line	Moderate
Weak Recommendations for Use			
Lidocaine Patches	One to three patches to the region of pain once a day for up to 12 h	Second line – peripheral neuropathic pain only (not central pain)	Low
Inconclusive Recommendations for Use			
Carbamazepine			
Lacosamide			
Lamotrigine			
Oxcarbazepine			
Topiramate			
***** Amitriptyline and imipramine are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls.[13]			

National Institute for Health and Care Excellence (NICE)

The NICE guidelines were updated in December 2014 and are similar to the IASP recommendations.[39] The guideline development group tasked with making recommendations categorized neuropathic pain into 3 broad types: central neuropathic pain, peripheral neuropathic pain and trigeminal neuralgia. The reviewers identified 115 studies with a total of 18,087 subjects for inclusion in the review. Quality of evidence was rated according the GRADE classification.[40] Primary outcomes measures included 30% or 50% reduction in pain intensity. The treatment recommendations are as follows:

- First line drugs include amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain, except for trigeminal neuralgia.[39]
- If initial treatment is not tolerated, try one of the remaining 3 drugs and consider switching again if the second and third drugs tried are also not effective or not tolerated.[39]
- Carbamazepine is recommended as initial treatment for trigeminal neuralgia.[39]
- Treatments that should not be used include lacosamide, lamotrigine, levetiracetam, oxcarbazepine or topiramate.[39]

Randomized Controlled Trials:

A total of 229 citations were manually reviewed from the initial literature search. After further review, 218 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 11 trials are summarized in the table below.

Table 2. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Boyle J et al.[7]

RCT, DB, PG

4 weeks</td>
<td>Pregablin 150 mg BID x 14 days followed by 300 mg BID x 14 days

Vs

Amitriptyline 25 mg BID x 14 days followed by 25 mg qam and 50 mg qhs x 14 days

Vs

Duloxetine 60mg qam x 14 days followed by 60 mg BID x 14 days

Vs

Placebo</td>
<td>Adults ≥ 18 y with DPN with LANSS score > 12 in T1 and T2 DM

N=83</td>
<td>Subjective pain as assessed by the VAS and BPI on Day 1, Day 14 and Day 28</td>
<td>Individual treatments effect on VAS and BPI compared to placebo[7]
<table>
<tr><th>Intervention</th><th>Mean Score on Visual Analog Scale (SE)</th><th>BPI Severity (SE)</th></tr>
<tr><td>Placebo</td><td>16.8 (2.0)</td><td>3.1 (0.4)</td></tr>
<tr><td>Pregablin 150mg BID</td><td>13.5* (2.1)</td><td>2.3* (0.4)</td></tr>
<tr><td>Pregablin 300mg BID</td><td>13.2 (1.7)</td><td>2.4 (0.4)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Placebo</td><td>29.6 (2.3)</td><td>3.5 (0.4)</td></tr>
<tr><td>Amitriptyline 25 mg BID</td><td>22.3 **(2.1)</td><td>2.7*(0.4)</td></tr>
<tr><td>Amitriptyline 25mg QAM and 50mg QHS</td><td>23.6 (2.4)</td><td>2.6 (0.4)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Placebo</td><td>23.3 (2.5)</td><td>3.4 (0.5)</td></tr>
<tr><td>Duloxetine 60mg Daily</td><td>16.3** (2.3)</td><td>2.5** (0.4)</td></tr>
<tr><td>Duloxetine 60mg BID</td><td>13.2***(2.2)</td><td>2.2 * (0.4)</td></tr>
<tr><td colspan="3">p < 0.05, ** p < 0.01, ***p< 0.001</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Kaur, H et al.[29]

RCT, DB, CO

6 wks for each drug</td>
<td>Amitriptyline 10, 25 or 50 mg QHS for 6 wks

Vs
Duloxetine 20, 40 or 60 mg QHS for 6 wks</td>
<td>Adults > 18- 75 y with T2 DM and with DPN > 1 month

N = 58</td>
<td>Reduction in the median pain score from baseline as assessed by VAS (numeric scale of 0-100)</td>
<td>Median VAS scores for each drug at baseline and 6 weeks[29]

<table>
<tr><th>Median VAS Pain Score</th><th>Amitriptyline</th><th>Duloxetine</th></tr>
<tr><td>Baseline</td><td>68</td><td>80</td></tr>
<tr><td>Week 6</td><td>50</td><td>30</td></tr>
<tr><td>P value (baseline to 6 weeks</td><td>P < 0.001</td><td>P < 0.001</td></tr>
</table>
</td>
</tr>
<tr>
<td>Razazian N et al.[31]

RCT, DB, PG

4 wks</td>
<td>Pregabalin 75 mg daily x 7 days followed by 75 mg Q12h x 3 wks

Vs

Venlafaxine 75 mg daily x 7 days followed by 150mg daily x 3 wks
Vs

Carbamazepine 100 mg q12h x 7 days followed by 200 mg q12h x 3 wks</td>
<td>Adults ≥ 18 y with T1 or T2 DM with DPN > 3 months and VAS > 40mm

N = 257

33 (~ 13%) patients withdrew due to adverse effects</td>
<td>Mean subjective pain scores as analyzed by VAS on days 2, 7, 14, and 35.</td>
<td>Mean VAS scores in treatment groups over time[31]

<table>
<tr><th></th><th>Baseline</th><th>Day 2</th><th>Day 7</th><th>Day 14</th><th>Day 35</th><th>p-value**</th></tr>
<tr><td>Carbamazepine</td><td>74.5</td><td>69.4</td><td>63.4</td><td>40.2</td><td>39.6</td><td>0.0001</td></tr>
<tr><td>Pregablin</td><td>82.3</td><td>80.2</td><td>69.7</td><td>35.6</td><td>33.4</td><td>0.0001</td></tr>
<tr><td>Venlafaxine</td><td>74.5</td><td>70.2</td><td>65.5</td><td>48.0</td><td>46.6</td><td>0.0001</td></tr>
<tr><td>p-value*</td><td>0.0001</td><td>0.0001</td><td>0.007</td><td>0.0001</td><td>0.0001</td><td></td></tr>
</table>
*One way ANOVA - pregabalin compared to carbamazepine and venlafaxine
**Repeated measurement ANOVA
</td>
</tr>
<tr>
<td>Tanenberg RJ et al.[41]

Phase 4, MC, OL, randomized, noninferiority

12 wks</td>
<td>Duloxetine 30 mg daily x 1 wk followed by 60 mg daily

Vs

Pregablin 50 mg po TID x 1 wk followed by 100 mg TID
*(Germany, Puerto Rico, US)

*Canada: Pregablin 75 mg BID x 1 wk followed by 150 mg BID

*Dosing varied by country depending on the prescribing recommendations for each nation</td>
<td>Adults > 18 y with T1 or T2 DM and DPN treated with gabapentin 900 mg/day > 5 weeks with an inadequate response to therapy (daily pain score > 4 on a scale of 1-10)

N = 407</td>
<td>To determine whether duloxetine is noninferior to pregabalin in the treatment of pain associated with DPN. Evaluated by improvement in the weekly mean of a daily 24-hour pain diary on a 0-10 point scale (0 = no pain; 10 = worst possible pain) from baseline to week 12.

(125 (31%) patients withdrew due to adverse effects, lack of efficacy, withdrawal of consent, protocol violation, or loss to follow up)</td>
<td>Changes in weekly mean of daily pain diary ratings in the ITT population[41]

<table>
<tr><th></th><th>Duloxetine</th><th>Pregabalin</th><th>Treatment Difference</th></tr>
<tr><td>Mean change in daily pain score</td><td>-2.6</td><td>-2.1</td><td>0.49
95% CI = -0.05 to 1.04
p = 0.08</td></tr>
</table>

Noninferiority would be declared if the mean improvement for duloxetine was no worse than the mean improvement for pregabalin, within statistical variability, by a margin of 0.8 unit.
</td>
</tr>
<tr>
<td>Tesfaye S et al.[32]

MC, RCT, DB, PG

8 wks initial therapy followed by additional 8</td>
<td>Phase 1: Initial therapy
Duloxetine 60 mg daily x 8 wks (Groups 1, 2)

Vs

Pregabalin 300 mg daily x 8 wks (Groups 3, 4)</td>
<td>Age > 18 y with T1 or T2 DM DPN > 3 mo not responding to standard doses of duloxetine or pregabalin and pain score ≥ 4 on BPI-MSF</td>
<td>24-hour average pain change in between high dose monotherapy or combination therapy as evaluated on BPI-MSF from baseline to week 8 or week 16</td>
<td>Phase 1 and Phase 2: Pain Reduction in BPI-MSF 24 hour average pain[32]

<table>
<tr><th></th><th>Number</th><th>Number (%) of responders</th><th>P value</th></tr>
<tr><td colspan="4">≥ 50% reduction in BPI-MSF</td></tr>
<tr><td>Duloxetine 60 mg /day (week 8)</td><td>375</td><td>151 (40.3)</td><td>-</td></tr>
<tr><td>Pregabalin 300 mg/day (week 8)</td><td>374</td><td>104 (27.8)</td><td>-</td></tr>
</table>
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</table>

<table>
<tr>
<td>wks for non-responders</td>
<td>Phase 2: Nonresponders - Combination/high-dose therapy

Duloxetine 120 mg daily (Group 1)
Vs
Duloxetine 60 mg daily Pregabalin 300 mg daily (Groups 2, 3)
Vs
Pregabalin 600 mg daily (Group 4)</td>
<td>Phase1 : Initial therapy
n = 804

Phase 2: Non-responders: Combination/high dose therapy
n = 343</td>
<td></td>
<td>
<table>
<tr><td colspan="3">Comparison: Duloxetine vs pregabalin</td><td>< 0.001</td></tr>
<tr><td>Combination Therapy -Duloxetine 60 mg/day and Pregabalin 300 mg/day (week 16)</td><td>165</td><td>86 (52.1)</td><td>-</td></tr>
<tr><td>High Dose Monotherapy – Duloxetine 120 mg/day OR Pregabalin 600 mg/day (week 16)</td><td>163</td><td>64 (39.3)</td><td>-</td></tr>
<tr><td colspan="3">Comparison: combination vs high dose therapy</td><td>0.068</td></tr>
<tr><td colspan="4">≥ 30% reduction in BPI-MSF</td></tr>
<tr><td>Duloxetine 60 mg /day (week 8)</td><td>375</td><td>195 (52.0)</td><td>-</td></tr>
<tr><td>Pregabalin 300 mg/day (week 8)</td><td>374</td><td>138 (36.0)</td><td>-</td></tr>
<tr><td colspan="3">Comparison: Duloxetine vs pregabalin</td><td><0.001</td></tr>
<tr><td>Combination Therapy -Duloxetine 60 mg/day and Pregabalin 300 mg/day (week 16)</td><td>165</td><td>102 (61.8)</td><td>-</td></tr>
<tr><td>High Dose Monotherapy – Duloxetine 120 mg/day OR Pregabalin 600 mg/day (week 16)</td><td>163</td><td>91 (55.8)</td><td>-</td></tr>
<tr><td colspan="3">Comparison: combination vs high dose therapy</td><td>0.565</td></tr>
</table>
</td>
</tr>
<tr>
<td>Mishra S et al.[41]

RCT, DB, PC

4 wks</td>
<td>Amitriptyline 50 mg daily x 1 wk followed by 75 mg daily x 1 wk, followed by 100 mg daily x 2 weeks

Vs

Gabapentin 900 mg daily x 1 wk; 1200 mg daily x 1 wk; 1800 mg daily in divided doses x 2 wks

Vs
Pregabalin 150 mg daily x 1 wk; 300 mg daily x 1 wk; 300mg BID x 2 weeks

Vs

Placebo</td>
<td>Adults with cancer related neuropathic pain

N = 120</td>
<td>Change in VAS value as compared to baseline measured each week for 4 weeks</td>
<td>Comparison of pain score in different groups at different time periods.[41]
<table>
<tr><td></td><td>Mean VAS</td><td>P value</td></tr>
<tr><td>Amitriptyline – week 1</td><td>7.8</td><td></td></tr>
<tr><td>Amitriptyline – week 2</td><td>7</td><td></td></tr>
<tr><td>Amitriptyline – week 3</td><td>4.9</td><td></td></tr>
<tr><td>Amitriptyline – week 4</td><td>3.2</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Gabapentin – week 1</td><td>7.5</td><td></td></tr>
<tr><td>Gabapentin – week 2</td><td>6.2</td><td></td></tr>
<tr><td>Gabapentin – week 3</td><td>5</td><td></td></tr>
<tr><td>Gabapentin – week 4</td><td>3.07</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Pregabalin – week 1</td><td>7.8</td><td></td></tr>
<tr><td>Pregabalin – week 2</td><td>6.2</td><td></td></tr>
<tr><td>Pregabalin – week 3</td><td>4.2</td><td></td></tr>
<tr><td>Pregabalin – week 4</td><td>2.5</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Placebo – week 1</td><td>7.47</td><td></td></tr>
<tr><td>Placebo – week 2</td><td>6</td><td></td></tr>
<tr><td>Placebo – week 3</td><td>4.3</td><td></td></tr>
<tr><td>Placebo – week 4</td><td>3.4</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="2">Comparison: Pregabalin to Amitriptyline Week 3</td><td>p = 0.003</td></tr>
<tr><td colspan="2">Comparison: Pregabalin to Amitriptyline Week 4</td><td>p = 0.024</td></tr>
<tr><td colspan="2">Comparison: Pregabalin to Gabapentin Week 4</td><td>P = 0.042</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Liu WQ et al.[42]

Randomized, OL, flexible dosing

6 mos</td>
<td>Amitriptyline monotherapy 10, 25, or 50 mg (at baseline and 3 months), 10, 25, 50, or 100 mg (at 6 months)

Vs

Amitriptyline adjuvant therapy 10, 25, or 50 mg (at baseline and 3 months), 10, 25, 50, or 100 mg (at 6 months)

Vs

Nortriptyline monotherapy 12.5, 25, 50, or 100 mg (at baseline, 3, and 6 months)

Vs

Nortriptyline adjuvant therapy 12.5, 25, 50, or 100 mg (at baseline, 3, and 6 months)

Vs
No pharmacological therapy (control)</td>
<td>Adults with peripheral neuropathy due to different etiologies enrolled in a tertiary care neuromuscular clinic.

N = 228</td>
<td>Quantitative adverse effects and discontinuation rates.</td>
<td>
<table>
<tr><th>Drug</th><th colspan="4">Amitriptyline</th><th colspan="4">Nortriptyline</th></tr>
<tr><th>Inter-vention</th><th colspan="2">Monotherapy N=42</th><th colspan="2">Adjuvant N= 47</th><th colspan="2">Monotherapy N = 50</th><th colspan="2">Adjuvant N = 56</th></tr>
<tr><th>Time</th><th>3 mos</th><th>6 mos</th><th>3 mos</th><th>6 mos</th><th>3 mos</th><th>6 mos</th><th>3 mos</th><th>6 mos</th></tr>
<tr><td>Number of Dropouts</td><td>6</td><td>16</td><td>7</td><td>13</td><td>12</td><td>13</td><td>11</td><td>15</td></tr>
<tr><td>Dry Mouth</td><td>5</td><td>5*</td><td>7</td><td>8</td><td>7</td><td>11*</td><td>10</td><td>12</td></tr>
<tr><td>Sedation</td><td>19</td><td>22</td><td>24</td><td>26</td><td>20</td><td>20</td><td>22</td><td>23</td></tr>
<tr><td>Dizziness</td><td>6</td><td>6</td><td>8</td><td>8</td><td>8</td><td>8</td><td>12</td><td>12</td></tr>
<tr><td>Fatigue</td><td>7</td><td>9</td><td>6</td><td>7</td><td>4</td><td>6</td><td>4</td><td>5</td></tr>
<tr><td>Weight Gain</td><td>9*</td><td>11*</td><td>10*</td><td>12*</td><td>1</td><td>1</td><td>4</td><td>6</td></tr>
</table>
*A significant difference with ANOVA testing between amitriptyline and nortriptyline cohorts (P < 0.05).
</td>
</tr>
<tr>
<td>Holbech JV et al.[42]

RCT,DB, PC,CO, MC

5 weeks for each of the 4 arms</td>
<td>Imipramine 75 mg daily (age > 70 y, 25 mg daily) x 5 wks

Vs

Pregabalin 150 mg BID (age > 70, 75mg BID) x 5 wks

vs

Imipramine 75 mg daily + Pregabalin 300 mg daily x 5 wks

Vs

Placebo x 5 wks</td>
<td>Adults > 20-85 y with painful polyneuropathy > 6 m of different etiologies with a pain rating of ≥ 4 on a NRS scale of 0-10

N = 73 randomized to medication

48 patients completed the trial</td>
<td>Effect on median weekly pain scores from baseline to week 5 using a NRS from 0 to 10. Modified ITT and PP analysis completed.</td>
<td>
Primary Outcome Measure- Total Pain Intensity from baseline to week 5[42]
<table>
<tr><th></th><th>Mean Baseline NRS</th><th>Mean Week 5 NRS</th><th>NRS Change</th><th>Treatment effect: NRS mean difference (95% CI)</th><th>P</th></tr>
<tr><td>ITT Population</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Combination vs:
Imipramine
Pregabalin
Placebo</td><td>6.4</td><td>4.4</td><td>-2.0</td><td>
-0.59 (-1.02 to -0.15)
-1.19 (-1.63 to -0.75)
-1.67 (-2.11 to -1.23)</td><td>
0.009
<0.001
<0.001</td></tr>
<tr><td>Imipramine vs:
Pregabalin
Placebo</td><td>6.4</td><td>5.0</td><td>-1.4</td><td>
-0.60 (-1.04 to -0.15)
-1.08 (-1.52 to -0.64)</td><td>
0.008
<0.001</td></tr>
<tr><td>Pregabalin vs:
Placebo</td><td>6.4</td><td>5.4</td><td>-1.1</td><td>
-0.48 (-0.92 to -0.04)</td><td>
0.032</td></tr>
<tr><td>Placebo</td><td>6.4</td><td>4.4</td><td>-2.0</td><td></td><td></td></tr>
<tr><td>PP Population</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Combination vs:
Imipramine
Pregabalin
Placebo</td><td>6.3</td><td>4.4</td><td>-0.8</td><td>
-0.60 (-1.07 to -0.14)
-1.21 (-1.67 to -0.74)
-1.63 (-2.09 to -1.16)</td><td>
0.011
<0.001
<0.001</td></tr>
<tr><td>Imipramine vs:
Pregabalin</td><td>6.3</td><td>5.1</td><td>-2.0</td><td>
-0.60 (-1.07 to -0.14)</td><td>
0.011</td></tr>
</table>
</td>
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</table>

Placebo				-1.02 (-1.48 to -0.56)	<0.001
Pregabalin vs: Placebo	6.3	5.5	-1.3	-0.42 (-0.88 to 0.05)	0.080
Placebo	6.3	5.6	-.07		

Min K, et al.[43]

OL, SC, CO

Not reported

Oxcarbazepine 150 mg BID and titrated up to 300 mg BID based on clinical response

Vs

Pregabalin 75 mg BID titrated up to 150 mg BID over 1-2 wks

Adults > 20 y with spinal cord injuries and neuropathic pain with a LANSS score ≥ 12 and VAS ≥ 3

N =55

Degree in pain reduction according to the presence or absence of pain (EPP vs EPA).

Differences of drug effect according to the presence or absence of evoked pain.[43]

Change in Variable before and after treatment	**Evoked Pain Present (n = 36)**			**Evoked Pain Absent (n =30)**		
	Oxcarbaze-pine	Pregabali n	*P*	Oxcarbazepine	Pregabalin	*P*
Electrical	1.5	2.6	0.063	3.8	3.4	0.195
Burning	2.3	2.1	0.819	4.8	4.3	0.680
Pricking	2.0	2.5	0.554	4.3	3.5	0.434
Numbness	1.8	2.3	0.416	3.0	2.2	0.321
Allodynia	0.6	2.3	0.000	2.1	-	-
Heat	0.1	2.1	0.000	2.3	-	-
Pressure	1.3	2.3	0.218	2.4	-	-

Solak Y, et al.[44]

RCT, CO

14 wks

Gabapentin 300 mg after each dialysis session (three times a wk)

Vs

Pregabalin 75 mg daily

Adults > 18 y receiving hemodialysis with neuropathic pruritus > 3 months with > 40 on SF-MPQ

N = 40

Determine the frequency of neuropathic pruritus as evaluated by SF-MPQ and VAS

Changes in SF-MPQ and VAS with gabapentin and pregabalin[44]

	Baseline	**After Gabapentin**	**P value**	**Baseline**	**After Pregabalin**	**P value**
SF-PMQ VAS	191. ± 3.9	9.2 ±4.4	< 0.001	18.6 ± 3.9	9.1 ±3.5	< 0.001
SF-MPQ PPI	2.9 ±0.9	1.3 ±0.8	< 0.001	2.8 ±0.8	1.4 ± 0.7	< 0.001
Pruritus VAS Score	5.84 ±1.38	1.43 ± 2.0	< 0.001	5.8 ± 1.4	1.36 ± 2.32	< 0.001

Raskin P et al[45]

RCT, DB PC, MC CO

2 x 6 wk treatment sequences with 2 wk washout in between – total of 14 wks

Pregabalin 50 mg TID x 1 wk increased to 100 mg TID x 6 wks

Vs

Placebo x 6 wks

Adults > 18 y with T1 or T2 DM and DPN ≥ 4 on a NRS and using NSAIDs

N = 301

Change in weekly mean DPN pain score from baseline to week 6

Weekly Mean Pain Scores from Week 1 through Week 6[45]

	Mean Pregabalin (95% CI) N = 272	**Mean Placebo (95% CI) N = 276**	**Mean Difference (95% CI)**	***P***
Week 1	5.10 (4.92-5.29)	5.27 (5.09-5.45)	-0.17 (-0.32 to -.02)	0.0293
Week 2	5.67 (5.47-5.87)	5.72 (5.52-5.92)	-0.05 (-0.24 to 0.14)	0.6014
Week 3	5.22 (5.02-5.42)	5.46 (5.26-5.66)	-.025 (-0.44 to -0.05)	0.0122
Week 4	4.99 (4.79-5.19)	5.26 (5.06-5.46)	-.027 (-0.47 to -0.08)	0.0061
Week 5	4.88 (4.68-5.08)	5.05 (4.85-5.25)	-0.17 (-0.36 to 0.03)	0.0983
Week 6	4.90 (4.69-5.10)	4.95 (4.75-5.16)	-0.05 (-0.26 to 0.15)	0.5987

Abbreviations: BPI = Brief Pain Inventory; BPI-MSF = Brief Pain Inventory-Modified Short Form; CI = Confidence Interval; CO = Cross Over; DB= Double Blind; DM = Diabetes Mellitus; DPN = Diabetic Peripheral Neuropathy; EPA = Evoked Pain Absent; EPP = Evoked Pain Present; ITT = Intention To Treat; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; MC = Multi-Center; N=number; mos = Months; NSAID = non-steroidal anti-inflammatory agent; NRS = Numeric Rating Scale; OL = Open Label; PC = Placebo Controlled; PG = Parallel Group; PP = Per Protocol; PPI = Present Pain Intensity; RCT = Randomized Clinical Trial; SC= Single Center; SF-PMQ = Short Form of McGill Pain Questionnaire; T1= Type 1; T2 = Type 2; VAS = Visual Analog Scale; wks= weeks; Y = Years

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Appendix 1: Current Preferred Drug List

ANTIEPILEPTICS

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVED OUT
ORAL	TABLET	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TABLET	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET	EPITOL	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	CARBAMAZEPINE ER	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	TEGRETOL XR	CARBAMAZEPINE	Y	
ORAL	TAB CHEW	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET DR	DEPAKOTE	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	CAP SPRINK	DEPAKOTE SPRINKLE	DIVALPROEX SODIUM	Y	Y
ORAL	CAP SPRINK	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DEPAKOTE ER	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DIVALPROEX SODIUM ER	DIVALPROEX SODIUM	Y	Y
ORAL	CAPSULE	GABAPENTIN	GABAPENTIN	Y	
ORAL	CAPSULE	NEURONTIN	GABAPENTIN	Y	
ORAL	TABLET	VIMPAT	LACOSAMIDE	Y	
ORAL	TABLET	LAMICTAL	LAMOTRIGINE	Y	Y
ORAL	TABLET	LAMOTRIGINE	LAMOTRIGINE	Y	Y
ORAL	TAB DS PK	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMOTRIGINE ER	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TABLET	KEPPRA	LEVETIRACETAM	Y	
ORAL	TABLET	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	ROWEEPRA	LEVETIRACETAM	Y	

ORAL	SOLUTION	KEPPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	TABLET	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	CAPSULE	DILANTIN	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTEK	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	ORAL SUSP	PHENYTOIN	PHENYTOIN	Y	
ORAL	ORAL SUSP	DILANTIN-125	PHENYTOIN	Y	
ORAL	TAB CHEW	DILANTIN	PHENYTOIN	Y	
ORAL	TAB CHEW	PHENYTOIN	PHENYTOIN	Y	
ORAL	TABLET	TOPAMAX	TOPIRAMATE	Y	
ORAL	TABLET	TOPIRAMATE	TOPIRAMATE	Y	
ORAL	CAPSULE	DEPAKENE	VALPROIC ACID	Y	Y
ORAL	CAPSULE	VALPROIC ACID	VALPROIC ACID	Y	Y
ORAL	SOLUTION	DEPAKENE	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SYRINGE	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)		Y
ORAL	TABLET	BRIVIACT	BRIVARACETAM	N	
ORAL	SOLUTION	BRIVIACT	BRIVARACETAM	N	
ORAL	CPMP 12HR	CARBAMAZEPINE ER	CARBAMAZEPINE	N	
ORAL	CPMP 12HR	CARBATROL	CARBAMAZEPINE	N	
ORAL	TABLET	APTIOM	ESLICARBAZEPINE ACETATE	N	
ORAL	TABLET	POTIGA	EZOGABINE	N	
ORAL	TABLET	GABAPENTIN	GABAPENTIN	N	
ORAL	TABLET	NEURONTIN	GABAPENTIN	N	
ORAL	SOLUTION	NEURONTIN	GABAPENTIN	N	
ORAL	SOLUTION	GABAPENTIN	GABAPENTIN	N	
ORAL	TAB ER 24H	GRALISE	GABAPENTIN	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	
ORAL	SOLUTION	VIMPAT	LACOSAMIDE	N	
ORAL	TAB ER 24H	KEPPRA XR	LEVETIRACETAM	N	
ORAL	TAB ER 24H	LEVETIRACETAM ER	LEVETIRACETAM	N	
ORAL	TAB SUSP	SPRITAM	LEVETIRACETAM	N	
ORAL	TAB ER 24H	OXTELLAR XR	OXCARBAZEPINE	N	

ORAL	ORAL SUSP	FYCOMPA	PERAMPANEL	N
ORAL	TABLET	FYCOMPA	PERAMPANEL	N
ORAL	SOLUTION	LYRICA	PREGABALIN	N
ORAL	CAPSULE	LYRICA	PREGABALIN	N
ORAL	CAP ER 24H	TROKENDI XR	TOPIRAMATE	N
ORAL	CAP SPR 24	QUDEXY XR	TOPIRAMATE	N
ORAL	CAP SPR 24	TOPIRAMATE ER	TOPIRAMATE	N
ORAL	CAP SPRINK	TOPAMAX	TOPIRAMATE	N
ORAL	CAP SPRINK	TOPIRAMATE	TOPIRAMATE	N

Antidepressants: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVED OUT
ORAL	TABLET	AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	Y	Y
ORAL	TABLET	DESIPRAMINE HCL	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	NORPRAMIN	DESIPRAMINE HCL	Y	Y
ORAL	TAB ER 24	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24	KHEDEZLA	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24	DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	V	Y
ORAL	TAB ER 24H	PRISTIQ	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	CAPSULE	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	ORAL CONC	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	CAPSULE DR	CYMBALTA	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	DULOXETINE HCL	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	IRENKA	DULOXETINE HCL	V	Y
ORAL	TABLET	IMIPRAMINE HCL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	TOFRANIL	IMIPRAMINE HCL	Y	Y
ORAL	CAPSULE	IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	V	Y
ORAL	CAP SA 24H	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	CAP24HDSPK	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	TAB DS PK	SAVELLA	MILNACIPRAN HCL		
ORAL	TABLET	SAVELLA	MILNACIPRAN HCL		
ORAL	CAPSULE	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	PAMELOR	NORTRIPTYLINE HCL	Y	Y
ORAL	SOLUTION	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y

ORAL	TABLET	PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	SURMONTIL	TRIMIPRAMINE MALEATE	Y	Y
ORAL	CAP ER 24H	EFFEXOR XR	VENLAFAXINE HCL	Y	Y
ORAL	CAP ER 24H	VENLAFAXINE HCL ER	VENLAFAXINE HCL	Y	Y
ORAL	TAB ER 24	VENLAFAXINE HCL ER	VENLAFAXINE HCL	V	Y
ORAL	TABLET	VENLAFAXINE HCL	VENLAFAXINE HCL	Y	Y

Topical Analgesics

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVED OUT
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	OINT. (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDODERM	LIDOCAINE	N	

Appendix 2: Abstracts

Boyle J. Eriksson ME. Gribble L. Gouni R. Johnsen S. Coppini DV. Kerr D. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 35(12):2451-8, 2012 Dec.
OBJECTIVE: Chronic diabetic peripheral neuropathic pain (DPNP) is difficult to treat, with treatment regimens often inadequate at controlling pain and limited by side effects and drug tolerance. Secondary parameters, such as quality of sleep and mood, may also be important for successful DPNP management. The objectives of this study were to compare the analgesic efficacy of pregabalin, amitriptyline, and duloxetine, and their effect on polysomnographic sleep, daytime functioning, and quality of life in patients with DPNP.
RESEARCH DESIGN AND METHODS: This was a double-blind, randomized, parallel group investigation of type 1 and 2 diabetic subjects with DPNP. Each treatment group had a single-blind, 8-day, placebo run-in followed by 14 days of lower-dose and 14 days of higher-dose medication. At the end of each dose titration period, subjective pain, sleep, and daytime functioning were assessed during a 2-day residential period.
RESULTS: All medications reduced pain when compared with placebo, but no one treatment was superior to any other. For sleep, pregabalin improved sleep continuity ($P < 0.001$), whereas duloxetine increased wake and reduced total sleep time ($P < 0.01$ and $P < 0.001$). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there was a significantly higher number of adverse events in the pregabalin treatment group.
CONCLUSIONS: There was no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin. However, there were significant differences in the secondary parameters, which may be of relevance when deciding the optimal treatment for DPNP.

Holbech, J. V., et al. (2015). Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain 156(5): 958-966.
Monotherapy with first-line drugs for neuropathic pain often fails to provide sufficient pain relief or has unacceptable side effects because of the need for high doses. The aim of this trial was to test whether the combination of imipramine and pregabalin in moderate doses would relieve pain more effectively than monotherapy with either of the drugs. This was a randomized, double-blind, placebo-controlled, crossover, multicenter trial consisting of four 5-week treatment periods in patients with painful polyneuropathy. Treatment arms were imipramine 75 mg/d vs pregabalin 300 mg/d vs combination therapy vs placebo. Patients with polyneuropathy and symptoms for more than 6 months, age 20 to 85 years, pain intensity >4 on a 0- to 10-point numeric rating scale (NRS) and pain at least 4 days a week were included in the trial. A total of 262 patients were screened for participation, 73 patients were randomized, and 69 patients were included in the data analysis. The effect on average pain in comparison with placebo was: combination (-1.67 NRS points, $P < 0.001$), imipramine (-1.08 NRS points, $P < 0.001$), and pregabalin (-0.48 NRS points, $P = 0.03$). The combination therapy had significantly lower pain scores than both monotherapies: combination vs imipramine ($P = 0.009$), combination vs pregabalin ($P < 0.001$). During combination therapy, the dropout rate was higher and the patients reported a higher rate and severity of side effects. Combination of moderate doses of the tricyclic antidepressant imipramine and pregabalin could be considered as an alternative to high-dosage monotherapy. However, the trial also emphasized that balance between efficacy and safety is an issue.

Kaur H. Hota D. Bhansali A. Dutta P. Bansal D. Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. Diabetes Care. 34(4):818-22, 2011 Apr.
OBJECTIVE: To compare the efficacy and safety of duloxetine and amitriptyline in painful diabetic neuropathy (PDN).
RESEARCH DESIGN AND METHODS: In this randomized, double-blind, cross-over, active-control trial, 58 patients received amitriptyline and duloxetine orally once daily at bedtime, each for 6 weeks with optional dose uptitration fortnightly. Single-blinded placebo washout was given for 2 weeks between the two

treatments and a single-blinded placebo run-out phase of 4 weeks was given at the end of the treatment period. Pain relief was measured by the patient's global assessment of efficacy, using a visual analog scale (0-100) as a primary end point, and overall improvement and adverse events were assessed as secondary outcome measures. Median pain score reductions of >50%, 25- 50%, and <25% were considered good, moderate, and mild responses, respectively.
RESULTS: There was a significant improvement in pain with both treatments compared with their baseline values (P < 0.001 for both). Good, moderate, and mild pain relief was achieved in 55, 24, and 15% of patients, respectively, on amitriptyline and 59, 21, and 9% of patients, respectively, on duloxetine. There were no significant differences in various other outcome measures between the groups. Of the reported adverse events, dry mouth was significantly more common with amitriptyline than duloxetine (55 vs. 24%; P < 0.01). Although, numerically, more patients preferred duloxetine, overall this was not statistically significant (48 vs. 36%; P = 0.18).
CONCLUSIONS: Both duloxetine and amitriptyline demonstrated similar efficacy in PDN. A large, multicentric clinical trialin other populations could possibly demonstrate the superiority of either drug.

Liu, W. Q., et al. (2014). Equivalency of tricyclic antidepressants in open-label neuropathic pain study. Acta Neurologica Scandinavica 129(2): 132-141.
OBJECTIVES: To compare adverse effects, tolerability and efficacy of the tricyclic antidepressants (TCAs) amitriptyline and nortriptyline in management of neuropathic pain due to peripheral neuropathy (PN).
MATERIALS & METHODS: We performed a prospective open-label flexible-dosing comparison of monotherapy or adjuvant therapy using amitriptyline or nortriptyline in PN-associated neuropathic pain. Primary outcomes were quantitative adverse effects and discontinuation rates. Secondary outcomes assessed changes in pain severity, quality of life, disability, sleep efficacy, mood and anxiety, and global improvement. Assessments occurred at 3 and 6 months after initiation. Our hypothesis was that nortriptyline would have better tolerance than amitriptyline.
RESULTS: A total of 228 PN patients were enrolled approximately equally for monotherapy and adjuvant therapy. Adverse effects and discontinuation rates were similar between amitriptyline and nortriptyline interventions. Weight gain was more common with amitriptyline, while nortriptyline use was associated with greater prevalence of dry mouth. Secondary outcome measures were similar in both groups, demonstrating improvement from baseline.
CONCLUSIONS: Amitriptyline and nortriptyline are equivalent for overall adverse effects and discontinuation rates. Either TCA should be equally considered for use in neuropathic pain due to PN. When used as monotherapy or as part of adjuvant therapy, either TCA can be expected to provide approximately 23-26% visual analog scale pain reduction if tolerated. Discontinuations due to inefficacy or adverse effects can be anticipated in 26-37% of patients initiated on either TCA for PN-associated neuropathic pain.

Min, K., et al. (2016). Symptom-Based Treatment of Neuropathic Pain in Spinal Cord-Injured Patients: A Randomized Crossover Clinical Trial. American Journal of Physical Medicine & Rehabilitation **95**(5): 330-338.
OBJECTIVE: The objective of this study was to identify the differences in medication effect according to pain characteristics in spinal cord-injured patients.
METHODS: This study is a prospective, randomized, crossover study. Fifty-five patients and 66 locations of neuropathic pain were included. Pain was classified into four spontaneous characteristics and three evoked pain characteristics. Oxcarbazepine (Na channel blocker) and pregabalin (calcium channel alpha2-delta ligand medication) were tried. Patients were divided into two groups: evoked pain present and evoked pain absent. Overall average visual analog scale was obtained.
RESULTS: Oxcarbazepine was significantly more effective for patients without evoked pain than in those with it for electrical, burning, and pricking pain. The effect of pregabalin was not different regarding the presence or absence of evoked pain for all pain categories, except burning pain. In patients with evoked pain, pregabalin was shown to be significantly more effective for electrical pain, allodynia, and heat hyperalgesia than oxcarbazepine. In the evoked pain absent group, oxcarbazepine showed greater improvement than pregabalin but was not significant.

CONCLUSIONS: In summary, the phenotype of neuropathic pain was associated with the efficacy of different pharmacologic treatments. Symptom-based treatment, therefore, can lead to more efficient analgesia.

Mishra S. Bhatnagar S. Goyal GN. Rana SP. Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. American Journal of Hospice & Palliative Medicine. 29(3):177-82, 2012 May.
Neuropathic pain is difficult to diagnose and difficult to treat with certainty. So the aim of the study was to evaluate comparative clinical efficacy of pregabaline with amitriptyline and gabapentin in neuropathic cancer pain. A total of 120 patients with cancer having severe neuropathic cancer pain were enrolled in the study after taking approval from Institutional Ethics Committee and divided in to 4 groups: group AT-amitriptyline, group GB-gabapentin, group PG-pregabalin, and group PL-placebo. Oral morphine was used for rescue analgesic for continued pain. Pain score (Visual Analogue scale) and secondary outcome measures such as intensity of lancinating, dysesthesia, and burning on numerical rating scale, Global satisfaction score (GSS), Eastern Co-operative Oncology Group scoring (ECOG), and adverse effects were assessed. At the end of study there was significant decrease in pain score in group PG as compared to the other groups; group AT (P = .003), group GB (P = .042), and group PL (P = .024). Percentage of patients with lancinating pain and dysesthesia were significantly less in group PG as compared to groups GB and PL. All the patients in group PL needed rescue morphine. After 4 visits, maximum improvement in ECOG scoring and GSS scoring was observed in group PG patients. Our results suggested that all antineuropathic drugs are effective in relieving cancer-related neuropathic pain. There was statistically and clinically significant morphine sparing effect of pregabaline in relieving neuropathic cancer pain and neuropathic symptoms as compared to other antineuropathic drugs.

Razazian, N., et al. (2014). Evaluation of the efficacy and safety of pregabalin, venlafaxine, and carbamazepine in patients with painful diabetic peripheral neuropathy. A randomized, double-blind trial. Neurosciences **19**(3): 192-198.
OBJECTIVE: To evaluate the efficacy and safety of carbamazepine, pregabalin, and venlafaxine in patients with painful diabetic neuropathy (PDN).
METHODS: Our study was performed as a randomized, double-blind, parallel-group clinical trial between December 2012 and December 2013 at Kermanshah University of Medical Sciences, Kermanshah, Iran. Two hundred and fifty-seven patients with clinically definite PDN were randomized to receive, carbamazepine, venlafaxine, or pregabalin. The primary outcome was subjective pain as assessed by the visual analogue scale (VAS). Secondary outcomes consisted of sleep, mood, and work interference assessments, and a percentage of patients achieving at least 50% reduction in pain intensity.
RESULTS: Means of VAS scores for carbamazepine, pregabalin, and venlafaxine treatment groups at the baseline (74.5, 82.3, and 74.5) and endpoint (39.6, 33.4, and 46.6) revealed significant reduction, although pregabalin was more efficacious than carbamazepine, and venlafaxine. Improvements in means scores of sleep, mood, and work interferences were identified in all treatment groups.
CONCLUSION: This study showed the efficacy of venlafaxine, pregabalin, and carbamazepine in pain reduction in patients with diabetic neuropathy, although pregabalin was shown to be superior to carbamazepine, and venlafaxine in relieving pain, no significant superiority was shown between carbamazepine, and venlafaxine.

Solak Y. Biyik Z. Atalay H. Gaipov A. Guney F. Turk S. Covic A. Goldsmith D. Kanbay M. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study. Nephrology. 17(8):710-7, 2012 Nov.
AIM: Pruritus is common in dialysis patients. Peripheral neuropathy is also prevalent in this patient population. However, the role of neuropathy in the genesis of uraemic itch has not been adequately studied to date. Therefore, we aimed to investigate the effects of gabapentin and pregabalin on uraemic pruritus along with neuropathic pain in patients receiving haemodialysis.

METHODS: This is a 14 week long randomized, prospective, cross-over trial. Haemodialysis patients with established neuropathy and/or neuropathic pain were included. Fifty patients were randomly assigned to gabapentin 300 mg after each haemodialysis session and pregabalin 75 mg daily. After 6 weeks of treatment, cross-over was performed and patients received the other drug for another 6 weeks. Short Form of McGill Pain Questionnaire and Visual Analogue Scale were used to evaluate pain and pruritus, respectively. At each week's visit, patients were interrogated in terms of adverse effects of study drugs. Baseline laboratory data and demographic characteristics were recorded from patient charts.
RESULTS: Forty (12 males, 28 females) out of 50 patients completed the study. Mean age was 58.2 +/- 13.7. Overall, 29 out of 40 patients (72.5%) had pruritus symptoms at baseline evaluation. Fifteen patients (37.5%) were diabetic. Thirty-one out of 40 patients (77.5%) had electromyography (EMG)-proven peripheral neuropathy. Twenty three patients (57.5%) had both EMG-proven neuropathy and pruritus. Gabapentin and pregabalin improved both neuropathic pain and pruritus significantly. There was no difference between the study drugs in terms of efficacy against pain and pruritus.
CONCLUSION: Treatment of neuropathic pain with either pregabalin or gabapentin effectively ameliorates uraemic itch.

Tanenberg RJ. Irving GA. Risser RC. Ahl J. Robinson MJ. Skljarevski V. Malcolm SK. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. Mayo Clinic Proceedings. 86(7):615-26, 2011 Jul.
OBJECTIVE: To determine whether duloxetine is noninferior to (as good as) pregabalin in the treatment of pain associated with diabetic peripheral neuropathy.
PATIENTS AND METHODS: We performed a 12-week, open-label study of patients with diabetic peripheral neuropathic pain who had been treated with gabapentin (>= 900 mg/d) and had an inadequate response (defined as a daily pain score of >= 4 on a numerical rating scale [0-10 points]). The first patient was enrolled on September 28, 2006, and the last patient visit occurred on August 26, 2009. Patients were randomized to duloxetine monotherapy (n=138), pregabalin monotherapy (n=134), or a combination of duloxetine and gabapentin (n=135). The primary objective was a noninferiority comparison between duloxetine and pregabalin on improvement in the weekly mean of the diary-based daily pain score (0- to 10-point scale) at end point. Noninferiority would be declared if the mean improvement for duloxetine was no worse than the mean improvement for pregabalin, within statistical variability, by a margin of -0.8 unit.
RESULTS: The mean change in the pain rating at end point was -2.6 for duloxetine and - 2.1 for pregabalin. The 97.5% lower confidence limit was a -0.05 difference in means, establishing noninferiority. As to adverse effects, nausea, insomnia, hyperhidrosis, and decreased appetite were more frequent with duloxetine than pregabalin; insomnia, more frequent with duloxetine than duloxetine plus gabapentin; peripheral edema, more frequent with pregabalin than with duloxetine; and nausea, hyperhidrosis, decreased appetite, and vomiting, more frequent with duloxetine plus gabapentin than with pregabalin.
CONCLUSION: Duloxetine was noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin

Tesfaye, S., et al. (2013). Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain 154(12): 2616-2625.
This multicentre, double-blind, parallel-group study in diabetic peripheral neuropathic pain addressed whether, in patients not responding to standard doses of duloxetine or pregabalin, combining both medications is superior to increasing each drug to its maximum recommended dose. For initial 8-week therapy, either 60 mg/day duloxetine (groups 1, 2) or 300 mg/day pregabalin (groups 3, 4) was given. Thereafter, in the 8-week combination/high-dose therapy period, only nonresponders received 120 mg/day duloxetine (group 1), a combination of 60 mg/day duloxetine and 300 mg/day pregabalin (groups 2, 3), or 600 mg/day pregabalin (group 4). Primary outcome (Brief Pain Inventory Modified Short Form [BPI-MSF] 24-hour average pain change after combination/high-dose therapy) was analyzed comparing combination (groups 2, 3 pooled) with high-dose monotherapy (groups 1, 4 pooled). Secondary end points included response rates, BPI-MSF severity items, and comparison of duloxetine and pregabalin in BPI-MSF average pain. Eight hundred four patients were evaluated for initial therapy and

339 for combination/high-dose therapy. There were no significant differences between combination and high-dose monotherapy regarding BPI-MSF average pain (mean change: combination: -2.35; high-dose monotherapy: -2.16; P = 0.370) and most secondary end points, which, however, consistently favoured combination therapy. Fifty-percent response rates were 52.1% for combination and 39.3% for high-dose monotherapy (P = 0.068). In exploratory analyses of the initial 8-week therapy uncorrected for multiple comparisons, 60 mg/day duloxetine was found superior to 300 mg/day pregabalin (P < 0.001). Both drugs and their combination were well tolerated. Although not significantly superior to high-dose monotherapy, combination therapy was considered to be effective, safe, and well tolerated.

Raskin, Philip MD; Huffman, Cynthia MD; Yurkewicz, Lorraine PhD; Pauer, Lynne MS; Scavone, Joseph M. MSc, PharmD; Yang, Ruoyong PhD; Parsons, Bruce MD, PhD Pregabalin in Patients With Painful Diabetic Peripheral Neuropathy Using an NSAID for Other Pain Conditions: A Double-Blind Crossover Study. Clinical Journal of Pain. 32(3):203-210, March 2016

Objectives: To evaluate pregabalin's efficacy and safety versus placebo to reduce pain in patients with diabetic peripheral neuropathy (DPN) using a concomitant nonsteroidal anti-inflammatory drug.

Materials and Methods: In a randomized, double-masked, 14-week, 2-period, crossover study, patients with painful DPN using a nonsteroidal anti-inflammatory drug for non-DPN-related pain received 150 to 300 mg/d pregabalin or placebo (period 1); 14-day washout; then, the opposite therapy (period 2). Endpoints included weekly change in DPN pain score, sleep interference, adverse events, and patient-reported outcomes.

Results: Patients with similar baseline characteristics were randomized (period 1) to 1 of the 2 following possible sequences: pregabalin->placebo (n=154) or placebo->pregabalin (n=147). Results of the primary efficacy measure, mean weekly DPN pain at endpoint, showed no significant difference between pregabalin and placebo. However, 1 sensitivity analysis (mixed-model repeated measures) found greater pain score reductions with pregabalin than placebo at weeks 2 to 4 and overall (all P<0.05). One secondary endpoint analysis, mean treatment difference in DPN-related sleep interference, favored pregabalin over placebo (P=0.0009). Other sensitivity and secondary analyses were nonsignificant. Treatment-emergent adverse events were consistent with the known safety profile of pregabalin.

Discussion: Pregabalin (vs. placebo) showed overall improvements in sleep, pain reduction in 1 sensitivity analysis, and was well tolerated. Potential factors that may have confounded the ability to detect a treatment difference in DPN pain reduction (high placebo response, carryover effect, short washout period, or pregabalin dose) are discussed in the context of future studies.

Source: Clinical Journal of Pain. 32(3):203-210, March 2016.

Appendix 3: Drug Information

Table 1. Dosing Recommendations for Non-analgesics Used to Manage Pain [46,47]

Medication	Starting Dose		Titration	Maximum Dosage	Duration of Adequate Trial
Tricyclic Antidepressants (TCA)					
Amitriptyline	12.5 mg QHS		Increase up to 25-50 mg Daily every 3-7 days	150 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Nortriptyline	10 mg QHS		Increase by 10 to 25 mg Daily every 3-7 days	150 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Imipramine	50 mg QHS		Increase 25 mg Daily every 3 to 7 days	200 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Desipramine	25 mg QHS		Increase 25 mg Daily every 3 to 7 days	200 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)					
Duloxetine	30 mg po Daily		Increase to 60 mg Daily after 1 week	120 mg Daily	4 weeks
Venlafaxine	37.5 mg Daily or BID		Increase by 75 mg each week	225 mg Daily	4-6 weeks
Milnacipran	12.5 mg Daily		Increase by 12.5 mg BID over 7 days to 50 mg BID	100 mg BID	4 weeks
Antiepileptics					
Gabapentin	100-300 mg QHS OR 100-300 mg TID		Increase by 100-300 mg TID every 1-7 days	1800-3600 mg per day in divided doses	4-8 weeks
Pregabalin	50 mg TID or 75 mg BID		Increase to 300 mg Daily after 3-7 days, then by 150 mg Daily over 3-7 days to 450 mg per day	600 mg Daily	4 weeks
Carbamazepine	100 mg BID		Increase by 100-200 mg as needed for pain control	600 mg BID	Attempt to reduce dose or discontinue use every 3 months
Topiramate	50 mg BID		Increase by 25 mg every 7 days	50 mg BID	4 weeks
Topical Agents					
Lidocaine 5% Patch	Maximum of 3 patches Daily for a max of 12 hours		None needed	Maximum of 3 patches Daily for a maximum of 12-18 hours	Immediate
Lidocaine Gel/Cream/Topical Solution (4%)	Apply 5 gms/6 in to affected area TID to QID		None needed	17-20 gms of ointment per day	Immediate

Abbreviations: BID = twice daily; gms = grams; in = inches; mg = milligrams; QHS = daily at bedtime; QID = four times a day; TID = three times a day

Table 2. Summary of Warnings and Precautions for Non-opiates Used to Manage Chronic Pain[46,47]

Warning/Precaution	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Milnacipran	Carbamazepine	Topiramate	Gabapentin, Pregabalin	Topical Lidocaine
CNS Depression (Confusion, Sedation, dizziness)	X	X	X		X	X	X	
Dry Mouth	X		X	X	X		X	
Blurred Vision	X				X		X	
Urinary Retention	X			X				
Constipation	X	X		X	X		X	
Orthostatic Hypotension	X	X						X
Use with Caution in Glaucoma	X	X	X	X				
Hypertension		X	X	X	X			
Cardiac Disease (MI, stroke, arrhythmia)	X		X	X	X			X
Peripheral Edema							X	
Nausea		X	X	X	X			
Local Erythema/Rash					X			X
Seizure Disorder	X	X	X	X				
SIADH/Hyponatremia		X		X	X			
Bone Marrow Depression*					X			
Stevens-Johnson Syndrome*					X	X		
Nonvertebral Bone Fracture	X							
Increased Risk of Suicidal Thoughts*	X	X	X					
Use with Caution in Hepatic Impairment	X	X	X	X	X	X		
Use with Caution in Renal Impairment	X	X	X	X			X	
Withdrawal Syndrome with Abrupt Discontinuation	X	X	X		X			

***Bold warnings indicate a black box warning associated with the adverse effect**

Table 3. Evidence for Efficacy for Non-opiate Medications in Specific Neuropathic/Chronic Pain Conditions [46,47]

Condition	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Milnacipran	Carbamazepine	Topiramate	Gabapentin	Pregabalin	Topical Lidocaine
Diabetic Neuropathy	X	X*	X			X	X	X*	X
Postherpetic Neuropathy	X						X*	X*	X*
Painful Polyneuropathy	X		X				X	X	X
Phantom Limb Pain							X		
Chemotherapy Induced Neuropathy		X			X		X	X	
HIV Neuropathy	X								
Central Post Stroke Pain	X	X						X	
Spinal Cord Injury Pain		X					X	X*	
Fibromyalgia	X	X*		X*				X*	
Migraine Headache Prophylaxis	X		X		X	X			
Chronic Musculoskeletal Pain	X	X*							
Trigeminal Neuralgia					X*				

***Drug has FDA approval for specific condition**

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 16, 2016

1. *carbamazepine.mp. or Carbamazepine/ 9087*
2. *divalproex.mp. or Valproic Acid/ 7559*
3. *Antiepileptics/ or Analgesics/ or gabapentin.mp. 56374*
4. *vimpat.mp. 17*
5. *lacosamide.mp. 435*
6. *lamotrigine.mp. 4030*
7. *levetiracetam.mp. 2169*
8. *oxcarbazepine.mp. 1360*
9. *phenytoin.mp. or Phenytoin/ 5464*
10. *valproic acid.mp. or Valproic Acid 8869*
11. *brivaracetam.mp. 82*
12. *esclicarbazepine.mp. 2*
13. *Epilepsies, Partial/ or ezogabine.mp. 4889*
14. *Antiepileptics/ or Analgesics/ or gabapentin.mp 56374*
15. *lacosamide.mp. 435*
16. *levetiracetam.mp. 2169*
17. *oxcarbazepine.mp. 1360*
18. *perampanel.mp. 133*
19. *pregabalin.mp. or Pregabalin/ 2041*
20. *topiramate.mp. 3614*
21. *amitriptyline.mp. or Amitriptyline/ 3124*
22. *Antidepressive Agents/ or desimpramine.mp. 25544*
23. *desvenlafaxine.mp. or Desvenlafaxine Succinate/ 277*
24. *doxepin.mp. or Doxepin/ 488*
25. *duloxetine.mp. or Duloxetine Hydrochloride/ 1731*
26. *imipramine.mp. or Imipramine/ 3366*
27. *levomilnacipran.mp. 34*
28. *milnacipran.mp. 524*
29. *nortriptyline.mp. or Nortriptyline/ 1176*
30. *protriptyline.mp. or Protriptyline/ 72*
31. *trimipramine.mp. or Trimipramine/ 148*
32. *venlafaxine.mp. or Venlafaxine Hydrochloride/ 3186*
33. *Lidocaine topical.mp. 286*
34. *Chronic pain.mp. or Chronic Pain/ 22185*
35. *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 -10241*
36. *35 and 34 2457*
37. *limit 36 to (english language and humans and humans and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews -year to 2012 current)) 229*

Appendix 5 Fee for Service Utilization of Selected Non-Analgesic Pain Medications (7/1/17 – 9/30/16)

Table 1. Lidocaine Patch

Drug	Total Claims	Paid Claims	Another Drug in PDL Class Paid	No Drugs within PDL Class Paid	Disposition of Claims Not Paid Within PDL Class				
					Patient Enrolled in CCO/IHS/Other*	Patient Lost Eligibility	PA Approved	PA Denied	PA Not Requested
Lidocaine	172	20 (12%)	5 (3%)	147 (85%)	60/24/13 (Total =97)	19	2	2	27

*CCO =Coordinated Care Organization, IHS = Indian Health Service

Table 2. Antiepileptics

Drug	Total Claims	Paid Claims	Another Drug in PDL Class Paid	No Drugs within PDL Class Paid	Disposition of Claims Not Paid Within PDL Class				
					Patient Enrolled in CCO/IHS/Other*	Patient Lost Eligibility	PA Approved	PA Denied	PA Not Requested
Gabapentin	1918	1917 (99%)	0	1 (1%)	1	0	0	0	0
Lyrica (Pregabalin)	205	78 (38%)	34 (17%)	(45%)	48/7/15 (Total = 70)	12	2	4	5

*CCO =Coordinated Care Organization, IHS = Indian Health Service

Table 3. Antidepressants

Drug	Total Claims	Paid Claims	Another Drug in PDL Class Paid	No Drugs within PDL Class Paid	Disposition of Claims Not Paid Within PDL Class				
					Patient Enrolled in CCO/IHS/Other*	Patient Lost Eligibility	PA Approved	PA Denied	PA Not Requested
Duloxetine	10369	10299 (99.4%)	21 (0.2 %)	49 (0.4%)	32/7/1 (Total = 40)	7	0	0	2
Amitriptyline	7359	7338 (99.7%)	5 (0.06%)	16 (0.2%)	8/0/1 (Total = 9)	6	0	0	1
Venlafaxine	5439	5432 (99.8%)	2 (0.03%)	5 (0.09%)	2/0/0 (Total = 2)	3	0	0	0
Imipramine	380	379 (99.8%)	0	1 (0.2%)	0/0/0	1	0	0	0

*CCO =Coordinated Care Organization, IHS = Indian Health Service

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of epilepsy?	**Yes: Approve for lifetime**	**No: Go to # 3**
3. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes: Approve for 90 days to lifetime**	**No: Pass to RPh. Deny; not funded by the OHP.**

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin
Funded	
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	X
Chemotherapy Induced Neuropathy	X
Non-funded	
Fibromyalgia	X

P&T Review: *3/17 (DM); 3/15; 5/09; 9/07; 11/07*
Implementation: *4/18/15; 1/11; 1/10*

Milnacipran

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Milnacipran

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes: Approve for 90 days to lifetime**	**No: Pass to RPh. Deny; not funded by the OHP.**

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	
Diabetic Neuropathy	
Postherpetic Neuropathy	
Painful Polyneuropathy	
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	X

Lidocaine Patch

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Lidocaine Patch

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes: Pass to RPh. Deny; medical appropriateness**	**No: Go to # 3**
3. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (refer to Table 1 for examples).	**Yes: Approve for 90 days to lifetime**	**No: Pass to RPh. Deny; not funded by the OHP.**

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Lidocaine Patch
Funded	
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	

P&T Review: *3/17 (DM)*
Implementation: *5/17*

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: “Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal.”	

P&T Review: *3/17 (DM); 7/16 (DM); 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*

Drugs Used for Non-Funded Pain Conditions

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature (e.g., major depressive disorder, epilepsy, diabetic neuropathy, post-herpetic neuralgia).

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Milnacipran and pregabalin

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
4. What diagnosis is being treated?	Record ICD10 code	
5. Is the drug requested pregabalin AND does the patient have a diagnosis of epilepsy (ICD10: G40101-G40311; G40401-G40509; G40802; G40804; G40901-G40919; R569 or S069X9S)?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
6. Is the diagnosis funded on the OHP list of prioritized services (see Table 1 below for examples)?	**Yes:** Approve for 90 days to 1 year	**No:** Pass to RPh. Go to #4

Approval Criteria

7. Pass to RPh:
    - For Bipolar affective disorder: there are no data to support use of any of these drugs for this indication (Deny Medical Appropriateness). Recommend other alternatives (lithium, valproate, carbamazepine, lamotrigine).
    - For Migraine prophylaxis: there are no data to support use of any of these drugs for this indication (Deny Medical Appropriateness). Recommend other alternatives (beta-blockers, calcium channel blockers, valproate, gabapentin, TCAs). Refer to American Academy of Neurology Guideline.
    - If clinically warranted, may DENY yesterday's date (Medical Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal.

    All other indications need to be evaluated to see if diagnosis is funded:
    - Funded neuropathies found in table (list is not all-inclusive) may be approved for 90 days with subsequent approvals dependent on documented positive response (documented response means that follow-up and response is noted in client's chart per clinic staff).
    - **Forward any neuropathy/neuralgia ICD-10 codes not found in Table 1 to the Lead Pharmacist. These codes will be forwarded to DMAP for consideration.**

Table 1.

NON-FUNDED DIAGNOSES	ICD10
DISORDERS OF SOFT TISSUE	
Myalgia and myositis, unspecified (includes fibromyalgia syndromes)	M609; M791; M797
Neuralgia, neuritis, and radiculitis, unspecified	M792
ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT	
Sacroiliitis, not elsewhere classified	M461
Inflammatory spondylopathies in diseases classified elsewhere	M4980
Cervical spondylosis without myelopathy	M47812
Thoracic spondylosis without myelopathy	M47814
Lumbosacral spondylosis without myelopath	M47817
Traumatic spondylopathy	M4830
Other allied disorders of spine	M489
Spondylosis of unspecified site, without mention of myelopathy	M47819
Intervertebral disc disorders*	M4640; M4647; M5020; M5030; M5080; M5090; M5104-M5107; M519; M5124-5127; M5134-5137; M5144-5147; M5184-5187; M961
Other disorders of cervical region	M5402, M5382
Pain in thoracic spine/Lumbago	M545-546
Backache, unspecified	M4327-4328; M533; M539; M5408; M5489; M549
Nonallopathic lesions not elsewhere classified	M9900-9908
Closed dislocation thoracic and lumbar vertebra	S33101A; S23101A
Sprains and strains of other and unspecified parts of back	S134XXA; S138XXA; S233XXA; S238XXA; S239XXA; S335XXA; S338XXA
CHRONIC PAIN (EXCLUDED DIAGNOSES)	
Chronic pain d/t trauma	G8921
Other chronic pain	G8929
Chronic pain syndrome	G894
FUNDED DIAGNOSES	**ICD10**
Hereditary and idiopathic peripheral neuropathy	G600-601; G603; G608-609
Diabetes with neurological manifestations	E1040; E1065; E1140; E1165

Herpes zoster with nervous system complications	B0221-B0229
Syringomyelia and syringobulbia	G950
Disorders of meninges, not elsewhere classified	G9612; G9619
Brachial neuritis or radiculitis NOS	M5412-5413
Other specified congenital anomalies of spinal cord	Q060-061; Q063; Q068

**= the following diagnoses are currently funded by OHP: Intervertebral disc disorders (M5000, M5104-5106); Other disorders of cervical region (M6788); and Backache, unspecified* (*M5414-5417)*
***= the following diagnoses require use of HERC guideline notes to determine coverage: Intervertebral disc disorders (M5020; M5125-5127); Backache, unspecified* (*M438X9; M532X7-532X8); and Congenital musculoskeletal deformities of sternocleidomastoid muscle (Q680)*

P&T Review: *3/15; 5/09; 9/07; 11/07*
Implementation: *10/1*

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Class Update: Skeletal Muscle Relaxants

Date of Review: March 2017 **Date of Last Review:** November 2014

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

Purpose for Class Update:
The purpose of this class review is to evaluate new evidence for the safety and efficacy of muscle relaxants in treating chronic neurologic conditions associated with spasticity, or in chronic or acute musculoskeletal conditions with or without muscle spasms.

Research Questions:
1. What is the comparative efficacy and effectiveness of skeletal muscle relaxants for 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 harms of skeletal muscle relaxants in neurologic conditions with spasticity or musculoskeletal conditions?
3. Are there certain sub-populations in which skeletal muscle relaxants may be beneficial or cause more harm?

Conclusions:
- There is no new evidence regarding the use of skeletal muscle relaxants in neurological conditions associated with spasticity.
- Moderate quality evidence shows tizanidine, cyclobenzaprine, and baclofen are more efficacious than placebo for short-term (5 to 7 days) pain relief of acute low back pain (LBP).[1]
- One high quality study showed that tizanidine, baclofen and cyclobenzaprine are more effective than placebo in reducing pain associated with acute LBP.[2]
- Three high quality studies revealed carisoprodol is no more effective than placebo in alleviating pain associated with acute LBP.[2]
- There is insufficient evidence to evaluate the effectiveness of skeletal muscle relaxants in chronic LBP.[1,2]
- Moderate quality evidence demonstrates that patients experience more adverse effects with skeletal muscle relaxants compared to placebo.[1]
- There is no new evidence regarding use of skeletal muscle relaxants in specific populations.

Recommendations:
- Evaluate comparative costs in executive session and make final PDL recommendations.
- Revise PA criteria to limit duration of skeletal muscle relaxant therapy to 3 months due to limited evidence demonstrating their efficacy beyond 5-7 days.

Previous Conclusions and Recommendations:

- 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.
- 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.

Background:

Skeletal muscle relaxants can be classified into 2 main categories: antispasticity and antispasmodic medications. The antispasticity agents include baclofen and dantrolene. Although the precise mechanism of action of baclofen is unknown, it is postulated baclofen inhibits synaptic reflexes at the spinal cord level.[3] Baclofen is Food and Drug Administration (FDA) approved to alleviate signs and symptoms of spasticity resulting from multiple sclerosis (MS) or spinal cord injuries; particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.[3] It is not indicated for the treatment of skeletal muscle spasm due to rheumatic diseases.[3] The efficacy of baclofen in stroke, cerebral palsy and Parkinson's disease has not been established.[3] In contrast, dantrolene causes skeletal muscle relaxation through a direct effect on skeletal muscle, most likely due to interfering with calcium release from the sarcoplasmic reticulum.[4] Dantrolene is FDA approved to control the manifestations of clinical spasticity resulting from upper neuron disorders due to spinal cord injury, cerebral palsy, or MS.[4] Similar to baclofen, dantrolene is not indicated for treatment of skeletal muscle spasm due to rheumatic disorders.[4] Dantrolene can cause fatal hepatotoxicity and the manufacturer has issued a black box warning notifying prescribers of this serious adverse effect.[4]

Antispasmodic muscle relaxants include carisoprodol, cyclobenzaprine, chlorzoxazone, metaxalone, methocarbamol, and orphenadrine. Cyclobenzaprine is structurally related to the tricyclic antidepressants (TCAs) and causes anticholinergic side effects similar to TCAs. Carisoprodol is metabolized to meprobamate, a drug that is primarily used to treat anxiety. The antispasmodics decrease muscle spasm by altering central nervous system (CNS) conduction resulting in reduced pain perception. Most patients will also experience sedation as a result of the drugs' effects on CNS physiology. Tizanidine, a centrally acting alpha agonist, is a unique agent in this class because it alleviates both spasms and spasticity. It has a short duration of effect, so it should be used at times when relief of spasticity is most important.[5] In general, antispasticity and antispasmodic agents are not interchangeable and should be not be substituted for each other.[6] **Table 1** outlines the FDA approved indications, dosing, and adverse effects of the skeletal muscle relaxants. The current list of preferred skeletal muscle relaxants is included in **Appendix 1**.

The evidence for effectiveness of the skeletal muscle relaxants is sparse. A 2000 Cochrane review assessed the effectiveness and safety of muscle relaxants for the long-term treatment of spasticity in spinal cord injury (SCI) patients.[7] Overall, there was insufficient evidence to make conclusions for antispastic treatment in SCI patients.[7] Another Cochrane review published in 2003 evaluated anti-spasticity agents in patients with MS and again found insufficient evidence for comparative effectiveness between these medications.[8] An additional 2003 Cochrane review evaluated the effectiveness of skeletal muscle relaxants in the treatment of nonspecific low back pain.[9] Eleven short term, placebo controlled, randomized trials of nonbenzodiazepene muscle relaxants were included in this

systematic review. The authors concluded there is moderate quality evidence that cyclobenzaprine, carisoprodol, orphenadrine and tizanidine are all more effective than placebo for reducing pain intensity in patients with acute low back pain (Relative Risk (RR) 0.80, 95% Confidence Interval (CI) 0.71 – 0.89).[9] At the time of this review there were no comparative trials between muscle relaxants and nonsteroidal anti-inflammatory agents (NSAIDs). Of note, adverse effects including drowsiness, headache, blurred vision, nausea, and vomiting, were significantly more prevalent in patients taking muscle relaxants compared to placebo (RR 1.50, 95% CI: 1.14-1.98).[9] Central nervous adverse effects such as dizziness and drowsiness occurred more frequently than other side effects (RR 2.04, 95% CIL 1.23-3.37).[9] Although skeletal muscle relaxants are somewhat effective in the short term management of nonspecific low back pain, their adverse effects require that they be used with caution.[9] This assessment is reinforced by the 2012 American Geriatrics Society (AGS) Beers Criteria update for potentially inappropriate medication use in older adults.[10] For this update, an interdisciplinary panel of AGS reviewers completed a systematic review and graded the evidence using the Cochrane scoring system to evaluate risk of bias.[11] Moderate quality evidence revealed that skeletal muscle relaxants are poorly tolerated by older adults due to anticholinergic and sedating adverse effects and should be avoided in the elderly.[10] Furthermore, there is insufficient evidence to support the effectiveness of muscle relaxants at doses tolerated by older adults.[10] When the 2015 update to the Beers criteria was published, no additional evidence was found to modify the 2012 recommendations for avoiding skeletal muscle relaxants in older adults.[12]

The third National Health and Nutrition Examination Survey (NHANES III) examined prevalence of patterns for prescription muscle relaxant use from 1988 through 1994.[13] This survey reported approximately two million U.S. adults used skeletal muscle relaxants for pain. Eight five percent patients used muscle relaxants for back pain or muscle disorders. The Oregon Health Evidence Review Commission (HERC) issued coverage guidance for pharmacological interventions in lower back pain in 2012.[14] The HERC guidance supported the use of skeletal muscle relaxants for treatment of acute back pain but not for chronic back pain. Until July 2016, not all types of back pain were funded conditions for Oregon Health Plan (OHP) patients. Due to new evidence, changes to the Prioritized List of Health Services were implemented July 1, 2016 to expand coverage for most back conditions. These changes also included recommendations to limit opiates to short term utilization and cautioned against long term opiate prescriptions.[15] Furthermore, nonpharmacologic therapies such as acupuncture, chiropractic and physical therapy are now recommended over surgery and narcotics.[15] A complete list of funded and nonfunded painful back conditions is listed in **Table 2.**

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

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
In the 2016 Agency for Healthcare Research and Quality (AHRQ) report focusing on noninvasive treatments for back pain, a total of 156 publications were reviewed including pharmacologic and nonpharmacologic treatments.[1] Pharmacologic interventions included acetaminophen, NSAIDs, opioids, benzodiazepines, corticosteroids, antidepressants, antiepileptics, and skeletal muscle relaxants. Seventeen studies evaluated skeletal muscle relaxants versus placebo (n = 12),

skeletal muscle relaxants versus an active medication (n = 2), and comparisons between skeletal muscle relaxants (n = 3).[1] Treatment duration for these trials was short term, ranging from 4 to 21 days. Most of the patients enrolled in the trials had non-specific LBP with at least moderate intensity pain at baseline (>5 on a 10 point rating scale).[1] Primary outcomes included reduction in pain intensity and improvements in back specific function. Pharmacological interventions in these trials included: tizanidine (number of trials = 7), cyclobenzaprine (n = 4), oral and IV orphenadrine (n = 3, 1, respectively), carisoprodol (n = 2), chlorzoxazone (n = 1), dantrolene (n = 1), and baclofen (n = 1). [1] Moderate quality evidence showed tizanidine, cyclobenzaprine, and baclofen were more effective than placebo for short-term pain relief over 5 to 7 days (RR 1.72, 95% CI 1.32 -2.22).[1] Low quality evidence found no difference in efficacy between carisoprodol versus cyclobenzaprine and tizanidine versus chlorzoxazone for acute LBP. [1] There was insufficient evidence to evaluate the efficacy of muscle skeletal relaxants versus placebo in management of chronic LBP.[1] In 8 trials, skeletal muscle relaxants were associated with increased risk of any adverse events compared to placebo (RR 1.50, 95% CI 1.14 – 1.98) as well as increased risk of central nervous system events such as sedation (RR 2.04, 95% CI 1.23 – 3.37).[1]

A 2016 systematic review was funded by the Australian Medical Research Council and GlaxoSmithKline to evaluate the efficacy and tolerability of skeletal muscle relaxants in the management of adults with LBP.[2] The reviewers searched for RCTs from 1972 through October 2015. Fifteen studies including 3362 participants met inclusion criteria. Six of the studies evaluated medications available in the United States; cyclobenzaprine, tizanidine, and carisoprodol, the rest of the studies included medications only available in Europe. The reviewers rated the quality of these studies as moderate to high.[2] The trials were short term (4-7 days) in adults with acute LBP. No evidence was found to evaluate skeletal muscle relaxant use in chronic LBP.[2] Three studies compared carisoprodol to placebo, 1 trial compared tizanidine to ibuprofen, 1 trial compared tizanidine to placebo, and 1 trial compared carisoprodol to cyclobenzaprine. The primary outcome was changes in pain intensity. The pain outcomes were converted to 0-100 scale (0: no pain - 100: worst possible pain) and were reported as mean differences (MD). Changes in MD by 10 points were considered minimally significant and by 20 points considered clinically significant.[2] Tizanidine was more effective than placebo in reducing pain intensity (MD = -25, 95% CI -37.1 to -13.1).[2] There was no significance in effectiveness noted between tizanidine and ibuprofen (MD = -4, 95% CI -18.8 to 10.8). [6] In a head-to-head trial comparing carisoprodol and cyclobenzaprine, no differences were noted in alleviating pain (MD = -5.0, 95 % CI -15.7 to 5.7).[2] The 3 placebo controlled carisoprodol trials also showed no significant differences in efficacy between drug and placebo (MD = -8.7, 95% CI -12.2 to -5.2; MD = -14, 95% CI -29.3 to 1.3; MD -4.2, 95% CI -7.0 to -.0.5).[2] Adverse events such as nausea, dizziness, and headaches were similar for muscle relaxants compared to placebo (n = 6 trial; 16% vs 14.1%; p = 0.5).[2] Of the 3 skeletal muscle relaxants included in this systematic review, tizanidine was more effective than placebo in reducing pain associated with acute LBP. Carisoprodol showed no benefit in efficacy when compared to placebo and no differences were noted between carisoprodol and cyclobenzaprine in alleviating pain.

In the 2015 CADTH review on long-term use of cyclobenzaprine, seven systematic reviews, four RCTs, and four practice guidelines were evaluated.[16] In the meta-analysis, the study population included patients with fibromyalgia (n = 2), myofascial pain (a chronic condition that affects the connective tissues or muscles; n = 1), mechanical neck disorders (n = 1), and back pain (n = 2). For the RCTs, there was one for neck pain, one for myofascial pain, and two for neck or back pain. For the four practice guidelines, two included fibromyalgia, one for chronic pain, and one for low back pain. There was insufficient evidence to determine if one skeletal muscle relaxant provided more pain relief than the others.[16] Another systematic review for non-specific LBP showed no difference in pain relief between cyclobenzaprine and carisoprodol and a low quality RCT showed a significant decrease in muscle spasm for cyclobenzaprine over NSAID use within two weeks.[16] There was a 2011 guideline that recommended skeletal muscle relaxants in addition to NSAIDS or monotherapy when first-line agents (NSAIDS and acetaminophen) has not reduced the pain, but only up to two weeks.[16] CADTH was unable to extract information on dosing, duration, and place in therapy based on the available literature.

New Guidelines:

American College of Physicians (ACP) Clinical Practice Guideline for Noninvasive Treatments of Back Pain

In early 2017, updated ACP guidelines were published in the Annals of Internal Medicine. The most recent publication provides treatment guidance for acute, subacute, and chronic low back pain.[17] Nonpharmacologic treatment with heat, massage, acupuncture or spinal manipulation are recommended as first line therapies. If pharmacologic therapy is warranted, NSAIDs or skeletal muscle relaxants are the treatments of choice for acute low back pain for short term use based on moderate quality evidence. Skeletal muscle relaxants are not recommended for management of chronic low back pain due to low quality evidence that showed no differences in any outcome between different muscle relaxants for treatment of chronic back pain. The adverse effects associated with muscle relaxants included sedation, drowsiness, and dizziness. Moderate quality evidence from 8 RCTs showed that muscle relaxants have an increased risk of central nervous effects compared to placebo (RR 2.04; 95% CI 1.14 to 1.98).[17]

Table 1. Skeletal muscle relaxants indications and adverse drug reactions[5,18]

Oral Medications	FDA indications	Oral Dosing	Adverse drug reactions (common)
Antispasticity Agents			
Baclofen	Spasticity from multiple sclerosis and spinal cord injuries	Initial 5 mg 3 times a day May increase by 5 mg every 3 days Do not exceed 20 mg 4 times daily (80 mg daily)	Drowsiness/Dizziness Nausea Weakness/Fatigue Confusion Hypotension Urinary Frequency
Dantrolene	Chronic spasticity due to spinal cord injury, cerebral palsy or multiple sclerosis	Initial 25 mg daily for 7 days Increase to 25 mg 3 times daily for 7 days, increase to 50 mg 3 times daily for 7 days, and then increase to 100 mg 3 times daily May increase to 100 mg 4 times daily Do not exceed 400 mg daily	Drowsiness/Dizziness Weakness Fatigue Diarrhea **Hepatotoxicity- Black Box Warning** Dysphagia Nausea Urinary Retention
Antispasmodic Agents			
Cyclobenzaprine	Muscle spasm associated with acute, painful musculoskeletal conditions. **Do not use longer than 2-3 weeks**	Tablet, immediate release: 5 mg 3 times daily; may increase up to 10 mg 3 times daily if needed. Not recommended in moderate to severe hepatic impairment	Drowsiness/Dizziness Blurred Vision Xerostomia
Carisoprodol	Relief of discomfort associated with acute musculoskeletal pain. **Do not use longer than 2-3 weeks**	250-350 mg 3 times daily at bedtime	Drowsiness/Dizziness Headache
Chlorzoxazone	Relief of discomfort associated with acute musculoskeletal pain.	250-500 mg 3 or 4 times daily, may increase to 750 mg 3 or 4 times daily. Consider dose reductions as symptoms improve	Drowsiness/Dizziness Urine Discoloration Paradoxical CNS stimulation Hepatic Toxicity
Metaxalone	Relief of discomfort associated with acute musculoskeletal pain	800 mg 3 to 4 times daily	Drowsiness/Dizziness Skin rash Nausea Vomiting Hemolytic Anemia Jaundice
Methocarbamol	Relief of discomfort associated with acute musculoskeletal pain.	1.5 grams 4 times daily for 2-3 days (up to 8 grams/day may be given in severe conditions), then decrease to 4-4.5 grams/day in 3-6 divided doses	Drowsiness/Dizziness Skin rash GI upset Jaundice Blurred Vision
Orphenadrine	Relief of discomfort associated with acute musculoskeletal pain.	100 mg twice daily	Drowsiness/Dizziness Tachycardia Blurred Vision Urinary retention
Combination Antispasticity and Antispasmodic Agents			
Tizanidine	Management of spasticity	Initial 2 mg up to 3 times daily (every 6 or 8 hours) as needed. May titrate to optimal effect in 2-4 mg increments per dose (with a minimum of 1-4 days between dose increases). Do not exceed 36 mg daily; single doses >16 mg have not been studied	Drowsiness/Dizziness Hypotension Hepatic Injury Xerostomia Bradycardia Weakness Hallucinations

Table 2: Funded and unfunded conditions of the back

Funded	Unfunded
Line 351: conditions of the back and spine with urgent surgical indications Line 407: Conditions of the back and spine	Line 532: conditions of the back and spine without urgent surgical conditions Line 562: Spastic dysphonia Line 611: Sprains and strains of adjacent muscles and joints, minor Line 663: Musculoskeletal conditions with no or minimally effective treatments or no treatment necessary

Randomized Controlled Trials:
A total of 74 citations were manually reviewed from the literature search. After manual review, 73 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in the table below. The full abstract is included in **Appendix 3**.

Table 2: Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Friedman et al.[19] RCT, DB, ITT, 3 group N = 323	Naproxen 500 mg BID + placebo x 10 days Vs Naproxen 500 mg BID + cyclobenzaprine 5 mg 1-2 tablets q8h prn x 10 days Vs Naproxen 500 mg BID + oxycodone 5 mg/acetaminophen 325 mg daily 1-2 tables q8h prn x 10 days	Age: 21-64 years old with Nontraumatic, nonradicular LBP of 2 weeks duration or less	Improvement in RMDQ between ED discharge and 1 week later	**Pain and Disability Improvement:**[19] Naproxen + placebo improved by a mean of 9.8 ; 98.3% CI: 7.9-11.7) Naproxen + cyclobenzaprine improved by a mean of 10.1; 98.3% CI: 9.0-13.2) Naproxen + oxycodone/acetaminophen improved by a mean of 11.1; 98.3% CI: 9.0-13.2) **Between group differences in mean RMDQ improvement were as follows:**[19]Cyclobenzaprine vs placebo = 0.3 (98.3% CI, −2.6 to 3.2; P = .77) Oxycodone/acetaminophen vs placebo = 1.3 (98.3% CI, −1.5 to 4.1; P = .28) Oxycodone/acetaminophen vs cyclobenzaprine = 0.9 (98.3% CI, −2.1 to 3.9; P = .45). Authors Conclusions: Adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 7 days[19]

Abbreviations: ED= Emergency Department, ITT= Intention to Treat, LBP = Low Back Pain, RCT = Randomized Clinical Trial; DB = Double Blinded; BID = twice daily dosing; RMDQ = Roland Morris Disability Questionnaire; n = sample size.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	BACLOFEN	BACLOFEN	Y
ORAL	TABLET	CYCLOBENZAPRINE HCL	CYCLOBENZAPRINE HCL	Y
ORAL	TABLET	TIZANIDINE HCL	TIZANIDINE HCL	Y
ORAL	TABLET	ZANAFLEX	TIZANIDINE HCL	Y
ORAL	CAP ER 24H	AMRIX	CYCLOBENZAPRINE HCL	N
ORAL	CAPSULE	DANTRIUM	DANTROLENE SODIUM	N
ORAL	CAPSULE	DANTROLENE SODIUM	DANTROLENE SODIUM	N
ORAL	CAPSULE	TIZANIDINE HCL	TIZANIDINE HCL	N
ORAL	CAPSULE	ZANAFLEX	TIZANIDINE HCL	N
ORAL	TABLET	CARISOPRODOL	CARISOPRODOL	N
ORAL	TABLET	CARISOPRODOL COMPOUND	CARISOPRODOL/ASPIRIN	N
ORAL	TABLET	CARISOPRODOL-ASPIRIN	CARISOPRODOL/ASPIRIN	N
ORAL	TABLET	CHLORZOXAZONE	CHLORZOXAZONE	N
ORAL	TABLET	CYCLOBENZAPRINE HCL	CYCLOBENZAPRINE HCL	N
ORAL	TABLET	FEXMID	CYCLOBENZAPRINE HCL	N
ORAL	TABLET	LORZONE	CHLORZOXAZONE	N
ORAL	TABLET	METAXALONE	METAXALONE	N
ORAL	TABLET	METHOCARBAMOL	METHOCARBAMOL	N
ORAL	TABLET	PARAFON FORTE DSC	CHLORZOXAZONE	N
ORAL	TABLET	ROBAXIN	METHOCARBAMOL	N
ORAL	TABLET	ROBAXIN-750	METHOCARBAMOL	N
ORAL	TABLET	SKELAXIN	METAXALONE	N
ORAL	TABLET	SOMA	CARISOPRODOL	N
ORAL	TABLET ER	ORPHENADRINE CITRATE	ORPHENADRINE CITRATE	N
ORAL	TABLET	CARISOPRODOL COMPOUND-CODEINE	CODEINE/CARISOPRODOL/ASPIRIN	N
ORAL	TABLET	CARISOPRODOL-ASPIRIN-CODEINE	CODEINE/CARISOPRODOL/ASPIRIN	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 4 2017

1. Baclofen.mp. or exp Baclofen/ 4198

2. carisoprodol.mp. or exp Carisoprodol/ 146

3. chlorzoxazone.mp. or exp Chlorzoxazone/ 584

4. cyclobenzaprine.mp. 143

5. dantrolene.mp. or exp Dantrolene/ 1248

6. Muscle Relaxants, Central/ or metaxalone.mp. 24

7. methocarbamol.mp. or exp Methocarbamol/ 69

8. orphenadrine.mp. or exp Orphenadrine/ 153

9. tizanidine.mp. 325

10. muscle relaxants

10. muscle spasticity 7063

11.back pain 32049

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 7484

13. 10 or 12 3521

14. exp Pain/ 369683

15. 13 or 14 388524

16. 11 and 15 2747

17. limit 16 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews), English, humans, 2013- current: 74

Appendix 3: Abstracts of Clinical Trials

Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low back pain

Importance: Low back pain (LBP) is responsible for more than 2.5 million visits to US emergency departments (EDs) annually. These patients are usually treated with nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, or skeletal muscle relaxants, often in combination.

Objective: To compare functional outcomes and pain at 1 week and 3 months after an ED visit for acute LBP among patients randomized to a 10-day course of (1) naproxen + placebo; (2) naproxen + cyclobenzaprine; or (3) naproxen + oxycodone/acetaminophen.

Design, Setting, and Participants: This randomized, double-blind, 3-group study was conducted at one urban ED in the Bronx, New York City. Patients who presented with nontraumatic, nonradicular LBP of 2 weeks' duration or less were eligible for enrollment upon ED discharge if they had a score greater than 5 on the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment on which 0 indicates no functional impairment and 24 indicates maximum impairment. Beginning in April 2012, a total of 2588 patients were approached for enrollment. Of the 323 deemed eligible for participation, 107 were randomized to receive placebo and 108 each to cyclobenzaprine and to oxycodone/acetaminophen. Follow-up was completed in December 2014.

Interventions: All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day. They were randomized to receive either 60 tablets of placebo; cyclobenzaprine, 5 mg; or oxycodone, 5 mg/acetaminophen, 325 mg. Participants were instructed to take 1 or 2 of these tablets every 8 hours, as needed for LBP. They also received a standardized 10-minute LBP educational session prior to discharge.

Main Outcomes and Measures: The primary outcome was improvement in RMDQ between ED discharge and 1 week later.

Results: Demographic characteristics were comparable among the 3 groups. At baseline, median RMDQ score in the placebo group was 20 (interquartile range [IQR], 17-21), in the cyclobenzaprine group 19 (IQR,17-21), and in the oxycodone/acetaminophen group 20 (IQR,17-22). At 1-week follow-up, the mean RMDQ improvement was 9.8 in the placebo group, 10.1 in the cyclobenzaprine group, and 11.1 in the oxycodone/acetaminophen group. Between-group difference in mean RMDQ improvement for cyclobenzaprine vs placebo was 0.3 (98.3% CI, −2.6 to 3.2; P = .77), for oxycodone/acetaminophen vs placebo, 1.3 (98.3% CI, −1.5 to 4.1; P = .28), and for oxycodone/acetaminophen vs cyclobenzaprine, 0.9 (98.3% CI, −2.1 to 3.9; P = .45).

Conclusions and Relevance: Among patients with acute, nontraumatic, nonradicular LBP presenting to the ED, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 1-week follow-up. These findings do not support use of these additional medications in this setting.

Skeletal Muscle Relaxants

Goal(s):

- Cover non-preferred drugs only for funded conditions.
- Restrict carisoprodol to short-term use due to lack of long-term studies to assess safety or efficacy and high potential for abuse.

Length of Authorization:

Up to 3 months

Requires PA:

- Non-preferred agents

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by the Oregon Health Plan?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded 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 and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Is drug requested carisoprodol?	**Yes:** Go to #5	**No:** Approve for up to 36 months

Approval Criteria		
5. Does total quantity of carisoprodol exceed 56 tablets in 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 cancer, end stage Parkinson's disease, 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 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 of age; or
  ○ renal failure; or
  ○ hepatic failure; or
  ○ take > 1400 mg per day?
	Yes: Document reason and approve long taper:
	
	• Authorize 18 tablets
	• Reduce dose over 9 days
	• 350 mg TID X 3 days, then
	• 350 mg BID X 3 days, then
	• 350 mg daily 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 daily x1 day, then evaluate

P&T Review: *5/17 (DM) 3/17; 11/14; 9/09; 2/06; 2/04; 11/01; 2/01; 9/00; 5/00; 2/00*
Implementation: *1/1/15, 1/1/14, 1/1/10, 11/18/04*

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

Drug Evaluation: Tramadol

Date of Review: March 2017
Generic Name: tramadol
PDL Class: Opioids, short acting and long acting

End Date of Literature Search: 02/10/2017
Brand Name (Manufacturer): Ultram
Dossier Received: no

Purpose of Review: The purpose of this review is to establish the place in therapy of tramadol for the management of acute and chronic non-cancer pain relative to other opioid therapy. Additionally, this paper will describe the risk for misuse, abuse, diversion, and dependence of tramadol relative to other opioids, which may affect coverage decisions.

Research Questions:

- What is the comparative efficacy or effectiveness of tramadol compared to other opioids in reducing acute or chronic non-cancer pain and improving functional outcomes in adult and pediatric patients?
- What is the evidence for comparative harms, safety concerns (cognitive impairment, sedation, and respiratory depression), unintended effects (euphoria and withdrawal cravings) and risk of misuse, abuse, dependence, and diversion of tramadol compared to other opioids in adult and pediatric patients treated for chronic non-cancer pain?
- Are there subpopulations of patients based on age (e.g., pediatric patients), race, comorbidities (e.g., renal or hepatic impairment, history of opioid abuse, alcohol dependence, mental health conditions, or pre-initiation functional level), concomitant drug therapies (benzodiazepines or marijuana use), or socio-economic status (e.g., Medicaid) who may be at a higher risk for harms or risk for misuse, abuse, dependence, and diversion with tramadol use?

Conclusions:

- There is low quality evidence that tramadol is more effective than placebo in reduction of pain and improved function for the treatment of chronic pain, chronic low back pain, and osteoarthritis. For the treatment of chronic low back pain, tramadol was associated with moderate effects on pain versus placebo (standardized mean difference [SMD] -0.55; 95% CI -0.66 to -0.44, with a mean difference of 1 point or less on a 0-10 pain scale) and small effects on function (SMD -0.18; 95% CI -029 to -0.07, mean difference of approximately 1 on the Roland-Morris Disability Questionnaire [RDQ]), which is well below the level considered clinically important.
- There is very low quality evidence that there is no difference in pain relief between sustained release tramadol and transdermal buprenorphine in patients with musculoskeletal pain.
- For the treatment of post-operative pain in children and adolescents, there is low quality evidence from 4 trials demonstrating no clear difference in the need for rescue analgesia between tramadol and morphine (RR 1.25; 95% CI 0.83 to 1.89). An accurate risk-benefit analysis is difficult since adverse events were poorly reported.

Author:

- There is insufficient long-term evidence of the comparative efficacy or safety of tramadol compared to other opioid therapies.
- Although tramadol has lower affinity for the μ-opioid receptor, there is insufficient evidence that tramadol has a lower addiction risk than other opioid analgesics. One RCT comparing buprenorphine patches to tramadol found no indication for abuse or diversion in either treatment group. An additional study with many limitations suggested that tramadol had significantly lower rates of abuse and dependence compared to hydrocodone (2.7% vs. 4.9%).
- Common adverse events that occur more frequently with tramadol than placebo are nausea (22.2% vs. 8.0%), constipation (18% vs. 5.3%), dizziness (13.2% vs. 4.6%) and somnolence (13.2% vs. 3.8%). Unique safety concerns associated with tramadol use include an increase in the risk of seizures and serotonin syndrome when used with other serotonergic medications. Those who are ultra-rapid CYP2D6 metabolizers appear to be more susceptible to opioid effects from tramadol, including dependency and sedation.

Recommendations:

- Maintain tramadol in current opioid prior authorization policy.

Background:

In recent years, there has been a growing understanding of significant harms associated with opioids, particularly at high doses, including addiction, abuse, and overdose. Opioid overdose has steadily increased from 2000 to 2015, with 91 Americans dying every day from opioid overdose.[1] Furthermore, there is a lack of high-quality evidence that opioids improve pain or function for chronic pain. Prevention, assessment, and treatment of chronic pain are challenging for clinicians. Pain can limit the ability to perform certain activities, decrease work productivity and quality of life. However, there are also serious harms associated with opioid use. Opioid analgesics are widely diverted and improperly used, which has resulted in a national epidemic of opioid-related deaths. The contributing factors associated with overdose can be divided into those associated with the opioid itself (e.g., potency, dose, or duration of action) and factors specific to the patient (e.g., older age, adolescence, depression, substance use disorder, or history of overdose).[2] As a result of the increase in opioid overdose, the Center for Disease Control and Prevention (CDC) released guidelines for prescribing opioids for chronic pain.[3] The CDC guidelines prefer nonpharmacological therapy and non-opioid analgesic therapy before turning to opioids. The maximum recommended dose of opioids should not exceed 90 morphine equivalents.[3] However, tramadol is not included in the guideline recommendations. Tapentadol, another mu receptor agonist and SNRI, is included in dosing recommendations with the following information: "*morphine milligram equivalent is based on degree of* μ*-receptor activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists."* [3]

Tramadol is an opioid medication that produces analgesic effects through a dual mechanism of action. Tramadol is pharmacologically similar to other opioids but has a lower affinity for μ-opioid receptors and also acts as a weak inhibitor of the neuronal reuptake of norepinephrine and serotonin.[4] It has been suggested that tramadol has a lower potential of abuse and dependence due to its relatively low affinity for μ-opioid receptor. The affinity for the μ-opioid receptor is 4000-fold less than that of morphine; however, tramadol has still been shown to cause significant withdrawal syndrome and can include both opioid and SNRI-associated withdrawal symptoms.[5] When initially approved in 1994, it was classified as a non-scheduled drug and was not regulated by the Drug Enforcement Administration (DEA). Preliminary data had demonstrated a low potential for abuse, and it was already being used extensively in Europe.[5] Following approval, post-marketing surveillance found that there were approximately 2 to 3 cases per 100,000 per month of drug abuse or diversion with tramadol, and data demonstrated that higher doses of tramadol resulted in reinforcement and abuse potential in opioid abusers.[6] In 2014, the DEA officially scheduled tramadol as a Schedule IV substance in the US.[7] The DEA reviewed available data and concluded that there is strong evidence tramadol and propoxyphene are similar in their abuse potential pattern and appropriate to schedule tramadol as such. Furthermore, they cited that tramadol produces similar pharmacological effects as other opioids, including analgesia and respiratory depression.[7] As tramadol also inhibits reuptake of serotonin and norepinephrine, additional safety concerns

need to be accounted for, including the risk of serotonin syndrome and an increased risk of seizures.[4,5] The most common adverse reactions with tramadol include nausea, dizziness, and vomiting. At therapeutic doses, tramadol does not cause clinically relevant respiratory depression.

Although tramadol is not FDA approved for children 17 years or younger, it is commonly used off-label because many think it is safer and less potent than other opioids. [8] In 2015, the Food and Drug Administration (FDA) released a drug safety communication to further investigate the use of tramadol in children, because of the rare but serious risk of slowed or difficult breathing in those thought to be ultra-rapid metabolizers.[8] The risk may be increased in children treated for pain after tonsillectomy or adenoidectomy surgery.

In general, tramadol has shown modest efficacy in pain reduction. Pain intensity measurements used in trials include the visual analogue scale (VAS scale, 0-100 or 0-10) and the numerical rating scale (NRS; 0-10). For acute pain, the minimum clinically important difference in the 10-point VAS is 1.4; (95% CI 1.2 to 1.6). The proposed thresholds for a meaningful difference in chronic pain are about 2.0 points on the 0 to 10 point scale or 20 points on the 0-100 point scale. The impact on disability is a key clinical outcome. Scales used to measure function include the Oswestry Disability Index (ODI) and the Roland Morris Disability Questionnaire (RDQ). Improvements greater than 20 points on the ODI and 5 points on the RDQ are considered clinical important differences.[9]

Table 1. Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin
Oral Bioavailability	75%
Distribution and Protein Binding	Volume of distribution 2.6 L/kg in males and 2.9 L/kg in females; protein binding 20%
Elimination	30% excreted in the urine as unchanged drug; 60% excreted as metabolites
Half-Life	6.7 hours
Metabolism	CYP2D6, CYP3A4

Methods:

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

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

An Agency for Healthcare Research and Quality systematic review appraised the evidence on the comparative benefits and harms of noninvasive treatments for low back pain and included systematic reviews and RCTs comparing pharmacological treatments, including opioids and tramadol.[9] For chronic low back pain, the authors found moderate quality evidence that both opioids and tramadol were more effective in pain relief and function than placebo or sham.[9] Tramadol was associated with moderate effects on pain versus placebo (Standardized Mean Difference (SMD) -0.55; 95% Confidence Interval -0.66 to -0.44, with a mean difference of 1 point or less on a 0-10 pain scale). Compared to placebo, opioids were associated with small effects (SMD -0.43; 95% CI -0.52 to -0.33 for a mean difference of approximately 1 point on a 0-10 pain scale).[9] Effects on function were small for tramadol (SMD -0.18; 95% CI -0.29 to -0.07, mean difference of approximately 1 on the Roland-Morris Disability Questionnaire [RDQ]) and opioids (SMD -0.26; 95% CI -0.37 to -0.15, mean difference of approximately 1 on the RDQ) compared to placebo.[9] The RDQ is a measurement used to assess the impact of opioids on disability and ranges from 0-24. Two trials compared tramadol (50 mg three times daily) to celecoxib 200 mg twice daily. One trial found a small advantage for celecoxib on the percent of patients with a reduction in pain scores of at least 30% (66% responder vs. 57% for tramadol).[9] The second trial found no significant difference between the two therapies. No trials directly compared tramadol to other opioids. Trials were not designed to assess long-term harms or the risk for overdose, abuse, or addiction.

A rapid response report from Canadian Agency for Drugs and Technologies Health (CADTH) reviewed the clinical effectiveness of tramadol and tramadol plus acetaminophen for the management of pain in adults compared to placebo or active treatment.[11,12] Four RCTs were identified comparing tramadol to placebo, one RCT compared tramadol with buprenorphine and one RCT compared tramadol with NSAIDs. Additionally, three systematic reviews were identified that showed greater pain reduction with tramadol or a tramadol combination product when compared with placebo. However, differences were only statistically significant in one systematic review that evaluated chronic low back pain (MD -0.55; 95% CI -0.66 to -0.44).[11] One systematic review for chronic low back pain did not find a statistically significant difference (MD -1.72; 95% CI -3.45 to 0.01) and the third systematic review, which evaluated painful diabetic neuropathy, did not report statistical analyses (≥30% pain reductions: 56.2% vs. 37.9% for tramadol combination vs. placebo, respectively).[11] There was an increase in adverse events with tramadol compared to placebo (RR 1.74; 95% CI 1.20 to 2.52). Common adverse events that occurred more frequently with tramadol than placebo were nausea (22.2% vs. 8.0%), constipation (18% vs. 5.3%), dizziness (13.2% vs. 4.6%), and somnolence (13.2% vs. 3.8%).[11] In another systematic review, improvement in pain intensity was greater with tramadol compared to celecoxib (63.2% vs. 49.9%), but adverse events were higher compared to celecoxib as well (30.4% vs. 14.4%).[11] One RCT in patients with musculoskeletal pain found no difference in change in VAS score between sustained release tramadol and transdermal buprenorphine.[11] The authors concluded that greater pain reduction and more adverse events are associated with tramadol compared with placebo.[11] A single RCT suggests that efficacy and safety with tramadol and buprenorphine were comparable. One non-randomized study compared the use of tramadol plus acetaminophen to transdermal fentanyl for the control of postoperative pain following corrective eye surgery. Transdermal fentanyl was significantly better at reducing pain, but was also associated with an increase in adverse events.[12]

A Cochrane systematic review evaluated the analgesic effectiveness, effect on physical function, duration of benefit, and the safety of oral tramadol in people with osteoarthritis.[13] Three placebo-controlled studies (n=362) reported a reduction in pain intensity compared to placebo (8.5 units less on a scale from 0-100; 95% CI -12.05 to -4.9) and a reduction in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, representing an improvement in pain, stiffness, and function (reduction in score by -0.34; 95% CI -0.49 to -0.19 on a scale of 0 to 10).[13] The most common adverse events reported in these short term studies (up to 3 months) were nausea, vomiting, dizziness, constipation, somnolence, tiredness, and headache. Patients on tramadol were more likely to develop minor (RR 2.27; 95% CI 1.77 to 2.66) and major adverse events (RR 2.6; 95% CI 1.96 to 3.63) compared to placebo.[13] There is insufficient evidence comparing tramadol to other drugs in the treatment of osteoarthritis and insufficient long term efficacy or safety data.

Another Cochrane review compared opioids to placebo or other treatments for chronic low back pain.[14] Tramadol was included in 5 trials (n=1378) resulting in low quality evidence of a significant reduction in pain compared to placebo (SMD -0.55; 95% CI -0.66 to -0.44) with a moderate effect size.[14] There was moderate quality evidence of improved function compared to placebo (SMD -0.18; 95% CI -0.29 to -0.07) with a small effect size.[14] Other opioids, including morphine, hydromorphone, and oxycodone) were also found to be superior to placebo for pain (SMD -0.43; 95% CI -0.52 to -0.33) and function (SMD -0.26; 95% CI -0.37 to -0.15). [14] One RCT (n=1583) provided very low quality evidence of little pain relief with tramadol 50 mg four times a day compared to celecoxib (RR 0.82; 95% 0.76 to 0.90). There are no RCTs evaluating the long term (longer than 4 months) safety or effectiveness of opioid therapy for treatment of chronic low back pain. As studies were short term only, there was limited evidence evaluating severe adverse effects, and trials were not designed to assess risk of misuse, abuse, addiction, overdose, or death.

A Cochrane systematic review evaluated the effectiveness and side effect profile of tramadol for postoperative pain relief in children and adolescents undergoing surgical procedures.[15] Twenty RCTs including 1170 patients were included in the analysis. The overall risk of bias in the trials was unclear because allocation concealment and blinding of outcome assessors were poorly described. Low quality evidence from 5 trials found that the need for rescue analgesia in the postoperative care unit was reduced in children receiving tramadol compared to placebo (RR 0.40; 95% CI 0.20 to 0.78).[15] There was low quality evidence from 4 trials which found no clear difference in the need for rescue analgesia between tramadol and morphine (RR 1.25; 95% CI 0.83 to 1.89).[15] Other comparators included in the studies are not currently available in the United States. Trials which included patients with moderate to severe pain did not use a validated pain scale, and results cannot be interpreted. Generally, adverse events were poorly reported. Those treated with tramadol, compared with placebo, did not have reduced postoperative nausea and vomiting (RR 0.84; 95% CI 0.28 to 2.52). [15] The authors concluded that the overall strength of the evidence is low or very low due to small studies and methodological problems. Tramadol appears to be slightly more effective than placebo in reducing pain in the postoperative setting, but evidence for the comparison to other opioids remains uncertain. An accurate risk-benefit analysis is difficult since adverse events were poorly reported. [15]

Guidelines:

Guidelines for the noninvasive treatment of acute, subacute, and chronic low back pain were published from the American College of Physicians (ACP) in 2017.[16] Recommendations were made based on a systematic review of RCTs evaluating reduction or elimination of low back pain, improvement in back specific and overall function, improvement in health-related quality of life, reduction in work disability and return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects. The guidelines recommend tramadol or duloxetine as second-line pharmacological therapy after NSAIDs and nonpharmacological treatment. Tramadol is recommended before opioids are considered due to the known risks and realistic benefits of opioids (weak recommendation; moderate-quality evidence). The guidelines specify that the risk of abuse with tramadol is similar to other opioids. However, moderate-quality evidence demonstrated tramadol had a moderate effect on pain and a small effect on function in the short term, while opioids were shown to have a small effect on both.[16]

The VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain found insufficient evidence to recommend for or against any specific opioid or opioid formulation, specifically for tramadol and other dual-mechanism opioids.[17] The guidelines recommend non-opioid therapy over opioid therapy and against long-term opioid therapy for pain in patients with untreated substance use disorder. Although the guidelines recommend against opioid doses over 90 mg morphine equivalent daily for treating chronic pain, they do not make any specific recommendations for or against tramadol therapy in relation to other long-acting

opioids. All recommendations for safety measures and risk mitigation strategies applied to tramadol as well, and authors found no evidence on the safety of tramadol that met inclusion criteria.

Dependence/Abuse Potential:
The literature describing tramadol dependence is mostly limited to case reports and case series. Data demonstrates that tramadol dependence may occur when used daily for more than a few weeks, but there is limited data comparing the abuse potential between tramadol and other opioids. Those who are ultra-rapid CYP2D6 metabolizers appear to be more susceptible to opioid effects from tramadol, including dependency and sedation.[6,18]

A CADTH health technology assessment evaluated the evidence for addition potential with tramadol compared to other opioids for the treatment of pain. The 2010 report identified 2 RCTs in which the addiction potential of tramadol was compared to buprenorphine patches and hydrocodone. The RCT comparing buprenorphine patches to tramadol for the treatment of osteoarthritis pain found no indication of abuse or diversion in either treatment group. Conclusions were not able to be made regarding the abuse potential of either therapy. The second 12-month trial compared the prevalence of tramadol abuse with nonsteroidal anti-inflammatory drugs (NSAIDs) and hydrocodone-containing analgesics in chronic noncancer pain. Individuals with current substance abuse problems were excluded. Abuse was assessed with the Abuse Index questionnaire which was not validated. After 12 months, 2.7% of tramadol users and 4.9% of hydrocodone users ($p<0.01$) were identified as abusing the drug, suggesting that tramadol had significantly lower rates of abuse and dependence compared to hydrocodone. However, there were many limitations to this study including unclear randomization and a lack of intention-to-treat analysis. Furthermore, those subjects at highest risk of abuse were not included in the trials. CADTH reported insufficient evidence to evaluate whether tramadol has a lower addiction risk than other opioid analgesics.

A post-marketing surveillance program reported that withdrawal symptoms were common following abrupt discontinuation of tramadol. Both typical signs and symptoms seen from withdrawal of other opioids (nausea, sweating, restlessness, anxiety, or insomnia) as well as atypical symptoms (confusion, paranoia, severe panic attacks, hallucinations, or numbness) were reported.[19] From 1995 through 2000, 422 cases of opiate withdrawal were observed for tramadol. There were 644 cases of positive, possible, or alleged abuse.

A retrospective analysis included data from the National Poison Data System for both tramadol and tapentadol exposures from June 2009 through December 2011.[20] A total of 8566 tramadol cases were reviewed. The most common reason for exposure to tapentadol was suspected suicide (43.4%) followed by intentional misuse (16.4%). The majority of patients experienced a mild outcome, and there were a total of 10 deaths following exposure to tramadol (0.1%). Compared to tapentadol, there was a significant increase in the risk of seizures (14% vs. 1.8%; RR 7.94; 95% CI 2.99 to 10.91) and vomiting (RR 1.96; 95% CI 1.07 to 3.60). For patients on tramadol, the rates of seizures were 14.6%, vomiting 9.0%, coma 1.2%, and respiratory depression was 1.6%.[20]

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Long-acting Opioid Analgesics

Goals:

- Restrict use of long-acting opioid analgesics to OHP-funded conditions with documented sustained improvement in pain and function and with routine monitoring for opioid misuse and abuse.
- Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk vs. benefit.
- Promote the safe use of long-acting opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.

Length of Authorization:

90 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

Table 1. Daily Dose Threshold (90 Morphine Milligram Equivalents per Day) of Opioid Products.

Opioid	90 MME/day	Notes
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose.)
Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

Table 2. Specific Long-acting Opioid Products Subject to Quantity Limits per FDA-approved Labeling.

Drug Product	Quantity Limit
AVINZA	1 dose/day
BELBUCA	2 doses/day
BUTRANS	1 patch/7 days
EMBEDA	2 doses/day
EXALGO	1 dose/day
Fentanyl patch	1 dose/72 hr

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day
OXYCONTIN	2 doses/day
TROXYCA ER	2 doses/day

Drug Product	Quantity Limit
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed opioid analgesics by only a single prescribing practice or prescriber?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

7. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
9. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #10
10. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.**	**Yes:** Go to #12 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
12. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun;24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).

10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *11/16 (AG); 05/16*
Implementation: *TBD*

Appendix 2: Search Strategy

# ▲	Searches	Results
2	opioid.mp. or Analgesics, Opioid/	59257
3	Chronic Pain/ or noncancer pain.mp.	7714
4	1 and 2 and 3	60
5	limit 4 to (english language and humans and yr="2007 -Current" and (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	9

☐	1	tramadol.mp. or Tramadol/	3328
☐	2	abuse potential.mp.	960
☐	3	addiction.mp.	23524
☐	4	dependence.mp. or Morphine Dependence/	105589
☐	5	Drug Overdose/ or overdose.mp.	11256
☐	6	withdrawal.mp.	50933
☐	7	2 or 3 or 4 or 5 or 6	179414
☐	8	1 and 7	343
☐	9	limit 8 to (english language and humans and yr="2005 -Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))	30

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Drug Class Update: Sedatives

Date of Review: March 2017 **Date of Last Review:** November 2014

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

Purpose for Class Update:
Evidence for the comparative effectiveness of sedatives was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2014. This review examines new comparative evidence of sedatives published since 2014. Though many other sedating medications are often used for sleep disorders, this review will only include medications listed in the Sedative PDL class (see **Appendix 1**). Drugs not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants such as trazodone, or atypical antipsychotics. Updates for current sedative prior authorization (PA) criteria are also proposed which restrict use of sedatives to funded conditions, prevent therapeutic duplication, and place quantity limits on sedative use.

Research Questions:
1. Is there any new comparative evidence which assesses efficacy or effectiveness of sedatives (non-benzodiazepine sedatives, benzodiazepine hypnotics, melatonin receptor agonists, orexin receptor antagonists, doxepin, or sedating antihistamines) for treatment of insomnia?
2. Is there new comparative evidence associated with safety of short- or long-term use of sedatives?
3. Are there any subpopulations (specifically elderly and patients with concomitant sleep apnea or mental health disorders) for which sedatives may be more effective or associated with more adverse effects?

Conclusions:
- There is insufficient comparative evidence that assesses differences in efficacy or effectiveness between sedative classes or between individual sedative agents. There is no new evidence for tasimelteon, diphenhydramine, or doxylamine for the treatment of insomnia. Evidence from one systematic review demonstrates similar improvement in total sleep time with short-term use of benzodiazepines, non-benzodiazepine sedatives, and sedating antidepressants compared to placebo (standardized mean difference [SMD] 0.44 to 0.64 corresponding to a small to moderate treatment effect).[1] In most cases, sedatives were studied for less than 1 month.[1]
- In the general adult population, total sleep time was improved with short-term use (4-6 weeks) of eszopiclone, zolpidem, suvorexant, and low-dose doxepin compared to placebo (weighted mean difference [MD] of 12 to 48 minutes; moderate quality evidence).[2] There was low quality evidence of no difference in total sleep time with zaleplon compared to placebo.[2]
- Sleep onset latency was also improved in adults taking eszopiclone, zolpidem, ramelteon, suvorexant, and doxepin compared to placebo (weighted MD of 6 to 19 minutes).[2] In the majority of trials the mean sleep latency remained greater than 30 minutes.[2]

- In elderly patients, there is low quality evidence that eszopiclone improves total sleep time (weighted MD 30 minutes, 95% CI 19.7 to 40.3) and wake time after sleep onset (weighted MD 22 minutes, 95% CI 13.6 to 29.6) compared to placebo.[2] Sleep onset latency is improved with zolpidem (weighted MD 18.3 minutes, 95% CI 5.4 to 31.5) and ramelteon (weighted MD 10 minutes, 95% CI 4.6 to 15.6) compared to placebo (low quality evidence).[2] Evidence from 1 systematic review also supports efficacy of doxepin for the treatment of insomnia in patients over 65 years of age.[3] There is insufficient evidence for other sleep outcomes or treatments.
- There is insufficient evidence to assess efficacy or safety of long-term use of sedatives. Few randomized control trials (RCTs) for non-benzodiazepine sedatives examine outcomes beyond 3 months, and study durations of benzodiazepines beyond 14 days were rare.[2] Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia.[2] In addition, the FDA has recently updated warnings for non-benzodiazepine sedatives that emphasize the risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.
- There is insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.[4]

Recommendations:
- Make benzodiazepine sedatives non-preferred due to limited efficacy data.
- Streamline and update prior authorization (PA) criteria (see **Appendix 4**) to restrict use of sedatives to OHP-funded conditions, to prevent therapeutic duplication, and to apply quantity limits of 30 tablets/60 days for all agents in the class.
- Apply quantity limits to zolpidem to reduce use above the maximum daily FDA recommended dose.
    - Zolpidem immediate release: 10 mg for males and 5 mg for females
    - Zolpidem extended release: 12.5 mg for males and 6.25 mg for females
- Evaluate comparative drug costs of other sedatives in the executive session to inform PDL status.

Previous Conclusions:
- There is no new comparative evidence for newer drugs for insomnia since the literature for this drug class was previously scanned.
- There is no comparative effectiveness or safety evidence for tasimelteon or suvorexant versus other newer drugs for insomnia.
- There is low quality 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. There is insufficient evidence for adverse drug events of tasimelteon in comparison to placebo.
- There is moderate quality 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. There is low quality evidence of no significant adverse drug events for suvorexant in comparison to placebo.

Previous Recommendations:
- Make tasimelteon non-preferred due to insufficient evidence for insomnia treatment outside the narrow FDA-approved indication and require a prior authorization for a funded OHP diagnosis.
- Compare costs of suvorexant and other newer drugs for insomnia in the executive session to inform PDL placement.

Background:
Sleep disorders encompass a wide variety of conditions including insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders.[5] This review will focus primarily on treatment of insomnia and circadian rhythm sleep-wake disorders. Other disorders are discussed only briefly.

Insomnia is one of the most common sleep disorders. Insomnia is defined as the subjective perception of difficulty with sleep which occurs despite adequate opportunity for sleep and causes functional impairment during the day.[6] Insomnia is often classified as short-term (typically <3 months in duration with an identifiable stressor), long-term (occurring ≥3 times per week for >3 months) or other (if criteria for short- and long-term criteria are not met). Diagnosis is primarily based on sleep history.[5,6] An estimated 30-50% of people experience insomnia symptoms, and insomnia disorder is diagnosed in approximately 4-22% of patients.[7] Insomnia is more common in elderly, females, individuals who are divorced or separated, those with shift work, and patients with lower socioeconomic status.[7] Insomnia symptoms have been associated with reduced health-related quality of life and cognitive decline in patients over 65 years of age.[7] Insomnia can also worsen outcomes for patients with comorbid conditions including cardiovascular disease, post-traumatic stress disorder, and depression.[7] Insomnia may also be associated with a wide variety of conditions, both medical and psychological. Identification and treatment of contributing factors and comorbid conditions (such as medical history, substance misuse and psychiatric conditions) are also important for management of insomnia symptoms.[6] Guidelines from the American Academy of Sleep Medicine for the evaluation and management of chronic insomnia in adults recommend psychological and behavioral treatment as first-line therapies.[6] These approaches may include relaxation therapy, stimulus control therapy, and sleep restriction therapy.[6] Good sleep hygiene is also typically recommended.[6] Pharmacological therapy may be added to behavioral therapy if additional treatment is necessary. Due to a lack of comparative evidence for pharmacological treatment, the American College of Physicians recommends decisions for short-term pharmacotherapy be based on individual risks and benefits of treatment.[8]

Circadian rhythm sleep-wake disorders are associated with a chronic or recurrent pattern of sleep-wake disturbances (> 3 months with the exception of jet lag disorder) and associated daytime distress or impairment.[5] Disorders may be classified as delayed, advanced, irregular, or non-24-hour sleep-wake phase disorders, shift work disorders, jet lag disorders and other disorders.[5] Treatment options recommended for circadian rhythm sleep-wake disorders include melatonin or light therapy.[9,10] Recommendations are also made to avoid sleep-promoting medications in elderly patients with dementia and irregular sleep-wake rhythm disorder based on increased risk of adverse events in this population.[10] Elderly patients, particularly those with baseline cognitive impairment, may be at increased risk for falls, adverse events including confusion and daytime sedation, medication interactions, or drug dependence.[10] No recommendations are made for other treatments due to insufficient evidence.[10]

FDA-approved medications for insomnia include drugs from a wide variety of classes such as benzodiazepines (temazepam, lorazepam, flurazepam, and estazolam), non-benzodiazepine hypnotic sedatives (zolpidem, eszopiclone, or zaleplon), melatonin receptor agonists (ramelteon), orexin receptor antagonists (suvorexant), antihistamines (doxylamine succinate and diphenhydramine) and antidepressants (doxepin).[7] Medications are only indicated for short-term use on an as needed basis but are frequently used routinely long-term. Other medications with sedating properties used off-label for treatment of insomnia include other benzodiazepines (midazolam), sedating antidepressants (trazodone, amitriptyline or mirtazapine) or atypical antipsychotics (quetiapine or olanzapine).[7] Improvement in symptom severity is typically measured by patient-reported improvement in severity, sleep symptoms, and quality of life. However, differences in efficacy are often difficult to evaluate due to a strong placebo response which is apparent with both subjective and objective measures of efficacy. One systematic review examining effect size of the placebo response in RCTs determined that approximately 64% of drug response could be attributed to a placebo effect.[11] Sleep outcomes which are commonly reported in trials include subjective change in sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Of these outcomes, change in total sleep time is generally considered most clinically significant.[2] However, there is no established

consensus on the minimum change in sleep time which correlates with clinical relevance to the patient. Objective assessment of sleep symptoms may also be measured via polysomnography, though subjective assessments may be more relevant to the patient. Other assessment scales include the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI) which document overall symptom severity.[2]

Common adverse effects associated with sedative medications include dizziness, daytime drowsiness, and somnolence. Non-benzodiazepine sedatives have also been associated with infrequent, but serious, adverse effect including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.[12] These warnings are included in the FDA labeling for zolpidem, eszopiclone, zaleplon, and ramelteon.[12] Suvorexant, an orexin receptor antagonist, carries similar warnings in addition to warnings for sleep paralysis, hallucinations, and other neurophychiatric symptoms.[12] Risk for daytime impairment may be higher in women or elderly who eliminate sedative more slowly from the body.[13] The FDA warns that patients with high levels of sedative in the bloodstream can be impaired even if they feel fully awake.[13] For zolpidem in particular, the FDA recommends maximum doses of 5 mg for immediate release products (or 6.25 mg extended release) for women and 10 mg (or 12.5 mg extended release) for men.[13] With long-term use of short- and intermediate-acting sedatives, rebound insomnia has also been noted upon discontinuation of treatment. Sedatives which have been associated with rebound insomnia include zolpidem, eszopiclone, zaleplon, and suvorexant.[14,15] In general, rebound effects were mild and resolved after a few nights.[7]

With the exception of obstructive sleep apnea, medical management of sleep disorders are not funded under the Oregon Health Plan (OHP). Sleep disorders, however, can worsen or exacerbate a funded comorbid condition such as depression or post-traumatic stress disorder (PTSD). In cases such as these, medical management of sleep disorders will be covered. Current policies are in place to restrict use of non-preferred agents to conditions funded by the OHP, to prevent therapeutic duplication of benzodiazepine sedatives, and to limit quantities of benzodiazepine sedatives to no more than 15 doses per 30 days. In quarter 3 of 2016 (July 1 to September 30), 656 patients had claims for sedatives listed in **Appendix 1**. Members with Medicare plans (benefit packages BMM, BMD, MND, or MED) and members with claims due to coordinated care organization (CCO) or Medicare enrollment (explanation of benefits codes 2017, 0154, 1109) were excluded from this population. Details are presented in **Appendix 2**. Immediate-release zolpidem tartrate, a preferred agent available without prior authorization (PA), was the most commonly prescribed sedative accounting for 68% of claims. Because sedatives are indicated for short-term or infrequent use, data were analyzed for the number of prescriptions which had been filled by patients over the course of 3 months. Results are shown in **Table 1**. Data indicates zolpidem was used infrequently for the majority of patients, with 25% (n=111) of patients prescribed less than 15 tablets in 30 days and 45% (n=203) of patients with only 1 claim in the quarter. A handful of patients (n=66) had greater than 3 claims per quarter indicating consistent and regular use of zolpidem.

Table 1. Patients prescribed immediate-release zolpidem tartrate with quantities >15 tablets/30 days.

Number of claims with >15 tablets/30 days	Patients (n=446)
6	1
5	0
4	8
3	57
2	68
1	203
0	109

Other agents commonly prescribed included temazepam (9% of claims) and triazolam (5% of claims). Of the non-preferred agents that required a PA (n=210), 44% (n=92) of claims were approved or a claim for an alternate sedative was received within 90 days of the original sedative claim (defined as the index event). Data were evaluated for potential explanations of patients without a paid claim within 90 days (n=118) of the original sedative claim. For these patients without a paid Medicaid claim within 90 days, 76% (n=90) had been enrolled in a CCO, had lost Medicaid eligibility, or had third-party insurance that may have paid for the sedative. In 2 cases, the PA had been approved but never filled; and for 26 patients, a PA had never been submitted by the prescriber. Interestingly, upon review of these charts, 9 of these claims were for doxylamine in women with a recent pregnancy diagnosis and 7 claims were for patients on treatment for comorbid depression, bipolar disorder or PTSD. These data indicate that a small population of patients are prescribed zolpidem continuously and implementation of a quantity limit would be feasible. No major safety or access issues were identified.

This review will only include medications listed in the Sedative PDL class (see **Appendix 1**). Drugs not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants or atypical antipsychotics. Some of these medications are addressed in other class reviews and are covered with other PA criteria. For example, lorazepam is included in PA criteria for the benzodiazepine class, and current PA criteria restrict use of low-dose quetiapine for insomnia.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
In 2015, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review to examine comparative efficacy of treatments for insomnia disorder in adults.[2] The review included evidence from 38 RCTs which assessed efficacy of pharmacologic interventions for treatment of insomnia.[2] RCTs were required to report sleep outcomes and have at least 4 weeks of follow-up.[2] In many cases, improvement in global sleep outcomes and severity (as measured by the Insomnia Severity Index, the Pittsburgh Sleep Quality Index, or the Patient Global Impression scale) could not be calculated as often trials failed to report baseline global sleep values.[12] Additional sleep outcomes included patient-reported sleep onset latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Overall, most RCTs were limited by small population size, large placebo response, and short duration. Many pharmacological treatments lacked eligible trials.[2] Few trials for benzodiazepines and antidepressants met inclusion criteria, primarily due to short treatment durations and lack of evidence assessing relevant clinical outcomes with these medications.[2] In addition, trials for suvorexant and zolpidem were studied at higher doses than what is now recommended by the FDA.[2] For example, zolpidem 10 to 15 mg was typically used in trials and the FDA recommended dose is now 5 mg.[2] Inclusion of these trials may result in overestimates of treatment effects.

Overall, in short-term placebo-controlled trials, sedative treatment improved sleep symptoms without serious adverse effects.[2] In placebo trials, both eszopiclone and zolpidem demonstrated greater improvements in sleep outcomes than zaleplon.[2] For eszopiclone, approximate change compared to placebo in sleep onset latency, total sleep time, and wake time after sleep onset was 19 minutes (95% CI 14.1 to 24.1), 45 minutes (95% CI 35.4 to 54.2), and 11 minutes (95% CI 1.7 to 19.8), respectively (moderate strength of evidence).[2] In older adults, there was low strength of evidence that eszopiclone improves total sleep time (weighted MD 30 minutes, 95% CI 19.7 to 40.3) and wake time after sleep onset (weighted MD 22 minutes, 95% CI 13.6 to 29.6), but not sleep onset latency.[2] For zolpidem, approximate sleep onset latency improved by 9-18 minutes and total sleep time improved by 23 to 48 minutes compared to placebo based on moderate strength evidence.[2] Results were similar for all formulations of zolpidem, though no direct comparisons were made.[2] Only extended-release (ER) zolpidem demonstrated an improvement in wake time after sleep onset (weighted MD 16 minutes, 95% CI not reported; low strength of evidence).[2] Similar improvements in sleep onset latency were seen in older adults (weighted MD 18.3 minutes, 95% CI 5.4 to 31.5; n=166; low strength evidence).[2] In adults with insomnia, global outcomes (defined as percentage of patients with a change in the Insomnia Severity Index score >6), were improved with suvorexant 15 to 20 mg compared to placebo (55% vs 42%; RR 1.3, 95% CI 1.2 to 1.5).[12] Sleep onset latency, total sleep time and wake time after sleep onset were also improved with suvorexant compared to placebo by 6 minutes, 16 minutes, and 5 minutes, respectively (moderate quality evidence from 2 RCTs).[12] Ramelteon did not clinically improve global or sleep outcomes compared to placebo in the general adult population (low quality evidence based on 5 RCTs).[2] In older adults, ramelteon improved sleep onset latency by 10 minutes (95% CI 4.6 to 15.6; low quality evidence based on 1 RCT).[12] There was insufficient evidence to demonstrate improvement in sleep latency with zaleplon, and low quality evidence from 2 RCTs demonstrating no difference in total sleep time compared with placebo.[2] There was insufficient evidence to evaluate sleep outcomes with temazepam in the general adult population, but one small study in older adults (n=168) did demonstrate improved sleep onset latency of 20 minutes (95% CI 8.2 to 31.6) compared with placebo (low strength of evidence).[12] Compared to placebo, doxepin 1 to 6 mg improved sleep onset latency an average of 15 minutes, total sleep time by 12-24 minutes, and wake time after sleep onset by 10-17 minutes (low to moderate strength of evidence).[2] However, in the majority of trials which reported improvements in sleep onset latency, the mean sleep onset latency for patients taking non-benzodiazepine sedatives, orexin receptor antagonists and melatonin agonists remained greater than 30 minutes.[12] Direct comparative evidence was limited. Only 4 RCTs compared psychological or behavioral therapy to pharmacologic treatment, and evidence was insufficient to evaluate differences in sleep-related outcomes.[2] One RCT (n=233) did demonstrate greater improvement in total sleep time with zolpidem 10 mg compared to temazepam 20 mg (weighted MD 27 minutes, 95% CI 2.1 to 51.9; low quality evidence).[2] There was insufficient evidence to determine differences in efficacy or safety for other doses, medications, or outcomes.[2] In short-term RCTs, adverse effects of non-benzodiazepine sedatives, ramelteon, suvorexant, and doxepin were not comparably different than placebo.[2] Safety of chronic long-term insomnia treatment in adults was evaluated using 12 observational studies.[2] Trials were limited to studies with a duration of at least 6 months and at least 100 patients without other major comorbid conditions.[2] In general, data indicates that long-term use of sedatives may be associated with increased risk of dementia (4% vs. 1.5%, HR 2.34, 95% CI 1.92 to 2.85).[2] Risks associated with specific medications include an increased risk of head injury or fracture requiring hospitalization with zolpidem (0.60% vs. 0.37%, adjusted HR 1.67, 95% CI, 1.19 to 2.34).[2] Incidence of both dementia and fractures increased in proportion to the dose of sedative prescribed.[2] One large observational study has also associated sedative use with an increased rate of incidental cancers.[2] The study examined incidence of all cancers with the exception of non-melanoma skin cancer. A higher incidence of cancer was associated with patients taking greater than 800 mg/year of zolpidem (HR 1.28, 95% CI 1.03 to 1.59) and greater than 240 mg or 1640 mg per year of temazepam (HR 1.28, 95% CI 1.03 to 1.59 and HR 1.99, 95% CI 1.57 to 2.52, respectively).[2] Two studies which examine effect of sedatives on mortality had inconsistent results.[2] These observational studies were limited by potential unmeasured or unknown confounders, and overall authors rated evidence as insufficient to determine differences in safety between interventions.[2]

Another systematic review of 25 RCTs specifically examined objective sleep outcomes from polysomnographic data.[1] Sedatives included in this review were non-benzodiazepine sedatives (n=851), benzodiazepines (n=152), antidepressants (n=351), and melatonin receptor agonists (n=433).[1] Of the patients included in these trials, 63.2% were female with an average age of 50.5 years (standard deviation [SD] 11.73).[1] Only 7 trials studied durations longer than 1 month, and only

2 studies included participants for longer than 3 months.[1] In order to compare results between classes, effect sizes were calculated using standardized mean differences (SMD) with small, medium, and large effects corresponding to values greater than 0.2, 0.5, and 0.8, respectively.[1] Use of SMD allows for comparisons between multiple evaluation tools and improvement scales. However, correlation of SMD to precise changes in total sleep time or sleep onset latency was not stated. Benzodiazepines, non-benzodiazepine receptor agonists, and antidepressants improved total sleep time by a SMD of 0.64 (95% CI 0.12 to 1.16; p=0.015), 0.52 (95% CI 0.33 to 0.71; p<0.001), and 0.44 (95% CI 0.29 to 0.59; p<0.001), respectively.[1] There was no difference in ramelteon, a melatonin receptor agonist, compared to placebo in total sleep time.[1] Patients treated with benzodiazepines (SMD -0.76, 95% CI -1.28 to -0.24; p=0.004) and non-benzodiazepine receptor agonists (SMD -0.46, 95% CI -0.61 to -0.31; p<0.001) had a greater change compared to placebo in sleep onset latency than patients on antidepressants (SMD -0.18, 95% CI -0.33 to -0.03, p=0.016).[1] Other sleep outcomes (including wake time after sleep onset and sleep efficacy) for benzodiazepines, non-benzodiazepine receptor agonists, and antidepressants achieved statistical significance with small to medium effect sizes compared to placebo.[1]

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a rapid response review summarizing efficacy and safety of sedatives for the treatment of insomnia, agitation, or delirium in adults over 65 years of age.[3] The review was limited to data from 3 RCTs that assessed sleep outcomes of doxepin versus placebo.[3] Severity of insomnia was reported using a variety of scales, and in order to compare differences between scales, results were calculated as SMD.[3] SMD evaluates effect sizes on a 0 to 1 scale with effect sizes of 0.2, 0.5 and 0.8 interpreted as small, medium, and large treatment effects.[3] Correlation of SMD to changes in sleep time or quality was not reported. Overall, compared to placebo, doxepin 1 mg, 3 mg, or 6 mg demonstrated a small to medium changes in wake time after sleep onset (SMD range: 0.37 to 0.78), total sleep time (SMD range: 0.33 to 0.97), sleep efficiency (SMD range: 0.41 to 0.98), and sleep quality (SMD: 0.5).[3] No difference was observed in sleep latency or initiation compared to placebo.[3] Authors concluded that doxepin is more effective than placebo for the treatment of insomnia in older adults, though exact correlation to improvements in sleep quality, insomnia severity, or total sleep time were not stated.[3] Rates of adverse events from these 3 RCTs were similar to placebo though evidence was limited by inclusion of a placebo run-in period and lack of reported relevant outcomes.[3]

<u>Discontinuation and taper strategies</u>

The Canadian Agency for Drugs and Technologies in Health (CADTH) completed a systematic review of interventions to promote discontinuation of benzodiazepines and manage withdrawal symptoms associated with discontinuation in patients with a history of long-term benzodiazepine use (>3 months).[4] Evidence from 3 systematic reviews, 5 RCTs, and 3 non-randomized trials were included in the review.[4] Adults in these trials were on average 41 to 79 years of age and were receiving benzodiazepines for a variety of treatments including insomnia, anxiety, panic disorders, or psychiatric disorders.[4] The precise number of patients receiving benzodiazepines for treatment of insomnia was not specified. Interventions included gradual dose-tapering, psychosocial therapy (including cognitive behavioral therapy), patient education, medication substitution, or simple interventions (defined as discontinuation letters from clinicians, self-help information or single consultations with physicians).[4] Most trials examined dose-tapering strategies in combination with nonpharmacological interventions or medication substitution.[4] In many cases, the exact dosing regimen was not specified though some studies used a 25% reduction in dose over 1-4 weeks until drug-free.[4] Due to inadequate reporting, the effectiveness of individual dose-tapering regimens could not be determined, and results of trials were not combined due to large differences in patient populations and interventions.[4] Overall, all nonpharmacological interventions improved the number of patients who successfully discontinued benzodiazepines. Patients who received simple interventions were more likely to successfully discontinue benzodiazepines or reduce benzodiazepine use (RR 2.3, 95% CI 1.3 to 4.2, p=0.008 and RR 2.04, 95% CI 1.5 to 2.8, p<0.001, respectively).[4] Patients who used cognitive behavioral therapy in addition to dose-tapering or supervised withdrawal were more likely to successfully discontinue benzodiazepine use (OR 5.06, 95% CI 2.68 to 9.57, p<0.00001, NNT=3) with reported discontinuation rates of 65 to 85% compared to 25 to 54% in patients with dose-tapering alone.[4] In one RCT, structured educational interventions in conjunction with dose-tapering also improved discontinuation rates compared to usual care (OR 8.3, 95% CI 3.3 to 20.9).[4] Two RCTs examined use of melatonin in combination with dose-tapering without a statistically significant benefit compared to placebo.[4] Other observational studies

evaluated use of pregabalin, hydroxyzine, or valerian as adjuvant treatment to tapering regimens, but quality of evidence was limited.[4] The evidence was further limited by patients included in these trials. In several RCTs, a large percentage of eligible patients (66-82%) declined to participate, limiting generalizability of these findings.[4]

Another systematic review, examining the effect of melatonin on discontinuation of benzodiazepines in adults, had similar findings as the previous review with no difference in discontinuation rates when melatonin 2-5 mg daily was used in combination with tapering strategies.[16] Six RCTs (n=332) examining benzodiazepines were included in the review.[16] One trial also included patients on zolpidem or zopiclone.[16] Tapering regimens varied between studies with total durations of 4 to 10 weeks.[16] Doses were typically decreased weekly or every 2 weeks by 25 to 50%.[16] Overall, there was no difference in discontinuation rates in patients taking melatonin versus placebo (OR 0.72, 95% CI 0.21 to 2.41, p=0.59).[16] Changes in sleep quality were reported in 4 trials, but pooled results were not calculated due to significant heterogeneity between studies.[16] Results were inconsistent, with 2 RCTs reporting improved sleep quality with melatonin and 2 trials reporting no difference in sleep quality compared to placebo.[16]

A systematic review by CADTH in 2015 examining discontinuation strategies of non-benzodiazepine sedative hypnotics including zolpidem, eszopiclone, zopiclone and zaleplon identified no additional systematic reviews or RCTs.[17]

New Guidelines:
In 2016, the American College of Physicians updated guidelines for treatment of insomnia based on evidence from the recent systematic review by AHRQ.[8] Recommended first-line therapy is cognitive behavioral therapy for insomnia (CBT-I; strong recommendation based on moderate quality evidence).[8] CBT-I consists of a combination of behavioral interventions such as sleep restriction, stimulus control, and education concerning good sleep hygiene.[8] Second-line therapy for insomnia includes pharmacological therapy. Guidelines recommend using an individualized evaluation of risks and benefits to decide whether to add pharmacological therapy in adults for which CBT-I was unsuccessful (weak recommendation based on low quality evidence).[8] Overall, authors determined that there was insufficient evidence to examine comparative efficacy of pharmacological treatments for insomnia.[8] In the general adult population, eszopiclone, zolpidem, suvorexant, and doxepin improved sleep outcomes compared to placebo.[8] These medications also improve sleep outcomes in adults greater than 55 years of age.[8] In one trial, ramelteon also demonstrated reduced sleep onset latency in older adults.[8] In general, evidence for these pharmacological treatments was of low to moderate quality. Evidence for other treatments including benzodiazepines was insufficient.[8] Data from observational studies indicates that sedative use may be associated with increased risk for dementia and fractures.[8] Post-marketing data also indicates that sedatives may be associated with rare but serious adverse effects such as cognitive and behavioral changes, driving impairment, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.[8] To minimize the risk for these adverse effects, the FDA recommends short-term use (maximum 4 to 5 weeks) of sedatives and lower doses of sedatives in women and older or debilitated adults.[8] There is insufficient evidence regarding long-term use of sedatives, and the FDA recommends further evaluation for patients whose symptoms do not improve within 7 to 10 days of treatment.[8]

In 2015, the American Academy of Sleep Medicine published updated guidelines for the treatment of intrinsic circadian rhythm sleep-wake disorders.[10] The guideline covers advanced and delayed sleep-wake phase disorders as well as non-24-hour and irregular sleep-wake rhythm disorders.[10] Trials were included in the systematic review if they describe symptoms consistent with a circadian rhythm sleep-wake disorder, even if diagnostic criteria were not strictly defined.[10] Therefore, patients with varied descriptions of insomnia, nighttime wakefulness, and daytime functional impairment were included in the review.[10] Overall, evidence for use of sedatives was insufficient to make recommendations for the majority of these disorders.[10] Pharmacological recommendations include the use of strategically timed melatonin in delayed sleep-wake phase disorder (weak recommendation) and non-24-hour sleep-wake rhythm disorder in blind adults (weak recommendation).[10] There is some evidence for use of melatonin in children or adolescents with irregular sleep-wake rhythm disorders (weak

recommendation).[10] Sedatives are not recommended in elderly patients with irregular sleep-wake rhythm disorders (strong recommendation), and clinicians should avoid use of melatonin in older patients with dementia for irregular sleep-wake rhythm disorders (weak recommendation).[10] The recommendation to avoid sedatives or hypnotics in older patients is based primarily on the lack of evidence supporting efficacy for these sleep disorders and the high risk for adverse effects, especially in an elderly patients with dementia.[10] The recommendation includes use of off-label antidepressants and antihistamines for sleep disorders.[10] Evidence supporting efficacy of trazodone in irregular sleep-wake rhythm disorder is limited, and use can be associated with adverse effects of priapism, orthostatic hypotension and cardiac arrhythmias.[10] Adverse effects associated with antihistamines include anticholinergic responses, daytime somnolence and cognitive impairment.[10]

Updates from the American Geriatrics Society for potentially inappropriate medication use in older adults make similar recommendations for sedative use in elderly patients.[18] Benzodiazepines (both short- and long-acting), non-benzodiazepine hypnotics without consideration of duration (eszopiclone, zolpidem, and zaleplon), high-dose doxepin (dose >6 mg/day) and antihistamines with anticholinergic properties (diphenhydramine and doxylamine) should be avoided in adults greater than 65 years of age due increased risk of adverse effects (strong recommendation with moderate quality evidence).[18] These medications may be appropriate for some circumstances and conditions, but evidence for efficacy in adults over 65 years of age for treatment of insomnia is limited.[18] Recommendations are also made to avoid use of these medications in patients with delirium (strong recommendation, moderate quality evidence), dementia or cognitive impairment (strong recommendation, moderate quality evidence), or history of falls or fractures (strong recommendation, high quality evidence).[18]

New Formulations or Indications:
No new formulations or indications were identified.

New FDA Safety Alerts:
In 2016, safety labeling for temazepam was updated to include a boxed warning describing risks from use with concomitant opioids.[13] Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.[13] Recommendations are made to reserve concomitant prescribing to patients for which alternate treatments are inadequate, limit dosage and duration to minimum amounts required, and monitor patients for respiratory depression and sedation.[13]

In 2016, safety labeling for zolpidem tartrate and zolpidem ER was updated to include a warning for hepatic encephalopathy in patients with hepatic insufficiency.[13] Patients with hepatic insufficiency do not clear zolpidem tartrate as rapidly and use in patients with severe hepatic impairment should be avoided.[13] In addition, warnings were updated to emphasize risk for central nervous system depression and next-day impairment, including drowsiness, prolonged reaction time, sleepiness, blurred or double vision, and impaired driving. In order to minimize risk, 7-8 hours of sleep is recommended.[13]

Randomized Controlled Trials:
A total of 156 citations were manually reviewed from the initial literature search. Only trials reporting new comparative evidence were considered for inclusion. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

Route	Formulation	BRAND	GENERIC	PDL
ORAL	TABLET	AMBIEN	ZOLPIDEM TARTRATE	Y
ORAL	TABLET	ZOLPIDEM TARTRATE	ZOLPIDEM TARTRATE	Y
ORAL	CAPSULE	HETLIOZ	TASIMELTEON	N
ORAL	CAPSULE	SONATA	ZALEPLON	N
ORAL	CAPSULE	ZALEPLON	ZALEPLON	N
ORAL	CAPSULE	Z-SLEEP	DIPHENHYDRAMINE HCL	N
ORAL	LIQUID	SLEEP TIME	DIPHENHYDRAMINE HCL	N
ORAL	SPRAY/PUMP	ZOLPIMIST	ZOLPIDEM TARTRATE	N
ORAL	SYRUP	MIDAZOLAM HCL	MIDAZOLAM HCL	N
ORAL	TAB MPHASE	AMBIEN CR	ZOLPIDEM TARTRATE	N
ORAL	TAB MPHASE	ZOLPIDEM TARTRATE ER	ZOLPIDEM TARTRATE	N
ORAL	TABLET	BELSOMRA	SUVOREXANT	N
ORAL	TABLET	ESZOPICLONE	ESZOPICLONE	N
ORAL	TABLET	LUNESTA	ESZOPICLONE	N
ORAL	TABLET	NIGHTTIME SLEEP AID	DIPHENHYDRAMINE HCL	N
ORAL	TABLET	ROZEREM	RAMELTEON	N
ORAL	TABLET	SILENOR	DOXEPIN HCL	N
ORAL	TABLET	SLEEP AID	DIPHENHYDRAMINE HCL	N
ORAL	TABLET	SLEEP AID	DOXYLAMINE SUCCINATE	N
ORAL	TABLET	SLEEP TABS	DIPHENHYDRAMINE HCL	N
SUBLINGUAL	TAB SUBL	EDLUAR	ZOLPIDEM TARTRATE	N
SUBLINGUAL	TAB SUBL	INTERMEZZO	ZOLPIDEM TARTRATE	N
SUBLINGUAL	TAB SUBL	ZOLPIDEM TARTRATE	ZOLPIDEM TARTRATE	N
ORAL	CAPSULE	FLURAZEPAM HCL	FLURAZEPAM HCL	
ORAL	CAPSULE	RESTORIL	TEMAZEPAM	
ORAL	CAPSULE	TEMAZEPAM	TEMAZEPAM	
ORAL	SYRUP	MIDAZOLAM HCL	MIDAZOLAM HCL	
ORAL	TABLET	ESTAZOLAM	ESTAZOLAM	
ORAL	TABLET	HALCION	TRIAZOLAM	
ORAL	TABLET	TRIAZOLAM	TRIAZOLAM	

Appendix 2. Drug Use Data for Sedatives from July through September 2016

Row Labels	Initially Paid		Paid Within 30 days		Paid Within 31-90 Days		Another Drug in PDL Class Paid Within 30 days		Another Drug in PDL Class Paid Within 31-90 days		No Drugs Within PDL Class Paid Within 90 Days		Total #	Total %
	#	%	#	%	#	%	#	%	#	%	#	%		
Sedatives	514	78%	10	2%	2	0%	9	1%	3	0%	118	18%	656	100%
Null	48	51%	0	0%	0	0%	6	6%	2	2%	39	41%	95	100%
MIDAZOLAM HCL	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%
TEMAZEPAM	16	28%	0	0%	0	0%	6	10%	2	3%	34	59%	58	100%
TRIAZOLAM	31	86%	0	0%	0	0%	0	0%	0	0%	5	14%	36	100%
Y	443	99%	2	0%	1	0%	0	0%	0	0%	0	0%	446	100%
ZOLPIDEM TARTRATE	443	99%	2	0%	1	0%	0	0%	0	0%	0	0%	446	100%
N	23	20%	8	7%	1	1%	3	3%	1	1%	79	69%	115	100%
BELSOMRA	2	67%	0	0%	0	0%	0	0%	0	0%	1	33%	3	100%
ESZOPICLONE	8	32%	1	4%	1	4%	2	8%	0	0%	13	52%	25	100%
ROZEREM	3	21%	2	14%	0	0%	0	0%	0	0%	9	64%	14	100%
SILENOR	0	0%	0	0%	0	0%	0	0%	0	0%	2	100%	2	100%
SLEEP AID	0	0%	0	0%	0	0%	0	0%	0	0%	15	100%	15	100%
UNISOM SLEEP AID	0	0%	0	0%	0	0%	0	0%	0	0%	5	100%	5	100%
ZALEPLON	3	14%	3	14%	0	0%	1	5%	0	0%	15	68%	22	100%
ZOLPIDEM TARTRATE ER	7	27%	2	8%	0	0%	0	0%	0	0%	17	65%	26	100%
WAL-SOM	0	0%	0	0%	0	0%	0	0%	1	33%	2	67%	3	100%
Grand Total	**514**	**78%**	**10**	**2%**	**2**	**0%**	**9**	**1%**	**3**	**0%**	**118**	**18%**	**656**	**100%**

Row Labels	Enrolled in CCO		Lost Eligibility		Has Other Insurance		Indian Health Service Coverage		PA Approved		PA Not Requested		Total #	Total %
	#	%	#	%	#	%	#	%	#	%	#	%		
Sedatives	44	37%	14	12%	24	20%	8	7%	2	2%	26	22%	118	100%
Null	18	46%	4	10%	9	23%	1	3%	0	0%	7	18%	39	100%
TEMAZEPAM	17	50%	4	12%	6	18%	1	3%	0	0%	6	18%	34	100%
TRIAZOLAM	1	20%	0	0%	3	60%	0	0%	0	0%	1	20%	5	100%
N	26	33%	10	13%	15	19%	7	9%	2	3%	19	24%	79	100%
BELSOMRA	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%
ESZOPICLONE	7	54%	2	15%	3	23%	0	0%	0	0%	1	8%	13	100%
ROZEREM	4	44%	1	11%	0	0%	1	11%	1	11%	2	22%	9	100%
SILENOR	1	50%	0	0%	0	0%	0	0%	1	50%	0	0%	2	100%
SLEEP AID	2	13%	0	0%	0	0%	6	40%	0	0%	7	47%	15	100%
UNISOM SLEEP AID	1	20%	0	0%	2	40%	0	0%	0	0%	2	40%	5	100%
ZALEPLON	2	13%	2	13%	5	33%	0	0%	0	0%	6	40%	15	100%
ZOLPIDEM TARTRATE ER	7	41%	5	29%	5	29%	0	0%	0	0%	0	0%	17	100%
WAL-SOM	1	50%	0	0%	0	0%	0	0%	0	0%	1	50%	2	100%
Grand Total	**44**	**37%**	**14**	**12%**	**24**	**20%**	**8**	**7%**	**2**	**2%**	**26**	**22%**	**118**	**100%**

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to December Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 09, 2016

1	exp Sleep Wake Disorders/	77864
2	exp "hypnotics and sedatives"/ or exp diazepam/ or exp lorazepam/ or exp midazolam/ or exp trazodone/ or exp quetiapine fumarate/	120719
3	zolpidem.mp.	2355
4	zaleplon.mp.	366
5	exp Sleep Aids, Pharmaceutical/	6649
6	exp Orexin Receptor Antagonists/ or suvorexant.mp.	264
7	ramelteon.mp. or exp Melatonin/	18003
8	tasimelteon.mp.	55
9	exp Doxylamine/	376
10	exp Temazepam/	676
11	exp Triazolam/	1261
12	exp Estazolam/	104
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	142189
14	1 and 13	5687
15	limit 14 to (english language and humans and yr="2014 -Current")	475
16	limit 15 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	156

Sedatives

Goal(s):

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent duplicate use of sedatives.
- Restrict long-term sedative use to due to insufficient evidence and to limit adverse effects.

Length of Authorization:

Up to 12 months (criteria specific)

Requires PA:

- Non-preferred sedatives
- Sedatives that exceed a total quantity of 30 doses within 60 days
- Concomitant use of more than one benzodiazepine hypnotic, more than one non-benzodiazepine sedative, or the combination of a benzodiazepine and non-benzodiazepine sedative in the prior 30 days.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #3
3. Does patient have diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5

Approval Criteria		
4. Is patient on CPAP?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics, due to depressant effect, are contraindicated.
5. Is the patient being treated for co-morbid: • Depression; • Anxiety or panic disorder; or • Bipolar disorder? **AND** Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Has the patient been treated with another non-benzodiazepine sedative or benzodiazepine hypnotic within the past 30 days?	**Yes:** Go to #7	**No:** Pass to RPh; Go to #8
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Document reason for switch and approve duplication for 30 days.	**No:** Pass to RPh. Deny; medical appropriateness. There is no evidence to support the concomitant use of two different sedatives.
8. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Go to #9

Approval Criteria		
9. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?	**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.	**No:** Deny; medical appropriateness

P&T/DUR Review: *3/17 (SS); 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *TBD; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Non-Benzodiazepine Sedatives

Goal(s):

- Approve only for OHP-funded conditions.
- Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is.
- Prevent adverse events associated with long-term sedative use. Clients coming onto the plan on chronic sedative therapy (continuously for >90) are "grandfathered." (Refer to criteria).
- See related Sedative Therapy Duplication edit. The safety and effectiveness of chronic sedative use is not established in the medical literature. There is a documented increased risk of serious adverse events in the elderly.

Length of Authorization:

6 months to 12 months (criteria specific)

Requires PA:

- Non-preferred sedatives

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does client have diagnosis of insomnia with sleep apnea?	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. Sedative/hypnotics, due to depressant effect, are contraindicated for this diagnosis and are not approvable.

Approval Criteria		
4. Is the client being treated for: • Co-morbid depression, • Anxiety, • Bipolar disorder or • Panic (i.e. 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 funded condition on the OHP and is there medical evidence of benefit of the prescribed sedative? All indications need to be evaluated as to see if they are funded or not.	Funded: Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	Not Funded: 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 Review: *11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Sedatives – Quantity Limit

Goal(s):

- Approve only for OHP-funded conditions.
- Treatment of uncomplicated insomnia is not funded, 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:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does client have diagnosis of insomnia with sleep apnea?	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; OR Panic disorder; 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 funded or not.	Funded: Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	Not Funded: 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 Review: *3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *7/1/14, 1/1/07, 7/1/06, 11/15/05*

Sedatives – Therapeutic Duplication

Goal(s):

- Prevent duplicate sedative use.
- Approve only for OHP-funded conditions.
- Treatment of uncomplicated insomnia is not covered; insomnia contributing to covered comorbid conditions is.
- Also see related Benzo Quantity edit and Non-benzo Sedative edit.
- The safety and effectiveness of chronic sedative use is not established in the medical literature.

Length of Authorization:

1 month

Requires PA:

- Concurrent therapy with more than one sedative drug in Class 47.
- The plan prohibits the client from receiving two oral sedative medications at the same time. POS system screens duplicate oral sedative claims in the prior 30 days. If client has a covered diagnosis, treatment with any single agent is approvable.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record the diagnosis, ICD10 code and reject the internal error code.	
2. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	Yes: Document reason for switch and approve duplication for 30 days.	No: Pass to RPh. Deny; medical appropriateness. There is no evidence to support the use of two different sedatives concurrently. Continuous use of a single sedative is approvable for covered diagnoses. (See benzo quantity limit sedative and non-benzo PA)

P&T/DUR Review: *5/18/06*
Implementation: *7/1/14*

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Drug Class Update: Vascular Endothelial Growth Factors

Date of Review: March 2017 **Date of Last Review:** January 2015

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

Purpose for Class Update:
Evidence for the anti-vascular endothelial growth factor (anti-VEGF) agents was last reviewed by the Oregon Pharmacy and Therapeutics Committee (P&T) in January 2015. Recently two medications (ranibizumab and aflibercept) have received expanded FDA indications for treatment of diabetic retinopathy in patients with diabetic macular edema. Ranibizumab has also been recently approved for choroidal neovascularization secondary to myopia. This review examines new comparative efficacy and safety data of anti-VEGF therapy for ocular conditions. Treatment of cancer with bevacizumab is not discussed.

Research Questions:
1. Is there any new comparative evidence to assess efficacy of anti-VEGF agents in the treatment of age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema, or diabetic retinopathy in patients with macular edema?
2. Is there any new comparative evidence to assess incidence and severity of short- or long-term harms associated with anti-VEGF agents?
3. Are there subpopulations of adults (specifically based on age, disease severity, or prior treatment experience) for which there are differences among anti-VEGF agents in efficacy or adverse effects?

Conclusions:
- There is high quality evidence based on data from multiple systematic reviews that there is no difference in best corrected visual acuity between ranibizumab and bevacizumab for neovascular AMD.[1-4]
- There is moderate quality evidence based on systematic reviews of 2 randomized controlled trials (RCTs) of no difference in visual acuity between ranibizumab and aflibercept at 1 or 2 years in patients with neovascular AMD.[3,4]
- There is no difference in efficacy between aflibercept and bevacizumab for treatment of neovascular AMD (low quality evidence based on indirect evidence).[4] There is no direct comparative evidence for pegaptanib sodium for the treatment of AMD.
- There is no difference between ranibizumab and bevacizumab in visual acuity for the treatment of macular edema due to retinal vein occlusion (moderate quality evidence).[4] There is no direct comparative evidence for other agents for the treatment of retinal vein occlusion.
- There is moderate quality evidence of no clinical meaningful difference in efficacy (defined as a change of >15 ETDRS letters) between anti-VEGF agents in patients treated for diabetic macular edema.[4,5]

- Patients with diabetic macular edema and worse visual acuity at baseline (<69 letters on the Early Treatment Diabetic Retinopathy Study scale [ETDRS]) may have improved visual acuity with aflibercept compared to bevacizumab (low quality evidence based on 1 RCT). [4,6] There is insufficient evidence to evaluate differences in other subpopulations of adults.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.[4,7] There was insufficient evidence for other treatments.
- There is no difference in serious ocular events (including endophthalmitis, eye pain, macular hole, macular edema, retinal hemorrhage or reduced visual acuity) between ranibizumab, bevacizumab or aflibercept (low quality evidence).[3,4]
- Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed. Several observational studies demonstrated an increased risk of mortality and cardiovascular events including venous thromboembolism (VTE) and stroke with bevacizumab compared to ranibizumab.[4] However, higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between bevacizumab and ranibizumab.[1,3,4,8] Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).

Recommendations:

- Evaluate comparative costs in the executive session to determine PDL status.
- Recommend PA criteria for non-preferred drugs which will apply to pharmacy and physician administered claims (see **Appendix 4**).

Previous Conclusions:

- There is high quality evidence of no difference between bevacizumab and ranibizumab for the treatment of neovascular age-related macular degeneration (AMD) in gain in visual acuity at one year (RR 0.90; 95% CI 0.73 to 1.11) or loss of visual acuity (RR 1.00; 95% CI 0.98 to 1.02). Two studies have confirmed that there is no difference in efficacy at two years.
- There is moderate quality evidence of no difference serious ocular adverse events between bevacizumab and ranibizumab in the treatment of neovascular AMD.
- For the treatment of neovascular AMD, there was moderate quality evidence of no significant difference in risk of death between bevacizumab and ranibizumab (3.7% vs. 3.4%; RR 1.10; 95% CI 0.78 to 1.57); p=0.59).
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema (DME) relative to laser treatment and sham injection, with similar improvements across agents.
- There is conflicting evidence regarding the comparative risk of serious systemic adverse events between bevacizumab and ranibizumab. A recent Cochrane Collaboration systematic review found low quality evidence of no difference in serious systemic adverse events (RR 1.08; 95% CI 0.90 to 1.31; p=0.41); however, when removing unpublished trials there was a significant difference favoring ranibizumab. The current evidence remains imprecise and suggests that if a difference does exist, it is likely to be small. There is evidence of no difference in arterial thrombotic events (RR 1.02; 95% CI 0.65 to 1.60) between ranibizumab and bevacizumab.
- There is insufficient comparative evidence to make conclusions on the relative efficacy and safety of pegaptanib or aflibercept.

Previous Recommendations:

- Overall, there is no difference in efficacy between ranibizumab and bevacizumab with potentially slight differences in systemic adverse events and no differences in mortality. Evaluate comparative costs in executive session to determine appropriate PDL placement. Maintain pegaptanib and aflibercept as non-preferred due to lower strength evidence.

Background:

Anti-vascular endothelial growth factor (anti-VEGF) agents are indicated for the treatment of a variety of retinal conditions characterized by abnormal blood vessel growth. Choroid neovascularization and macular edema can be caused by a variety of ocular conditions and diseases. They are commonly present in age-related macular degeneration (AMD), diabetic retinopathy, retinal vein occlusion, and myopia. Though the mechanism of treatment for all these conditions is similar, the exact etiology and risk factors for choroidal neovascularization vary by disease state.

Ranibizumab and aflibercept are both approved for neovascular AMD, macular edema due to retinal vein occlusion, diabetic macular edema, and diabetic retinopathy associated with macular edema. Ranibizumab is the only agent FDA-approved for treatment of myopic choroidal neovascularization, and pegaptanib octasodium is only FDA-indicated for AMD. Bevacizumab is primarily indicated for treatment of cancer, but it is used off-label for retinal conditions. In these diseases, vascular damage can trigger inflammatory responses, expression of vascular endothelial growth factor (VEGF), and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.[9] Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.[9] Use of anti-VEGF agents in these conditions can help inhibit angiogenesis and preserve vision in these populations. In many RCTs, the visual acuity is evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A change of 10-15 letters on the ETDRS chart (corresponding to approximately 2-3 lines) is considered clinically significant.[4] Definitions for mild, moderate, or significant visual impairment can vary, but stable vision is typically defined as a loss of 15 letters or less.[1] Moderate visual changes correspond to 15 letters or more and severe vision loss is typically defined as a loss of greater than 30 letters (or 6 lines on the ETDRS chart).[1]

Age-related macular degeneration is defined as a chronic, progressive retinal disease eventually leading to visual impairment. It is most common in adults greater than 50 years of age and affects approximately 2-6% of older adults in the United States.[9-12] The exact etiology of age-related macular degeneration is unknown, but it is thought to be caused by a combination of genetic and environmental factors.[12] Incidence increases with age and is more common in white patients compared to other ethnic races.[10] Other risk factors include previous cataract surgery, darker iris pigmentation, prolonged sunlight exposure, smoking history, significant family history, and nutritional factors.[9,12] Severe visual symptoms are often only associated with late disease and onset of neovascular changes. Visual symptoms can manifest as progressive or sudden visual distortion of objects, difficulties with light adaptation, perceived flashes of light, or central vision impairment.[9,12] Disease may also be classified as wet (referring to the presence of neovascular changes) or dry (characterized by primarily presence of acellular debris). If untreated, approximately 5% of patients with early disease will progress to late-stage disease within 5 years.[12] Guidelines from the American Academy of Ophthalmology recommend anti-VEGF agents as first-line therapy to manage AMD associated with neovascular changes to slow disease progression.[13]

Anti-VEGF agents are also used to treat diabetic macular edema. In patients with uncontrolled diabetes, chronic exposure to elevated glycemic levels can result in damage to the microvasculature of the eye causing macular edema and retinopathy. Retinopathy is often asymptomatic but can cause progressive visual changes and impairment if untreated. Retinopathy may be classified as proliferative or non-proliferative disease, and it can occur in conjunction with or separately from development of macular edema.[9] Proliferative diabetic retinopathy is more commonly associated with neovascularization and preretinal or

vitreous hemorrhage.[9] Risk factors for retinopathy include ethnicity (Hispanic, African American, and Asian patients), uncontrolled diabetes, longer disease duration, history of cataract surgery, and comorbid dyslipidemia or hypertension.[9] Guidelines from the American Diabetes Association and American Academy of Ophthalmology recommend laser photocoagulation as first-line therapy in patients with proliferative diabetic retinopathy.[14,15] Anti-VEGF agents are recommended in patients with diabetic macular edema.[14,15] Recently, the indications for both ranibizumab and aflibercept were expanded to include patients with diabetic retinopathy associated with diabetic macular edema. Approval of anti-VEGF agents in patients with retinopathy was based on secondary analyses of trials in patients with diabetic macular edema. The majority of patients included in these trials had moderate to severe nonproliferative diabetic retinopathy.[16,17] More patients treated with aflibercept and ranibizumab had an improvement greater than or equal to 2 steps on the diabetic retinopathy severity scale (DRSS) compared to patients given laser photocoagulation therapy or sham injections. The DRSS classifies retinopathy into 5 categories based on observable findings upon dilated ophthalmoscopy (i.e. presence of microaneurysms, intraretinal hemorrhages, venous beading, neovascularization or other vascular abnormalities).[18] Categories include no apparent retinopathy, mild non-proliferative diabetic retinopathy, moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy.[18]

Macular edema may also occur as a result of retinal vein occlusion. Risk factors for retinal vein occlusion include older age, hypertension, arteriosclerosis and diabetes.[19] Obstruction of retinal veins leads to decreased circulation, retinal vascular leakage, macular edema, and an increase in intraocular pressure.[19] Depending on the severity and location of the occlusion, visual symptoms may resolve without treatment.[19] However, untreated persistent macular edema may cause progressive visual loss.[19] Guidelines from the American Academy of Ophthalmology recommend use of anti-VEGF agents in patients with macular edema due to retinal vein occlusion in order to reduce vision loss and prevent neovascular complications.[19] Other treatment options include intraocular corticosteroids and peripheral panretinal photocoagulation for patients with neovascularization of the iris and retina.[19]

Myopia, also known as nearsightedness or shortsightedness, is a common eye condition affecting approximately 2% of the United States population.[7] Patients with myopia are able to see close objects clearly, have difficulty seeing objects at a distance.[7] Patients with pathologic myopia have progressive elongation of the eyeball which eventually leads to thinning of the retinal epithelium and choroid.[7] In approximately 5-10% of patients with pathologic myopia, choroidal neovascularization is also present.[7] Approximately 90% of patients with myopic choroidal neovascularization will have progressive vision loss and macular atrophy eventually leading to blindness.[7] Current standard of care for myopic choroidal neovascularization includes verteporfin photodynamic therapy which has demonstrated stabilization of disease for up to 1 year.[7] However, treatment has shown little benefit beyond 1 year.[7] Other treatment options include laser photocoagulation and surgery, but the efficacy of these treatments is limited by high rates of disease recurrence.[7] Anti-VEGF agents have also been used off-label for the treatment of myopic choroidal neovascularization and have shown promising short-term results. In 2016, ranibizumab was the first anti-VEGF agent FDA-approved for the treatment of myopic choroidal neovascularization.[20] It was approved on the basis of results from one RCT demonstrating improvement in vision over the course of 1 year.[20]

In the Oregon fee-for-service Medicaid population, these medications are given as intravitreal injections and are billed as physician administered drugs. They are not currently billed through pharmacy claims and are not restricted by prior authorization. In the past year (October 2015 to September 2016), 268 medical claims were submitted for anti-VEGF agents. Members with Medicare plans or members eligible for only labor and delivery services, emergency medical treatment, or coverage of Medicare part B premiums were excluded from this population. Bevacizumab, the current preferred agent, accounted for 85% of claims (n=229). Of the patients using bevacizumab, approximately 33% had a diagnosis of cancer within the previous year. There were 33 claims (12%) for aflibercept and 16 claims (6%) for ranibizumab during this time.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
In 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) performed a systematic review of the anti-VEGF agents for treatment of ocular conditions.[4] The review included 30 RCTs evaluating bevacizumab, ranibizumab and aflibercept for neovascular AMD (13 studies), diabetic macular edema (5 studies), retinal vein occlusion (9 studies), or choroidal neovascularization secondary to pathologic myopia (3 studies).[4] The primary outcome in these trials was improvement in best corrected visual acuity, typically measured by a gain of 15 or more letters on the ETDRS scale.[4] In neovascular AMD, there was no difference in the number of patients who experienced a gain of greater than 15 ETDRS letters between ranibizumab and bevacizumab (OR 1.13, 95% CI 0.96 to 1.34) or ranibizumab and aflibercept (OR 1.01, 95% CI 0.75 to 1.37).[4] In addition, there were no differences between ranibizumab and bevacizumab when comparing the mean difference in best corrected visual acuity (OR 0.51, 95% CI –0.82 to 1.83), the proportion of patients who had a loss of greater than 15 ETDRS letters (OR 0.95, 95% CI 0.70 to 1.27), or the number of patients who progressed to legal blindness (OR 0.46, 95% CI 0.07 to 3.26).[4] Similarly, no difference in these visual outcomes was observed between ranibizumab and aflibercept.[4] No trials directly compared aflibercept and bevacizumab in AMD, though results from a network meta-analysis indicate that there is no statistically significant difference between anti-VEGF agents.[4] In patients with retinal vein occlusion, there was no difference between ranibizumab and bevacizumab in vision gain (OR 1.03, 95% CI, 0.55 to 1.94) or mean difference in best corrected visual acuity (standardized mean difference [SMD] 0.00, 95% CI –0.30 to 0.30).[4] Data were lacking for other comparisons in patients with retinal vein occlusion.[4] Direct comparative data for patients with choroidal neovascularization secondary to pathologic myopia was limited to 2 small RCTs (n=80) comparing ranibizumab and bevacizumab which observed no difference in best corrected visual acuity (SMD: –0.13, 95% CI –0.57 to 0.31).[4] No evidence was found for other anti-VEGF agents. In diabetic macular edema, direct evidence was limited to a single comparative study. Vision gain, measured as greater than 15 ETDRS letters at 1 year, was statistically less common with bevacizumab and ranibizumab compared to aflibercept (OR 0.60, 95% CI 0.40 to 0.80 and OR 0.70, 95% CI 0.44 to 0.98, respectively).[4] Comparisons between bevacizumab and ranibizumab were not statistically significant.[4] Mean difference from baseline in best corrected visual acuity was a 13.3 letter improvement with aflibercept compared to a mean 11.2 letter improvement with ranibizumab and 9.7 letter improvement with bevacizumab.[4] These differences were primarily driven by a subgroup of patients in the aflibercept group who had worse visual acuity at baseline (initial letter score <69). These patients exhibited a greater relative improvement in best corrected visual acuity when on aflibercept compared to bevacizumab (6.50 letters, 95% CI 2.90 to 10.10; p<0.001) or ranibizumab (4.70 letters, 95% CI 1.40 to 8.00; p=0.003). However, these differences did not achieve a clinically significant difference of 10 to 15 ETDRS letters. There was no significant difference in vision loss (> 15 ETDRS letters) between agents.[4] At 2 years, the difference in visual acuity between ranibizumab and aflibercept was no longer statistically significant.[6]

Harms examined in the CADTH report included adverse events (including increases in intraocular pressure), serious adverse events (particularly arterial thromboembolism, bacterial endophthalmitis and retinal detachment), withdrawals due to adverse events, and mortality.[4] In neovascular AMD, direct comparative data was not available for comparisons of aflibercept and bevacizumab. In addition, safety data in patients with retinal vein occlusion were limited to a few small RCTs in patients taking ranibizumab or bevacizumab. No comparative safety data were available in patients with choroidal neovascularization. Overall, no difference was observed between agents with regard to these adverse effects in patients with neovascular AMD, diabetic macular edema, or retinal vein occlusion.[4] However, harms were infrequently reported and studies were not powered adequately to determine differences in these rare adverse effects.[4] These results must be interpreted with caution. Authors do note that because bevacizumab is not marketed for intravitreal injection, improper handling or preparation may result in increased risk of microbial contamination.[4] To further evaluate safety of bevacizumab compared to other anti-VEGF agents, an additional 24 observational studies were included in the review.[4] Data included one large cohort study with more than 383,000 injections of bevacizumab or ranibizumab which demonstrated no difference in risk of endophthalmitis (adjusted OR 0.66, 95% CI 0.39 to 1.09; p=0.11).[4] Evidence regarding the cardiovascular safety of anti-VEGF agents was mixed. Several observational studies demonstrated an increased risk of mortality and cardiovascular events including VTE and stroke with bevacizumab compared to ranibizumab.[4] However, these studies also had significant confounding factors including lack of reported cardiovascular risk factors, selection biases, and unequal follow-up times which may bias results in favor or ranibizumab.[4] Higher quality observational studies failed to demonstrate any difference in cardiovascular events between bevacizumab and ranibizumab.[4] Therefore, the authors concluded that if properly prepared and stored, bevacizumab is not associated with greater risk of adverse effects compared to other anti-VEGF agents.[4] Overall, bevacizumab was recommended as the preferred first-line therapy because it demonstrated equivalent efficacy and safety to other anti-VEGF agents and was associated with lower costs.[4] Ranibizumab or aflibercept may be used in patients non-responsive to bevacizumab (defined as no improvement after 3 months or < 15 letters improvement after 6 months of therapy) or in patients at high risk for cardiovascular disease.[4] High risk for cardiovascular disease was defined as individuals with clinical evidence of atherosclerosis, have undergone coronary or arterial revascularization, or have prior history of myocardial infarction (MI), cerebrovascular accident (CVA), or peripheral arterial disease.[4]

A systematic review by the Cochrane Collaboration examined direct comparative evidence for efficacy and safety of ranibizumab or aflibercept for the treatment of neovascular AMD.[3] Evidence was derived from 2 high quality RCTs (n=2457 patients, 2457 eyes).[3] Patients included in these trials were on located in the United States, Canada, Europe, Latin America, Asia Pacific and the Middle East.[3] After 1 year of treatment, the best-corrected visual acuity (measured using the ETDRS scale) was similar between treatments (MD -0.15 letters, 95% CI -1.47 to 1.17; high quality evidence).[3] The number of patients who achieved significant improvements in the ETDRS scale (>15 letters) was 32% for both groups (RR 0.97, 95% CI 0.85 to 1.11; high quality evidence), and there was no difference in the proportion of patients who lost 15 or more letters (RR 0.89, 95% CI 0.61 to 1.30; high quality evidence).[3] In addition, there was no difference in quality of life measures at 1 year (MD -0.39, 95% CI -1.71 to 0.93; high quality evidence).[3] Similarly, after 2 years, there was no difference between aflibercept and ranibizumab in the mean change in best corrected visual acuity from baseline (7.2 vs. 7.9 ETDRS letters) or the proportion of patients with greater than 15 letter improvement (RR 0.98, 95% CI 0.85 to 1.12; high quality evidence).[3] Overall safety of ranibizumab and aflibercept was comparable.[3] The rate of serious adverse events was similar in patients treated with aflibercept or ranibizumab at 1 year (RR 0.99, 95% CI 0.79 to 1.25, moderate quality evidence).[3] There was no difference between groups in the rate of arterial thrombotic events, vascular death, non-fatal MI and non-fatal stroke.[3] Serious ocular events occurred rarely and results failed to achieve statistical differences (RR 0.62, 95% CI 0.36 to 1.07, moderate quality evidence due to imprecision), though events were less common in the aflibercept group.[3] There is moderate quality evidence of no difference in risk for specific adverse events between groups at 1 year, including risk of congestive heart failure events (RR 0.77, 95% CI 0.20 to 2.97), retinal hemorrhage (RR 0.65, 95 % CI 0.16 to 2.60), and non-ocular hemorrhagic events (RR 2.30, 95% CI 0.42 to 12.70).[3] These events were rare, imprecise, and failed to achieve statistical significance, leading to uncertainty in the true estimate of effect.[3] In addition, differences in these all events at 2 years failed to achieve statistical significance.[3] Another systematic review reported similar outcomes, with no clinical difference in efficacy or safety between ranibizumab and aflibercept.[8]

A systematic review conducted in 2015 compared bevacizumab to ranibizumab for the treatment of neovascular AMD.[2] Six high quality RCTs were included in the meta-analysis (n=2612 patients).[2] The majority of patients included in these trials were on average 76 to 79 years of age.[2] Overall, there was no difference between bevacizumab and ranibizumab in the mean change in best-corrected visual acuity after follow-up of 1 year (MD -0.40, 95% CI -1.48 to 0.69, p=0.47) or 2 years (weighted MD -1.16, 95% CI -2.82 to 0.51, p=0.17).[2] Serious adverse events were slightly more common with bevacizumab than ranibizumab at 1 year (18.6% vs 14.9%; RR 1.24, 95% CI 1.04 to 1.48; p=0.02; NNH=27) and 2 years (35.6% vs 29.7%; RR 1.20, 95% CI 1.05 to 1.37; p=0.008; NNH=17).[2] Though there was no difference in individual risk of death, MI, stroke, or VTE, increased risk of serious adverse events appeared to be primarily driven by a higher rate of VTE in patients treated with bevacizumab.[2] Other high quality systematic reviews reported similar outcomes, with no difference in clinical efficacy or safety between bevacizumab or ranibizumab treatment for neovascular AMD.[8,21]

In 2016, a systematic review evaluated safety and efficacy of anti-VEGF agents for the treatment of neovascular AMD.[1] Outcomes examined included visual acuity (measured by the change in ETDRS letters), quality of life and adverse events (especially thrombotic events, infection, bleeding, and death) at 1 and 2 years.[1] Five publications from 4 studies evaluated efficacy of bevacizumab versus ranibizumab.[1] Data from these trials were not pooled in a meta-analysis, but overall, there was no difference between groups in the proportion of patients with clinically significant vision changes (> 15 letters on the ETDRS chart) or mean change in best-corrected visual acuity score (low quality evidence).[1] Similarly, in trials which reported adverse effects, there was no difference in risk of death, arterial thrombotic events (including MI or stroke), endophthalmitis or infection.[1] Adverse events that were more common with bevacizumab than ranibizumab included serious systemic adverse events (40% vs 32%, RR 1.30, 95% CI 1.07 to 1.57; p=0.009; NNH=12, 1 RCT for 2 years), and serious ocular events at 12 to 18 months (3 vs 1%, RR 2.77, 95% CI 1.18 to 6.54; p=NR; NNH=50, 3 RCTs).[1] Serious systemic adverse events included hypertension, arteriothrombotic events, systemic hemorrhage, congestive heart failure, VTE, or vascular death.[22] Specific ocular events included endophthalmitis, uveitis, retinal/choroidal detachment, retinal tear, ocular vessel embolism or occlusion and vitreous hemorrhage.[1] Evidence from 7 RCTs evaluated different dosing regimens of ranibizumab. Regimens included doses of 0.3 mg, 0.5 mg, and 2 mg administered monthly, quarterly, or on an as needed basis over the course of 1 to 2 years.[1] Overall, there was insufficient evidence to assess changes in vision or serious adverse effects with different dosing regimens due to lack of reported comparative outcomes.[1] Low quality evidence from 1 RCT (n=353) indicates that fixed monthly regimens of 0.3 mg may be more effective than quarterly injections of 0.3 mg (MD -3.9 letters, 95% CI -7.7 to -0.9) or 0.5 mg (MD -5.2 letters, 95% CI -8.6 to -1.7) ranibizumab.[1] The proportion of patients who had an improvement of greater than 15 ETDRS letters was 14% in patients given quarterly injections compared to 29% with monthly injections.[1] Similarly, 8% of patients given 0.3 mg quarterly compared to 3% receiving 0.3 mg monthly injections progressed to legal blindness (20/200) in 12 months.[1] Statistical significance for these outcomes was not reported.[1] Evidence from 2 RCTs compared aflibercept to ranibizumab.[1] Overall, aflibercept and ranibizumab demonstrated similar efficacy in the mean change in best-corrected visual acuity and proportion of patients with a gain of 15 or more ETDRS letters (moderate quality evidence).[1] Adverse events were similar between groups though events were infrequent and studies were not powered to evaluate these outcomes.[1] There was insufficient evidence evaluating differences in dosing regimens of aflibercept (given monthly or every 2 months).[1] Evidence comparing different regimens of bevacizumab (either monthly or as needed dosing) was limited to 2 RCTs.[1] Overall, changes in visual acuity were similar between groups, though statistical significance was not assessed for the majority of outcomes (low quality evidence).[1] There was no comparative data on adverse effects between patients taking bevacizumab monthly or as needed.[1] Authors do note that bevacizumab is not formulated for intravitreal injections and requires compounding which may increase risk of infections due to potential contamination.[1]

Two systematic reviews have examined comparative efficacy and safety of different dosing regimens of ranibizumab in neovascular AMD.[8,23] Patients in these reviews were treated with injections of 0.5 mg ranibizumab on a scheduled basis or with a 1-3 months of scheduled doses followed by as needed treatment for patients with progressive disease.[8] The efficacy of ranibizumab when given alone or in conjunction with photodynamic therapy was also examined.[8] Evidence examining difference in ranibizumab regimens included data from 6 RCTs.[8] Patients were on average 73 to 80 years of age and were followed for 1 to 2 years.[8]

The authors found a slight statistical benefit when ranibizumab was administered as needed compared to a scheduled regimen (2 RCTs, weighted MD 1.97 letters, 95% CI 0.14 to 3.794, p=0.04, I^2=0%) and combination treatment of ranibizumab plus photodynamic therapy versus ranibizumab alone (4 RCTs, weighted MD 2.74, 95% CI 0.26 to 5.21, p=0.03, I^2=0%), though differences were not clinically significant.[8] Another systematic review which examined differences in dosing regimens of ranibizumab (either scheduled monthly doses or therapy given as needed depending on diseases progression) reached similar conclusions.[23] The meta-analysis included similar studies (3 RCTs, n=1844) and found no clinical difference in best corrected visual acuity between groups after 2 years (weighted MD 1.9, 95% CI 0.5 to 3.3, p=0.008, I^2=0%).[23] At 2 years, the total number of intravitreal injections was significantly less in patients treated on an as needed basis compared to patients receiving scheduled monthly therapy (MD 8.4, 95% CI 7.9 to 8.9, p<0.00001, I^2=95%).[23] Heterogeneity between these trials was significant, but results all demonstrated consistently fewer injections when therapy was given as needed.

A Cochrane review in 2016 examined the efficacy of anti-VEGF agents for the treatment of choroidal neovascularization due to pathological myopia.[7] The review included 6 RCTs or quasi-RCTs (n=594) which compared anti-VEGF agents to photodynamic therapy, placebo, or other anti-VEGF agents.[7] Direct comparative evidence between anti-VEGF agents was limited to 2 trials which evaluated bevacizumab and ranibizumab.[7] Treatment was primarily given as 1 injection followed by as needed treatment depending on disease activity upon optical imaging.[7] Compared to photodynamic therapy, the current standard of care, anti-VEGF agents improved mean visual acuity by approximately 7 and 13 ETDRS letters at 1 and 2 years, respectively.[7] The proportion of patients achieving a clinically significant improvement in visual acuity (corresponding to >3 ETDRS lines) was also greater in patients given anti-VEGF agents after 1 year (RR 1.86, 95% CI 1.27 to 2.73, 226 people, moderate quality evidence) and 2 years of treatment (RR 3.43, 95% CI 1.37 to 8.56, 92 people, low quality evidence) compared to those receiving photodynamic therapy.[7] In 1 of these trials, patients in the control groups were allowed to receive anti-VEGF treatment after 3 months, which may lead to a more conservative estimate of efficacy.[7] Similar improvements were seen with bevacizumab compared to laser photocoagulation therapy with mean improvements of approximately 11 and 14 ETDRS letters after 1 and 2 years (low quality evidence).[7] In 2 RCTs directly comparing bevacizumab and ranibizumab, there was no difference in change in visual acuity after 1 year (RR 0.79, 95% CI 0.50 to 1.27, P=0.33, moderate quality evidence).[7] Adverse events were rarely reported, and no serious adverse events occurred in patients randomized to control groups.[7] Differences in adverse events failed to achieve statistical significance, though adverse events were more common in patients treated with anti-VEGF therapy (RR 1.82, 95% CI 0.23 to 14.71, p=0.14). Serious systemic adverse events occurred in 15 patients (4.2%) taking anti-VEGF agents, and ocular adverse events occurred in 5 patients (1.4%).[7]

Similar results were documented in another systematic review of anti-VEGF agents for the treatment of choroidal neovascularization in conditions unrelated to AMD.[24] This review included both RCTs and comparative non-randomized trials. Of the 16 included studies, 13 (n=1017) were in patients with myopic choroidal neovascularization.[24] The majority of patients included in these trials were female and 35 to 67 years of age.[24] Mean baseline best corrected visual acuity was between 81 and 99 letters.[24] Three study regimens required 3 monthly loading doses and continued treatment in all studies was based on clinical assessment at follow-up visits.[24] Patients received an average of 1.6 to 4.72 injections over the course of these studies.[24] Due to significant heterogeneity between studies, results were not pooled in a meta-analysis. However, in myopic choroidal neovascularization, the proportion of patients with a clinical improvement of greater than 15 letters ranged from 27% to 70% in patients taking anti-VEGF therapy compared to 14% to 20% in patients given photodynamic therapy.[24] Evidence was limited by quality of the included trials, limited population size, and significant methodological heterogeneity between studies.[24] Differences in baseline visual acuity and treatment regimens may have contributed to the wide difference in treatment outcomes. In trials directly comparing bevacizumab and ranibizumab, no statistical difference in best corrected visual acuity was reported between groups.[24]

A systematic review examined safety of anti-VEGF agents in patients with diabetic macular edema and consistent exposure to anti-VEGF agents (i.e. receiving monthly injections for at least 2 years).[25] Four RCTs (n=1078) of aflibercept and ranibizumab versus sham treatment were included in the review.[25] Outcomes examined included risk of MI, CVA, VTE, and mortality.[25] The mean age of patients enrolled in trials was 61 to 64 years.[25] Baseline cardiovascular risk

factors were not evaluated, though patients with recent stroke or MI (within 3 to 6 months) were excluded from these trials.[25] Compared to sham-laser treatment, patients treated with anti-VEGF therapy had a higher risk of all-cause mortality (OR 2.57, 95% CI 1.31 to 5.05, p=0.006), CVA (OR 2.33, 95% CI 1.04 to 5.22), and vascular-related death (OR 2.23, 95% CI 1.01 to 4.89, p=0.05).[25] Risk for VTE and MI failed to achieve statistical significance.[25] All outcomes were graded as moderate quality evidence.[25] In addition, similar outcomes were observed in subgroup analyses of ranibizumab 0.5 mg and 0.3 mg doses, and no difference was observed between patients receiving either ranibizumab or aflibercept.[25]

A systematic review published in 2016 examined the comparative efficacy and safety of anti-VEGF agents in patients with diabetic macular edema. The review included updated evidence from 8 systematic reviews and 4 RCTs.[5] Overall, due to quality of included trials and lack of direct comparative data, evidence for improvements in visual acuity was graded as low quality.[5] Overall, authors concluded that in patients with good baseline visual acuity (>69 ETDRS letters), ranibizumab, aflibercept, and bevacizumab were equally effective at improving visual acuity at 6 to 12 months.[5] Results from 1 RCT indicate that in patients with worse baseline visual acuity (<69 ETDRS letters), aflibercept may have improved visual acuity at 1 year compared to ranibizumab or bevacizumab (MD 4.7 and 6.5 letters, respectively).[5] The clinical significance of these differences remains unclear. Regarding adverse effects, there were no significant differences between agents.[5] However, studies were not powered to examine these rare events and many studies excluded patients at high risk for thrombotic events.[5] Authors note that all intravitreal injections have an increased risk of endophthalmitis with reported rates of 0.05 to 1.6%, but direct comparative evidence between agents is lacking.[5]

New Guidelines:
Guidance from the National Institute for Health and Care Excellence (NICE) for the use of aflibercept in patients with diabetic macular edema was published in 2015.[26] Recommendations were based on evidence from 2 RCTs evaluating change in best corrected visual acuity at 1 year.[26] The clinical and cost effectiveness was evaluated in the total population and in subgroups of patients with prior cataract surgery and baseline central retinal thickness less than 400 micrometers.[26] Clinically, aflibercept demonstrated a significant improvement in the best corrected visual acuity compared to laser photocoagulation when given every 4 or 8 weeks.[26] Subgroup analyses demonstrated that in patients with a central retinal thickness of less than 400 micrometers, differences failed to achieve statistical significance.[26] The analysis was limited due to the small population of patients with central retinal thickness less than 400 micrometers (n=78) and lack of balanced baseline characteristics in this subgroup.[26] Based on cost-effectiveness results, NICE guidance recommends initiation of aflibercept only in patients with a central retinal thickness greater than 400 micrometers.[26]

In the past few years, the American Academy of Ophthalmology has updated guidelines on the use of anti-VEGF agents in retinal vein occlusion, neovascular AMD and diabetic retinopathy. Guidelines recommend anti-VEGF agents as a first-line therapy for the treatment of macular edema associated with branched or central retinal vein occlusion (strong recommendation based on good quality evidence).[19] No specific recommendations are made for any particular agent. Intraocular steroids have also demonstrated benefit in treatment of macular edema due to retinal vein occlusion and are recommended as a second-line treatment due to their associated with increased risk of cataracts and glaucoma (strong recommendation based on good quality evidence).[19] Similar recommendations are made in guidelines for the treatment of neovascular AMD.[13] Anti-VEGF agents are recommended as first-line therapy in patients with neovascular AMD (strong recommendation based on good quality evidence), but no recommendations are made for any particular agent or treatment regimen.[13] Guidelines for diabetic retinopathy state anti-VEGF agents may be used for the treatment of retinopathy associated with clinically significant macular edema regardless of retinopathy severity (strong recommendation based on good quality evidence).[15] Anti-VEGF agents are first-line therapy in patients with central macular edema.[15] They may be used as monotherapy or in combination with focal laser treatment or panretinal photocoagulation.[15] Anti-VEGF agents are not recommended for treatment of mild or moderate severity retinopathy alone (strong recommendation based on good quality evidence).[15] Though

evidence is limited, treatment may be considered in patients with high-risk proliferative diabetic retinopathy with or without macular edema (strong recommendation based on observational studies).[15] Guidelines note that treatment decision should be based on the individual risks and benefits of the patient.[15]

New Formulations or Indications:
In 2016, bevacizumab labeling was updated to include a new indication for treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer either in combination with carboplatin and paclitaxel, in combination with carboplatin and gemcitabine, and as monotherapy following combination therapy.[27]

Since 2015, aflibercept and ranibizumab were FDA-approved for treatment of diabetic retinopathy in patients with diabetic macular edema, and ranibizumab achieved approval for the treatment of myopic choroidal neovascularization.[20,28]

A new formulation for pre-filled 0.5 mg syringes of ranibizumab was also approved in 2015.[20]

New FDA Safety Alerts:
In 2016, labeling for aflibercept was updated to include contraindications for hypersensitivity reactions including rash, pruritus, urticarial, or severe anaphylactic/anaphylactoid reactions.[27]

Randomized Controlled Trials:
A total of 324 citations were manually reviewed from the initial literature search. After further review, 314 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). If multiple publications presented results from the same trial, the publication with the most recent results and longest follow-up was included. Data supporting the use of aflibercept and ranibizumab for recently FDA-approved indications of diabetic retinopathy in patients with diabetic macular edema and for ranibizumab in patients with treatment of myopic choroidal neovascularization are also included. The remaining 10 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Berg K, et al. 2016.[29] DB, MC, NI, RCT Duration: 2 years N=441	1. Ranibizumab 0.5 mg 2. Bevacizumab 1.25 mg T&E protocol: Intravitreal injections given monthly until achievement of inactive disease then injections were extended by 2 weeks at a time up to 12 weeks. Treatment periods were shortened in 2 week periods with disease recurrence.	Treatment naïve adults >50 years of age with neovascular AMD and BCVA between 20/25 and 20/320.	Mean change in BCVA at 2 years (measured by ETDRS chart)	Ranibizumab: 6.6 letters (SD 15.2) Bevacizumab: 7.4 letters (SD 16.0) MD 0.8 letters (95% CI -4.1 to 2.5; p=0.634)

Chakravarthy U, et al. 2015.[30] MC, NI, RCT Duration: 2 years N=628	1. Ranibizumab 0.5 mg continuous monthly intravitreal injections 2. Ranibizumab 0.5 mg intravitreal injections for 3 months followed by retreatment with active disease 3. Bevacizumab 1.25 mg continuous monthly intravitreal injections 4. Bevacizumab 1.25 mg intravitreal injections for 3 months followed by retreatment with active disease	Treatment naïve adults ≥50 years of age with neovascular AMD and BCVA ≥25 letters	BCVA at 2 years	Ranibizumab (Groups 1 and 2): 67.8 letters (SD 17.0) Bevacizumab (Groups 3 and 4): 66.1 letters (SD 18.4) MD –1.37 letters (95% CI –3.75 to 1.01; p=0.26) Continuous treatment (Groups 1 and 3): 66.6 (SD 17.9) Retreatment upon disease recurrence (Groups 2 and 4): 37.3 (SD 17.5) MD –1.63 letters (95% CI –4.01 to 0.75; p=0.18)
Wiley HE, et al. 2016.[31] DB, 3-month crossover, RCT Duration: 9 months N=56	1. Ranibizumab 0.3 mg monthly 2. Bevacizumab 1.25 mg monthly	Adults with type 1 or 2 diabetes and DME	Mean change in BCVA (ETDRS chart) at 3 months	Ranibizumab: 6.6 letters (95% CI 4.5 to 8.7) Bevacizumab: 5.3 letters (95% CI 3.2 to 7.4) MD 1.3 letters (95% CI 0.07 to 2.5; P=0.039)
Wells JA, et al. 2016.[6] MC, NI, RCT Duration: 2 years N=660	1. Aflibercept 2.0 mg 2. Bevacizumab 1.25 mg 3. Ranibizumab 0.3 mg Treatment was given monthly for 12 months then every 1-4 months thereafter depending on disease stability. Addition of focal grid laser photocoagulation could be added at 6 months with persistent disease activity.	Adults with DME and BCVA of 20/32 to 20/320 on the Snellen chart	Mean change in visual acuity at 2 years (post-hoc exploratory analysis)	1. Aflibercept 12.8 letters (SD 12.4) 2. Bevacizumab 10.0 letters (SD 11.8) 3. Ranibizumab 12.3 letters (SD 10.5) Aflibercept vs. bevacizumab: MD 2.7 (95% CI 0.3 to 5.2; P=0.02) Aflibercept vs. ranibizumab: MD 0.7 (95% CI -1.3 to 2.8; P=0.47) Ranibizumab vs. bevacizumab: MD 2.0 (95% CI -0.4 to 4.4; P=0.11)
Bressler SB, et al. 2016.[32] DB, MC, RCT Duration: 5 years N=450	1. Laser photocoagulation + very deferred ranibizumab (1.5 to 3 years later) 2. Ranibizumab + prompt laser photocoagulation 3. Laser photocoagulation + triamcinolone + very deferred ranibizumab (1.5 to 3 years later) 4. Ranibizumab + deferred laser photocoagulation (≥6 months later)	Adults with DME and BCVA of 20/32 to 20/320 on the Snellen chart	Mean change in BCVA at 5 years (post-hoc exploratory analysis)	1. 5 letters (SD 14) 2. 8 letters (SD 13) 3. 7 letters (SD 14) 4. 10 letters (SD 13) Compared to ranibizumab + deferred laser 1. MD 4.4 (95% CI 1.2 to 7.6; p=0.001) 2. MD 2.0 (95% CI -1.6 to 5.7; p=0.186)

				3. MD 2.8 (95% CI -0.9 to 6.5; p=0.067)
Pece A, et al. 2015.[33] RCT Mean duration: 19 months N=80	1. Bevacizumab 0.5 mg 2. Ranibizumab 1.25 mg Treatment was once then as needed upon presence of active lesions, progressive disease, or worsening of BCVA >1 line (5 letters)	Adults with myopic CNV and BCVA >20/400 on the Snellen chart	Mean change in BCVA	Bevacizumab: 55 letters (SD 26) Ranibizumab: 58 letters (SD 21) OR 2.46 (95% CI 0.88 to 6.83; p=0.138)
Brown DM, et al. 2015.[34] DB, MC, RCT Duration: 2 years N=466	1. Aflibercept 2 mg every 4 weeks 2. Aflibercept 2 mg every 8 weeks after 5 monthly doses 3. Macular laser photocoagulation at baseline and upon follow-up if clinically significant macular edema was present	Adults with retinopathy, DME and BCVA of 73-24 letters (20/40 to 20/320)	Proportion of patients with ≥ 2 step improvement in the DRSS score (pre-specified exploratory outcome)	1. 37.0% (95% CI NR); p<0.0001 vs. laser 2. 37.1% (95% CI NR); p<0.0001 vs. laser 3. 15.6% (95% CI NR) Aflibercept vs. laser photocoagulation ARR 22%, NNT=5
Brown DM, et al. 2015.[34] DB, MC, RCT Duration: 2 years N=406	1. Aflibercept 2 mg every 4 weeks 2. Aflibercept 2 mg every 8 weeks after 5 monthly doses 3. Macular laser photocoagulation at baseline and upon follow-up if clinically significant macular edema was present	Adults with retinopathy, DME and BCVA of 73-24 letters (20/40 to 20/320)	Proportion of patients with ≥ 2 step improvement in the DRSS score (pre-specified exploratory outcome)	1. 29.3% (95% CI NR); p=0.0004 vs. laser; ARR 21.1%, NNT=5 2. 32.6%(95% CI NR); p<0.0001 vs. laser; ARR 24.4%, NNT=4 3. 8.2%
Ip MS, et al. 2015.[16] DB, MC, RCT Duration: 3 years N=759	1. Ranibizumab 0.3 mg monthly 2. Ranibizumab 0.5 mg monthly 3. Sham injections monthly Patients randomized to sham injections could receive ranibizumab 0.5 mg monthly after 25 months	Adults with retinopathy, DME and BCVA of 20/40 to 20/320	Proportion of patients with ≥ 2 or ≥3 step improvement in the DRSS score (post-hoc exploratory outcome)	1. 38.9% (95% CI NR); p<0.0001 vs. sham injections 2. 39.3% (95% CI NR); p<0.0001 vs. sham injections 3. 23.8% (95% CI NR) Ranibizumab vs: sham injections ARR 15%, NNT=7
Wolf S, et al. 2014.[35]	1. Ranibizumab 0.5 mg on day 1 and at 1 month with further treatment based on change in VA	Adults with myopic CNV and BCVA of	Mean change in BCVA at 1-3 months (ETDRS letters)	1. 10.5 letters (SD 8.2), p<0.00001 vs. verteporfin photodynamic therapy 2. 10.6 letters (SD 7.3), p<0.00001 vs. verteporfin photodynamic therapy

Phase 3, Superiority and NI, DB, MC, RCT Duration: 1 year N=244	2. Ranibizumab 0.5 mg on Day 1 with further treatment based on presence of active disease upon exam 3. Verteporfin photodynamic therapy on Day 1 with further treatment based on active disease upon exam. Cross-over treatment with ranibizumab was permitted after 3 months.	24-78 ETDRS letters		3. 2.2 letters (SD 9.5) Noninferiority between ranibizumab groups achieved

Abbreviations: AMD = age-related macular degeneration; ARR = absolute risk reduction; BCVA = best corrected visual acuity; CNV= choroidal neovascularization; DB = double blind; DME = diabetic macular edema; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; MC = multicenter; MD = mean difference; NI = noninferiority; NNT = number needed to treat; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAVEN	VIAL	AVASTIN	BEVACIZUMAB	Y
INTRAOCULR	SYRINGE	MACUGEN	PEGAPTANIB SODIUM	N
INTRAOCULR	VIAL	EYLEA	AFLIBERCEPT	N
INTRAOCULR	SYRINGE	BEVACIZUMAB	BEVACIZUMAB	N
INTRAOCULR	VIAL	LUCENTIS	RANIBIZUMAB	N
INTRAOCULR	VIAL	LUCENTIS	RANIBIZUMAB	N

Appendix 2: Abstracts of Comparative Clinical Trials

Berg K, et al. 2016.[29]
Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results

Purpose: To compare the efficacy and safety of bevacizumab (Avastin; F. Hoffmann-La Roche Ltd, Basel, Switzerland) versus ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) for neovascular age-related macular degeneration (nAMD) after 2 years when using a treat-and-extend protocol. Design: Multicenter, randomized, noninferiority trial with a noninferiority limit of 5 letters. Participants: Patients 50 years of age or older with previously untreated nAMD in 1 eye and best-corrected visual acuity 20/25 to 20/320. Methods: Patients were assigned randomly to receive intravitreal injections with either ranibizumab 0.5 mg or bevacizumab 1.25 mg. Injections were given every 4 weeks until inactive disease was achieved. The treatment interval then was extended by 2 weeks at a time up to a maximum of 12 weeks. In the event of a recurrence, the treatment interval was shortened by 2 weeks at a time. Main Outcome Measure: Mean change in visual acuity at 2 years. Results: Of a total of 441 randomized patients, 339 patients (79%) completed the 2-year visit. According to perprotocol analysis at 2 years, bevacizumab was equivalent to ranibizumab, with 7.4 and 6.6 letters gained, respectively (95%confidence interval [CI] of mean difference, 4.1 to 2.5; P=0.634). Intention-to-treat analysis was concordant, with a gain of 7.8 letters for bevacizumab and 7.5 letters for ranibizumab (95%CI of mean difference, 3.2 to 2.7; P=0.873). The 2-year results did not show any significant difference in mean central retinal thickness, with a decrease of113 mmfor bevacizumab and122 mm for ranibizumab (95%CI of mean difference, 32 to 15; P=0.476). There was a statistically significant difference between the drugs regarding the number of treatments given, with 18.2 injections for bevacizumab and 16.0 injections for ranibizumab (95%CI of mean difference, 3.4 to1.0; P<0.001). The number of serious adverse events was similar between the groups over the course of the study. Conclusions: At 2 years, bevacizumab and ranibizumab had an equivalent effect on visual acuity and reduction of central retinal thickness when administered according to a treat-and-extend protocol for nAMD. There was no significant difference in the number of serious adverse events between the treatment groups.

Chakravarthy U, et al. 2015.[30]
A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)

Background: Bevacizumab (Avastin®, Roche), which is used in cancer therapy, is the 'parent' molecule from which ranibizumab (Lucentis®, Novartis) was derived for the treatment of neovascular age-related macular degeneration (nAMD). There were reports in the literature on the effectiveness of bevacizumab in treating nAMD, but no trials. The cost per dose of bevacizumab is about 5–10% that of ranibizumab. This trial was a head-to-head comparison of these two drugs.
Objective: To compare the clinical effectiveness and cost-effectiveness of ranibizumab and bevacizumab, and two treatment regimens, for nAMD.
Design: Multicentre, factorial randomised controlled trial with within-trial cost–utility and cost-minimisation analyses from the perspective of the UK NHS. Participants, health professionals and researchers were masked to allocation of drug but not regimen. Computer-generated random allocations to combinations of ranibizumab or bevacizumab, and continuous or discontinuous regimen, were stratified by centre, blocked and concealed.
Setting: Twenty-three ophthalmology departments in NHS hospitals
Participants: Patients ≥ 50 years old with active nAMD in the study eye with best corrected distance visual acuity (BCVA) ≥ 25 letters measured on a Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Previous treatment for nAMD, long-standing disease, lesion diameter > 6000 µm, thick blood at the fovea and any other confounding ocular disease were exclusion criteria. One eye per participant was studied; the fellow eye was treated according to usual care, if required.

Interventions: Ranibizumab and bevacizumab were procured commercially. Doses were ranibizumab 0.5 mg or bevacizumab 1.25 mg. The repackaged bevacizumab was quality assured. All participants were treated at visits 0, 1 and 2. Participants randomised to the continuous regimen were treated monthly thereafter. Participants randomised to the discontinuous regimen were not retreated after visit 2 unless pre-specified criteria for active disease were met. If retreatment was needed, monthly injections over 3 months were mandated.
Main outcome measures: The primary outcome was BCVA. The non-inferiority margin was 3.5 letters. Secondary outcomes were contrast sensitivity; near visual acuity; reading index; neovascular lesion morphology; generic and disease-specific patient-reported outcomes, including macular disease-specific quality of life; survival free from treatment failure; resource use; quality-adjusted life-years (QALYs); and development of new geographic atrophy (GA) (outcome added during the trial). Results are reported for the study eye, except for patient-reported outcomes.
Results: Between 27 March 2008 and 15 October 2010, 610 participants were allocated and treated (314 ranibizumab, 296 bevacizumab; at 3 months, 305 continuous, 300 discontinuous). After 2 years, bevacizumab was neither non-inferior nor inferior to ranibizumab [–1.37 letters, 95% confidence interval (CI) –3.75 to +1.01 letters] and discontinuous treatment was neither non-inferior nor inferior to continuous treatment (–1.63 letters, 95% CI –4.01 to +0.75 letters). Lesion thickness at the fovea was similar by drug [geometric mean ratio (GMR) 0.96, 95% CI 0.90 to 1.03; p = 0.24] but 9% less with continuous treatment (GMR 0.91, 95% CI 0.85 to 0.97; p = 0.004). Odds of developing new GA during the trial were similar by drug [odds ratio (OR) 0.87, 95% CI 0.61 to 1.25; p = 0.46] but significantly higher with continuous treatment (OR 1.47, 95% CI 1.03 to 2.11; p = 0.033). Safety outcomes did not differ by drug but mortality was lower with continuous treatment (OR 0.47, 95% CI 0.22 to 1.03; p = 0.05). Continuous ranibizumab cost £3.5M per QALY compared with continuous bevacizumab; continuous bevacizumab cost £30,220 per QALY compared with discontinuous bevacizumab. These results were robust in sensitivity analyses.
Conclusions: Ranibizumab and bevacizumab have similar efficacy. Discontinuing treatment and restarting when required results in slightly worse efficacy. Safety was worse with discontinuous treatment, although new GA developed more often with continuous treatment. Ranibizumab is not cost-effective, although it remains uncertain whether or not continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at £20,000 per QALY threshold. Future studies should focus on the ocular safety of the two drugs, further optimisation of treatment regimens and criteria for stopping treatment.

Wiley HE, et al. 2016.[31]
A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema

Purpose: To investigate the comparative efficacy of bevacizumab (Avastin) and ranibizumab (Lucentis; both Genentech, Inc, South San Francisco, CA) for diabetic macular edema (DME) using a crossover study design. Design: Randomized, double-masked, 36-week, 3-period crossover clinical trial. Participants: Fifty-six subjects with DME involving the center of the macula in one or both eyes. Methods: Monthly intravitreous injections of bevacizumab (1.25 mg) or ranibizumab (0.3 mg). Main Outcome Measures: Comparison of mean changes in visual acuity and central retinal thickness, tested using a linear mixed-effects model. Results: Based on the linear mixed-effects model, the 3-month estimated mean improvement in visual acuity was 5.3 letters for bevacizumab and 6.6 letters for ranibizumab (difference, 1.3 letters; P ¼ 0.039). Estimated change in optical coherence tomography (OCT) central subfield mean thickness (CSMT) was 89 mm for bevacizumab and 137 mm for ranibizumab (difference, 48 mm; P < 0.001). Incorporating cumulative treatment benefit, the model yielded a predicted 36-week (9-month) average improvement in visual acuity of 7.1 letters (95% confidence interval [CI], 5.0e9.2) for bevacizumab and 8.4 letters (95% CI, 6.3e10.5) for ranibizumab, and a change in OCT CSMT of 128 mm (95% CI, 155 to 100) for bevacizumab and 176 mm (95% CI, 202 to 149) for ranibizumab. There was no significant treatment-by-period interaction (i.e., treatment difference was constant in all 3 periods), nor was there a significant differential carryover effect from one period to the next. Conclusions: This trial demonstrated a statistically significant but small relative clinical benefit of ranibizumab compared with bevacizumab for treatment of DME, using a markedly reduced sample size relative to a full comparative efficacy study. The effects on visual acuity and central retinal thickness for the 2 drugs are consistent with those reported at 1 year for the concurrent parallel-group trial by the Diabetic Retinopathy Clinical Research

Network testing bevacizumab, ranibizumab, and aflibercept for DME. The 3-period crossover design allowed for meaningful and efficient comparison, suggesting that this approach may be useful for future comparative efficacy studies of antievascular endothelial growth factor drugs for DME.

Wells JA, et al. 2016.[6]
Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial

Purpose: To provide 2-year results comparing anti-vascular endothelial growth factor (VEGF) agents for center-involved diabetic macular edema (DME) using a standardized follow-up and retreatment regimen. Design: Randomized clinical trial. Participants: Six hundred sixty participants with visual acuity (VA) impairment from DME. Methods: Randomization to 2.0-mg aflibercept, 1.25-mg repackaged (compounded) bevacizumab, or 0.3mg ranibizumab intravitreous injections performed up to monthly using a protocol-specific follow-up and retreatment regimen. Focal/grid laser photocoagulation was added after 6 months if DME persisted. Visits occurred every 4 weeks during year 1 and were extended up to every 4 months thereafter when VA and macular thickness were stable. Main Outcome Measures: Change in VA, adverse events, and retreatment frequency. Results: Median numbers of injections were 5, 6, and 6 in year 2 and 15, 16, and 15 over 2 years in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global P ¼ 0.08). Focal/grid laser photocoagulation was administered in 41%, 64%, and 52%, respectively (aflibercept vs. bevacizumab, P < 0.001; aflibercept vs. ranibizumab, P ¼ 0.04; bevacizumab vs. ranibizumab, P ¼ 0.01). At 2 years, mean VA improved by 12.8, 10.0, and 12.3 letters, respectively. Treatment group differences varied by baseline VA (P ¼ 0.02 for interaction). With worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3, and 16.1 letters, respectively (aflibercept vs. bevacizumab, P ¼ 0.02; aflibercept vs. ranibizumab, P ¼ 0.18; ranibizumab vs. bevacizumab, P ¼ 0.18). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively (P > 0.10, for pairwise comparisons). Anti-Platelet Trialists' Collaboration (APTC) events occurred in 5% with aflibercept, 8% with bevacizumab, and 12% with ranibizumab (global P ¼ 0.047; aflibercept vs. bevacizumab, P ¼ 0.34; aflibercept vs. ranibizumab, P ¼ 0.047; ranibizumab vs. bevacizumab, P ¼ 0.20; global P ¼ 0.09 adjusted for potential confounders). Conclusions: All 3 anti-VEGF groups showed VA improvement from baseline to 2 years with a decreased number of injections in year 2. Visual acuity outcomes were similar for eyes with better baseline VA. Among eyes with worse baseline VA, aflibercept had superior 2-year VA outcomes compared with bevacizumab, but superiority of aflibercept over ranibizumab, noted at 1 year, was no longer identified. Higher APTC event rates with ranibizumab over 2 years warrants continued evaluation in future trials.

Bressler SB, et al. 2016.[32]
Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema

PURPOSE: To compare long-term vision and anatomic effects of ranibizumab with prompt or deferred laser vs laser or triamcinolone D laser with very deferred ranibizumab in diabetic macular edema (DME). DESIGN: Randomized clinical trial. METHODS: Eight hundred and twenty-eight study eyes (558 [67%] completed the 5-year visit), at 52 sites, with visual acuity 20/32 to 20/320 and DME involving the central macula were randomly assigned to intravitreous ranibizumab (0.5 mg) with either (1) prompt or (2) deferred laser; (3) sham injection D prompt laser; or (4) intravitreous triamcinolone (4 mg) D prompt laser. The latter 2 groups could initiate ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. The main outcome measures were visual acuity, optical coherence central subfield thickness, and number of injections through5years. RESULTS: At 5 years mean (± standard deviation) change in Early Treatment Diabetic Retinopathy Study visual acuity letter scores from baseline in the ranibizumab D deferred laser (N=111), ranibizumab D prompt laser (N= 124), laser/very deferred ranibizumab (N=198), and triamcinolone D laser/very deferred ranibizumab (N=125) groups were 10 ± 13, 8 ± 13, 5 ± 14, and 7 ± 14, respectively. The difference (95% confidence interval) in mean change between ranibizumab D deferred laser and laser/very deferred ranibizumab and triamcinolone D laser/very deferred ranibizumab was 4.4 (1.2–7.6, P <0.001) and 2.8 (L0.9 to 6.5, P=0.067), respectively, at 5 years. CONCLUSIONS: Recognizing

limitations of follow-up available at 5 years, eyes receiving initial ranibizumab therapy for center-involving DME likely have better long-term vision improvements than eyes managed with laser or triamcinolone D laser followed by very deferred ranibizumab for persistent thickening and vision impairment.

Pece A, et al. 2015.[33]
A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV

Aims: The aim was to compare the efficacy of intravitreal therapy with bevacizumab and ranibizumab for choroidal neovascularization (CNV) in pathologic myopia (PM). Methods: This was a prospective multicenter randomized non-blinded trial. Results: In seven centers, 78 eyes were randomized 1:1 to treatment with bevacizumab (group B, 40 eyes) or ranibizumab (group R, 38 eyes) given with an "on demand" regimen (PRN). The mean follow-up was 19 months (SD 2, range 12–24). The mean BCVA at baseline was 0.60 logMAR (20/80 Snellen equivalent, Seq) and 50 letter score (ls). Mean final BCVA was 0.51 LogMAR (20/63 Seq) and 57 ls (p= 0.0009 and p=0.0002, respectively). In group B, mean basal BCVA was 0.52 logMAR (20/63 Seq) and 54 ls, and final BCVA was 0.51 logMar (20/63 Seq) and 57 ls. In group R, mean basal BCVA was 0.62 logMAR (20/80 Seq) and 45 ls, and the final values were 0.50 logMAR (20/63 Seq) and 58 ls. Statistical comparison of the two groups showed no significant difference (logMAR p=0.90 and letters p=0.78). Multivariate analysis showed no influence of age or previous photodynamic treatment (PDT) on final visual changes. The mean number of treatments in the first year was 2.7 in group B and 2.3 in group R (p=0.09). Conclusion: Myopic CNV equally benefits from on-demand intravitreal injection of either bevacizumab or ranibizumab; the therapeutic effect is independent of previous PDT and age.

Brown 2015[34]
Intravitreal Aflibercept for Diabetic Macular Edema 100-Week Results From the VISTA and VIVID Studies

Purpose: To compare efficacy and safety of 2 dosing regimens of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME). Design: Two similarly designed, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}. Participants: Patients (eyes; n=872) with type 1 or 2 diabetes mellitus who had DME with central involvement. Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. Main Outcome Measures: The primary end point was mean change from baseline in best-corrected visual acuity (BCVA) at week 52. This report presents the 100-week results including mean change from baseline in BCVA, proportion of eyes that gained ≥15 letters, and proportion of eyes with a ≥2-step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score. Results: Mean BCVA gain from baseline to week 100 with IAI 2q4, IAI 2q8, and laser control was 11.5, 11.1, and 0.9 letters (P < 0.0001) in VISTA and 11.4, 9.4, and 0.7 letters (P < 0.0001) in VIVID, respectively. The proportion of eyes that gained ≥15 letters from baseline at week 100 was 38.3%, 33.1%, and 13.0% (P < 0.0001) in VISTA and 38.2%, 31.1%, and 12.1% (P≤0.0001) in VIVID. The proportion of eyes that lost ≥15 letters at week 100 was 3.2%, 0.7%, and 9.7% (P≤0.0220) in VISTA and 2.2%, 1.5%, and 12.9% (P≤0.0008) in VIVID. Significantly more eyes in the IAI 2q4 and 2q8 groups versus those in the laser control group had a ≥2 step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%; P < 0.0001) and VIVID (29.3% and 32.6% vs. 8.2%; P≤0.0004). In an integrated safety analysis, the most frequent serious ocular adverse event was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control). Conclusions: In both VISTA and VIVID, the 52-week visual and anatomic superiority of IAI over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Safety in these studies was consistent with the known safety profile of IAI**.**

Ip MS, et al. 2015.[16]
Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy
Purpose: To assess the effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity when administered for up to 3 years, evaluate the effect of delayed initiation of ranibizumab therapy on DR severity, and identify baseline patient characteristics associated with the development of proliferative DR (PDR).

Design: Exploratory analyses of phase III, randomized, double-masked, sham-controlled multicenter clinical trials.
Participants: Adults with diabetic macular edema (DME) (N = 759), baseline best-corrected visual acuity 20/40 to 20/320 Snellen equivalent, and central foveal thickness ≥275 mm.
Methods: Patients were randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections. Sham participants could switch to 0.5 mg ranibizumab during the third year (sham/0.5 mg crossover). Baseline risk factors were evaluated to explore potential associations with development of PDR. Time to first development of PDR was analyzed by Kaplan-Meier methods to calculate cumulative probabilities by group.
Main Outcome Measures: Study eye change on the Early Treatment Diabetic Retinopathy Study severity scale and a composite clinical outcome evaluating progression to PDR based on photographic changes plus clinically important events defining PDR.
Results: At month 36, a greater proportion of ranibizumab-treated eyes had ≥2- or ≥3-step DR improvement compared with sham/0.5 mg crossover. A ≥3-step improvement was achieved at 36 months by 3.3%, 15.0%, and 13.2% of sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab-treated eyes, respectively (P < 0.0001). Through 36 months, 39.1% of eyes in the sham/0.5 mg group developed PDR, as measured by composite outcome, compared with 18.3% and 17.1% of eyes treated with 0.3 or 0.5 mg ranibizumab, respectively. The presence of macular capillary nonperfusion at baseline seems to be associated with progression to PDR in ranibizumab treated eyes but did not meaningfully influence visual acuity improvement in eyes with DME after ranibizumab therapy.
Conclusions: Ranibizumab, as administered to patients with DME for 12 to 36 months in these studies, can both improve DR severity and prevent worsening. Prolonged delays in initiation of ranibizumab therapy may limit this therapeutic effect. Although uncommon, the development of PDR still occurs in a small percentage of eyes undergoing anti-vascular endothelial growth factor therapy and may be related to the presence of macular nonperfusion.

Wolf S, et al. 2014.[35]
RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia

Objective: To compare the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients with visual impairment due to myopic choroidal neovascularization (CNV). Design: Phase III, 12-month, randomized, double-masked, multicenter, active-controlled study. Participants: Patients (N ¼ 277) with visual impairment due to myopic CNV. Methods: Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n ¼ 106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n ¼ 116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n ¼ 55). Main Outcome Measures: Mean average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3 (primary) and 6, mean BCVA change and safety over 12 months. Results: Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 (group I: þ10.5, group II: þ10.6 vs. group III: þ2.2 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; both P<0.0001). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: þ11.7 vs. group I: þ11.9 ETDRS letters; P<0.00001). Mean BCVA change from baseline to month 12 was þ13.8 (group I), þ14.4 (group II), and þ9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred. Conclusions: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was noninferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1, 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 29, 2016

1	exp Bevacizumab/	8913
2	aflibercept.mp.	1014
3	pegaptanib.mp.	594
4	exp Ranibizumab/	2302
5	exp Vascular Endothelial Growth Factors/	43787
6	1 or 2 or 3 or 4 or 5	50503
7	exp Retinal Diseases/	66915
8	exp Macular Degeneration/	16476
9	7 or 8	66915
10	6 and 9	5982
11	limit 10 to yr="2015 -Current"	1075
12	limit 11 to (english language and humans)	946
13	limit 12 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	324

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes**: Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve for 12 months, or for length of the prescription, whichever is less
4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 12 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *3/17 (SS)*
Implementation: *TBD*

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Salem, Oregon 97301-1079
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Class Update: Tetracyclines

Date of Review: March 2017 **Date of Last Review:** May 2015

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

Purpose for Class Update:
Current Oregon Health Plan (OHP) fee-for-service (FFS) drug policy for tetracyclines limit the use of these antibiotics to one 14-day supply every 6 months to prevent use for non-funded conditions like acne or rosacea. However, this drug policy may cause unnecessary delay therapy in patients with skin and soft tissue infections (e.g., MRSA infections), osteomyelitis, or other conditions like chronic suppression for non-removable infected prostheses or other foreign body. A class update will be performed with the purpose of identifying if there is a need to change the current drug policy.

Research Questions:
1. Is there evidence to support extended therapy of tetracyclines beyond 14 days? For which clinical indications does the evidence support extended use?
2. Are there any safety concerns when using extended therapy of tetracyclines for chronic suppression or other indications?
3. Is there any new evidence for differences in efficacy or effectiveness or safety between the tetracycline agents?

Conclusions:
- There is no new comparative evidence for differences in efficacy/effectiveness or safety between tetracycline antibiotic formulations.
- There is insufficient evidence to support extended use of tetracycline antibiotics beyond 14 days outside of acne and rosacea. However, some exceptions may include bacillary angiomatosis, glanders, and bone and joint infections (e.g., osteomyelitis) for those not candidates for surgical intervention.
- There is insufficient evidence to support differences in safety or efficacy of Doryx® (doxycycline hyclate delayed-release tablets) and other oral delayed-release doxycycline formulations.
- There is insufficient evidence to address the safety of extended therapy with tetracycline antibiotics. Tetracyclines should generally be avoided in pregnant women or children under the age of 8 years.
- Doxycycline is the most commonly used tetracycline and is recommended as first- or second-line options for multiple indications or as part of combination therapy based on low quality evidence.
- From 7/1/2016 to 9/30/2016, there were 45 denied claims that did not result in a PA request and treatment was not received. Of the 27 denied claims for preferred products, 44% (n=12) of claims were associated with an unfunded condition (acne, rosacea, Hidradenitis suppurativa) and were prescribed for more than 14 days. The remaining claims were associated with funded conditions, including skin and soft tissue infections and upper respiratory tract infections.

Recommendations:

- Evaluate comparative costs in executive session.
- Change quantity limit to allow two 14 day supplies in a 3 month timeframe.

Previous Conclusions:

- Doxycycline is the most commonly recommended tetracycline and is recommended for multiple indications as first line, second line, or as part of combination therapy based on limited, low quality evidence.
- Tetracycline is recommended for select indications based on expert opinion and low quality evidence.
- Minocycline is a potential agent for methicillin-susceptible *S. aureus* (MSSA) and MRSA in non-pregnant adults and children over 7 years based on limited, low quality evidence.
- The majority of members (69.2%) received a single prescription with an average of a 13-day supply. A minority of members (17.8%) received more than two tetracycline prescriptions.
- Most tetracycline claims were for short-term therapy (57%), followed by medium-term duration (28%) and long-term duration (15%).
- Members with claims data indicating treatment of tetracyclines for only unfunded conditions comprised 27.9% of the total study population and represented 43.3% of the total prescription drug expenditures ($28,439).
- When a funded condition for a tetracycline was identified, 86% of members received only short-term treatment.

Previous Recommendations:

- Restrict use of all (preferred and non-preferred) tetracycline antibiotics to a 14-day supply every 6 months.
- Make tetracycline antibiotic therapy exceeding 14 days every 6 months subject to prior authorization to verify the presence of an OHP funded condition.

Background:

Tetracycline antibiotics work by entering the bacterial cell wall, binding reversibly to the 30s ribosomal subunit to inhibit protein synthesis.[1] They are indicated for a variety of infections caused by many aerobic gram-positive and gram-negative bacteria, including sexually transmitted diseases, respiratory tract infections, urinary tract infections (UTI), skin and soft tissue infections (SSTI), acne vulgaris, rosacea, as well as a variety of less common infections (e.g., anthrax). For most indications, duration of treatment does not exceed 14 days. Extended therapy is indicated most commonly for acne and rosacea.[2] Rosacea and most mild forms of acne fall below the current Oregon Health Plan (OHP) funded line on the Prioritized List of Health Services.[3] The only funded form of acne is acne conglobata in the presence of recurrent abscesses or communicating sinuses. [3] In the tetracycline class, doxycycline is one of the most active agents and used most often clinically. Doxycycline can be administered twice daily, has both intravenous and oral formulations, can be given with food, and is less likely to cause photosensitivity. However, the spectrum of activity is similar between the agents in the class. Tetracyclines should generally be avoided in pregnant women or children under the age of 8 years.[1] Recent changes in generic manufacturing of tetracyclines has resulted in significant price increases for both oral tetracycline and oral doxcycline products.[4]

Demeclocycline is a tetracycline that antagonizes the actions of vasopressin at the collecting duct in the nephron, producing diuresis by inhibiting ADH-induced water reabsorption in the distal portion of the convoluted tubules.[5] The use of demeclocycline is limited to treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

In 2015, a drug use evaluation of OHP FFS patients showed that the majority of members (69.2%) received a single prescription per year with an average 13-day supply dispensed.[6] Approximately 28% of prescriptions were associated with unfunded diagnoses and a small number (15%) of members received chronic therapy. As a result of this, a policy was implemented to restrict use of all tetracyclines to a 14-day supply every 6 months to limit extended therapy for unfunded conditions. Claims that exceed this limit require prior authorization to confirm treatment for an OHP-funded condition. [6]

Tetracyclines are one of the few classes with oral agents available to cover community-acquired methicillin resistant *staphylococcus aureus* (MRSA).[7] Current Infectious Disease Society of America (IDSA) guidelines recommend doxycycline as a preferred empiric treatment option for purulent moderate skin and soft tissue infections (SSTI) when MRSA is suspected or confirmed.[8] Other oral options include clindamycin and sulfamethoxazole-trimethoprim. However, resistance rates are higher for clindamycin than the other agents. Treatment duration of tetracyclines for common conditions is usually 5-10 days. According to the guidelines, a duration of longer than 14 days is only recommended for the treatment of bacillary angiomatosis and glanders, in which treatment can extend up to 6 months. For recurrent skin abscesses, an additional 5- to 10-day course of an active antibiotic is recommended. Additionally, due to the excellent bioavailability of doxycycline, IDSA guidelines recommend it as an oral treatment option for vertebral osteomyelitis.[9] Duration of therapy for osteomyelitis can extend to 3 months. For those with osteomyelitis not suitable for surgery, long-term suppressive therapy may be used after initial parenteral therapy. For bone and joint infections caused by *staphylococcus aureus* in patients who not candidates for surgical intervention, up to 6-12 weeks of combination therapy with doxycycline can be considered.[7,10] Uncomplicated cystitis or pyelonephritis due to MRSA is uncommon and extended therapy of tetracyclines is not routinely recommended for the treatment of complicated or uncomplicated urinary tract infections.[11]

Methods:

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

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A systematic review from the Cochrane Collaboration was completed in 2015 to assess the efficacy and safety of treatments for rosacea.[12] Overall, oral tetracycline and low dose doxycycline (40 mg) were associated with improvements in populopustular rosacea compared with placebo and isotretinoin was associated with improvement compared to doxycycline. There is high quality evidence from 2 studies that oral doxycycline (40 mg) compared to placebo was associated with 2 grades of improvement among 90 of 269 participants (33% vs. 21%; RR 1.63; 95% CI 1.22-2.18) over 16 weeks. [12] There was no statistically significant difference in effectiveness between 100 mg and 40 mg doxycycline, but there were fewer adverse effects with the lower dose (RR 0.25; 95% CI 0.11 to 0.54) Evidence only supports doxyxcline for papulopustular rosacea (subtype 2). [12] Currently rosacea falls below the funding line on the Oregon Health Plan's prioritized list.

Guidelines:
None identified.

New Safety Alerts:
None identified.

New Formulations or Indications:
In May, 2016 the FDA approved Doryx® MPC (doxycycline hyclate) delayed-release (DR) tablets for the treatment of rickettsial infections, sexually transmitted infections, respiratory tract infections, other bacterial infections, ophthalmic infections, anthrax, severe acne and prophylaxis of malaria.[13] It is available as 60 mg and 120 mg DR tablets. This new formulation was approved around the same time doxycycline hyclate DR tablets became available as a generic tablet. Doryx® MPC incorporates a modified polymer coat designed to further delay the release of doxycycline. Doryx® MPC 120 mg is equivalent to doxycycline DR 100 mg and 60 mg MPC is equivalent to 50 mg due to a reduced bioavailability. There is no evidence of clinical superiority of Doryx MPC compared to doxycycline delayed release. Approval was based on pharmacokinetic data from phase 1 clinical trials.[14]

Randomized Controlled Trials:
A total of 30 citations were manually reviewed from the literature search. After manual review, 30 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Drug Use Evaluation:

Methods:
FFS paid and denied claims were evaluated from 7/1/2016 and 9/30/2016 to determine the disposition of the PA and potential effects from the quantity limit (Table 1). Categories are mutually exclusive but members requesting different medications during the reporting period may be counted on more than one row. Claims that resulted in no drugs within the class paid for within 90 days of the index event (first request) were further evaluated for a follow up PA or reason for no paid claim (Table 2). Members with Medicare plans were excluded. Patient profiles for denied claims with no PA requested were further reviewed for diagnosis and duration.

Results:
Table 1 includes data on requests for tetracycline antibiotics including paid claims or paid claims for an alternative in the class. The majority of claims were for doxycycline, a preferred product. Approximately 60% of claims resulted in paid drug claim for the requested product or an alternative in the class within 90 days. However, the other 40% (n=260) resulted in no paid claim within 90 days after the index event, with a little over half of those from non-preferred agents (doxycycline tablet and minocycline). Of those claims that did not result in drug treatment, 75% of those can be explained by another source of payment (Table 2). A PA was never requested after a total of 45 claims (17%), which could be a result of the quantity limit in place. Only 8 of the PA requests were denied.

For preferred products only, there were 27 denied claims that did not result in a PA request. Of these claims, 12 of them (44%) were associated with an unfunded condition (acne, rosacea, and Hidradenitis suppurativa). All of these claims were for extended therapy (>29 days). However, the remaining denied

claims (56%) were associated with a funded condition, including sinusitis, skin or soft tissue infection, bite wound, prostatitis, pneumonia). Only 2 of these claims were for treatment beyond 14 days.

Table 1: Outcome of Paid and Denied Claims from 7/1/2016 to 9/30/2016

	Initially Paid		Paid Within 30 days		Paid Within 31-90 Days		Another Drug in PDL Class Paid Within 30 days		Another Drug in PDL Class Paid Within 31-90 days		No Drugs Within PDL Class Paid Within 90 Days		Total #	Total %
Row Labels	#	%	#	%	#	%	#	%	#	%	#	%		
Tetracyclines, Oral	300	47%	39	6%	0	0%	37	6%	1	0%	260	41%	637	100%
Y	286	66%	19	4%	0	0%	9	2%	1	0%	121	28%	436	100%
DOXYCYCLINE HYCLATE	160	68%	8	3%	0	0%	6	3%	1	0%	61	26%	236	100%
DOXYCYCLINE MONOHYDRATE	122	65%	10	5%	0	0%	3	2%	0	0%	53	28%	188	100%
TETRACYCLINE HCL	4	33%	1	8%	0	0%	0	0%	0	0%	7	58%	12	100%
N	14	7%	20	10%	0	0%	28	14%	0	0%	139	69%	201	100%
DEMECLOCYCLINE HCL	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%
DOXYCYCLINE HYCLATE	0	0%	0	0%	0	0%	2	40%	0	0%	3	60%	5	100%
DOXYCYCLINE IR-DR	0	0%	1	33%	0	0%	0	0%	0	0%	2	67%	3	100%
DOXYCYCLINE MONOHYDRATE	6	5%	11	10%	0	0%	25	23%	0	0%	69	62%	111	100%
MINOCYCLINE HCL	8	10%	8	10%	0	0%	1	1%	0	0%	62	78%	79	100%
ORACEA	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%
SOLODYN	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%

Table 2: Denied Claims from 7/1/2016 to 9/30/2016

Row Labels	Enrolled in CCO		Lost Eligibility		Has Other Insurance		Indian Health Service Coverage		PA Approved		PA Denied		PA Not Requested		Total #	Total %
	#	%	#	%	#	%	#	%	#	%	#	%	#	%		
Tetracyclines, Oral	82	32%	32	12%	82	32%	11	4%	0	0%	8	3%	45	17%	260	100%
Y	42	35%	13	11%	28	23%	7	6%	0	0%	4	3%	27	22%	121	100%
DOXYCYCLINE HYCLATE	20	33%	5	8%	19	31%	0	0%	0	0%	0	0%	17	28%	61	100%
DOXYCYCLINE MONOHYDRATE	18	34%	8	15%	9	17%	7	13%	0	0%	2	4%	9	17%	53	100%
TETRACYCLINE HCL	4	57%	0	0%	0	0%	0	0%	0	0%	2	29%	1	14%	7	100%
N	40	29%	19	14%	54	39%	4	3%	0	0%	4	3%	18	13%	139	100%
DEMECLOCYCLINE HCL	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	1	100%
DOXYCYCLINE HYCLATE	0	0%	1	33%	0	0%	0	0%	0	0%	0	0%	2	67%	3	100%
DOXYCYCLINE IR-DR	1	50%	0	0%	1	50%	0	0%	0	0%	0	0%	0	0%	2	100%
DOXYCYCLINE MONOHYDRATE	16	23%	11	16%	26	38%	4	6%	0	0%	1	1%	11	16%	69	100%
MINOCYCLINE HCL	23	37%	7	11%	24	39%	0	0%	0	0%	3	5%	5	8%	62	100%

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	CAPSULE	MORGIDOX	DOXYCYCLINE HYCLATE	Y
ORAL	CAPSULE	VIBRAMYCIN	DOXYCYCLINE HYCLATE	Y
ORAL	TABLET	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	TABLET	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	SUSP RECON	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	Y
ORAL	SUSP RECON	VIBRAMYCIN	DOXYCYCLINE MONOHYDRATE	Y
ORAL	CAPSULE	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	Y
ORAL	CAPSULE	TETRACYCLINE HCL	TETRACYCLINE HCL	Y
ORAL	SYRUP	VIBRAMYCIN	DOXYCYCLINE CALCIUM	N
ORAL	TABLET DR	DORYX	DOXYCYCLINE HYCLATE	N
ORAL	TABLET DR	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	N
ORAL	CAP IR DR	DOXYCYCLINE IR-DR	DOXYCYCLINE MONOHYDRATE	N
ORAL	CAP IR DR	ORACEA	DOXYCYCLINE MONOHYDRATE	N
ORAL	CAPSULE	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	N
ORAL	TABLET	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	N
ORAL	TABLET	DEMECLOCYCLINE HCL	DEMECLOCYCLINE HCL	N
ORAL	CAPSULE	MINOCYCLINE HCL	MINOCYCLINE HCL	N
ORAL	TAB ER 24H	MINOCYCLINE HCL ER	MINOCYCLINE HCL	N
ORAL	TAB ER 24H	SOLODYN	MINOCYCLINE HCL	N
ORAL	TABLET	MINOCYCLINE HCL	MINOCYCLINE HCL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

# ▲	Searches	Results
1	tetracyclines.mp. or Tetracyclines/	3142
2	doxycycline.mp. or Doxycycline/	9726
3	minocycline.mp. or Minocycline/	5175
4	limit 3 to (english language and humans and yr="2015 -Current" and (controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	30
5	from 4 keep 19, 24-25	3

Abbreviated Drug Review

Drug Product		
Cholbam® (cholic acid) capsule (oral)	Claims: 0	Wholesale Acquisition Cost: $49,650/month for 20 kg patient [based on 50 mg (#90): $24,825]

Indications

- **Bile acid synthesis disorders**: Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs)
- **Peroxisomal disorders**: Adjunctive treatment of peroxisomal disorders (PDs), including Zellweger spectrum disorders, in patients who exhibit manifestations of hepatic disease, steatorrhea, or complications from decreased fat soluble vitamin absorption.

Dosage

- 10-15 mg/kg/day in 1 or 2 divided doses
- Children 3 weeks of age or older and adults

Background

- Bile acid synthesis is complex requiring at least 17 enzymes.
- Cholic acid is an endogenous bile acid synthesized in the liver facilitates fat absorption, absorption of fat-soluble vitamins, and enhances bile flows.
- Disorders of bile acid synthesis are rare and clinical severity is variable. These disorders can be primary or secondary:
  - SEDs are primary enzyme defects involved in the synthesis of cholic acid and other primary bile acids.
  - PDs are secondary metabolic defects that impact primary bile acid synthesis.
- Impaired bile acid synthesis is associated with insufficient bile acid secretion from the hepatocyte, which results in accumulation of intermediate hepatotoxic bile acids. Accumulation may lead to cholestasis, bile acid plugs, giant cell hepatitis and cirrhosis, or death.

Efficacy

- The primary study is an unpublished, non-randomized, open-label, non-controlled, compassionate-use study (average duration 145 weeks).
- Supplemental data are from a post-hoc subgroup analysis of responders, an extension study, and case series reports.
- Data were evaluated for 50 patients with bile acid synthesis disorders and 29 patients with peroxisomal disorders.
- Blood and urine samples were monitored every 3-6 months; liver biopsy was performed in some patients every 6 months.
- A patient was consider a "Responder" to treatment if they were alive at last follow-up, and
  - **a)** met ≥2 lab criteria; or **b)** met ≥1 lab criterion and had increased body weight by 10% or stable at >50th percentile
- SED: 62% responders; 22% non-responders; 16% data not available
- PD: 0% responders; 76% non-responders; 24% data not available
  - (modified "Responder" criteria that removed lab criteria showed 2/29 patients responded)

Laboratory Criteria

- ALT/AST reduced to <50 U/L, or baseline level reduced by 80%
- Total bilirubin reduced to ≤1 mg/dL
- No evidence of cholestasis on liver biopsy

Safety

- Gastrointestinal: exacerbation of cholestasis (≤14%)
- Hepatic: increased serum bilirubin (≤14%); increased serum transaminases (≤14%)

Evidence Gaps/Limitations

The safety and effectiveness of cholic acid on *extrahepatic manifestations* of bile acid synthesis disorders due to SEDs or PDs, including Zellweger spectrum disorders, have not been established.

Recommendation

Refer claims to DMAP Medical Director through Prior Authorization.

References

- Center for Drug Evaluation and Research. Medical Review: Application number 205750Orig1s000 http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed May 23, 2015.
- Cholbam (cholic acid) [prescribing information]. Baltimore, MD: Asklepion Pharmaceuticals; March 2015.

Exondys 51 (eteplirsen)		
Estimated prevalence of patients with Duchenne muscular dystrophy (DMD) and an exon 51 mutation is approximately 1 in 27,000 people	Claims: 0	Wholesale Acquisition Cost: $6400/month for a 30 kg patient

Indications

- DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

Dosage

- 30 mg/kg once weekly intravenous infusion given over 35 to 60 minutes
- Available as 100 mg/2 mL and 500 mg/10 mL single dose vials

Background

- DMD is a rare genetic disorder caused by the absence of a functional dystrophin protein. In approximately 13% of patients with DMD, the cause is a mutation in exon 51 of the pre-mRNA. Eteplirsen binds to exon 51 of dystrophin pre-mRNA leading to exclusion of this exon and formation of a partially functional, truncated dystrophin protein.
- DMD is characterized by progressive muscle deterioration leading to pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications lead to wheelchair dependence and death before the age of 20. There is currently no curative treatment.

Efficacy

- Eteplirsen was evaluated in 3 studies. The primary outcome was dystrophin protein level in muscle tissue, measured as a percentage of normal levels in healthy patients without DMD. Clinical outcomes included change in 6-minute walking distance. All patients in these trials were ambulatory and on a stable dose of corticosteroids for at least 6 months.
- Study 1 was a double-blind, randomized, dose-response, placebo-controlled study for 24 weeks. It included 12 white, male, pediatric patients (age range 7-13, mean 9.4 years) with a mean 6-minute walking distance at baseline of 363 meters. Dystrophin levels at baseline were unknown. Patients were randomized (1:1:1) to eteplirsen 50 mg/kg weekly, eteplirsen 30 mg/kg weekly, or placebo. After 24 weeks, patients were enrolled in a long-term extension study at 30 or 50 mg/kg/week for up to 4 years (Study 2).
    - Study 1: No difference was observed in the 6-minute walk distance at 24 weeks compared to placebo. Change in dystrophin level from baseline could not be assessed.
    - Study 2: At 180 weeks (3.5 years), patients treated with eteplirsen had an average dystrophin level that was 0.93% of the normal protein level in health patients.
- Study 3 was an open-label study including 13 male patients treated with eteplirsen 30 mg/kg weekly for 48 weeks (mean age of 8.9 years).
    - Study 3: Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).

Safety

Adverse events reported in patients receiving eteplirsen with greater than 10% frequency included vomiting, confusion, excoriation, contact dermatitis, arthralgia, rash, upper respiratory tract infection, balance disorders, and catheter site pain. Because few patients were enrolled in these trial, the exact frequency of these events is unclear.

Evidence Gaps/Limitations

- There is no evidence supporting improvement in clinical or functional outcomes with treatment of eteplirsen. The minimally significant difference in dystrophin level which correlates to clinical outcomes has not been established. It is unclear whether changes less than 1% of normal would result in clinically significant outcomes.
- There is no data available to assess efficacy or safety in specific populations including females, ethnic minorities, or in other types of DMD.
- Continued approval for this indication is dependent on further confirmatory trials which demonstrate clinical benefit.

Recommendation

Refer claims to DMAP Medical Director through Prior Authorization

References

- Duchenne and Becker muscular dystrophies. In: DynaMed [internet database]. Ipswich, MA: EBSCO Publishing. Updated December 30, 2016. Accessed February 7, 2017.
- Exondys 51 (eteplirsen injection) [prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc; 2016.
- Food and Drug Administration Center for Drug Evaluation and Research. Exondys 51 Summary Review. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed February 3, 2017.

Trade Name (generic) Spinraza (Nusinersen)		
Estimated OHP Population: 1-5 patients Estimated Number of Live Births in OHP FFS: 27,100	Claims: 1-2 (estimated)	OHP Wholesale Acquisition Cost (WAC): Loading Dose Phase = $500,000 Maintenance Dose Phase = $375,000/year

Indications

- Spinal muscular atrophy in pediatrics and adults

Dosage

- Loading Dose - total of 4 doses as follows: 12 mg intrathecal once every 14 days for 3 doses; then 12 mg once 30 days after the third dose.[1]
- Maintenance Dose: 12 mg intrathecal once every 4 months.[1]

Administration of this drug should be directed by healthcare professionals experienced in performing lumbar punctures.

Background

Spinal muscular atrophy (SMA) is due to degeneration of motor neurons in the spinal cord, which causes progressive weakness, atrophy of skeletal muscles and hypotonia. SMA is one of the most frequent autosomal recessive diseases and the most common genetic cause of childhood mortality.[2] The phenotype is extremely variable, and patients are classified as SMA type 0-IV based on age at onset and clinical course. All types of SMA are caused by mutations in the survival motor neuron gene (SMN1). SMA Type I is the most common and severe type of SMA and occurs primarily in infants under 6 months of age.[3] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. SMA type 4 generally occurs in the third decade of life and is the mildest form of the disease. The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[3]

SMA Type	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	Prenatal	Respiratory failure at birth	Weeks	N/A
I	0-6 months	Never able to sit unassisted	<2 years	3.2 – 7.1 (45% of cases)
II	6 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
III	18 - 36 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5 – 4.6 (30 % of cases)
IV	30 years	Ambulatory	Normal	N/A (5% of cases)

*Natural history may vary depending on supportive interventions

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. Carrier testing is available and the incidence is estimated as 1:40 to 1:60.[3] There is no known cure for SMA. Management focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Difficulties in feeding and swallowing can lead to gastrointestinal complications and malnutrition.

Efficacy

Nusinersen is the first Food and Drug Association (FDA) approved therapy for treatment of SMA. This drug was fast tracked for FDA approval and phase III trial data for nusinersen has not yet been published. Nusinersen is an antisense oligonucleotide which increases exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) leading to production of full-length SMN protein. As a result, the amount of functional SMN protein increases and improves motor function in SMA patients who are deficient in SMN protein.

A phase 2, open-label, dose-escalation study assessed safety and efficacy in patients with infantile-onset SMA (EMBRACE).[4] Subjects enrolled in the trial were between 3 weeks and 7 months old with SNM1 homozygous gene deletion or mutation and SMA symptoms.[4] Clinical efficacy included event free survival and change from baseline of 2 motor function assessments: the Hammersmith Infant Neurological Exam Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function test. HINE-2 measures seven different areas of infant development motor milestones as evaluated by a pediatric neurologist. Increase in score indicates improved function with a maximum score between 2 to 4 points for each category and a total maximum score of 26.[4] CHOP-INTEND is a validated 16 item scale (0-64 points) specifically designed to evaluate motor function by physical therapists in infants with SMA.[4] Twenty patients were included in the trial and followed from 2 to 32 months. The first 4 participants received a loading dose of 6 mg on days 1, 15 and 85 followed by 12 mg on day 253 and every 4 months thereafter. The next 16 subjects received 12 mg doses on the same schedule. There were 77 serious adverse events reported in 16 participants, all considered by study investigators not related or unlikely related to the study drug, with the most common being respiratory distress or failure or respiratory infections, which are commonplace in infants with spinal muscular atrophy.[4] Incremental improvements in developmental motor milestones on the HINE-2 were observed for 16 of 19 participants at the last visit compared with baseline.[4] Change in HINE-2 score from baseline to last visit was significant for both dosing cohorts

combined (p=0.0002) and for participants in the 12 mg dose group (p<0.0001).[4] The data for HINE-2 score changes in the 6-12 mg cohort were not reported. Motor function, assessed using the CHOP-INTEND scale, showed a mean increase of 11.5 points from baseline to last visit overall (p=0.008; n=18), with 14 of 18 infants having an improvement.[4] In the 12 mg group, 12 of 14 participants had an increase from baseline to last visit (mean increase 15.2 points; p=0.0013).[4] The study did not mention the CHOP-INTEND score changes for the 6-12 mg group and did not mention individual scores before and after treatment. A second Phase II trial (NURTURE) focused on the efficacy of nusinersen in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA is currently ongoing with anticipated results in 2019.

ENDEAR, is a phase 3, multicenter, randomized, double blind, multiple dose, placebo controlled study of nusinersen in 121 patients with infantile-onset SMA.[5] Participants were diagnosed with SMA symptoms before 6 months of age. The study is still ongoing and expected to reach completion July 2017.[5] The nusinersen dose used in the study is 12 mg intrathecally. The primary efficacy endpoint is responder analysis of motor milestones using the HINE-2 exam. A responder is defined as a patient who improved in more milestones than worsened. Survival analyses were completed on the intent-to-treat population. Eighty two patients were included in the interim efficacy population. A greater percentage of subjects achieved a HINE motor milestone response in the nusinersen group (40%; n=21 of 52) compared to the control group (0%; n=0 of 30) which was statistically significant (p <0.0001).[6] An analysis of overall survival found a lower percentage of subjects in the nusinersen group (15%) died compared with the control group (32%), although this was not statistically significant.[6] One additional Phase III trial (CHERISH) is currently ongoing in patients aged 2 to 12 years with later onset SMA with an estimated completion date of May 2017.[7]

Safety

The most common adverse reactions that were observed in patients were lower respiratory infection (43% with nusinersen vs 29% with placebo), upper respiratory infection (39% vs 34%) and constipation (30% vs 22%).[1] Coagulation abnormalities and thrombocytopenia have been observed after administration of nusinersen. Renal toxicity including potentially fatal glomerulonephritis has also been observed. Per the manufacturer, lab testing of platelets, prothrombin time and quantitative spot urine protein testing is recommended at baseline and prior to each dose of nusinersen.[1] For urinary protein concentrations > 0.2 g/L is it is recommended to consider repeat testing and further evaluation.[1]

Evidence Gaps/Limitations

Nusinersen is effective at improving motor function in infants with SMA. The long term impact on survival is not well documented due to the ongoing data collection in the phase III RCTs. Evidence regarding efficacy in adults is not published. Long term safety data is currently unavailable. As nusinersen is the first drug FDA approved to treat SMA, there are no comparator medications.

Recommendation

Implement prior authorization criteria to insure nusinersen is used for funded conditions.

References

1. Prescribing Information Spinraza™ (nusinersen) Intrathecal Injection. Cambridge, MA. Biogen, Inc. December 2016. https://www.spinraza.com/en_us/home.html. Accessed February 15, 2017.
2. Wirth B. An Update of the Mutation Spectrum of the Survival Motor Neuron Gene (smn1) in Autosomal Recessive Spinal Muscular Atrophy (sma). *Hum Mutat*. 2000;15(3):228-237. doi:10.1002/(SICI)1098-1004(200003)15:3<228::AID-HUMU3>3.0.CO;2-9.
3. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve*. 2015;51(2):157-167. doi:10.1002/mus.24497.
4. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388(10063):3017-3026. doi:10.1016/S0140-6736(16)31408-8.
5. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Infants With Spinal Muscular Atrophy - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/show/NCT02193074. Accessed February 15, 2017.
6. Spinraza Drug Information Submitted to the FDA for Approval. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000RiskR.pdf. Accessed February 15, 2017.
7. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Patients With Later-onset Spinal Muscular Atrophy - Tabular View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/record/NCT02292537. Accessed February 17, 2017.

Nusinersen

Goal(s):

- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:

- Up to 12 months

Requires PA:

- Nusinersen

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to # 2	
2. Does the patient have Spinal Muscular Atrophy documented by genetic testing?	Yes: Go to # 3	No: Pass to RPh. Deny; medical appropriateness.
3. Is the drug being prescribed by a neurologist?	Yes: Approve up to 12 months	No: Pass to RPh. Deny; medical appropriateness.

P&T Review: 3/17 (DM)
Implementation

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

Policy Evaluation: Metabolic Monitoring of Antipsychotics in Children

Purpose: In October 2012, Oregon implemented a RetroDUR policy to improve metabolic monitoring for pediatric Medicaid patients who are on an antipsychotic drug. Faxed reminders were sent to physicians regarding annual glucose monitoring for children on antipsychotic drugs without claims for metabolic monitoring in the previous 12 months.[1] Providers also received a report card which compared their monitoring rates to other providers in the state.[1] The purpose of this review is to examine the impact of this RetroDUR policy on rates of metabolic monitoring for children taking antipsychotics and to identify areas for potential policy change.

Research Questions:

1. After implementation of the RetroDUR, was there a change in the proportion of children on antipsychotics who received yearly glucose monitoring (blood glucose or hemoglobin A1c [HbA1c])?
2. After implementation of the RetroDUR, was there any change in monitoring of other metabolic laboratory parameters, including triglycerides or high density lipoprotein (HDL)?
3. Was there any change in the rate of new diabetes diagnoses after implementation of the RetroDUR?
4. Were there any subgroups of patients based on drug therapy (i.e. drug, dose, or duration), patient characteristics (i.e. age or mental health diagnosis), or prescriber characteristics (i.e. provider specialty) who receive more routine metabolic glucose monitoring?

Conclusions:

- After implementation of the RetroDUR, there was only a modest change in glucose monitoring (Figure 2). In the year following implementation of the policy, approximately 50.3% of patients lacked glucose monitoring compared to 54.1% of patients without monitoring before implementation of the policy (mean difference=4.2%).
- There was no difference in monitoring rate of other metabolic laboratory parameters or in the rate of new diabetes diagnoses before or after implementation of the RetroDUR.
- Rates of glucose monitoring in subgroup populations based on drug therapy, patient, or prescriber characteristics were also similar before and after implementation of the RetroDUR.

Recommendations:

- Because there was minimal change in metabolic monitoring rates detected after implementation of the RetroDUR, discontinue the policy.

Author: Sarah Servid, Pharm.D.

Date: March 2017

Background:
Metabolic adverse effects including hyperglycemia, dyslipidemia, and weight gain are commonly associated with first- and second-generation antipsychotics. Second-generation antipsychotics carry labeling warnings from the U.S. Food and Drug Administration (FDA) for metabolic changes which may be associated with increased long-term risk for type 2 diabetes mellitus and cardiovascular and cerebrovascular diseases.[1,2] In 2004, the American Diabetes Association (ADA) and American Psychiatric Association (APA) released a consensus statement that recommends periodic metabolic monitoring for all patients on antipsychotic medications.[2] Upon initiation or modification of an antipsychotic regimen, baseline assessments of personal and family history of obesity, weight or body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose and fasting lipid profile are recommended.[2] Further evaluation of fasting plasma glucose is recommended at 12 weeks and annually thereafter.[2] Lipid assessment is recommended at 12 weeks followed by an assessment every 5 years. However, in children less than 10 years of age, there is no established criteria to define lipid abnormalities in young children, and as a result, lipid monitoring is not used regularly.[3] In children, more frequent metabolic monitoring is recommended if weight gain exceeds the 90th percentile for BMI or waist circumference for their age.[3,4] More frequent monitoring may also be necessary in patients at high risk for metabolic side effects or those who have worsening hyperglycemia or dyslipidemia while on therapy.[2]

However, despite these known risks, monitoring of metabolic adverse events remains low.[5,6] Data from a large cohort of Medicaid patients in 2012 demonstrated that monitoring in pediatric patients on an antipsychotic was lower than rates for adults for glucose (OR 0.41, 95% CI 0.38 to 0.44) and lipids (OR 0.56, 95% CI 0.52 to 0.61) .[7] Similarly, in 2011, a large nationwide cohort (n=52,407) demonstrated that rates of glucose testing and HbA1c testing in pediatric patients (ages 5-18) after initiation of an antipsychotic was suboptimal with rates of 15.6% and 1.6%, respectively.[8] In a population of pediatric Medicaid patients from California, Missouri and Oregon (n=5,370), 2 years following the release of the consensus guidelines, glucose screening was performed in only 31.6% of patients (95% CI 30.4% to 32.9%) and lipid testing was performed in 13.4% of patients (95% CI 12.5% to 14.4%).[6] Overall, patients in Oregon were less likely to have glucose testing (adjusted odds ratio [AOR] 0.81, 95% CI 0.65 to 1.02) and lipid testing (AOR 0.57, 95% CI 0.42 to 0.77) performed compared to children in California.[6]

In an effort to increase monitoring rates, several states have implemented programs to evaluate physician monitoring of their pediatric patients on antipsychotic therapy. In 2009, one state mental health authority began an initiative to improve metabolic monitoring rates by conducting education for prescribers, initiating audits on metabolic monitoring, and providing feedback to mental health center leaders regarding their monitoring.[9] Provider education included access to lectures by experts, discussions about improving monitoring, access to articles on antipsychotic monitoring, yearly data summaries on monitoring and prescribing practices, and quarterly letters describing the quality initiative.[9] The program included 10 community mental health centers with over 15,000 patients.[9] Data were collected on a random sample of 595 adults and 310 children over the course of 2 years.[9] Rates of yearly monitoring for glucose, lipids, weight, and waist circumference varied significantly between centers but did not demonstrate an overall improvement over the course of the study.[9] Another quality improvement program, conducted in the United Kingdom, utilized a yearly audit-based targeted screening program with feedback for providers regarding data on their relative and absolute performance compared to practice standards.[10] Each individual mental health Trust participating in the program developed a local action plan.[10] Resources provided to the centers included reference documents with information about testing results and resources for staff related to aspects of physical health, diet, exercise and smoking cessation.[10] Data were collected from a sample of patients each year on monitoring of 4 parameters: blood pressure, obesity or BMI, plasma glucose and lipids.[10] Over the course of the study, patients without monitoring for any of these parameters decreased from 46% to 14%.[10] Rates of patients with documented monitoring of all 4 parameters increased from 11% to 34%.[10] Patients with a known diagnosis of diabetes or dyslipidemia were more likely to have monitoring in all 4 categories.[10]

In October 2012, Oregon implemented a RetroDUR policy for metabolic monitoring in pediatric Medicaid patients who are on an antipsychotic drug. A detailed description of the program is available at the following website: http://www.orpdl.org/drugs.[1] The goal of this program is to improve monitoring rates in

children taking an antipsychotic. For children on antipsychotic drugs without claims for metabolic monitoring in the previous 12 months, reminders were sent to physicians regarding annual glucose monitoring.[1] Providers also received a report card which compared their monitoring rates to other providers in the state.[1] The purpose of this review is to examine the impact of this RetroDUR policy on rates of metabolic monitoring for children taking antipsychotics and to identify areas for potential policy change.

Methods:

This observational before-and-after analysis compared patients in a historical control group before the implementation of the RetroDUR from October 2011 to September 2012 to patients after implementation of the policy from October 2012 to September 2013. Patients included in the study were in the FFS population, 18 years of age or less, and had at least one paid pharmacy claim for an antipsychotic with a minimum 5 days' supply (identified as the index event). Included members could be enrolled in a Coordinated Care Organization (CCO), but were required to be enrolled in Medicaid for at least 75% of the time in the year prior to the index event. If a patient had multiple claims for an antipsychotic within this time frame, the index event was defined as the earliest paid pharmacy claim during this time with a minimum 5 days' supply. Antipsychotics included in the program are listed in Table A1 and include both first- and second-generation antipsychotic medications. With implementation of the RetroDUR policy, this index event would trigger a report sent to the provider if there was no claim for of metabolic monitoring within the previous 12 months. In order to examine the impact of this policy, information was collected on metabolic monitoring in the 12 months prior to the index event in the historical control and compared to metabolic monitoring rates after implementation of the policy. Metabolic monitoring in these patients was identified via CPT code (Table A2).

Patients were excluded from the study if they had Medicare part D coverage (identified via benefit packages BMM, BMD, MND, or MED) or a prior diagnosis of diabetes. Antipsychotics or formulations brought to market after implementation of the RetroDUR were not included in subgroup analyses. Diagnosis of diabetes was identified via pharmacy claims for diabetic medications in the 1 year prior to the index event or medical claims indicating a diabetes diagnosis in the 2 years prior to the index event. Pharmacy claims data included patients who received insulin or oral hypoglycemic/antihyperglycemics (with the exception of metformin) during 1 year prior to the index event.[1] See Table A3 for a list of included medications. Medical claims indicating a diabetes diagnosis included patients with at least 2 face-to-face encounters in an outpatient setting or non-acute inpatient setting, on different dates of service, with a diagnosis of diabetes or one face-to-face encounter in an acute inpatient or ED during the 2 years prior to the index event.[1] ICD codes used to identify diabetes diagnosis are listed in Table A4 and CPT codes for encounter data are listed in Table A5.

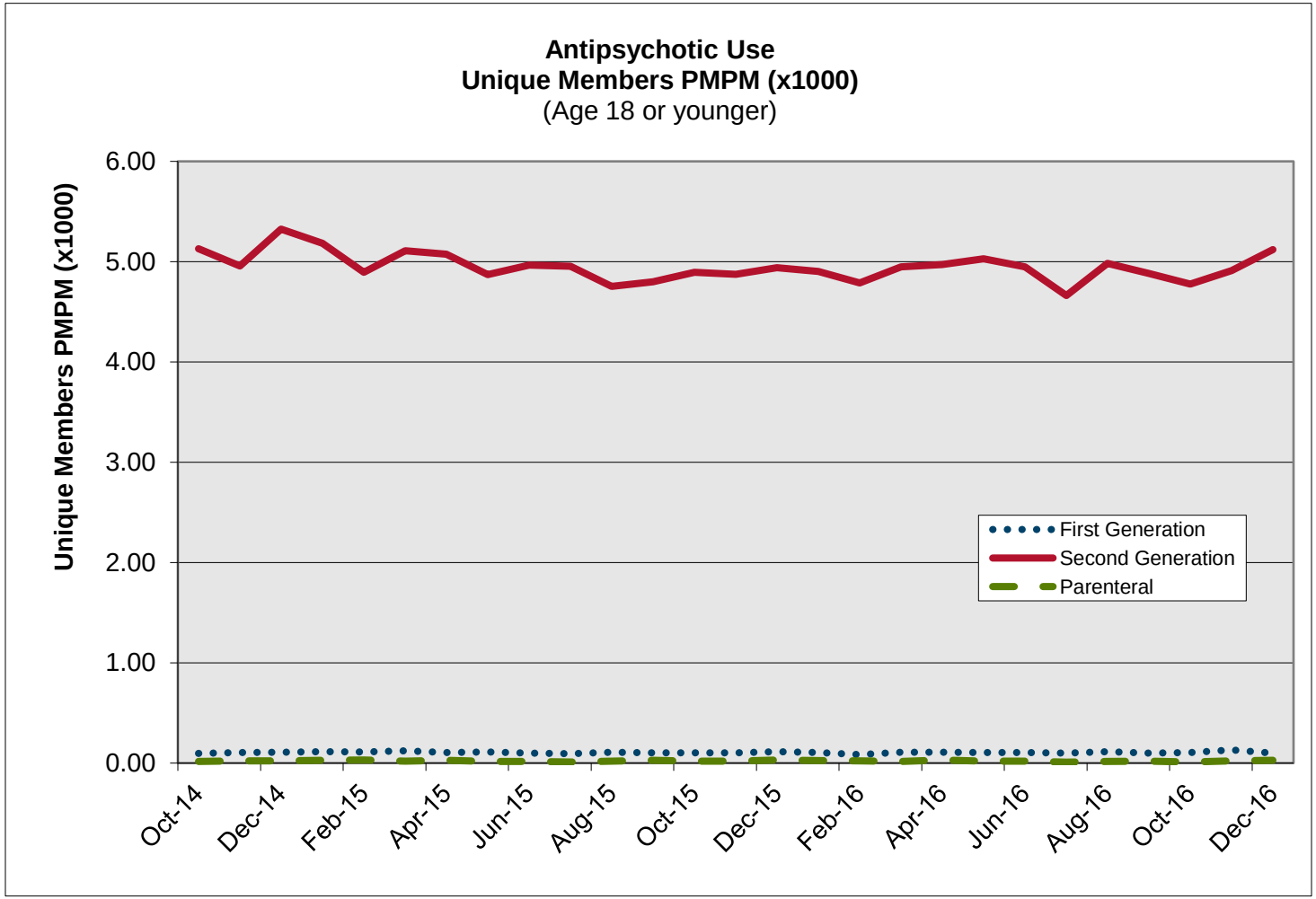
Data assessed at the index event included baseline demographics (age, gender and ethnicity), prescribing provider specialty, mental health diagnoses, and type of medication. Diagnoses were identified by ICD-9 and ICD-10 codes (Table A6) and assessed within 12 months before or 3 months after the index event. Provider specialty was identified using the National Provider Identifier (NPI) number and the associated taxonomy. Subgroup analyses included patients stratified by dose and duration of therapy. Duration of therapy was defined as the proportion of days covered (PDC) by at least 1 antipsychotic prescription over the course of 365 days. Short-term therapy corresponds to a PDC of 33% (120 days) or less, intermittent therapy corresponds to a PDC of 34-80% (121-292 days), and long-term therapy corresponds to a PDC greater than 80% (>293 days). Intermittent therapy may indicate therapy of medium duration or low adherence to continuously prescribed therapy. Additional subgroup analyses will include stratification by medication type, provider specialty, and diagnoses. Differences in dose were identified based on FDA approved doses. Medications prescribed above the maximum FDA approved dose were defined as high dose and medications within the FDA dosing range were classified as standard doses (See Table A2). Maximum approved doses for pediatric use are often dependent on weight, age of the child, or indication. In the case of indication-specific dosing, the highest approved for a particular age was used. If there is no established dose in pediatric patients, maximum adult doses are referenced.

Results:

Utilization

Figure 1 shows the recent utilization of antipsychotic medications by unique members from October 2014 through October 2016. Data is stratified by first generation antipsychotics, second generation antipsychotics, and parenteral antipsychotics. These medications are carve out medications and represent all pediatric members with FFS coverage regardless of CCO enrollment. Overall, use of second generation antipsychotics is more frequent than first generation or parenteral forms. Use of these medications over time has remained consistent.

Figure 1: Unique patient count of children (age ≤18 years) who utilized antipsychotics (PMPM) from October 2014 to present stratified by PDL class (first generation, second generation, and parenteral antipsychotics).



Patient demographics

Table 1 shows demographics of Medicaid members with a claim for an antipsychotic in the year prior to and following implementation of the RetroDUR. There was a total of 4132 patients with an index event in the year before implementation of the RetroDUR and 3838 patients in the following year. Patient demographics were similar in both groups. The mean age was approximately 13 years, 33% were female, and 63-65% of the population was white. Based on the proportion of days covered, 42-45% of patients were taking antipsychotics long-term and 33% of patients were taking antipsychotics intermittently. Less than 5% of the population received prescriptions for antipsychotics at doses greater than the maximum amount recommended by the FDA. The most common diagnoses for these patients are listed in Table 2. The majority of patients had multiple mental health diagnoses.

Evaluation of Monitoring Rates

After implementation of the RetroDUR, there was only a modest change in glucose monitoring (Figure 2). In the year following implementation of the policy, approximately 50.3% of patients lacked glucose monitoring compared to 54.1% of patients without monitoring before implementation of the policy (mean difference=4.2%). Similarly, there was no apparent change in the rates of newly diagnosed diabetes over time or in monitoring of lipid parameters (Figure 2). To evaluate changes in glucose monitoring for specific subpopulations claims were stratified by drug therapy (i.e. drug, dose, or duration), patient characteristics (i.e. age or mental health diagnosis), or prescriber characteristics (i.e. provider specialty). For the majority of subgroups rates were similar before and after implementation of the RetroDUR (Tables 1-4).

Prior studies indicate that interventions including academic detailing and education for providers may increase metabolic monitoring rates for patients on antipsychotics. However, in our patient population, monitoring rates were only slightly improved upon initiation of this RetroDUR. The policy included yearly reminders sent to physicians about pediatric patients whose claims history indicated they did not have metabolic monitoring within 1 year. The reminder included information about recommended standards of care and compared their monitoring rates to other providers in the state. Other types of interventions may have a greater potential to influence monitoring rates in this population. More intensive academic detailing, provider education, and audits may provide limited improvement. However, the costs of intensive and detailed interventions must be weighed against their potential benefit.

Figure 2. Change in glucose monitoring, lipid monitoring, and rates of newly diagnosed type 2 diabetes over time, described as the percent of patients without monitoring within 12 months after an antipsychotic claim. Patients with dual eligibility and prior evidence of diabetes were excluded.

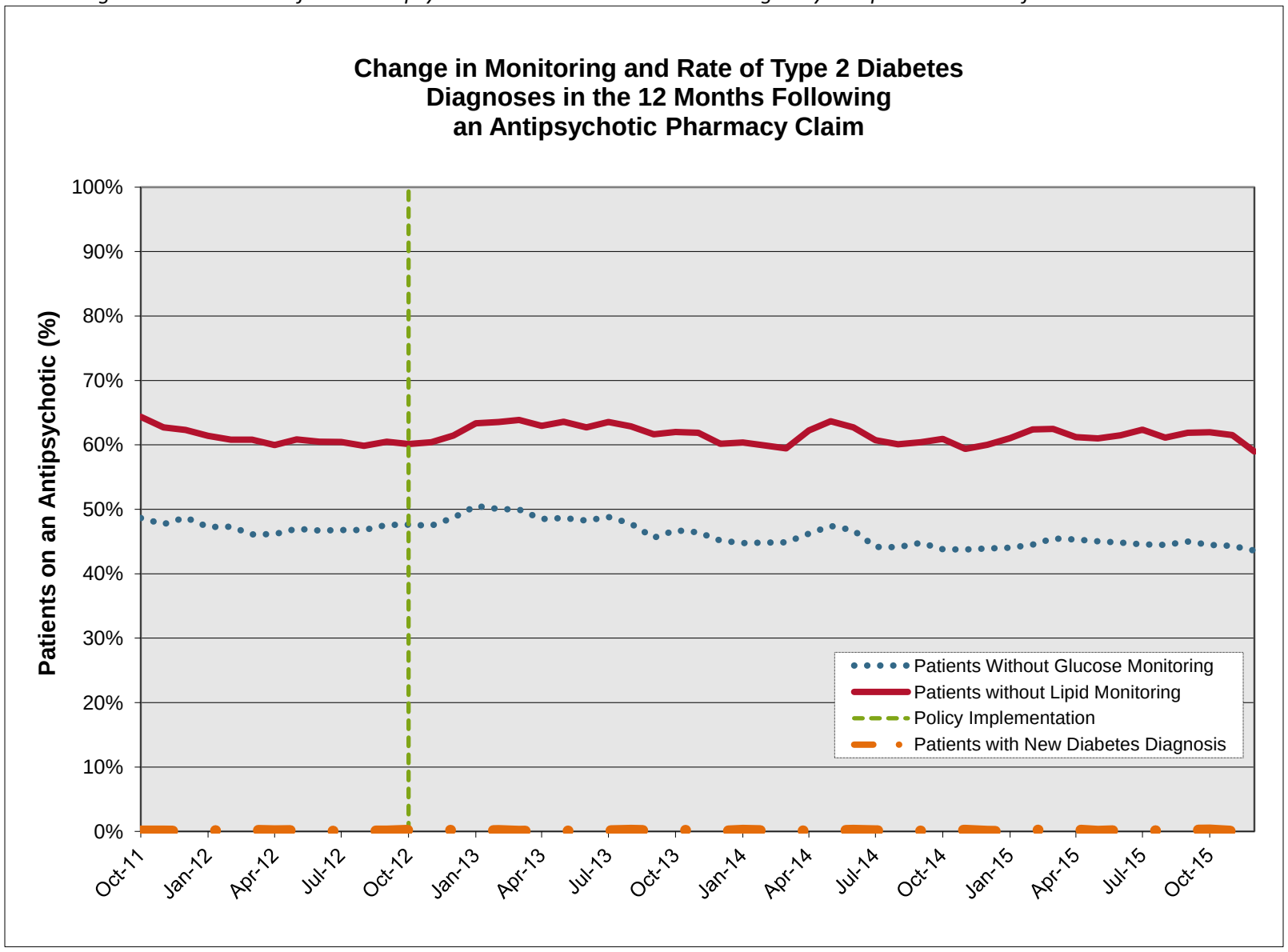


Table 1. Subgroup analysis of glucose or HbA1c monitoring rates categorized by baseline demographics.

	Before Program				After Program				
	Population Characteristics		**Population Without Monitoring**		**Population Characteristics**		**Population Without Monitoring**		**Change in Monitoring Rates**
N=	**4,132**		**2,237**	54.1%	**3,838**		**1,929**	50.3%	4.2%
Mean age (range)	12.7	(1-18)	11.9	(1-18)	12.8	(2-18)	12.1	(3-18)	
0-5	143	3.5%	114	79.7%	114	3.0%	81	71.1%	8.7%
6-9	802	19.4%	535	66.7%	708	18.4%	470	66.4%	0.3%
10-15	2,002	48.5%	1,100	54.9%	1,936	50.4%	939	48.5%	6.4%
16-18	1,185	28.7%	488	41.2%	1,080	28.1%	439	40.6%	0.5%
Female	1,353	32.7%	643	47.5%	1,266	33.0%	564	44.5%	3.0%
White	2,698	65.3%	1,481	54.9%	2,423	63.1%	1,229	50.7%	4.2%
Duration									
Short-term (PDC <33%)	905	21.9%	521	57.6%	881	23.0%	470	53.3%	4.2%
Intermittent (PDC 33-80%)	1,357	32.8%	763	56.2%	1,282	33.4%	693	54.1%	2.2%
Long-term (PDC >80%)	1,870	45.3%	953	51.0%	1,675	43.6%	766	45.7%	5.2%
High dose (> maximum FDA approved dose)	177	4.3%	85	48.0%	182	4.7%	75	41.2%	6.8%

Note: Max dose and age range calculations taken on index claim only

Table 2. Subgroup analysis of glucose or HbA1c monitoring rates categorized by diagnosis. Patients may have more than one diagnoses.

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	4,132		2,237	54.1%	3,838		1,929	50.3%	4.2%
ADHD	4,190	101.4%	2,358	56.3%	3,905	101.7%	1,947	49.9%	6.4%
Adjustment and Acute Reactions	3,096	74.9%	1,535	49.6%	2,698	70.3%	1,273	47.2%	2.4%
Affective Disorders, Excluding Bipolar	3,252	78.7%	1,376	42.3%	3,429	89.3%	1,385	40.4%	1.9%
Autism Spectrum Disorders	1,025	24.8%	539	52.6%	1,287	33.5%	646	50.2%	2.4%
Bipolar	213	5.2%	60	28.2%	205	5.3%	56	27.3%	0.9%
Developmental Disorders	1,384	33.5%	733	53.0%	1,269	33.1%	599	47.2%	5.8%
Disruptive Behavior Disorders	1,457	35.3%	702	48.2%	1,390	36.2%	608	43.7%	4.4%
Other Mental Health Diagnosis	973	23.5%	291	29.9%	1,121	29.2%	329	29.3%	0.6%
Other Psychotic Disorders	3,040	73.6%	1,273	41.9%	2,972	77.4%	1,176	39.6%	2.3%
Personality Disorders	223	5.4%	77	34.5%	347	9.0%	123	35.4%	-0.9%
PTSD	2,139	51.8%	933	43.6%	2,012	52.4%	744	37.0%	6.6%
Schizophrenia	338	8.2%	94	27.8%	308	8.0%	107	34.7%	-6.9%
Sleep Disorders	285	6.9%	159	55.8%	309	8.1%	154	49.8%	6.0%

Table 3. Subgroup analysis of glucose or HbA1c monitoring rates categorized by medications.

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	4,132		2,237	54.1%	3,838		1,929	50.3%	4.2%
Antipsychotics, 1st Gen	31	0.8%	14	45.2%	47	1.2%	18	38.3%	6.9%
Antipsychotics, 2nd Gen									
ARIPIPRAZOLE	1,299	31.4%	635	48.9%	1,178	30.7%	532	45.2%	3.7%
OLANZAPINE	223	5.4%	82	36.8%	249	6.5%	85	34.1%	2.6%
QUETIAPINE FUMARATE	569	13.8%	259	45.5%	455	11.9%	208	45.7%	-0.2%
RISPERIDONE	1,808	43.8%	1,172	64.8%	1,710	44.6%	1,004	58.7%	6.1%
ZIPRASIDONE HCL	147	3.6%	54	36.7%	126	3.3%	51	40.5%	-3.7%
OTHER	51	1.2%	19	37.3%	65	1.7%	25	38.5%	-1.2%
Antipsychotics, Parenteral	4	0.1%	2	50.0%	8	0.2%	6	75.0%	-25.0%

Table 4. Provider specialty subgroup analyses of glucose or HbA1c monitoring rates after implementation of the RetroDUR.

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	4,132		2,237	54.1%	3,838		1,929	50.3%	4.2%
Physician-psychiatric/neurology	1,584	38.3%	728	46.0%	1,449	37.8%	672	46.4%	-0.4%
NP-psychiatry/mental health	306	7.4%	173	56.5%	398	10.4%	178	44.7%	11.8%
Physician-family medicine	207	5.0%	126	60.9%	206	5.4%	110	53.4%	7.5%
NP-family	92	2.2%	53	57.6%	70	1.8%	33	47.1%	10.5%
Facility-mental health/pediatric	21	0.5%	12	57.1%	65	1.7%	32	49.2%	7.9%
Facility-mental health	5	0.1%	1	20.0%	6	0.2%	1	16.7%	3.3%
Other	138	3.3%	83	60.1%	142	3.7%	84	59.2%	1.0%
Unavailable	1,779	43.1%	1,061	59.6%	1,502	39.1%	819	54.5%	5.1%

Limitations:

Several limitations exist as a result of the retrospective nature of this study. First, data is based on claims history which may not accurately reflect true patient diagnoses or correlate with actual medication adherence. Use of proportion of days covered attempts to estimate the frequency which a patient takes a prescription, but accuracy of this method has not been validated. Second, provider specialization was identified using the National Provider Identifier (NPI) number and the associated taxonomy which may be inaccurate, out-of-date, or incomplete for some providers. The retrospective nature of the study also does not allow for potential unknown confounders which may influence results of the analysis. Potential confounders include changes in the population over time or changes in the general monitoring patterns of providers. It is unclear whether the small change observed after implementation of the policy was a result of the policy or simply a gradual change in practice over time. Estimates of maximum pediatric dose were made based on approved FDA dosing. However, many antipsychotics don't have data supporting dose in pediatric patients. If data are available, doses are often based on weight or age. If pediatric dosing data was lacking, the maximum adult dose was used which may not be appropriate for all children and may result in overestimated maximum doses.

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Table A1: Antipsychotics included in the RetroDUR grouped by PDL class. If pediatric dosing was unavailable, maximum dose in adults was used.

Medication	Maximum FDA approved dose
1st Generation	
- Chlorpromazine HCl	500 mg/day
- Fluphenazine HCl	40 mg/day
- Haloperidol	15 mg/day
- Haloperidol lactate	15 mg/day
- Loxapine	250 mg/day
- Loxapine succinate	250 mg/day
- Perphenazine	8 mg/day
- Pimozide	10 mg/day
- Thioridazine HCl	800 mg/day
- Thiothixene	60 mg/day
- Trifluroperazine HCl	15 mg/day 40 mg/day
2nd Generation	
- Asenapine maleate	20 mg/day
- Aripiprazole	20 mg/day
- Brexpiprazole	4 mg/day
- Cariprazine HCl	6 mg/day
- Clozapine	900 mg/day
- Iloperidone	24 mg/day
- Lurasidone HCl	160 mg/day
- Olanzapine	20 mg/day
- Paliperidone	12 mg/day
- Quetiapine fumarate	800 mg/day
- Risperidone	3 mg/day
- Ziprasidone	160 mg/day
Parenteral Antipsychotics	
- Aripiprazole	30 mg/day, 400 mg/month
- Aripiprazole lauroxil	882 mg/month
- Chlorpromazine HCl	40 mg/day (Age <5 years), 75 mg/day (Age 5-12 years), 500 mg/day (Age > 12 years)
- Fluphenazine decanoate	100 mg/month
- Fluphenazine HCl	10 mg/day
- Haloperidol Decanoate	450 mg/month

- Haloperidol lactate	20 mg/day
- Olanzapine	30 mg/day
- Olanzapine pamoate	300 mg every 2 weeks, 405 mg/month
- Paliperidone palmitate	234 mg/month
- Risperidone microspheres	50 mg every 2 weeks
- Ziprasidone mesylate	40 mg/day
Miscellaneous Classes	
- Molindone HCl	225 mg/day
- Olanzapine/fluoxetine	12/50 mg/day
- Perphenazine/amitriptyline	12 mg/day perphenazine
- Prochlorperazine	25 mg/day

Table A2. CPT codes used to identify metabolic screening

Description	CPT
Glucose tests	80047 basic metabolic panel w/calcium, ionized 80048 basic metabolic panel w/calcium, total 80050 general health panel 80053 comprehensive metabolic panel 80069 renal function panel 82947 glucose assay 82948 reagent strip/blood glucose 82950 glucose test 82951 glucose tolerance test 82952 glucose tolerance test –added samples 82962 glucose test (home use)
HbA1c	83036 A1c 83037 A1c home use
Lipid tests	84478 triglycerides 82465 serum cholesterol 80061 lipid panel 83718 direct lipoprotein (HDL) 83704 lipoprotein bld, by NMR 83701 lipoportein bld, high resolution fractionation 83700 lipoprotein bld, electrophoretic 83721 LDL cholesterol 83719 blood lipoprotein (VLDL)

Table A3. Diabetic medications included in the RetroDUR to evaluate diagnosis of diabetes mellitus

DPP-4 inhibitors
- SITAGLIPTIN PHOS/METFORMIN HCL
- SITAGLIPTIN PHOSPHATE
- ALOGLIPTIN BENZ/METFORMIN HCL
- ALOGLIPTIN BENZ/PIOGLITAZONE
- ALOGLIPTIN BENZOATE
- LINAGLIPTIN
- LINAGLIPTIN/METFORMIN HCL
- SAXAGLIPTIN HCL
- SAXAGLIPTIN HCL/METFORMIN HCL
- SITAGLIPTIN PHOS/METFORMIN HCL
GLP-1 receptor agonists
- EXENATIDE
- ALBIGLUTIDE
- DULAGLUTIDE
- EXENATIDE MICROSPHERES
- LIRAGLUTIDE
Insulins
- INSULIN ASPART
- INSULIN ASPART PROT/INSULN ASP
- INSULIN DETEMIR
- INSULIN GLARGINE,HUM.REC.ANLOG
- INSULIN LISPRO
- INSULIN LISPRO PROTAMIN/LISPRO
- INSULIN NPH HUM/REG INSULIN HM
- INSULIN NPH HUMAN ISOPHANE
- INSULIN REGULAR, HUMAN
- INSULIN ZINC HUMAN RECOMBINANT
- INSULIN DEGLUDEC
- INSULIN DETEMIR
- INSULIN GLARGINE,HUM.REC.ANLOG
- INSULIN GLULISINE
SGLT-2 Inhibitors
- CANAGLIFLOZIN
- CANAGLIFLOZIN/METFORMIN HCL
- DAPAGLIFLOZIN PROPANEDIOL
- DAPAGLIFLOZIN/METFORMIN HCL
- EMPAGLIFLOZIN
- EMPAGLIFLOZIN/LINAGLIPTIN
- EMPAGLIFLOZIN/METFORMIN HCL
Sulfonylureas
- GLIMEPIRIDE
- GLIPIZIDE
- GLYBURIDE
- CHLORPROPAMIDE

- GLYBURIDE,MICRONIZED - TOLAZAMIDE - TOLBUTAMIDE
Thiazolidinediones - PIOGLITAZONE HCL - PIOGLITAZONE HCL/GLIMEPIRIDE - PIOGLITAZONE HCL/METFORMIN HCL - ROSIGLITAZONE MALEATE
Miscellaneous Antidiabetic Agents - ACARBOSE - GLIPIZIDE/METFORMIN HCL - GLYBURIDE/METFORMIN HCL - MIGLITOL - NATEGLINIDE - PRAMLINTIDE ACETATE - REPAGLINIDE - REPAGLINIDE/METFORMIN HCL

Table A4. ICD codes to identify diabetes

Category	ICD Version	Code	Description
Diabetes Mellitus	9	357.2	Polyneuropathy in diabetes
Diabetes Mellitus	9	250.x	Diabetes mellitus
Diabetes Mellitus	9	249.x	Secondary diabetes mellitus
Diabetes Mellitus	9	790.2x	Abnormal glucose
Diabetes Mellitus	9	648.0x	Diabetes mellitus complicating pregnancy childbirth or the puerperium
Diabetes Mellitus	9	648.8x	Abnormal glucose tolerance of mother complicating pregnancy childbirth or the puerperium
Diabetes Mellitus	9	362.0x	Diabetic retinopathy
Diabetes Mellitus	10	E09.x	Drug or chemical induced diabetes mellitus
Diabetes Mellitus	10	E11.x	Type 2 diabetes mellitus
Diabetes Mellitus	10	E13.x	Other specified diabetes mellitus
Diabetes Mellitus	10	O24.x	Diabetes mellitus in pregnancy, childbirth and the puerperium (Type 1 and 2)

Table A5. Claim/encounter data used to identify visit type

Description	CPT code	UB Revenue
Outpatient visit	99201-99205, 99211-99215, 99217-99220, 99241-99245, 99341-99345, 99347-99350, 99384-99387, 99394-99397, 99401-99404, 99411, 99412, 99420, 99429, 99455, 99456	051x, 0520-0523, 0526-0529, 057x-059x, 082x-085x, 088x, 0982, 0983
Nonacute inpatient visit	99304-99310, 99315, 99316, 99318, 99324-99328, 99334-99337	0118, 0128, 0138, 0148, 0158, 019x, 0524, 0525, 055x, 066x
Acute inpatient visit	99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291	010x, 0110-0114, 0119, 0120-0124, 0129, 0130-0134, 0139, 0140-0144, 0149, 0150-0154, 0159, 016x, 020x,021x, 072x, 080x, 0987

ED visit	99281-99285	045x, 0981

Table A6. Diagnosis codes used to identify mental health disorders.

Category	ICD-9 Code	Description
ADHD	3140	Attention deficit disorder of childhood
ADHD	31400	Attention deficit disorder without mention of hyperactivity
ADHD	31401	Attention deficit disorder with hyperactivity
ADHD	3149	Unspecified hyperkinetic syndrome
Adjustment and Acute Reactions	308	Acute reaction to stress
Adjustment and Acute Reactions	3080	Predominant disturbance of emotions
Adjustment and Acute Reactions	3081	Predominant disturbance of consciousness
Adjustment and Acute Reactions	3082	Predominant psychomotor disturbance
Adjustment and Acute Reactions	3083	Other acute reactions to stress
Adjustment and Acute Reactions	30830	DSM other acute reactions to stress
Adjustment and Acute Reactions	3084	Mixed disorders as reaction to stress
Adjustment and Acute Reactions	3089	Unspecified acute reaction to stress
Adjustment and Acute Reactions	309	Adjustment reaction
Adjustment and Acute Reactions	3090	Adjustment disorder with depressed mood
Adjustment and Acute Reactions	30900	DSM brief depressive reaction
Adjustment and Acute Reactions	3091	Prolonged depressive reaction
Adjustment and Acute Reactions	3092	Predominant disturbance other emotions as adjustment reaction
Adjustment and Acute Reactions	30921	Separation anxiety disorder
Adjustment and Acute Reactions	30922	Emancipation disorder of adolescence and early adult life
Adjustment and Acute Reactions	30923	Specific academic or work inhibition
Adjustment and Acute Reactions	30924	Adjustment disorder with anxiety
Adjustment and Acute Reactions	30928	Adjustment disorder with mixed anxiety and depressed mood
Adjustment and Acute Reactions	30929	Other adjustment reactions with predominant disturbance of other emotions
Adjustment and Acute Reactions	3093	Adjustment disorder with disturbance of conduct
Adjustment and Acute Reactions	30930	DSM adjustment reaction disorder
Adjustment and Acute Reactions	3094	Adjustment disorder with mixed disturbance of emotions and conduct
Adjustment and Acute Reactions	30940	DSM adjustment reaction disorder
Adjustment and Acute Reactions	3098	Other specified adjustment reactions
Adjustment and Acute Reactions	30982	Adjustment reaction with physical symptoms
Adjustment and Acute Reactions	30983	Adjustment reaction with withdrawal
Adjustment and Acute Reactions	30989	Other specified adjustment reactions
Adjustment and Acute Reactions	3099	Unspecified adjustment reaction
Adjustment and Acute Reactions	30990	DSM unspecified adjustment reaction
Adjustment and Acute Reactions	313	Disturbance emotions specific to childhood & adolescence
Adjustment and Acute Reactions	3130	Overanxious disorder specific to childhood & adolescence
Adjustment and Acute Reactions	31300	DSM overanxious disorder of childhood & adolescence
Adjustment and Acute Reactions	3131	Misery and unhappiness disorder specific to childhood and adolescence
Adjustment and Acute Reactions	3132	Sensitivity shyness & social withdrawal disorder
Adjustment and Acute Reactions	31321	Shyness disorder of childhood
Adjustment and Acute Reactions	31322	Introverted disorder of childhood
Adjustment and Acute Reactions	31323	Selective mutism

Adjustment and Acute Reactions	3133	Relationship problems specific to childhood and adolescence
Adjustment and Acute Reactions	3138	Other/mixed emotional disturb child/adolescence
Adjustment and Acute Reactions	31381	Oppositional defiant disorder
Adjustment and Acute Reactions	31382	Identity disorder of childhood or adolescence
Adjustment and Acute Reactions	31383	Academic underachievement disorder of childhood or adolescence
Adjustment and Acute Reactions	31389	Other emotional disturbances of childhood or adolescence
Adjustment and Acute Reactions	3139	Unspecified emotional disturbance of childhood or adolescence
Affective Disorders, Excluding Bipolar	2962	Major depressive disorder single episode
Affective Disorders, Excluding Bipolar	29620	Major depressive affective disorder, single episode, unspecified
Affective Disorders, Excluding Bipolar	29621	Major depressive affective disorder, single episode, mild
Affective Disorders, Excluding Bipolar	29622	Major depressive affective disorder, single episode, moderate
Affective Disorders, Excluding Bipolar	29623	Major depressive affective disorder, single episode, severe, without mention of psychotic behavior
Affective Disorders, Excluding Bipolar	29624	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior
Affective Disorders, Excluding Bipolar	29625	Major depressive affective disorder, single episode, in partial or unspecified remission
Affective Disorders, Excluding Bipolar	29626	Major depressive affective disorder, single episode, in full remission
Affective Disorders, Excluding Bipolar	2963	Major depressive disorder recurrent episode
Affective Disorders, Excluding Bipolar	29630	Major depressive affective disorder, recurrent episode, unspecified
Affective Disorders, Excluding Bipolar	29631	Major depressive affective disorder, recurrent episode, mild
Affective Disorders, Excluding Bipolar	29632	Major depressive affective disorder, recurrent episode, moderate
Affective Disorders, Excluding Bipolar	29633	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior
Affective Disorders, Excluding Bipolar	29634	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior
Affective Disorders, Excluding Bipolar	29635	Major depressive affective disorder, recurrent episode, in partial or unspecified remission
Affective Disorders, Excluding Bipolar	29636	Major depressive affective disorder, recurrent episode, in full remission
Affective Disorders, Excluding Bipolar	2980	Depressive type psychosis
Affective Disorders, Excluding Bipolar	30000	Anxiety state, unspecified
Affective Disorders, Excluding Bipolar	30001	Panic disorder without agoraphobia
Affective Disorders, Excluding Bipolar	30002	Generalized anxiety disorder
Affective Disorders, Excluding Bipolar	30009	Other anxiety states
Affective Disorders, Excluding Bipolar	3004	Dysthymic disorder
Affective Disorders, Excluding Bipolar	30040	DSM neurotic depression
Affective Disorders, Excluding Bipolar	30113	Cyclothymic disorder
Affective Disorders, Excluding Bipolar	311	Depressive disorder, not elsewhere classified
Autism Spectrum Disorders	2990	Autistic disorder
Autism Spectrum Disorders	29900	Autistic disorder, current or active state
Autism Spectrum Disorders	29901	Autistic disorder, residual state
Bipolar	2960	Bipolar I disorder single manic episode
Bipolar	2961	Manic disorder, recurrent episode
Bipolar	2964	Bipolar I disorder most recent episode manic
Bipolar	2965	Bipolar I disorder most recent episode depressed
Bipolar	2966	Bipolar I disorder most recent episode mixed
Bipolar	2967	Bipolar I disorder, most recent episode (or current) unspecified
Bipolar	2968	Other and unspecified bipolar disorders
Developmental Disorders	315	Specific delays in development
Developmental Disorders	3150	Specific developmental reading disorder
Developmental Disorders	31500	Developmental reading disorder, unspecified

Developmental Disorders	31501	Alexia
Developmental Disorders	31502	Developmental dyslexia
Developmental Disorders	31509	Other specific developmental reading disorder
Developmental Disorders	3151	Mathematics disorder
Developmental Disorders	31510	DSM specific arithmetic disorder
Developmental Disorders	3152	Other specific developmental learning difficulties
Developmental Disorders	3153	Developmental speech or language disorder
Developmental Disorders	31531	Expressive language disorder
Developmental Disorders	31532	Mixed receptive-expressive language disorder
Developmental Disorders	31534	Speech and language developmental delay due to hearing loss
Developmental Disorders	31535	Childhood onset fluency disorder
Developmental Disorders	31539	Other developmental speech or language disorder
Developmental Disorders	3154	Developmental coordination disorder
Developmental Disorders	3155	Mixed development disorder
Developmental Disorders	31550	DSM mixed specific develop dis
Developmental Disorders	3158	Other specified delays in development
Developmental Disorders	3159	Unspecified delay in development
Developmental Disorders	31590	DSM unspecified delays in development
Developmental Disorders	316	Psychic factors associated with diseases classified elsewhere
Developmental Disorders	3160	Psychic factors associated with diseases classified elsewhere
Developmental Disorders	31600	DSM psychic factors associated with diseases classified elsewhere
Developmental Disorders	317	Mild intellectual disabilities
Developmental Disorders	318	Other specified mental retardation
Developmental Disorders	3180	Moderate intellectual disabilities
Developmental Disorders	31800	DSM moderate mental retardation
Developmental Disorders	3181	Severe intellectual disabilities
Developmental Disorders	31810	DSM severe mental retardation
Developmental Disorders	3182	Profound intellectual disabilities
Developmental Disorders	31820	DSM profound mental retardation
Developmental Disorders	319	Unspecified intellectual disabilities
Disruptive Behavior Disorders	3120	Undersocialized conduct disorder aggressive type
Disruptive Behavior Disorders	31200	Undersocialized conduct disorder, aggressive type, unspecified
Disruptive Behavior Disorders	31201	Undersocialized conduct disorder, aggressive type, mild
Disruptive Behavior Disorders	31202	Undersocialized conduct disorder, aggressive type, moderate
Disruptive Behavior Disorders	31203	Undersocialized conduct disorder, aggressive type, severe
Disruptive Behavior Disorders	3121	Undersocialized conduct disorder unaggressive
Disruptive Behavior Disorders	31210	Undersocialized conduct disorder, unaggressive type, unspecified
Disruptive Behavior Disorders	31211	Undersocialized conduct disorder, unaggressive type, mild
Disruptive Behavior Disorders	31212	Undersocialized conduct disorder, unaggressive type, moderate
Disruptive Behavior Disorders	31213	Undersocialized conduct disorder, unaggressive type, severe
Disruptive Behavior Disorders	3122	Socialized conduct disorder
Disruptive Behavior Disorders	31220	Socialized conduct disorder, unspecified
Disruptive Behavior Disorders	31221	Socialized conduct disorder, mild
Disruptive Behavior Disorders	31222	Socialized conduct disorder, moderate
Disruptive Behavior Disorders	31223	Socialized conduct disorder, severe

Disruptive Behavior Disorders	3123	Disorders of impulse control NEC
Disruptive Behavior Disorders	31230	Impulse control disorder, unspecified
Disruptive Behavior Disorders	31231	Pathological gambling
Disruptive Behavior Disorders	31232	Kleptomania
Disruptive Behavior Disorders	31233	Pyromania
Disruptive Behavior Disorders	31234	Intermittent explosive disorder
Disruptive Behavior Disorders	31235	Isolated explosive disorder
Disruptive Behavior Disorders	31239	Other disorders of impulse control
Disruptive Behavior Disorders	3124	Mixed disturbance of conduct and emotions
Disruptive Behavior Disorders	3128	Other specified disturbances of conduct NEC
Disruptive Behavior Disorders	31281	Conduct disorder, childhood onset type
Disruptive Behavior Disorders	31282	Conduct disorder, adolescent onset type
Disruptive Behavior Disorders	31289	Other conduct disorder
Disruptive Behavior Disorders	3129	Unspecified disturbance of conduct
Disruptive Behavior Disorders	V40	Mental and behavioral problems
Disruptive Behavior Disorders	V403	Other behavioral problems
Disruptive Behavior Disorders	V4039	Other specified behavioral problem
Disruptive Behavior Disorders	V409	Unspecified mental or behavioral problem
Other Mental Health Diagnosis	2930	Delirium due to conditions classified elsewhere
Other Mental Health Diagnosis	2931	Subacute delirium
Other Mental Health Diagnosis	3003	Obsessive-compulsive disorders
Other Mental Health Diagnosis	30081	Somatization disorder
Other Mental Health Diagnosis	30082	Undifferentiated somatoform disorder
Other Mental Health Diagnosis	3009	Unspecified nonpsychotic mental disorder
Other Mental Health Diagnosis	3014	Obsessive-compulsive personality disorder
Other Mental Health Diagnosis	306	Physiological malfunction arise from mental factors
Other Mental Health Diagnosis	3060	Musculoskeletal malfunction arising from mental factors
Other Mental Health Diagnosis	3061	Respiratory malfunction arising from mental factors
Other Mental Health Diagnosis	3062	Cardiovascular malfunction arising from mental factors
Other Mental Health Diagnosis	3063	Skin disorder arising from mental factors
Other Mental Health Diagnosis	3064	Gastrointestinal malfunction arising from mental factors
Other Mental Health Diagnosis	3066	Endocrine disorder arising from mental factors
Other Mental Health Diagnosis	3067	Disorder of organs of special sense arising from mental factors
Other Mental Health Diagnosis	3068	Other specified psychophysiological malfunction
Other Mental Health Diagnosis	3069	Unspecified psychophysiological malfunction
Other Mental Health Diagnosis	3071	Anorexia nervosa
Other Mental Health Diagnosis	30751	Bulimia nervosa
Other Mental Health Diagnosis	3077	Encopresis
Other Mental Health Diagnosis	V6284	Suicidal ideation
Other Psychotic Disorders	2938	Other spec transient mental d/o due conditions classified elsewhere
Other Psychotic Disorders	29381	Psychotic disorder with delusions in conditions classified elsewhere
Other Psychotic Disorders	29382	Psychotic disorder with hallucinations in conditions classified elsewhere
Other Psychotic Disorders	29383	Mood disorder in conditions classified elsewhere
Other Psychotic Disorders	29384	Anxiety disorder in conditions classified elsewhere
Other Psychotic Disorders	29389	Other specified transient mental disorders due to conditions classified elsewhere, other

Other Psychotic Disorders	2969	Other and unspecified episodic mood disorder
Other Psychotic Disorders	29690	Unspecified episodic mood disorder
Other Psychotic Disorders	29699	Other specified episodic mood disorder
Other Psychotic Disorders	2971	Delusional disorder
Other Psychotic Disorders	2973	Shared psychotic disorder
Other Psychotic Disorders	2978	Other specified paranoid states
Other Psychotic Disorders	2979	Unspecified paranoid state
Other Psychotic Disorders	2981	Excitative type psychosis
Other Psychotic Disorders	2983	Acute paranoid reaction
Other Psychotic Disorders	2988	Other and unspecified reactive psychosis
Other Psychotic Disorders	2989	Unspecified psychosis
Other Psychotic Disorders	29890	DSM unspecified atypical psychosis
Other Psychotic Disorders	29910	Childhood disintegrative disorder, current or active state
Other Psychotic Disorders	2998	Other spec pervasive developmental disorders
Other Psychotic Disorders	29980	Other specified pervasive developmental disorders, current or active state
Other Psychotic Disorders	29981	Other specified pervasive developmental disorders, residual state
Other Psychotic Disorders	29990	Unspecified pervasive developmental disorder, current or active state
Other Psychotic Disorders	29991	Unspecified pervasive developmental disorder, residual state
Other Psychotic Disorders	3108	Other nonpsychotic mental disorder following organic brain damage
Other Psychotic Disorders	3109	Unspecified nonpsychotic mental disorder following organic brain damage
Personality Disorders	3010	Paranoid personality disorder
Personality Disorders	30110	Affective personality disorder, unspecified
Personality Disorders	30112	Chronic depressive personality disorder
Personality Disorders	3013	Explosive personality disorder
Personality Disorders	30150	Histrionic personality disorder, unspecified
Personality Disorders	30159	Other histrionic personality disorder
Personality Disorders	3016	Dependent personality disorder
Personality Disorders	3017	Antisocial personality disorder
Personality Disorders	3018	Other personality disorders
Personality Disorders	30181	Narcissistic personality disorder
Personality Disorders	30182	Avoidant personality disorder
Personality Disorders	30183	Borderline personality disorder
Personality Disorders	30184	Passive-aggressive personality
Personality Disorders	30189	Other personality disorders
Personality Disorders	3019	Unspecified personality disorder
PTSD	30981	Posttraumatic stress disorder
Schizophrenia	295	Schizophrenic disorders
Schizophrenia	2950	Simple type schizophrenia
Schizophrenia	29500	Simple type schizophrenia, unspecified
Schizophrenia	29501	Simple type schizophrenia, subchronic
Schizophrenia	29502	Simple type schizophrenia, chronic
Schizophrenia	29503	Simple type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29504	Simple type schizophrenia, chronic with acute exacerbation
Schizophrenia	29505	Simple type schizophrenia, in remission
Schizophrenia	2951	Disorganized type schizophrenia

Schizophrenia	29510	Disorganized type schizophrenia, unspecified
Schizophrenia	29511	Disorganized type schizophrenia, subchronic
Schizophrenia	29512	Disorganized type schizophrenia, chronic
Schizophrenia	29513	Disorganized type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29514	Disorganized type schizophrenia, chronic with acute exacerbation
Schizophrenia	29515	Disorganized type schizophrenia, in remission
Schizophrenia	2952	Catatonic type schizophrenia
Schizophrenia	29520	Catatonic type schizophrenia, unspecified
Schizophrenia	29521	Catatonic type schizophrenia, subchronic
Schizophrenia	29522	Catatonic type schizophrenia, chronic
Schizophrenia	29523	Catatonic type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29524	Catatonic type schizophrenia, chronic with acute exacerbation
Schizophrenia	29525	Catatonic type schizophrenia, in remission
Schizophrenia	2953	Paranoid type schizophrenia
Schizophrenia	29530	Paranoid type schizophrenia, unspecified
Schizophrenia	29531	Paranoid type schizophrenia, subchronic
Schizophrenia	29532	Paranoid type schizophrenia, chronic
Schizophrenia	29533	Paranoid type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29534	Paranoid type schizophrenia, chronic with acute exacerbation
Schizophrenia	29535	Paranoid type schizophrenia, in remission
Schizophrenia	2954	Schizophreniform disorder
Schizophrenia	29540	Schizophreniform disorder, unspecified
Schizophrenia	29541	Schizophreniform disorder, subchronic
Schizophrenia	29542	Schizophreniform disorder, chronic
Schizophrenia	29543	Schizophreniform disorder, subchronic with acute exacerbation
Schizophrenia	29544	Schizophreniform disorder, chronic with acute exacerbation
Schizophrenia	29545	Schizophreniform disorder, in remission
Schizophrenia	2955	Latent schizophrenia
Schizophrenia	29550	Latent schizophrenia, unspecified
Schizophrenia	29551	Latent schizophrenia, subchronic
Schizophrenia	29552	Latent schizophrenia, chronic
Schizophrenia	29553	Latent schizophrenia, subchronic with acute exacerbation
Schizophrenia	29554	Latent schizophrenia, chronic with acute exacerbation
Schizophrenia	29555	Latent schizophrenia, in remission
Schizophrenia	2956	Schizophrenic disorders residual type
Schizophrenia	29560	Schizophrenic disorders, residual type, unspecified
Schizophrenia	29561	Schizophrenic disorders, residual type, subchronic
Schizophrenia	29562	Schizophrenic disorders, residual type, chronic
Schizophrenia	29563	Schizophrenic disorders, residual type, subchronic with acute exacerbation
Schizophrenia	29564	Schizophrenic disorders, residual type, chronic with acute exacerbation
Schizophrenia	29565	Schizophrenic disorders, residual type, in remission
Schizophrenia	2957	Schizoaffective disorder
Schizophrenia	29570	Schizoaffective disorder, unspecified
Schizophrenia	29571	Schizoaffective disorder, subchronic
Schizophrenia	29572	Schizoaffective disorder, chronic

Schizophrenia	29573	Schizoaffective disorder, subchronic with acute exacerbation
Schizophrenia	29574	Schizoaffective disorder, chronic with acute exacerbation
Schizophrenia	29575	Schizoaffective disorder, in remission
Schizophrenia	2958	Other specified types of schizophrenia
Schizophrenia	29580	Other specified types of schizophrenia, unspecified
Schizophrenia	29581	Other specified types of schizophrenia, subchronic
Schizophrenia	29582	Other specified types of schizophrenia, chronic
Schizophrenia	29583	Other specified types of schizophrenia, subchronic with acute exacerbation
Schizophrenia	29584	Other specified types of schizophrenia, chronic with acute exacerbation
Schizophrenia	29585	Other specified types of schizophrenia, in remission
Schizophrenia	2959	Unspecified schizophrenia
Schizophrenia	29590	Unspecified schizophrenia, unspecified
Schizophrenia	29591	Unspecified schizophrenia, subchronic
Schizophrenia	29592	Unspecified schizophrenia, chronic
Schizophrenia	29593	Unspecified schizophrenia, subchronic with acute exacerbation
Schizophrenia	29594	Unspecified schizophrenia, chronic with acute exacerbation
Schizophrenia	29595	Unspecified schizophrenia, in remission
Sleep Disorders	3074	Specific disorders of sleep of nonorganic origin
Sleep Disorders	30740	Nonorganic sleep disorder, unspecified
Sleep Disorders	30741	Transient disorder of initiating or maintaining sleep
Sleep Disorders	30742	Persistent disorder of initiating or maintaining sleep
Sleep Disorders	30745	Circadian rhythm sleep disorder of nonorganic origin
Sleep Disorders	30746	Sleep arousal disorder
Sleep Disorders	30747	Other dysfunctions of sleep stages or arousal from sleep
Sleep Disorders	30748	Repetitive intrusions of sleep
Sleep Disorders	30749	Other specific disorders of sleep of nonorganic origin
Sleep Disorders	327	Organic sleep disorders
Sleep Disorders	3270	Organic disorders initiating & maintaining sleep
Sleep Disorders	32730	Circadian rhythm sleep disorder, unspecified
Sleep Disorders	32731	Circadian rhythm sleep disorder, delayed sleep phase type
Sleep Disorders	32732	Circadian rhythm sleep disorder, advanced sleep phase type
Sleep Disorders	32733	Circadian rhythm sleep disorder, irregular sleep-wake type
Sleep Disorders	32734	Circadian rhythm sleep disorder, free-running type
Sleep Disorders	32735	Circadian rhythm sleep disorder, jet lag type
Sleep Disorders	32737	Circadian rhythm sleep disorder in conditions classified elsewhere
Sleep Disorders	32739	Other circadian rhythm sleep disorder
Sleep Disorders	7805	Sleep disturbances
Sleep Disorders	78050	Sleep disturbance, unspecified
Sleep Disorders	V694	Lack of adequate sleep