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 21, 2019 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302
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	R. Citron (OSU)
	D. Department Update	D. Weston (OHA)
	E. Legislative Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	T. Klein (Chair)
	A. GLP-1 Receptor Agonists Literature Scan	
	1. Public Comment	
	III. DUR ACTIVITIES	
1:20 PM	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (DXC)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Reviews	K. Sentena (OSU)
	1. Updates on Testosterone Therapy	
	2. Basal Insulin Update	
	IV. DUR OLD BUSINESS	
1:45 PM	A. Calcium/Vitamin D Prior Authorization Update	K. Sentena (OSU)
	1. Prior Authorization Update	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

1:50 PM	B. Hydroxyprogesterone Prior Authorization Update 1. Prior Authorization Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
1:55 PM	C. Benzodiazepine Prior Authorization Update 1. Prior Authorization Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:00 PM	D. Cannabidiol Prior Authorization Update 1. Prior Authorization Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
	V. PREFERRED DRUG LIST NEW BUSINESS	
2:05 PM	A. Tetracycline Class Update and New Drug Evaluation 1. Class Update 2. Nuzyra™ (omadacycline) New Drug Evaluation 3. Seysara™ (sarecycline) New Drug Evaluation 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
2:25 PM	B. Hereditary Angioedema Agents Class Review 1. Class Review/Prior Authorization 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:45 PM	C. Endometriosis Class Review 1. Class Review/Prior Authorization 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:05 PM	BREAK	
	VI. DUR NEW BUSINESS	
3:15 PM	A. Mental Health Clinical Advisory Group 1. MHCAG Overview 2. MHCAG Schizophrenia Algorithm 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	A. Parish (OHA) K. Cheng (MHCAG) G. Fussell (MHCAG)

3:40 PM	B. Antipsychotics for Schizophrenia Drug Use Evaluation 1. Drug Use Evaluation and Literature Scan 2. Provider Education Opportunities 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU) S. Servid (OSU)
4:00 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
	IX. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
Kelley Burnett, DO	Physician	Pediatrician / Associate Medical Director	Grants Pass	December 2019
Dave Pass, MD	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2019
Tracy Klein, PhD, FNP	Public	Nurse Practitioner	Portland	December 2020
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director	Coos Bay	December 2020
William Origer, MD	Physician	Residency Faculty	Albany	December 2020
James Slater, PharmD	Pharmacist	Pharmacy Director	Beaverton	December 2020
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021

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and

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 24, 2019
1:00 p.m. – 5:00 p.m.
DXC Building, 4070 27th Ct
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: Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; William Origer, MD; Stacy Ramirez, PharmD; Jim Rickards, MD, MBA; James Slater, PharmD; Cathy Zehrung, RPh

Members Present by Phone: Kelley Burnett, DO

Staff Present: Roger Citron, RPh; Richard Holsapple, RPh; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Renae Wentz, MD; Dee Weston; Jonnaliz Corbett; Trevor Douglass, DC, MPH

Staff Present by Phone: N/A

**Audience: ***Margaret Olmon, AbbVie; *Elise Conlee, Greenwich Biosciences; *Paul Williams, Genentech; *Stuart O'Broonth, Gilead; Paul Bonham, Avexis; *Valerie Ng, Invidior; Georgette Dzwilewski, Invidior, Tim McFerrero; Don Noper, Dova; Keri Smith, ViiV; Heather Hays, Array Biopharma; *Chris Conner, BMS; Camille Kerr, Amgen; Alex Bithy, Bioverativ; Katie Peters, Oregon State University; Jeana Colabianchi, Sunovio; *Ryan Flynn, Dova; Bobbi Su Duim, BMS; *Sylvia Churchill, Amgen; Laura Jeffcoat; Danielle Shannon, WVP Health; Meridith Bradshaw; *Chioma Ezenduka, UCB; *Ryan Fowler, Pfizer; Andrew Yu, Novartis; Mark Pledge, Novartis; Amy Burns, AllCare CCO; Lisa Boyle, WVP Health, *Colin Roberts, OHSU

*Provided public testimony

Written testimony provided: Posted to OSU Website

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.
B. No new conflicts of interest were declared.
C. Election of Chair & Vice Chair

Tracy Klein was nominated as chair.
ACTION: Motion to approve, 2nd, all in favor

Caryn Mickelson was nominated as vice chair.
ACTION: Motion to approve, 2nd, all in favor

D. Approval of agenda and November 2018 minutes presented by Mr. Citron.
ACTION: Motion to approve, 2nd, all in favor

E. Department Update: Dee Weston reported she did not have any updates on behalf of the OHA
F. Legislative Update: Trevor Douglass said the OHA was tracking a number of bills, but nothing to report at this time and he will arrange for an update at the March P&T meeting

II. CONSENT AGENDA TOPICS

A. P&T Operating Procedures
B. P&T Methods
C. OHA onboarded the new committee members and updated the operating procedures and methods. The changes are available in the packet beginning on page 8 and Posted to OSU Website.
D. Fibromyalgia Indication Review
E. Erythropoiesis Stimulating Agents Literature Scan

III. DUR OLD BUSINESS

A. Hepatitis C Direct Acting Antivirals

IV. DUR NEW BUSINESS

A. Substance Use Disorder Class Update/Drug Use Evaluation
Dr. Moretz and Dr. Servid presented the proposal to:
- Make lofexidine non-preferred on the Preferred Drug List (PDL) and implement Prior Authorization (PA) criteria to ensure appropriate utilization.
- Add extended release subcutaneous buprenorphine injection (Sublocade) to PA criteria for buprenorphine and buprenorphine/naxolone products (Appendix 6).
- No PA or PDL changes recommended based on utilization.
- Evaluate comparative costs in executive session.

ACTION: revise the PA criteria to document concomitant naloxone use when available and upon approval of the PA. Include messaging recommending concomitant naloxone prescribing if needed. The committee also requested staff evaluate MAT continuation over a longer period >6 months. Collect, evaluate co-prescribing information with naloxone and evaluate further non-pharmacological therapy.

The committee recommended a newsletter regarding best practices/pearls for MAT, including new therapies and recommendations for co-prescribing naloxone and psychosocial support.

Motion to approve, 2nd, all in favor

V. PREFERRED DRUG LIST NEW BUSINESS

A. Antiepileptics Class Update
Dr. Moretz presented the proposal to:
- Implement PA criteria to ensure medically appropriate utilization of cannabidiol and stiripentol.
- Revise clobazam criteria to include Dravet Syndrome as an indication (based on 2012 NICE guidance) and add renewal criteria.
- Review comparative drug costs in the executive session.

ACTION: amended to reorder #4 and #5 in cannabidiol PA criteria and add a question confirming concurrent use of other antiepileptic therapy to cannabidiol initial and renewal criteria.

The committee asked staff to evaluate use of solution formulations and whether they are actually needed for the patients they are prescribed.

Motion to approve, 2nd, all in favor

B. Drugs for Thrombocytopenia Class Review
Dr. Sentena presented the proposal to:
- Add the Thrombocytopenia Class to the PMPDP.
- Implement proposed PA criteria for non-preferred drugs.
- Evaluate costs in executive session to determine PDL status.

ACTION: amend proposed PA criteria to: confirm presence of chronic liver disease prior to approval in question #5; revise approval duration to be 3 months with initial approval and 12 months upon renewal; and add evaluation of LFTs. The committee also asked to monitor requests to ensure PA is not causing undue delay in surgical procedures.

Motion to approve, 2nd, all in favor

C. Influenza Antivirals Class Update
Dr. Servid presented the proposal to:

- Make baloxavir marboxil non-preferred and subject to prior authorization criteria due to lack of available evidence in high risk patients and concerns with potential resistance.
- Review comparative costs in executive session.

ACTION: Motion to approve, 2nd, all in favor

D. Biologics for Autoimmune Conditions Class Update
Dr. Moretz presented the proposal to:

- Modify PA criteria reflect updated indications and age ranges for specific biologics.
- Modify PA criteria to include tildrakizumab for use in moderate-to-severe plaque psoriasis for adults.
- Modify PA criteria to include baricitinib for use in moderate-to-severe rheumatoid arthritis for adults.
- Evaluate comparative costs in executive session.

ACTION: for questions which require DMARD step therapy (e.g.#13), add language specifying that the patient has tried/failed "or had inadequate response" to these treatments and amend criteria to support continued therapy with DMARDs in combination with biologics where appropriate. The committee also requested staff perform a DUE of biologic utilization.

Motion to approve, 2nd, all in favor

E. Colony Stimulating Factors Class Update
Dr. Sentena presented the proposal to:

- Make no changes to the PMPDP based on clinical evidence.
- Evaluate comparative drug costs in executive session.

ACTION: Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; William Origer, MD; Stacy Ramirz, PharmD; Jim Rickards, MD, MBA; James Slater, PharmD; Cathy Zehrung, RPh

Members Present by Phone: Kelley Burnett, DO; James Slater, PharmD

Staff Present: Roger Citron, RPh; Richard Holsapple, RPh; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Renae Wentz, MD; Dee Weston; Jonnaliz Corbett; Trevor Douglass, DC, MPH

Staff Present by Phone: N/A

VII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Hepatitis C Direct Acting Antivirals
   Recommendation: update the recommendation made at the November P&T meeting, which was to optimize Mavyret use when fibrosis restrictions are removed, and instead to continue to prefer glecaprevir/pibrentasvir (Mavyret™), sofosbuvir/velpatasivr (both brand Epclusa® and the authorized generic), and elbasvir/grazoprevir (Zepatier®) as recommended regimens for hepatitis C for their respective FDA-approved indications.
B. Erythropoiesis Stimulating Agents Literature Scan
   Recommendation: no changes to the PMPDP
C. Substance Use Disorder Class
   Recommendation: no changes to the PMPDP
D. Antiepileptics Class Update
   Recommendation: no changes to the PMPDP
E. Thrombocytopenia Class Review
   Recommendation: make eltrombopag (Promacta®) and romiplostim (Nplate™) preferred and fostamatinib (Tavalisse™), lusutrombopag (Mulpleta®) and avatromopag (Doptelet®) non-preferred on the PMPDP.
F. Influenza Class
   Recommendation: no changes to the PMPDP
G. Biologics for Autoimmune Conditions Class
   Recommendation: maintain tildrakizumab-asmn (Ilumya™) and baricitinib (Olumiant®) as non-preferred on the PMPDP and no other changes.
H. Colony Stimulating Factors Class Update
   Recommendation: make filgrastim-sndz (Zarxio®) non-preferred on PMPDP.

ACTION: Motion to approve items, 2nd, all in favor

VIII. ADJOURN

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Diabetes, GLP-1 Receptor Agonists

Date of Review: May 2019

Date of Last Review: July 2018
Literature Search: 01/14/19 – 01/30/19

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

Conclusions:
- The majority of previous evidence supports clinically similar hemoglobin A1c (HbA1c) lowering within the glucagon-like peptide-1 (GLP-1) receptor agonists (RA) class.[1] This updated review supports these findings. Cardiovascular (CV) evidence for this class has no new published data, and previous findings are available in **Appendix 6**.
- A Cochrane systematic review in patients with diabetes and chronic kidney disease (CKD) demonstrated more HbA1c lowering for patients treated with GLP-1 RAs compared to placebo by a mean difference (MD) of -0.53% (95% CI, -1.01 to -0.06; P=0.029) in patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 (moderate evidence).[7]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on review of the clinical data.
- Evaluate cost in executive session.

Summary of Prior Reviews and Current Policy
- Evidence has demonstrated similar HbA1c lowering between the different classes of anti-diabetic treatments.[8] Data on efficacy and harms supports the use of metformin as first-line therapy in patients with type 2 diabetes (T2DM) requiring medication.[9,10] There is no consensus on the most appropriate second-line therapy.
- The Drug Effectiveness Review Project found that there was moderate evidence of more HbA1c lowering with daily lixisenatide compared to daily liraglutide and more HbA1c lowering with once-weekly exenatide compared to exenatide twice daily.[1] The differences were 0.5% to 0.6% suggesting benefit in patients close to goal HbA1c.
- Liraglutide is indicated to reduce the risk of CV events in patients with established CVD based on a small benefit over placebo.[2,3] Liraglutide, compared to placebo, in patients with type 2 diabetes (T2DM) taking standard therapy and with a history of cardiovascular disease (CVD) or at high risk of CVD, over the time period of 3.5 years demonstrated an actual risk reduction [ARR] in composite CV events (death from CV causes, nonfatal myocardial infarction [MI], or nonfatal stroke) of 1.9% and number needed to treat [NNT] of 53 favoring and reduction in CV death also favored liraglutide (ARR 1.3%/ NNT 77).[2] Cardiovascular studies of exentatide extended release (ER), semaglutide and lixisenatide demonstrated neutral effects on the composite CV endpoint compared to placebo. [4–6] Dulaglutide CV safety studies are ongoing and albiglutide has been discontinued.

- Daily exenatide (Byetta) is the only preferred GLP-1 RA and accounts for 6% of the market share. The majority of the utilization is for liraglutide.
- Current prior authorization criteria require metformin and sulfonylurea trial, or have contraindications to these treatments, for GLP-1 RA approval.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

Cochrane – Insulin and Glucose-lowering Agents for Treating People with Diabetes and Chronic Kidney Disease
A systematic review and meta-analysis by Cochrane analyzed efficacy and safety of insulin and other antidiabetic treatments in people with diabetes and CKD.[7] Forty-four trials were included in the review, two of these trials evaluated the use of GLP-1 receptor agonists. Both studies included liraglutide compared to placebo in patients with an eGFR of less than 60 mL/min/1.73 m^2. Trials were found to be at low risk of bias for all domains except attrition bias which was high in both studies, and both trials were funded by industry. Fasting blood glucose (FBG) and HbA1c reduction were the primary outcomes, and death was an important secondary outcome.[7] Hypoglycemia and discontinuations due to adverse events were safety outcomes.

Mean HbA1c lowering was greater for GLP-1 RAs compared to placebo, MD -0.53% (95% CI, -1.01 to -0.06; P=0.029) based on moderate evidence.[7] FBG was reduced by 1.08 mmol/L (95% CI, -1.71 to -0.45; P=0.0008) in one trial and not reported by the other trial (very low quality evidence).[7] Liraglutide was not found to have any effect on the risk of death compared to placebo (relative risk [RR] 3.91; 95% CI, 0.44 to 34.58) based on low quality evidence. Liraglutide had no effect on hypoglycemia risk compared to placebo in patient with eGFR 30 to less than 60 mL/min/1.73m^2 (RR 0.79; 95% CI, 0.51 to 1.21; P=0.28).[7] Discontinuation rates were 48% with liraglutide compared to 11% for placebo in the one trial that reported discontinuation rates (ARR 37%/NNH 3).[7]

Conclusions for the use of GLP-1 RAs in patients with diabetes and CKD are limited by only two studies of liraglutide available for analysis. Limited evidence suggests liraglutide is effective in HbA1c reduction in this patient population; however, tolerability may be limited by high discontinuation rates.

After review, four systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11–13]

New Guidelines:
No high-quality guidelines were identified.

Additional Guidelines for Clinical Context:

American Diabetes Association – Standards in Medical Care 2019

GLP-1 RAs are part of the annual update by the American Diabetes Association.[9] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

Metformin is recommended as the first line treatment for patients with T2DM.[9] GLP-1 RAs are recommended as a second line treatment for patients with the following characteristics: need to minimize hypoglycemia, compelling need to minimize weight gain or promote weight loss. In patients with established atherosclerotic cardiovascular disease (ASCVD) GLP-1 RAs with proven CV benefit (i.e., liraglutide, semaglutide, and exenatide ER [in this order based on evidence]) are recommended as second line treatment.[9] In patients with heart failure (HF) or chronic kidney disease (CKD) GLP-1 RAs, with CV benefit, are recommended if SGLT-2 inhibitors are not tolerated or contraindicated.

American College of Endocrinology

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a T2DM management algorithm in 2019, which included guidance on GLP-1 RAs.[10] Similar to the ADA recommendations, this management algorithm was authored by a majority of authors with industry affiliations and the methods for guideline development were not disclosed. GLP-1 RAs are recommended as monotherapy, after metformin. Preference may be given to GLP-1 RAs in patients with CVD and CKD. GLP-1 RAs are also recommended as combination therapy in patients taking one or more anti-diabetic therapies.

New Formulations:

No new formulations identified.

New FDA Safety Alerts:

No new FDA safety alerts identified.

References:

1. McDonagh M, Blazina I, Holmes R, Lazur BH. Newer diabetes medications and combinations. Final update 3 report prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University, Portland, Oregon, October 2017.
2. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *Journal of Medicine*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.
3. Victoza Prescribing Information. Novo Nordisk. Plainsboro, NJ. 2017.
4. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225.
5. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917.

6. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141.
7. Lo C, Toyama T, Wang Y, et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev*. 2018;9:CD011798. doi:10.1002/14651858.CD011798.pub2.
8. Canadian Agency for Drugs and Technologies in Health. New drug for type 2 diabetes: second-line therapy-science report. Ottawa: CADTH Sep.(CADTH therapeutic review; vol.4, no.1b).
9. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S90-S102. doi:10.2337/dc19-S009.
10. Garber A, Abrahamson M, Barzilay J, Bonde L, et al. Consensus statement by the American Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm- 2019 executive summary. *Endocrine Practice*. 2019;25:69-90.
11. Peterson SC, Barry AR. Effect of Glucagon-like Peptide-1 Receptor Agonists on All-cause Mortality and Cardiovascular Outcomes: A Meta-analysis. *Curr Diabetes Rev*. 2018;14(3):273-279. doi:10.2174/1573399813666170414101450.
12. Al Yami MS, Alfayez OM, Alsheikh R. Update in Cardiovascular Safety of Glucagon Like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes. A Mixed Treatment Comparison Meta-Analysis of Randomised Controlled Trials. *Heart Lung Circ*. 2018;27(11):1301-1309. doi:10.1016/j.hlc.2018.03.018.
13. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6(2):105-113. doi:10.1016/S2213-8587(17)30412-6.
14. Guja C, Frías JP, Somogyi A, et al. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. *Diabetes Obes Metab*. 2018;20(7):1602-1614. doi:10.1111/dom.13266.
15. Jabbour SA, Frías JP, Hardy E, et al. Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial. *Diabetes Care*. 2018;41(10):2136-2146. doi:10.2337/dc18-0680.
16. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects with Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care*. 2018;41(2):258-266. doi:10.2337/dc17-0417.
17. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286. doi:10.1016/S2213-8587(18)30024-X.
18. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(5):370-381. doi:10.1016/S2213-8587(18)30023-8.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
exenatide	BYETTA	PEN INJCTR	Y
dulaglutide	TRULICITY	PEN INJCTR	N
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N
exenatide microspheres	BYDUREON PEN	PEN INJCTR	N
exenatide microspheres	BYDUREON	VIAL	N
liraglutide	VICTOZA 2-PAK	PEN INJCTR	N

liraglutide	VICTOZA 3-PAK	PEN INJCTR	N
lixisenatide	ADLYXIN	PEN INJCTR	N
semaglutide	OZEMPIC	PEN INJCTR	N

Appendix 2: New Comparative Clinical Trials

A total of 28 citations were manually reviewed from the initial literature search. After further review, 23 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 5 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Guja, et al[14] (DURATION 7) MC, DB, Phase 3, PC	Exenatide ER 2 mg weekly + insulin glargine (E) vs. Placebo weekly + insulin glargine ± metformin for both groups	Adult patients with type 2 diabetes that were inadequately controlled on titrated insulin glargine ± metformin (n=464)	Change from baseline HbA1c at week 28	E: -0.96% P: -0.23% LSMD – 0.73% (95% CI, -0.93% to -0.53%) P<0.001
Jabbour, et al[15] (DURATION 8) Phase 3, MC, DB	Exenatide 2 mg weekly + dapagliflozin daily vs. Exenatide 2 mg weekly vs. Dapagliflozin	Adult patients with type 2 diabetes that were inadequately controlled on metformin monotherapy that participated in an open label extension study following original study duration of 28 weeks (n=695)	Safety endpoints such as hypoglycemia, abnormal vital signs and reported adverse events at 52-weeks.	No major safety findings emerged. No episodes of major hypoglycemia (loss of consciousness, seizure, or coma resolving after glucose administration, event requiring third party assistance, or concentration < 3.0 mmol/L) were reported. Efficacy endpoints were exploratory and therefore not reported.
Ahmann, et al[16] (SUSTAIN 3) Phase 3a, OL, NI, PG, RCT	Semaglutide 1.0 mg (S) vs. Exenatide ER 2.0 mg (ER)	Adult patients with type 2 diabetes that were taking oral antidiabetic drugs (96% biguanides, sulfonylureas 48%) (n=813)	Change from baseline in HbA1c at week 56	S: -1.5% E: -0.9% ETD -0.62% (95% CI, -0.80 to -0.44) P<0.0001 for noninferiority and superiority

Pratley, et al[17] (SUSTAIN-7) PG, Phase 3b, OL, NI, RCT	Semaglutide 0.5 mg weekly (S 0.5) vs. Dulaglutide 0.75 mg weekly (D 0.75) Semaglutide 1.0 mg weekly (S 1.0) vs. Dulaglutide 1.5 mg weekly (D 1.5)	Adult patients with inadequately controlled type 2 diabetes on metformin	Change from baseline in HbA1c at week 40	S 0.5: -1.5% D 0.75: -1.1% ETD 0.4% (95% CI, -0.55 to -0.25) P<0.0001 for noninferiority and superiority S 1.0: -1.8% D 1.5: -1.4% ETD -0.41% (95% CI, -0.57 to -0.25) P<0.0001 for noninferiority and superiority
Ludvik, et al[18] (AWARD -10) Phase 3b, DB, PC, MC	Dulaglutide 1.5 mg weekly (D1.5) vs. Dulaglutide 0.75 mg weekly (D.75) vs. Placebo weekly (P) + SGLT-2 inhibitor in each group (most commonly dapagliflozin or empagliflozin)	Adult patients with type 2 diabetes inadequately controlled with a SGLT-2 inhibitor ± metformin (n=424)	Change from baseline HbA1c at 24 weeks	D1.5: -1.34% D.75: -1.21% P: -0.54% D1.5 vs. P: LSMD -0.79% (95% CI, -9.2 to -5.4) P<0.0001 D.75 vs. P: LSMD -0.66% (-0.84 to -0.49) P<0.001)

Abbreviations: DB = double-blind; E= extended release; ETD = estimated treatment difference; HbA1c = hemoglobin A1c; LSMD = least-squares mean difference; MC = multi-center; NI = noninferiority; OL = open label; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; SGLT-2 = sodium-glucose cotransporter-2

Appendix 3: Abstracts of Comparative Clinical Trials

Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study.

Guja C, Frías JP, Somogyi A, Jabbour S, Wang H, Hardy E, Rosenstock J

AIMS:

To compare the efficacy and safety of adding the glucagon-like peptide-1 receptor agonist exenatide once weekly (QW) 2 mg or placebo among patients with type 2 diabetes who were inadequately controlled despite titrated insulin glargine (IG) ± metformin.

METHODS:

This multicentre, double-blind study (ClinicalTrials.gov identifier: NCT02229383) randomized (1:1) patients with persistent hyperglycaemia after an 8-week titration phase (glycated haemoglobin [HbA1c] 7.0%-10.5% [53-91 mmol/mol]) to exenatide QW or placebo. The primary endpoint was HbA1c change from baseline to week 28. Secondary endpoints included body weight, 2-hour postprandial glucose, and mean daily IG dose.

RESULTS:

Of 464 randomized patients (mean: age, 58 years; HbA1c, 8.5% [69 mmol/mol]; diabetes duration, 11.3 years), 91% completed 28 weeks. Exenatide QW + IG vs placebo + IG significantly reduced HbA1c (least-squares mean difference, -0.73% [-8.0 mmol/mol]; 95% confidence interval, -0.93%, -0.53% [-10.2, -5.8 mmol/mol]; P < .001; final HbA1c, 7.55% [59 mmol/mol] and 8.24% [67 mmol/mol], respectively); body weight (-1.50 kg; -2.17, -0.84; P < .001); and 2-hour postprandial glucose (-1.52 mmol/L [-27.5 mg/dL]; -2.15, -0.90 [-38.7, -16.2]; P < .001). Significantly more exenatide QW + IG-treated patients vs placebo + IG-treated patients reached HbA1c <7.0% (<53 mmol/mol) (32.5% vs 7.4%; P < .001); daily IG dose increased by 2 and 4 units, respectively. Gastrointestinal and injection-site adverse events were more frequent with exenatide QW + IG (15.1% and 7.8%, respectively) than with placebo + IG (10.8% and 3.0%, respectively); hypoglycaemia incidence was similar between the exenatide QW + IG (29.7%) and placebo + IG (29.0%) groups, with no major hypoglycaemic events.

CONCLUSIONS:

Among patients with inadequate glycaemic control, exenatide QW significantly improved glucose control and decreased body weight, without increased hypoglycaemia or unexpected safety findings.

Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial.

Jabbour SA, Frías JP, Hardy E, Ahmed A, Wang H, Öhman P, Guja C

Abstract

OBJECTIVE:

Among patients with type 2 diabetes uncontrolled with metformin, exenatide once weekly (QW) plus dapagliflozin combination produced greater reductions in glycemia, weight, and systolic blood pressure (SBP) at 28 weeks than exenatide QW or dapagliflozin alone (DURATION-8). Here, we investigated the safety and maintenance of efficacy at 52 weeks, after a 24-week extension.

RESEARCH DESIGN AND METHODS:

This phase 3, multicenter, double-blind study randomized adults with type 2 diabetes (with glycated hemoglobin [HbA_{1c}] 8.0-12.0% [64-108 mmol/mol] and on metformin ≥1,500 mg/day) to exenatide QW (2-mg subcutaneous injection) plus once-daily dapagliflozin (10-mg oral tablet), exenatide QW plus oral placebo, or dapagliflozin plus injected placebo. Extension-period *P*values were nominal.

RESULTS:
Of 1,375 patients screened, 695 were randomized (mean baseline HbA_{1c} 9.3% [78 mmol/mol]); 81.2% completed the study, and 75.3% completed treatment. At 52 weeks, HbA_{1c} reductions were greater with exenatide QW plus dapagliflozin (least squares mean change -1.75% [-19.1 mmol/mol]) versus exenatide QW (-1.38% [-15.1 mmol/mol]; *P* = 0.006) or dapagliflozin (-1.23% [-13.4 mmol/mol]; *P* < 0.001); mean HbA_{1c} values were 6.9% (52 mmol/mol), 7.2% (55 mmol/mol), and 7.4% (57 mmol/mol), respectively. Weight and SBP reductions were greater with exenatide QW plus dapagliflozin (-3.31 kg and -4.5 mmHg) versus exenatide QW (-1.51 kg and -0.7 mmHg; both *P* < 0.001) but similar to those with dapagliflozin (-2.28 kg and -2.7 mmHg; *P* = 0.057 and *P* = 0.100, respectively). The exenatide QW plus dapagliflozin regimen was well tolerated with no unexpected safety findings; more patients treated with exenatide QW experienced gastrointestinal and injection site-related adverse events. No major hypoglycemia occurred.
CONCLUSIONS:
Among patients with type 2 diabetes uncontrolled with metformin, exenatide QW plus dapagliflozin provided sustained improvements in glycemia, weight, and SBP over 52 weeks, with no unexpected safety findings.

Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial.
Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, Annett MP, Aroda VR
Abstract
OBJECTIVE:
To compare the efficacy and safety of once-weekly semaglutide 1.0 mg s.c. with exenatide extended release (ER) 2.0 mg s.c. in subjects with type 2 diabetes.
RESEARCH DESIGN AND METHODS:
In this phase 3a, open-label, parallel-group, randomized controlled trial, 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomized (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. The primary end point was change from baseline in HbA_{1c} at week 56.
RESULTS:
Mean HbA_{1c} (8.3% [67.7 mmol/mol] at baseline) was reduced by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER (estimated treatment difference vs. exenatide ER [ETD] -0.62% [95% CI -0.80, -0.44] [-6.78 mmol/mol (95% CI -8.70, -4.86)]; *P* < 0.0001 for noninferiority and superiority). Mean body weight (95.8 kg at baseline) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD -3.78 kg [95% CI -4.58, -2.98]; *P* < 0.0001). Significantly more subjects treated with semaglutide (67%) achieved HbA_{1c} <7.0% (<53 mmol/mol) versus those taking exenatide ER (40%). Both treatments had similar safety profiles, but gastrointestinal adverse events were more common in semaglutide-treated subjects (41.8%) than in exenatide ER-treated subjects (33.3%); injection-site reactions were more frequent with exenatide ER (22.0%) than with semaglutide (1.2%).
CONCLUSIONS:
Semaglutide 1.0 mg was superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight after 56 weeks of treatment; the drugs had comparable safety profiles. These results indicate that semaglutide treatment is highly effective for subjects with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs.

Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial.
Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators

Abstract

BACKGROUND:

Despite common mechanisms of actions, glucagon-like peptide-1 receptor agonists differ in structure, pharmacokinetic profile, and clinical effects. This head-to-head trial compared semaglutide with dulaglutide in patients with inadequately controlled type 2 diabetes.

METHODS:

This was an open-label, parallel-group, phase 3b trial done at 194 hospitals, clinical institutions or private practices in 16 countries. Eligible patients were aged 18 years or older and had type 2 diabetes with HbA_{1c} 7·0-10·5% (53·0-91·0 mmol/mol) on metformin monotherapy. Patients were randomly assigned (1:1:1:1) by use of an interactive web-response system to once a week treatment with either semaglutide 0·5 mg, dulaglutide 0·75 mg, semaglutide 1·0 mg, or dulaglutide 1·5 mg subcutaneously. The primary endpoint was change from baseline in percentage HbA_{1c}; the confirmatory secondary endpoint was change in bodyweight, both at week 40. The primary analysis population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment and before the onset of rescue medication. The safety population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment. The trial was powered for HbA_{1c} non-inferiority (margin 0·4%) and bodyweight superiority. This trial is registered with ClinicalTrials.gov, number NCT02648204.

FINDINGS:

Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0·5 mg, 299 to dulaglutide 0·75 mg, 300 to semaglutide 1·0 mg, and 299 to dulaglutide 1·5 mg. 72 (6%) patients withdrew from the trial (22 receiving semaglutide 0·5 mg, 13 receiving dulaglutide 0·75 mg, 21 receiving semaglutide 1·0 mg, and 16 receiving dulaglutide 1·5 mg). From overall baseline mean, mean percentage HbA_{1c} was reduced by 1·5 (SE 0·06) percentage points with semaglutide 0·5 mg versus 1·1 (0·05) percentage points with dulaglutide 0·75 mg (estimated treatment difference [ETD] -0·40 percentage points [95% CI -0·55 to -0·25]; p<0·0001) and by 1·8 (0·06) percentage points with semaglutide 1·0 mg versus 1·4 (0·06) percentage points with dulaglutide 1·5 mg (ETD -0·41 percentage points [-0·57 to -0·25]; p<0·0001). From overall baseline mean, mean bodyweight was reduced by 4·6 kg (SE 0·28) with semaglutide 0·5 mg compared with 2·3 kg (0·27) with dulaglutide 0·75 mg (ETD -2·26 kg [-3·02 to -1·51]; p<0·0001) and by 6·5 kg (0·28) with semaglutide 1·0 mg compared with 3·0 kg (0·27) with dulaglutide 1·5 mg (ETD -3·55 kg [-4·32 to -2·78]; p<0·0001). Gastrointestinal disorders were the most frequently reported adverse event, occurring in 129 (43%) of 301 patients receiving semaglutide 0·5 mg, 133 (44%) of 300 patients receiving semaglutide 1·0 mg, 100 (33%) of 299 patients receiving dulaglutide 0·75 mg, and in 143 (48%) of 299 patients receiving dulaglutide 1·5 mg. Gastrointestinal disorders were also the most common reason for discontinuing treatment with semaglutide and dulaglutide. There were six fatalities: one in each semaglutide group and two in each dulaglutide group.

Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial.

Ludvik B, Frías JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, García-Pérez LE, Woodward DB, Milicevic Z

Abstract

BACKGROUND:

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors improve glycaemic control and reduce bodyweight in patients with type 2 diabetes through different mechanisms. We assessed the safety and efficacy of the addition of the once-weekly GLP-1 receptor agonist dulaglutide to the ongoing treatment regimen in patients whose diabetes is inadequately controlled with SGLT2 inhibitors, with or without metformin.

METHODS:

AWARD-10 was a phase 3b, double-blind, parallel-arm, placebo-controlled, 24-week study done at 40 clinical sites in Austria, Czech Republic, Germany, Hungary, Israel, Mexico, Spain, and the USA. Eligible adult patients (≥18 years) with inadequately controlled type 2 diabetes (HbA_{1c} concentration ≥7·0% [53 mmol/mol] and ≤9·5% [80 mmol/mol]), a BMI of 45 kg/m^2 or less, and taking stable doses (>3 months) of an SGLT2 inhibitor (with or without metformin) were randomly assigned (1:1:1) via an interactive web-response system to subcutaneous injections of either dulaglutide 1·5 mg, dulaglutide 0·75 mg, or placebo once per week for 24 weeks. Patients and investigators were masked to dulaglutide and placebo assignment, and those assessing outcomes were masked to study drug assignment. The primary objective was to test for the superiority of dulaglutide (1·5 mg or 0·75 mg) versus placebo for change in HbA_{1c} concentration from baseline at 24 weeks. All analyses were done in the intention-to-treat population, defined as all randomly assigned patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02597049.

FINDINGS:

Between Dec 7, 2015, and Feb 3, 2017, 424 patients were randomly assigned to dulaglutide 1·5 mg (n=142), dulaglutide 0·75 mg (n=142), and placebo (n=140). One patient in the dulaglutide 0·75 mg group was excluded from the analysis because they did not receive any dose of the study drug. The reduction in HbA_{1c} concentration at 24 weeks was larger in patients receiving dulaglutide (least squares mean [LSM] for dulaglutide 1·5 mg -1·34% [SE 0·06] or -14·7 mmol/mol [0·6]; dulaglutide 0·75 mg -1·21% [0·06] or -13·2 mmol/mol [0·6]) than in patients receiving placebo (-0·54% [0·06] or -5·9 mmol/mol [0·6]; p<0·0001 for both groups vs placebo). The LSM differences were -0·79% (95% CI -0·97 to -0·61) or -8·6 mmol/mol (-10·6 to -6·7) for dulaglutide 1·5 mg and -0·66% (-0·84 to -0·49) or -7·2 mmol/mol (-9·2 to -5·4) for dulaglutide 0·75 mg (p<0·0001 for both). Serious adverse events were reported for five (4%) patients in the dulaglutide 1·5 mg group, three (2%) patients in the dulaglutide 0·75 mg group, and five (4%) patients in the placebo group. Treatment-emergent adverse events were more common in patients treated with dulaglutide than in patients who received placebo, mainly because of an increased incidence of gastrointestinal adverse events. Nausea (21 [15%] patients in the dulaglutide 1·5 mg group vs seven [5%] in the dulaglutide 0·75 mg group vs five [4%] in the placebo group), diarrhoea (eight [6%] vs 14 [10%] vs four [3%]), and vomiting (five [4%] vs four [3%] vs one [1%]) were more common with dulaglutide than with placebo. One episode of severe hypoglycaemia was reported in the dulaglutide 0·75 mg group. Two (1%) patients receiving dulaglutide 1·5 mg died, but these deaths were not considered to be related to study drug; no deaths occurred in the other groups.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to January Week 3 2019

Search Strategy:

#	Searches	Results
1	exenatide.mp.	2582
2	dulaglutide.mp.	158
3	exenatide microspheres.mp.	4
4	liraglutide.mp. or LIRAGLUTIDE/	1774
5	lixisenatide.mp.	256

6	1 or 2 or 3 or 4 or 5	4019
7	limit 6 to (english language and humans)	2702
8	limit 7 to yr="2018 -Current"	183
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	35

Appendix 5: Key Inclusion Criteria

Population	Adult patients with type 2 diabetes
Intervention	GLP-1 receptor agonist
Comparator	Placebo or active treatment
Outcomes	HbA1c lowering or cardiovascular composite endpoint or cardiovascular death
Timing	NA
Setting	Outpatient

Appendix 6: Cardiovascular Trials of GLP-1 Receptor Agonists Compared to Placebo

Study	Population	CV Death, Nonfatal MI, or Nonfatal Stroke	CV Death
Marso, 2016 SUSTAIN-6 Semaglutide N=3,297	Established CV disease (age ≥ 50 years) or CV risk factors (age ≥ 60 years) HbA1c: 8.7% Duration of diabetes: 14 y	Event rate (2.1 y FU): 6.6% vs. 8.9% HR 0.74 (95% CI, 0.58 to 0.95) For noninferiority *moderate strength of evidence*	Event rate (2.1 y FU): 2.7% vs.2.8% HR 0.98 (95% CI, 0.65 to 1.48) *insufficient evidence*
Pfeffer, 2015 ELIXA Lixisenatide N=6,068	Recent acute coronary syndrome HbA1c: 7.7% Duration of diabetes: 9.3 y	Not reported – used an alternated composite endpoint of unstable angina, CV death, nonfatal MI or stroke. No difference compared to placebo was found.	Event rate (2.1 y FU) 5.1% vs. 5.2% HR 0.98 (95% CI, 0.78 to 1.22) *moderate strength of evidence*
Marso, 2016 LEADER Liraglutide N=9,340	Established CV disease (age ≥ 50 years) or CV risk factors (age ≥ 60 years) HbA1c: 8.7% Duration of diabetes: 13 y	Event rate (3.8 y FU): 13.0% vs. 14.9% HR 0.87 (95% CI, 0.78 to 0.97) *moderate strength of evidence*	Event rate (3.8 y FU): 4.7% vs. 6.0% HR 0.78 (95% CI, 0.66 to 0.93) *moderate strength of evidence*
Holman, 2018 EXSCEL Exenatide ER	Adult patients (mean age of 62 years) with T2DM (73.1% with established CV disease) HbA1c: 8.0%	Event rate (3.2 y FU): 11.4% vs. 12.2% HR 0.91 (95% CI, 0.83 to 1.00)	Event rate (3.2 y FU): 4.6% vs. 5.2% HR 0.88 (95% CI, 0.76 to 1.02)

N=14,752	Duration of diabetes: 12.0 y	For noninferiority *moderate strength of evidence*	*moderate strength of evidence*

Abbreviations: CI = confidence interval; CV = cardiovascular; ER = extended release; FU = follow-up; HR = hazard ratio; HbA1c = hemoglobin A1c; T2DM = type 2 diabetes mellitus

Appendix 6: Prior Authorization Criteria

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All GLP-1 receptor agonists

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 Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the request for semaglutide or dulaglutide?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the request for the Bydureon BCISE™ formulation of exenatide extended-release?	**Yes:** Go to #7	**No:** Go to #8
7. Is the patient using prandial or basal insulin?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months
8. Is the patient currently taking insulin?	**Yes:** Go to #9	**No:** Approve for up to 12 months
9. Is the patient requesting exenatide (Byetta or Bydureon®), liraglutide, albiglutide, or lixisenatide (including combination products) and using basal insulin?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. The safety and efficacy of other insulin formations with GLP-1 agonists have not been studied.

Initiating Metformin

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

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *7/18 (KS), 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *8/15/18; 4/1/17; 2/15; 1/14*

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

Pharmacy Utilization Summary Report: July 2017 - June 2018

Eligibility	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Total Members (FFS & Encounter)	982,276	963,901	959,096	961,528	962,260	963,814	961,458	959,824	963,504	965,503	964,592	965,132	964,407
FFS Members	143,784	127,100	130,304	128,336	118,961	126,786	121,061	121,425	120,975	121,038	113,512	117,714	124,250
OHP Basic with Medicare	33,513	33,453	33,651	33,710	33,679	33,770	33,777	34,033	34,222	34,378	34,471	34,742	33,950
OHP Basic without Medicare	12,903	12,546	12,333	12,541	11,983	12,096	12,068	12,220	12,198	12,207	11,665	11,817	12,215
ACA	97,368	81,101	84,320	82,085	73,299	80,920	75,216	75,172	74,555	74,453	67,376	71,155	78,085
Encounter Members	838,492	836,801	828,792	833,192	843,299	837,028	840,397	838,399	842,529	844,465	851,080	847,418	840,158
OHP Basic with Medicare	40,894	40,986	41,036	41,080	41,162	41,174	41,156	41,089	41,117	41,143	41,324	41,337	41,125
OHP Basic without Medicare	63,104	62,676	62,828	63,025	63,731	63,827	63,767	63,431	63,435	63,126	63,424	63,149	63,294
ACA	734,494	733,139	724,928	729,087	738,406	732,027	735,474	733,879	737,977	740,196	746,332	742,932	735,739

Gross Cost Figures for Drugs	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	YTD Sum
Total Amount Paid (FFS & Encounter)	$72,029,611	$75,314,146	$69,873,976	$73,603,576	$73,141,976	$69,942,707	$81,013,640	$71,385,681	$79,035,903	$75,856,741	$78,440,498	$74,028,787	$893,667,242
Mental Health Carve-Out Drugs	$7,994,622	$8,116,140	$7,101,216	$7,573,468	$7,267,459	$7,024,290	$7,925,880	$7,114,041	$7,699,583	$7,636,156	$7,949,798	$7,576,709	$90,979,363
OHP Basic with Medicare	$52	$117	$28	$282	$61	$36	$2,895	$73	$2,609	$1,634	$56	$39	$7,881
OHP Basic without Medicare	$3,269,113	$3,296,574	$2,949,813	$3,121,094	$3,033,932	$3,000,440	$3,288,065	$3,030,699	$3,240,618	$3,203,077	$3,345,086	$3,223,092	$38,001,604
ACA	$4,647,640	$4,737,982	$4,095,532	$4,394,267	$4,171,299	$3,965,588	$4,579,910	$4,029,443	$4,405,855	$4,375,942	$4,552,295	$4,301,753	$52,257,505
FFS Physical Health Drugs	$2,856,515	$2,972,081	$2,967,326	$2,845,998	$2,635,234	$2,706,510	$3,521,373	$2,968,893	$3,004,677	$2,903,874	$2,990,389	$2,735,644	$35,108,514
OHP Basic with Medicare	$221,915	$230,877	$228,850	$240,239	$235,632	$206,537	$261,269	$237,179	$251,186	$240,326	$274,031	$226,547	$2,854,588
OHP Basic without Medicare	$859,906	$1,008,347	$1,051,314	$956,368	$858,129	$889,590	$1,255,857	$950,128	$933,292	$932,768	$1,010,605	$855,795	$11,562,099
ACA	$1,653,334	$1,602,312	$1,564,084	$1,533,731	$1,404,305	$1,495,023	$1,868,898	$1,643,837	$1,680,967	$1,580,602	$1,567,066	$1,523,564	$19,117,723
FFS Physician Administered Drugs	$2,082,331	$2,583,756	$1,764,141	$1,352,033	$1,815,498	$1,360,070	$2,450,824	$2,339,225	$1,809,194	$1,853,179	$1,957,838	$2,194,317	$23,562,406
OHP Basic with Medicare	$543,695	$473,335	$339,008	$383,087	$541,113	$463,671	$550,060	$434,513	$492,228	$523,152	$560,636	$483,646	$5,788,145
OHP Basic without Medicare	$477,386	$352,217	$250,921	$328,100	$505,351	$268,999	$505,480	$884,038	$312,254	$124,008	$320,822	$575,974	$4,905,551
ACA	$807,310	$859,055	$939,393	$433,080	$518,851	$439,866	$1,027,953	$680,910	$665,501	$565,613	$659,938	$708,178	$8,305,648
Encounter Physical Health Drugs	$47,782,398	$49,831,031	$46,937,164	$50,080,296	$49,507,372	$48,085,551	$54,083,522	$48,003,498	$54,562,989	$51,499,038	$53,568,221	$50,425,411	$604,366,490
OHP Basic with Medicare	$122,099	$126,317	$116,447	$132,723	$126,622	$111,214	$134,511	$137,547	$153,062	$114,537	$127,575	$123,356	$1,526,010
OHP Basic without Medicare	$13,239,133	$13,898,476	$12,753,905	$13,403,252	$13,336,909	$12,472,539	$13,938,922	$12,377,504	$14,282,133	$13,405,709	$13,913,421	$13,277,609	$160,299,511
ACA	$33,748,181	$35,062,542	$33,290,216	$35,831,239	$35,338,766	$34,801,718	$39,242,489	$34,805,139	$39,391,812	$37,253,185	$38,810,949	$36,410,240	$433,986,476
Encounter Physician Administered Drugs	$11,313,745	$11,811,138	$11,104,129	$11,751,780	$11,916,414	$10,766,287	$13,032,040	$10,960,024	$11,959,459	$11,964,494	$11,974,253	$11,096,706	$139,650,469
OHP Basic with Medicare	$228,244	$221,555	$187,399	$205,590	$196,286	$200,279	$321,526	$249,954	$305,538	$265,565	$274,365	$247,727	$2,904,029
OHP Basic without Medicare	$2,689,638	$2,666,593	$2,239,817	$2,235,790	$2,615,123	$2,274,434	$3,105,425	$2,432,078	$2,486,025	$2,868,124	$2,754,276	$2,387,990	$30,755,314
ACA	$8,264,210	$8,718,513	$8,497,940	$8,998,398	$8,834,046	$8,121,208	$9,421,168	$8,157,585	$9,000,625	$8,546,843	$8,806,602	$8,344,821	$103,711,959

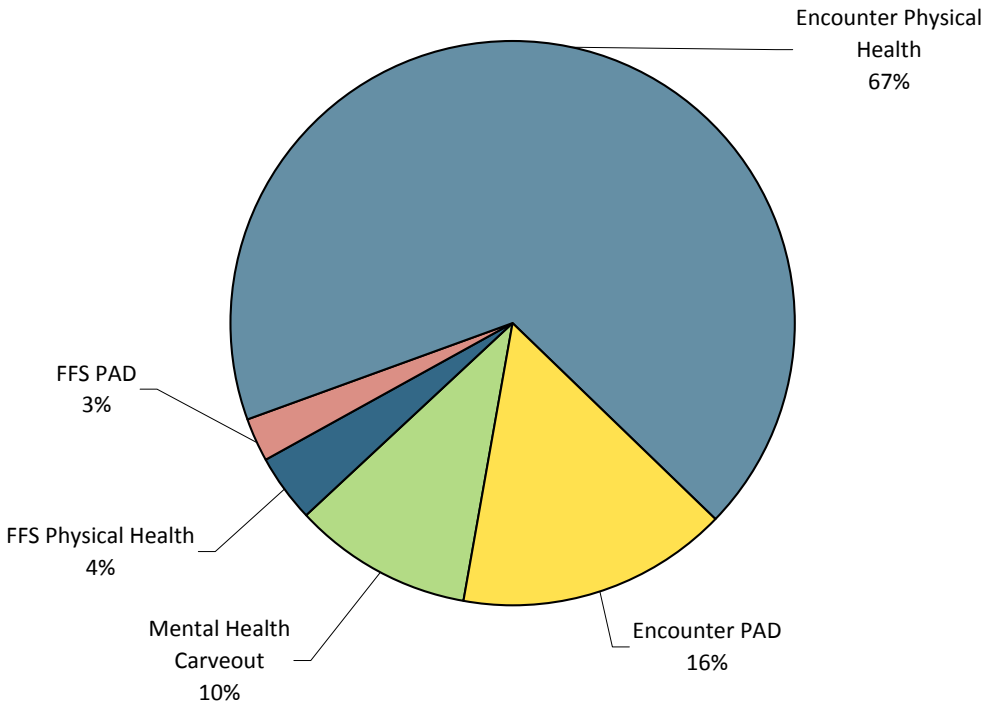
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

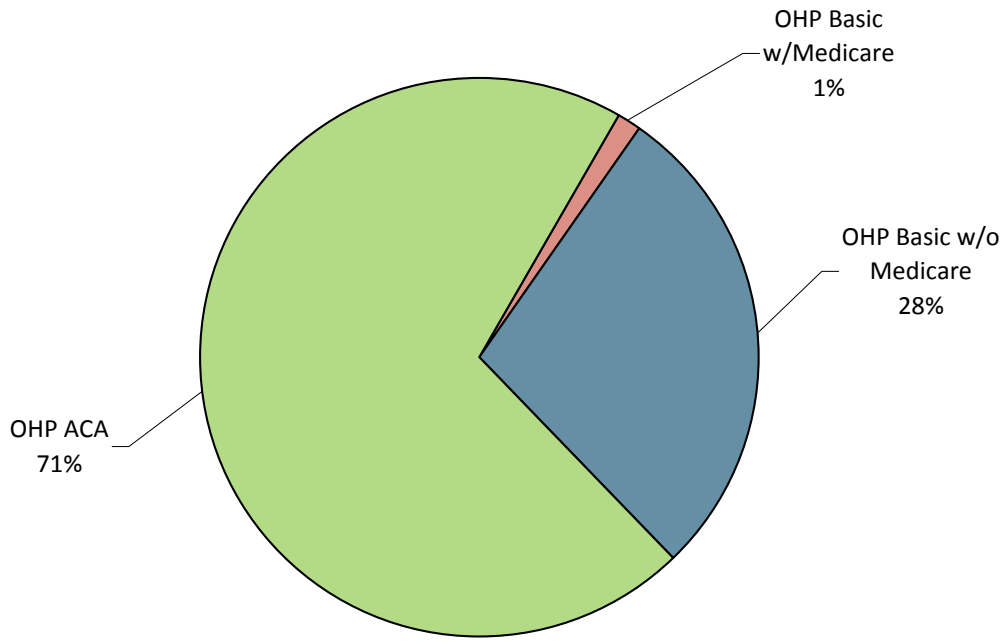
Last Updated: January 16, 2019

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

Pharmacy Utilization Summary Report: July 2017 - June 2018

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

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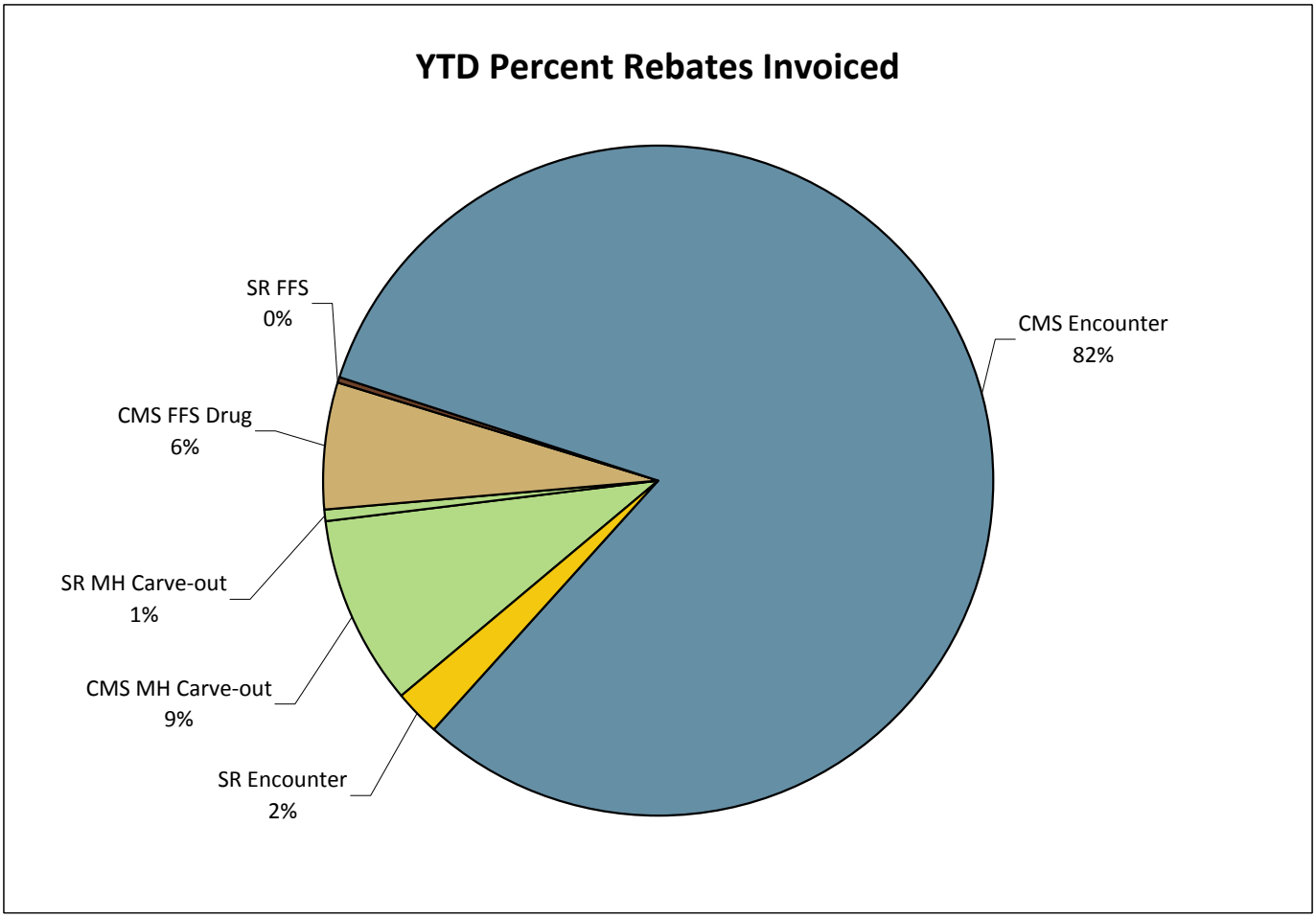
Pharmacy Utilization Summary Report: July 2017 - June 2018

Quarterly Rebates Invoiced	2017-Q3	2017-Q4	2018-Q1	2018-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$100,247,399	$100,809,477	$108,331,628	$107,134,843	$416,523,348
CMS MH Carve-out	$9,379,357	$8,960,881	$9,707,244	$9,880,816	$37,928,299
SR MH Carve-out	$608,802	$662,252	$531,804	$562,257	$2,365,115
CMS FFS Drug	$6,501,121	$5,700,097	$6,899,883	$6,436,309	$25,537,410
SR FFS	$178,107	$185,410	$213,924	$198,535	$775,975
CMS Encounter	$81,320,124	$82,677,713	$89,057,284	$87,232,300	$340,287,421
SR Encounter	$2,259,888	$2,623,124	$1,921,489	$2,824,627	$9,629,127

Quaterly Net Drug Costs	2017-Q3	2017-Q4	2018-Q1	2018-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$116,970,334	$115,878,781	$123,103,596	$121,191,183	$477,143,894
Mental Health Carve-Out Drugs	$13,223,819	$12,242,084	$12,500,457	$12,719,590	$50,685,949
FFS Phys Health + PAD	$8,546,923	$6,829,836	$8,980,380	$8,000,396	$32,357,534
Encounter Phys Health + PAD	$95,199,593	$96,806,862	$101,622,759	$100,471,197	$394,100,411



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

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Pharmacy Utilization Summary Report: July 2017 - June 2018

Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$73.33	$78.13	$72.85	$76.55	$76.01	$72.57	$84.26	$74.37	$82.03	$78.57	$81.32	$76.70	$77.23
Mental Health Carve-Out Drugs	$8.14	$8.42	$7.40	$7.88	$7.55	$7.29	$8.24	$7.41	$7.99	$7.91	$8.24	$7.85	$7.86
FFS Physical Health Drugs	$19.87	$23.38	$22.77	$22.18	$22.15	$21.35	$29.09	$24.45	$24.84	$23.99	$26.34	$23.24	$23.64
FFS Physician Administered Drugs	$14.48	$20.33	$13.54	$10.54	$15.26	$10.73	$20.24	$19.26	$14.96	$15.31	$17.25	$18.64	$15.88
Encounter Physical Health Drugs	$56.99	$59.55	$56.63	$60.11	$58.71	$57.45	$64.35	$57.26	$64.76	$60.98	$62.94	$59.50	$59.94
Encounter Physician Administered Drugs	$13.49	$14.11	$13.40	$14.10	$14.13	$12.86	$15.51	$13.07	$14.19	$14.17	$14.07	$13.09	$13.85

Claim Counts	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Total Claim Count (FFS & Encounter)	988,885	1,031,039	986,261	1,050,832	1,019,796	1,005,197	1,115,794	969,901	1,074,499	1,046,973	1,083,932	1,012,976	1,032,174
Mental Health Carve-Out Drugs	147,058	153,238	144,363	153,641	149,558	145,490	159,751	141,713	155,473	153,703	159,261	149,562	151,068
FFS Physical Health Drugs	61,524	62,965	59,027	60,714	56,901	56,437	66,818	59,084	61,645	59,049	59,882	56,041	60,007
FFS Physician Administered Drugs	18,691	19,537	18,383	17,933	16,851	16,397	26,169	20,723	21,307	20,295	20,693	18,756	19,645
Encounter Physical Health Drugs	655,677	683,627	654,401	701,816	682,550	675,691	738,482	643,519	720,858	700,310	726,633	679,527	688,591
Encounter Physician Administered Drugs	105,935	111,672	110,087	116,728	113,936	111,182	124,574	104,862	115,216	113,616	117,463	109,090	112,863

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$72.84	$73.05	$70.85	$70.04	$71.72	$69.58	$72.61	$73.60	$73.56	$72.45	$72.37	$73.08	$72.15
Mental Health Carve-Out Drugs	$54.36	$52.96	$49.19	$49.29	$48.59	$48.28	$49.61	$50.20	$49.52	$49.68	$49.92	$50.66	$50.19
FFS Physical Health Drugs	$46.43	$47.20	$50.27	$46.88	$46.31	$47.96	$52.70	$50.25	$48.74	$49.18	$49.94	$48.82	$48.72
FFS Physician Administered Drugs	$111.41	$132.25	$95.97	$75.39	$107.74	$82.95	$93.65	$112.88	$84.91	$91.31	$94.61	$116.99	$100.01
Encounter Physical Health Drugs	$72.87	$72.89	$71.73	$71.36	$72.53	$71.17	$73.24	$74.60	$75.69	$73.54	$73.72	$74.21	$73.13
Encounter Physician Administered Drugs	$106.80	$105.77	$100.87	$100.68	$104.59	$96.83	$104.61	$104.52	$103.80	$105.31	$101.94	$101.72	$103.12

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$30.80	$30.78	$29.81	$29.55	$30.00	$29.44	$29.26	$28.52	$28.60	$27.97	$27.82	$27.61	$29.18
Mental Health Carve-Out Drugs	$30.38	$29.10	$24.89	$24.66	$23.78	$23.45	$23.77	$23.88	$23.06	$22.62	$22.76	$22.75	$24.59
FFS Physical Health Drugs	$23.54	$23.33	$24.57	$23.96	$23.10	$24.08	$24.44	$24.71	$23.42	$22.74	$22.71	$22.98	$23.63
Encounter Physical Health Drugs	$31.58	$31.86	$31.43	$31.17	$32.00	$31.23	$30.94	$29.94	$30.29	$29.63	$29.40	$29.10	$30.71

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$662.78	$641.48	$584.52	$570.56	$621.65	$638.76	$668.21	$709.76	$733.04	$719.21	$737.46	$739.29	$668.89
Mental Health Carve-Out Drugs	$893.22	$899.82	$900.64	$928.66	$933.46	$964.37	$981.02	$1,012.10	$1,003.27	$1,021.42	$1,010.48	$1,033.83	$965.19
FFS Physical Health Drugs	$398.60	$398.98	$391.85	$343.34	$372.32	$379.86	$447.35	$416.95	$430.89	$438.75	$457.70	$433.05	$409.14
Encounter Physical Health Drugs	$663.95	$638.99	$574.82	$561.00	$614.71	$632.74	$660.89	$709.42	$733.55	$714.62	$734.24	$736.19	$664.59

Multi-Source Drug Use Percentage	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Multi-Source Drug Use Percentage	94.1%	94.0%	93.4%	93.3%	93.8%	94.0%	94.0%	94.1%	94.2%	94.2%	94.3%	94.2%	94.0%
Mental Health Carve-Out Drugs	97.2%	97.3%	97.2%	97.3%	97.3%	97.4%	97.3%	97.3%	97.3%	97.3%	97.3%	97.2%	97.3%
FFS Physical Health Drugs	93.9%	93.6%	93.0%	92.8%	93.4%	93.3%	93.3%	93.5%	93.8%	93.6%	93.7%	93.7%	93.5%
Encounter Physical Health Drugs	93.5%	93.2%	92.6%	92.4%	93.0%	93.4%	93.3%	93.4%	93.5%	93.6%	93.7%	93.6%	93.3%

Preferred Drug Use Percentage	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Avg Monthly
Preferred Drug Use Percentage	86.45%	86.21%	87.10%	86.91%	86.72%	86.68%	87.09%	86.96%	86.86%	86.63%	86.73%	86.56%	86.7%
Mental Health Carve-Out Drugs	74.85%	74.82%	74.74%	74.66%	74.47%	74.52%	74.51%	74.36%	74.45%	74.17%	74.23%	73.93%	74.5%
FFS Physical Health Drugs	95.36%	95.35%	95.48%	95.38%	95.54%	95.48%	95.75%	95.61%	95.59%	95.53%	95.46%	95.76%	95.5%
Encounter Physical Health Drugs	88.18%	87.90%	89.06%	88.88%	88.68%	88.57%	89.04%	88.96%	88.79%	88.62%	88.75%	88.57%	88.7%

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 16, 2019

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,526,404	15.4%	4,686	$1,179	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,347,177	6.5%	1,312	$1,789	V
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,194,862	3.3%	629	$1,900	Y
4	REXULTI	Antipsychotics, 2nd Gen	$1,083,731	3.0%	1,006	$1,077	V
5	VRAYLAR	Antipsychotics, 2nd Gen	$825,691	2.3%	751	$1,099	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$643,836	1.8%	116	$5,550	V
7	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$608,530	1.7%	1,693	$359	V
8	SAPHRIS	Antipsychotics, 2nd Gen	$578,640	1.6%	819	$707	Y
9	FLUOXETINE HCL	Antidepressants	$533,066	1.5%	32,260	$17	Y
10	DULOXETINE HCL	Antidepressants	$505,805	1.4%	29,787	$17	V
11	SERTRALINE HCL	Antidepressants	$478,520	1.3%	42,528	$11	Y
12	ATOMOXETINE HCL*	ADHD Drugs	$442,849	1.2%	5,198	$85	Y
13	BUPROPION XL	Antidepressants	$438,452	1.2%	22,629	$19	V
14	TRAZODONE HCL	Antidepressants	$423,533	1.2%	38,366	$11	
15	TRINTELLIX	Antidepressants	$404,229	1.1%	1,084	$373	V
16	VIIBRYD	Antidepressants	$382,559	1.1%	1,491	$257	V
17	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$371,411	1.0%	106	$3,504	Y
18	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$369,577	1.0%	422	$876	Y
19	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$364,653	1.0%	1,989	$183	
20	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$331,894	0.9%	2	$165,947	
21	VENLAFAXINE HCL ER	Antidepressants	$297,106	0.8%	1,739	$171	V
22	ARISTADA	Antipsychotics, Parenteral	$294,156	0.8%	151	$1,948	Y
23	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$273,493	0.8%	1,784	$153	V
24	ESCITALOPRAM OXALATE	Antidepressants	$266,424	0.7%	24,323	$11	Y
25	LAMOTRIGINE	Antiepileptics (oral & rectal)	$264,206	0.7%	22,935	$12	Y
26	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$252,490	0.7%	17,434	$14	
27	HUMIRA PEN*	Biologics for Autoimmune Conditions	$241,162	0.7%	78	$3,092	Y
28	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$233,112	0.6%	14,226	$16	V
29	AMITRIPTYLINE HCL	Antidepressants	$232,957	0.6%	14,996	$16	Y
30	CITALOPRAM HBR	Antidepressants	$217,194	0.6%	22,366	$10	Y
31	VENLAFAXINE HCL ER	Antidepressants	$197,775	0.6%	14,937	$13	Y
32	CONCERTA*	ADHD Drugs	$184,513	0.5%	795	$232	N
33	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$182,621	0.5%	15,436	$12	Y
34	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$161,572	0.5%	612	$264	V
35	ENBREL*	Biologics for Autoimmune Conditions	$160,162	0.4%	32	$5,005	Y
36	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$155,536	0.4%	13	$11,964	Y
37	FETZIMA	Antidepressants	$149,976	0.4%	413	$363	V
38	ADVATE	Antihemophilia Factors	$147,782	0.4%	8	$18,473	
39	ORKAMBI*	Cystic Fibrosis	$146,653	0.4%	13	$11,281	N
40	BUPROPION HCL SR	Antidepressants	$141,994	0.4%	10,678	$13	Y
		Top 40 Aggregate:	**$22,056,303**		**349,843**	**$5,951**	
		All FFS Drugs Totals:	**$35,865,047**		**662,189**	**$534**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- 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

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$371,411	3.0%	106	$3,504	Y
2	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$364,653	2.9%	1,989	$183	
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$331,894	2.7%	2	$165,947	
4	HUMIRA PEN*	Biologics for Autoimmune Conditions	$241,162	2.0%	78	$3,092	Y
5	CONCERTA*	ADHD Drugs	$184,513	1.5%	795	$232	N
6	ENBREL*	Biologics for Autoimmune Conditions	$160,162	1.3%	32	$5,005	Y
7	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$155,536	1.3%	13	$11,964	Y
8	ADVATE	Antihemophilia Factors	$147,782	1.2%	8	$18,473	
9	ORKAMBI*	Cystic Fibrosis	$146,653	1.2%	13	$11,281	N
10	LANTUS SOLOSTAR*	Diabetes, Insulins	$141,134	1.1%	410	$344	Y
11	Rituximab Injection	Physican Administered Drug	$133,776	1.1%	31	$4,315	
12	BIKTARVY	HIV	$132,036	1.1%	53	$2,491	Y
13	MAKENA*	Progestational Agents	$130,673	1.1%	42	$3,111	Y
14	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$130,349	1.1%	37	$3,523	
15	GENVOYA	HIV	$127,530	1.0%	54	$2,362	Y
16	Injection, Nivolumab	Physican Administered Drug	$124,339	1.0%	47	$2,646	
17	NOVOLOG FLEXPEN	Diabetes, Insulins	$121,339	1.0%	253	$480	Y
18	Factor Viii Recombinant Nos	Physican Administered Drug	$117,929	1.0%	4	$29,482	
19	Inj Pembrolizumab	Physican Administered Drug	$116,956	0.9%	48	$2,437	
20	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$111,526	0.9%	377	$296	Y
21	Factor Viii Pegylated Recomb	Physican Administered Drug	$111,195	0.9%	4	$27,799	
22	Etonogestrel Implant System	Physican Administered Drug	$106,329	0.9%	171	$622	
23	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$104,921	0.8%	1,908	$55	Y
24	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$103,604	0.8%	1,660	$62	Y
25	LANTUS	Diabetes, Insulins	$103,444	0.8%	298	$347	Y
26	HYDROXYPROGESTERONE CAPROAT	Progestational Agents	$101,477	0.8%	48	$2,114	N
27	Drugs Unclassified Injection	Physican Administered Drug	$94,351	0.8%	4,692	$20	
28	Mirena, 52 Mg	Physican Administered Drug	$93,198	0.8%	153	$609	
29	VYVANSE*	ADHD Drugs	$91,716	0.7%	637	$144	Y
30	NUVARING	STC 63 - Oral Contraceptives	$90,608	0.7%	359	$252	
31	FLOVENT HFA	Corticosteroids, Inhaled	$87,258	0.7%	511	$171	Y
32	Aflibercept Injection	Physican Administered Drug	$84,798	0.7%	174	$487	
33	TRUVADA	HIV	$76,925	0.6%	65	$1,183	Y
34	ACTEMRA*	Biologics for Autoimmune Conditions	$76,817	0.6%	20	$3,841	N
35	HUMIRA*	Biologics for Autoimmune Conditions	$75,992	0.6%	16	$4,749	Y
36	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$75,737	0.6%	273	$277	Y
37	TRIUMEQ	HIV	$74,597	0.6%	35	$2,131	Y
38	SUBOXONE*	Substance Use Disorders, Opioid & Alcohol	$74,562	0.6%	452	$165	Y
39	VITAMIN D3	Calcium/Vit D Replacement, Oral	$73,162	0.6%	7,834	$9	Y
40	AFINITOR	Antineoplastics	$72,362	0.6%	5	$14,472	
		Top 40 Aggregate:	**$5,264,407**		**23,707**	**$8,267**	
		All FFS Drugs Totals:	**$12,362,535**		**194,110**	**$547**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- 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 16, 2019

ProDUR Report for October through December 2018
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	12	7	0	5	0.01%	58.33%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,498	311	0	1,187	1.27%	20.76%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	179	52	0	127	0.10%	29.05%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	78,388	14,160	192	64,025	68.30%	18.06%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	24,425	6,279	8	18,095	21.23%	25.71%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	723	128	0	589	0.60%	17.70%
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	4	4	0	0	0.01%	100.00%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	1,011	265	0	746	0.80%	26.21%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	652	155	2	493	0.50%	23.77%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	52	30	0	22	0.02%	57.69%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,752	2,187	3	5,546	6.73%	28.21%
		Totals	**114,696**	**23,578**	**205**	**90,835**	**99.57%**	**20.56%**

ProDUR Report for October through December 2018

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,370	253	1,117	11,897	11.5%	18.5%
ER	Hydrocodone/APAP	23	10	13	2,620	0.9%	43.5%
ER	Oxycodone	83	36	47	1,991	4.2%	43.4%
ER	Oxycodone/APAP	7	2	5	523	1.3%	28.6%
ER	Tramadol	22	11	11	837	2.6%	50.0%
ER	Buspirone (Buspar)	2,267	377	1,890	27,183	8.3%	16.6%
ER	Lorazepam	547	146	401	14,406	3.8%	26.7%
ER	Alprazolam	316	56	260	6,752	4.7%	17.7%
ER	Diazepam	224	44	180	5,396	4.2%	19.6%
ER	Lamictal (Lamotrigine)	4,294	745	3,549	35,208	12.2%	17.3%
ER	Abilify (Aripiprazole)	2,913	488	2,425	22,910	12.7%	16.8%
ER	Seroquel (Quetiapine)	3,485	690	2,795	25,133	13.9%	19.8%
ER	Risperdal (Risperidone)	1,936	376	1,559	13,929	13.9%	19.4%
ER	Wellbutrin (Bupropion)	4,440	695	3,745	48,008	9.2%	15.7%
ER	Zoloft (Sertraline)	5,370	940	4,430	54,069	9.9%	17.5%
ER	Prozac (Fluoxetine)	3,932	594	3,338	43,560	9.0%	15.1%
ER	Celexa (Citalopram)	2,214	278	1,937	27,169	8.1%	12.6%

ProDUR Report for October through December 2018

Early Refill Reason Codes

DUR Alert	Month	# Overrides	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	CC-Other
ER	October	3,733	109	287	1,090	8	2,239	0	142
ER	November	2,958	114	244	874	2	1,724	0	104
ER	December	2,939	147	288	849	6	1,648	1	133
	Total =	**9,630**	**370**	**819**	**2,813**	**16**	**5,611**	**1**	**379**

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

Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	637			
		Unique Patients Identified	891			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	272			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$11,799			
	Lamotrigine ER to IR	Unique Prescribers Identified	363			
		Unique Patients Identified	652			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	110			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$27,266			

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

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	88	12		
		Total Faxes Successfully Sent	34	3		
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	5			
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	4			
		Prescriptions Unchanged after 3 Months of Fax Sent	3			
		Safety Monitoring Profiles Identified	3			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$8,879			

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	46			
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	9			
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	85			
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5			
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed	19			
		RetroDUR_Letters Sent To Providers	2			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
	Lock-In	RetroDUR_Profiles Reviewed	52			
		RetroDUR_Letters Sent To Providers	3			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
		Locked In	3			
	Polypharmacy	RetroDUR_Profiles Reviewed	16			
		RetroDUR_Letters Sent To Providers	3			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			

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Updates on Testosterone Therapy

Jisha Jacob, Pharm D, OSU College of Pharmacy, Drug Use Research and Management

Aggressive direct-to-consumer advertising and development of more convenient formulations of testosterone (subsequently referred to as *T*) have played an important role in the dramatic increase of T prescribing rates in the United States.[1] The annual rate of T initiation has increased 3- to 4-fold from beginning in the year 2000 through 2011.[2,3] The largest change was with the topical T formulation with a 5-fold increase observed during the decade.[1] Increased utilization of T has been attributed to guideline nonadherence when initiating and monitoring testosterone therapy and an overall increase in routine population-level screening for testosterone deficiency and use of testosterone replacement therapy (TRT) for off-label indications.[4] The purpose of this review is to evaluate recent evidence focused on risks associated with TRT.

Background

The 2018 Clinical Practice Guidelines published by the Endocrine Society recommend against screening for testosterone deficiency (TD) in the general population due to the lack of clear benefit of early detection of androgen deficiency and long-term testosterone therapy in asymptomatic patients.[5] A diagnosis of hypogonadism should only be made in men with clinical symptoms suggestive of TD and consistently low serum T concentrations.[5] In general, the Endocrine Society recommends 300 ng/dL as the lower limit of the normal range for total testosterone level.

Symptoms of low T are variable. Sexual symptoms include diminished sexual libido, decreased frequency of sexual thoughts, decreased frequency of nocturnal erections, and erectile dysfunction (ED). Nonspecific symptoms include fatigue, decreased energy, depressed mood, irritability, and decreased sense of well-being. Low serum T concentrations may also be accompanied by other objective signs such as anemia, decreased bone-mineral density (BMD), reduced muscle strength and mass, increased body fat mass, and weight gain.

Testosterone levels are subject to circadian variation and are generally the highest in the morning. Therefore, measurement of testosterone levels should be performed in the morning as the normal ranges from serum testosterone are based on morning blood samples. There is no general consensus on the absolute level of low T below which a man can be considered androgen-deficient. For these reasons, the diagnosis should be based on both presence of clinical symptoms and confirmed low T levels

Low T levels can result from testicular failure caused by disruption of one or more levels of hypothalamic-pituitary-gonadal (HPG) axis.[5] Primary hypogonadism results from abnormalities at the testicular or gonadal level, whereas defects of the hypothalamus or pituitary could lead to secondary hypothyroidism. Examples of primary causes include genetic disorders, testicular trauma or chemotherapy and secondary causes include pituitary tumors and hyperprolactinemia. Distinguishing between primary and secondary hypogonadism is important as TD can be reversible in some cases of secondary hypogonadism by managing the underlying condition (e.g., obesity) or discontinuing the offending medication (e.g., opioids).

In general, testosterone levels tend to decline by 0.4-2% annually in men after the age of 30. Due to the extensive use of TRT in age-related hypogonadism, the Food and Drug Administration (FDA) published a statement in 2014 notifying providers that there is insufficient safety and efficacy data on the use of TRT for age-related hypogonadism.[6] Currently, the use of TRT is FDA-approved for men who have hypogonadism due to primary or secondary causes. The use of TRT is contraindicated in patients with pre-existing breast/prostate cancer, prostate-specific antigen (PSA) >4 ng/dL, hematocrit over 50%, untreated severe sleep apnea, severe lower urinary tract symptoms, uncontrolled or poorly controlled heart failure, or in those desiring fertility.[5] A thorough urological evaluation is recommended in patients with prostate nodule or induration or serum PSA level > 4 ng/mL or serum PSA level > 3 ng/mL in men at high risk for prostate cancer (e.g., African-Americans or men with first-degree relatives with prostate cancer) prior to initiation of TRT.[5]

The goal of TRT is to provide symptom relief by restoring serum T concentrations to levels within normal range of 300-1000 ng/dL.[5] Once initiated, monitoring recommendations for TRT include assessment of serum T levels, clinical response and adverse effects at 3 months following initiation and then annually thereafter. Common adverse effects associated with TRT include acne, gynecomastia, peripheral edema, and polycythemia. However, the serious concerns identified with TRT are an increased incidence of cardiovascular (CV) events and prostate cancer. It was these risks that prompted the FDA to issue a safety alert in January 2014 regarding TRT.

Oregon Health Plan (OHP) Fee-for service (FFS) policy requires prior authorization for all testosterone products. Covered indications include testicular hypofunction, hypopituitarism and related disorders, AIDS-related cachexia, and gender dysphoria.

Cardiovascular Events

The use of TRT in TD has been in clinical practice for over 70 years, however, there has been an increasing concern regarding the CV risks associated with TRT. The data available on the CV safety profile of TRT is conflicting. Earlier data supported the view that a low serum T level is associated with increased CV risk and therefore, TRT can have beneficial impact on CV risk reduction.[7] However, some studies within the last decade have suggested increased CV risk with the use of exogenous testosterone therapy. As a result, in 2014, the FDA released a statement mandating labeling changes for all testosterone products to inform patients about the possible increased risk of heart attacks and strokes associated with TRT.[6] Additionally, health care providers were also advised to prescribe TRT only for men with low T levels caused by primary or secondary hypogonadism, and not age-related hypogonadism.

The statement released by the FDA was based on five observational studies[8-13] and 2 meta-analyses[14-15]. The five observational studies were retrospective cohort studies that yielded conflicting results. Two of these studies[8-9] found statistically significant CV harm with TRT, two studies[10-11]found a decreased risk of all-cause mortality with TRT, and one study[12] was inconclusive. Due to the conflicting results and the retrospective nature of these studies, the generalizability of these results is limited.

Additional evidence from a meta-analysis that included 27 placebo-controlled testosterone studies of 12 weeks duration or longer showed an increase in CV events in the TRT group when compared with the placebo group.[13] However, this analysis only included trials that reported 1 or more CV events. As a result, failure to include any trials that did not show increased CV risk could have skewed the analysis. Furthermore, the results from 2 out of the 27 studies contributed to a third of the CV outcomes in the TRT group. Additionally, 18 of the 23 events reported in one of the studies would not generally qualify as CV events (e.g., edema, elevated blood pressure, chest pain and tachycardia with fatigue).[13] The high number of adverse events reported in one study could likely be due to the use of an unapproved oral formulation of micronized T at very high doses in men with cirrhosis of the liver, resulting in serum T concentrations approximately 20 times the upper limit of the normal range.[13] Therefore, the increased CV risk could potentially

be due to methodological issues, inclusion/exclusion criteria challenges and varying formulations of T included in trials.[13]

Recently, several systematic reviews and meta-analyses have been published to examine the association between TRT and CV disease and mortality. One analysis evaluated the association between exogenous TRT (injection, oral, or topical) and risk of serious CV events. It included 39 randomized controlled trials (RCTs) and 10 observational studies, including those mentioned above.[15] The included trials represented 5451 men, of which 3230 received exogenous T and 2221 received placebo. The duration of trials ranged from 6 weeks to 3 years and the mean ages of participants were 50-60 years. The findings of this systematic review did not reveal any significant association between TRT and myocardial infarction (MI) (odds ratio [OR] 0.87; 95% confidence interval [CI], 0.39-1.93; 16 RCTs), stroke (OR 2.17; 95% CI, 0.63-7.54; 9 RCTs), or mortality (OR 0.88; 95% CI, 0.55-1.41; 20 RCTs). Due to presence of high clinical trial heterogeneity, a pooled analysis was not conducted using data from the observational studies.[15]

Another analysis, The Testosterone Trials, were a multi-center set of 7 double-blind, placebo-controlled trials designed to determine whether testosterone would benefit older men.[16] Men 65 years of age or older (n=790) with serum T levels less than 275 ng/dL were assigned to receive either testosterone gel or placebo gel for 1 year. The primary endpoints included improvements in sexual function, physical function and fatigue. Results showed a modest benefit in sexual function and physical function in symptomatic older men with low T levels. Seven major CV events (MI, stroke, or death from CV causes) were observed in each study group during the treatment period. Two events in the testosterone group and nine events in the placebo group were observed in the subsequent year. However, given that the study was not designed to investigate CV events, it is not possible to draw a definitive conclusion on the impact of TRT on cardiovascular risk.[16]

Prostate Cancer

The theory of prostate cancer being an androgen-dependent disease was established by the work of Charles Huggins in 1941.[17] This is based on the concept that development of prostate relies on androgen stimulation and high levels of testosterone could contribute to the acceleration of prostate growth, not only in benign disease but also in cancer.[17,18] Furthermore, testosterone suppression, by the means of orchiectomy followed by use of medical castration with LHRH agonists, has historically been considered first line therapy for advanced prostate cancer since the 1980s.[17] However, this does not take into account that malignant prostate tumors become increasingly prevalent as men age and experience a decline in serum T levels. Therefore, the question of whether high levels of endogenous testosterone or testosterone supplementation stimulates the development of prostate cancer continues to remain controversial.

A recent systematic review and meta-analysis evaluated the possible relationship between endogenous and exogenous testosterone and prostate-specific antigen (PSA) and prostate cancer.[19] This meta-analysis examined the link between prostate cancer with endogenous testosterone levels and exogenous testosterone separately. Twenty prospective cohort studies that reported risk estimates for prostate cancer and endogenous testosterone levels were included. The meta-analysis results showed a summary relative risk (SRR) of prostate cancer for an increase of 5 nmol/L of testosterone of 0.88 (95% CI 0.96, 1.02). Additionally, 26 placebo-controlled randomized trials of TRT that reported data on PSA levels and/or prostate cancer were included. The overall difference in PSA levels after TRT initiation was 0.10 ng/mL (95% CI -0.28 to 0.48) and the SRR of prostate cancer as an adverse effect of TRT initiation was 0.87 (95% CI 0.30 to 2.50). These results did not reveal a statistical difference between endogenous testosterone levels and prostate cancer or between TRT and an increased risk of prostate cancer and/or change in PSA levels.

Conclusion

Studies have not demonstrated a clear association between testosterone therapy and CV events or prostate cancer. Given the limitations of currently available evidence on benefit-risk profile, current OHP policy restricts the use of testosterone therapy in patients with symptomatic hypogonadism due to primary or secondary causes.

For patients with a qualifying indication for testosterone replacement, preferred OHP FFS products are topical testosterone gel, testosterone cypionate and testosterone enanthate

Peer Reviewed by: Jason Hedges, M.D., Ph.D., Associate Professor, Department of Urology, Oregon Health and Science University

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Basal Insulin Update

Kathy Sentena, Pharm D, OSU College of Pharmacy, Drug Use Research and Management

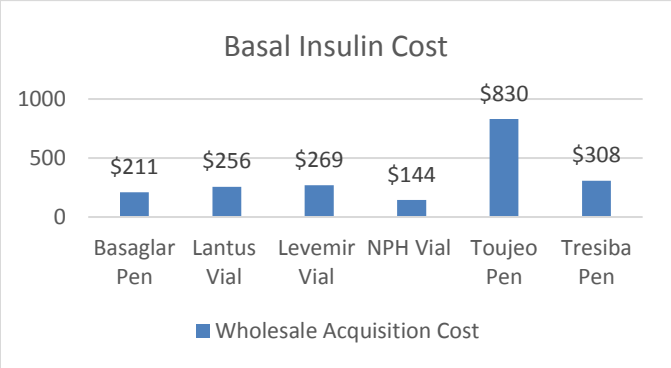
Introduction

The focus of this newsletter is using basal insulin in patients with type 2 diabetes mellitus (T2DM) in light of dramatic cost increases within the long-acting insulin market and the introduction of the first follow-on insulin product. With the incidence of diabetes doubling in Oregon over the past 20 years, the healthcare system has been substantially impacted.[1] In Oregon alone, it is estimated that approximately 287,000 adults have diabetes, costing the state $2.2 billion dollars annually on medical expenditures.[1] Effectiveness, safety and cost considerations of using basal insulin therapy will be discussed below.

The Cost of Basal Insulins

The long-acting insulin analogs have experienced a trend of escalating costs with increases in wholesale prices of more than 160% in the past five years.[2] A 2016 analysis found that the cost of insulin tripled between 2002 to 2013, with the cost of analog insulin consistently double that of human insulin.[3,4] This translates to an average cost to patients of approximately $400-$500 a month (Figure 1).[3,5,6] There is evidence of underuse of insulin due to high costs, which subsequently has resulted in poor glycemic control.[7] Additionally, utilization of lower cost neutral protamine Hagedorn (NPH) insulin continues to decline.

Figure 1. Comparative Costs for Basal Insulin[6]



Basal Insulins: NPH vs. Long-Acting Insulin Analogs

With the approval of insulin glargine (Lantus) in 2000 there has been the perception of superiority of long-acting insulin analogs over intermediate acting, NPH insulin. Clinical trial data suggests a modest benefit in reduced risk of nocturnal hypoglycemia with long-acting insulin analogs (glargine, detemir and degludec) compared to NPH insulin, without clinically significant differences in hemoglobin A1c (HbA1c) lowering. This is supported by evidence from a Cochrane Systematic Review (Table 1).[8] However, the incidence of severe hypoglycemia with long-acting insulin analogs and NPH in patients with T2DM is similar.[9] This was substantiated by a recent observational, retrospective review which analyzed the comparative hypoglycemia rates of long-acting insulin analogs (glargine or detemir) to NPH insulin and found no statistically significant difference in the incidence of emergency department (ED) visits/hospitalizations between the two groups (Table 1).[9] There is a lack of evidence to support clinically relevant differences for most outcomes when comparing long-acting insulin analogs to NPH and additional comparative evidence between NPH and concentrated insulins (insulin glargine U-300) and ultra-long acting insulin (insulin degludec) is needed.[8]

Table 1. Clinical Trial Data

Source	Outcome	Comparator	Results
Cochrane[8]	Nocturnal hypoglycemia†	LA insulin analogs vs. NPH	LA insulin: 24% NPH: 39% P<0.05*
Observational, Retrospective Trial[9]	ER visits or hospitalizations	LA insulin analogs vs. NPH	LA insulin: 39 (2%) NPH: 354 (1.5%) P>0.05

Key: * Data not pooled but individual comparisons were statistically significant, † Most commonly defined as an event taking place while sleeping, between bedtime and getting up
Abbreviations: LA- long-acting; NPH - neutral protamine Hagedorn

Follow-on Insulin vs. Biosimilars

Follow-on insulins and biosimilars may offer a cost advantage of approximately 20% to 30% less than their reference insulin for some patients; however, many reference insulin manufacturers offer incentives that provide a price advantage over follow-on insulin products. Therefore, the most cost-effective option will be dependent upon patient-specific health care coverage.

Clinically, follow-on products are similar to their reference biologic (insulin); however, biologics are complex molecules derived from a living source with small changes in manufacturing influencing efficacy and safety.[10] Exact duplication is not possible, and therefore, follow-ons and biosimilars are not considered to be generically equivalent to their reference product.[11] Additionally, regulations for follow-on and biosimilars differ as outlined below:

- Follow-on biologics:
  - Copy of reference biologic approved via the Food, Drug and Cosmetic (FD&C) Act as a new drug application and biologics submitted under the Public Health Service (PHS) Act as a biologic license application (BLA)[10]
- Biosimilars:
  - Biological product licensed by the Food and Drug Administration (FDA) which are highly similar to an already FDA-approved biological product which have been shown to have no clinically meaningful difference from the reference product (e.g., safety, purity, and potency)
  - Therapies submitted under the PHS Act as a BLA

Follow-on insulins are now available in the United States. Follow-on insulins are not interchangeable without the intervention of a healthcare provider. Currently there are no interchangeable biosimilars approved in the United States.[11]

Basaglar

Basaglar (insulin glargine U-100) was the first follow-on insulin to be approved by the FDA.[12] Two non-inferiority trials compared it to the reference insulin, Lantus (insulin glargine U-100), to provide evidence for the approval.[13,14] Efficacy and harms data found Basaglar to be similar to Lantus in patients with type 1 diabetes mellitus (T1DM) and T2DM. The Drug Effectiveness Review Project (DERP) also found Basaglar to be equivalent to Lantus.[15] Due to the equivalency findings between Basaglar and Lantus, switching between the two products can be done on a unit-per-unit conversion but must be authorized by a provider. When switching to non-glargine insulin formulations, conversion data for Lantus is applied to Basaglar. [16]

Oregon Health Plan (OHP) Fee-For-Service (FFS) Policy

OHP FFS preferred intermediate and long-acting products are NPH vials, insulin detemir pens (Levemir Flextouch), insulin glargine pens (Lantus Solostar), and insulin glargine vials (Lantus)

- Lantus (vials and pens) represent the most cost-effective basal insulin option for OHP FFS patients
- NPH is the most cost-effective option for most patients with other types of insurance coverage

Switching Basal Insulins

It may be appropriate to switch patients from one insulin to another based on a variety of factors such as: efficacy concerns, tolerability or cost. Many insulins can be switched on a unit-per-unit basis and some conversions require a dose reduction. Switching from a long-acting insulin to NPH may also necessitate the need to divide the total units between AM and PM doses or 2/3 in the morning and 1/3 before dinner or bedtime.[16]

Unit-per-unit conversions:

- insulin glargine (Lantus or Basaglar) to once-daily NPH
- NPH to insulin detemir
- Insulin glargine U-100 to U-300
- Insulin glargine (U-100 or U-300) to insulin detemir
- Any long- or intermediate-acing insulin to insulin degludec

A dose reduction of 20% conversions:

- Insulin glargine U-300 to NPH, insulin detemir or insulin glargine U-100
- Changes from twice daily to a once daily insulin dosing schedule

Key Take Home Points

- Incidence of severe hypoglycemia has been shown to be similar for NPH and long-acting insulin analogs in patients with T2DM, without clinically significant differences in hemoglobin A1c (HbA1c) lowering.
- The most cost-effective long-acting insulin is dependent upon the patient's specific healthcare coverage, and may or may not be a follow-on insulin.

Peer Reviewed By: Robert Hughes, DO, Family Medicine, Samaritan Health Services and Nanette Bultemeier, PharmD, BCPS, BC-ADM, CDE, Clinical Pharmacy Specialist and Katelyn Boel, PharmD, PGY2 Pharmacy Resident, Providence Medical Group

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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

Prior Authorization Criteria Update: Calcium/Vitamin D Replacement, Oral

Purpose of Update:

The calcium/vitamin D class was last reviewed in March of 2016. At that time prior authorization (PA) criteria was created to designate specific vitamin D and calcium supplements as preferred and provide coverage for the following patients: pregnant, nutrient deficient, diagnosis of osteopenia or osteoporosis, and patients 65 years of age or older who are at risk for falls (see Appendix 1). The purpose of this update is to determine the appropriateness of designating a vitamin D solution (drops) as a preferred drug.

Guidelines recommend that infants receive supplemental vitamin D to ensure adequate levels for proper growth. Guidelines recommend vitamin D 400 IU daily for infants from birth up to 12 months and 400-600 IU daily for infants 12-24 months.[1-3] Human breast milk contains small amounts of vitamin D, and therefore, supplementation is recommended. Infants who receive formula may require vitamin D supplementation dependent upon the micronutrient composition of the formula. Fortification of foods with vitamin D and increased exposure to sunlight contributes to appropriate vitamin D levels in children as they age.[2] Currently, multi-vitamin pediatric formulations, including drops, with 400 IU vitamin D are available without a prior authorization (PA).

Recommendation:

- It is recommended that a vitamin D solution suitable for infants is added to the preferred drug list.
- Evaluate costs in executive session.

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Appendix 1. Current Preferred Drug List Status

Generic	Brand	FormDesc	PDL
calcium carbonate	CALCI-MIX	CAPSULE	Y
calcium carbonate	CALCIUM CARBONATE	ORAL SUSP	Y
calcium carbonate	CALCIUM	TABLET	Y
calcium carbonate	CALCIUM 500	TABLET	Y
calcium carbonate	CALCIUM CARBONATE	TABLET	Y
calcium carbonate	OYSCO-500	TABLET	Y
calcium carbonate	OYSTER SHELL CALCIUM	TABLET	Y
calcium carbonate/vitamin D3	CALCIUM	TAB CHEW	Y
calcium carbonate/vitamin D3	CALCIUM 500 + VIT D	TAB CHEW	Y
calcium carbonate/vitamin D3	OS-CAL 500+D	TAB CHEW	Y
calcium carbonate/vitamin D3	CALCIUM 500-VIT D3	TABLET	Y
calcium carbonate/vitamin D3	CALCIUM 600 + VIT D	TABLET	Y
calcium carbonate/vitamin D3	OS-CAL 500-VIT D3	TABLET	Y
cholecalciferol (vitamin D3)	DECARA	CAPSULE	Y
cholecalciferol (vitamin D3)	MAXIMUM D3	CAPSULE	Y
cholecalciferol (vitamin D3)	VITAMIN D3	CAPSULE	Y
cholecalciferol (vitamin D3)	DIALYVITE VITAMIN D3 MAX	TABLET	Y
cholecalciferol (vitamin D3)	VITAMIN D	TABLET	Y
cholecalciferol (vitamin D3)	VITAMIN D3	TABLET	Y
ergocalciferol (vitamin D2)	DRISDOL	CAPSULE	Y
ergocalciferol (vitamin D2)	VITAMIN D2	CAPSULE	Y
calcium carb/D3/magnesium/zinc	CAL MAG ZINC-D3	TABLET	N
calcium carb/magnesium oxid/D3	CALCIUM MAGNESIUM + D	TABLET	N
calcium carb/vit D3/minerals	CALCIUM +D & MINERALS	TAB CHEW	N
calcium carb/vit D3/minerals	CALCIUM 600+MINERALS	TABLET	N
calcium carb/vitamin D3/vit K1	CALCIUM SOFT CHEW	TAB CHEW	N
calcium carbonate	CALCI-CHEW	TAB CHEW	N
calcium carbonate	CALCIUM	TAB CHEW	N
calcium carbonate	CORAL CALCIUM	TABLET	N
calcium carbonate/vitamin D2	CALCIUM CARBONATE W/VITAMIN D	TABLET	N
calcium carbonate/vitamin D3	CALCIUM 250-VIT D3	TABLET	N
calcium carbonate/vitamin D3	CALCIUM 500 + VIT D	TABLET	N
calcium carbonate/vitamin D3	CALCIUM 500-VIT D3	TABLET	N
calcium carbonate/vitamin D3	CALCIUM 600 + VIT D	TABLET	N
calcium carbonate/vitamin D3	CALCIUM 600-VIT D3	TABLET	N
calcium carbonate/vitamin D3	OS-CAL 500-VIT D3	TABLET	N
calcium carbonate/vitamin D3	OYSCO 500-VIT D3	TABLET	N
calcium carbonate/vitamin D3	OYSCO D	TABLET	N

calcium carbonate/vitamin D3	OYSTER SHELL + D	TABLET	N
calcium carbonate/vitamin D3	OYSTER SHELL CALCIUM W-VIT D	TABLET	N
calcium carbonate/vitamin D3	OYSTER SHELL CALCIUM-VIT D3	TABLET	N
calcium citrate	CALCITRATE	TABLET	N
calcium citrate	CITRACAL LIQUITAB	TABLET EFF	N
calcium citrate/vitamin D3	CALCET	TAB CHEW	N
calcium citrate/vitamin D3	CALCITRATE + VIT D	TABLET	N
calcium citrate/vitamin D3	CALCIUM CITRATE - VITAMIN D	TABLET	N
calcium citrate/vitamin D3	CALCIUM CITRATE - VITAMIN D3	TABLET	N
calcium citrate/vitamin D3	CALCIUM CITRATE-VITAMIN D3	TABLET	N
calcium citrate/vitamin D3	CITRUS CALCIUM + D	TABLET	N
calcium citrate/vitamin D3	CITRUS CALCIUM-VITAMIN D3	TABLET	N
calcium glubionate	CALCIONATE	SYRUP	N
calcium gluconate	CALCIUM GLUCONATE	TABLET	N
calcium lactate	CALCIUM LACTATE	TABLET	N
calcium phosphate dibas/vit D3	CALVITE P&D	TABLET	N
calcium phosphate dibas/vit D3	RISACAL-D	TABLET	N
calcium/mag/D3/B12/FA/B6/boron	FOLGARD OS	TABLET	N
calcium/mag/D3/B12/FA/B6/boron	TL G-FOL OS	TABLET	N
calcium/mag/D3/B12/FA/B6/boron	CALCIUM-FOLIC ACID PLUS D	WAFER	N
calcium/magnesium/zinc	CALCIUM/MAGNESIUM/ZINC	TABLET	N
calcium/magnesium/zinc	CALCIUM-MAGNESIUM-ZINC	TABLET	N
cholecalciferol (vitamin D3)	DIALYVITE VITAMIN D	CAPSULE	N
cholecalciferol (vitamin D3)	VITAMIN D3	CAPSULE	N
cholecalciferol (vitamin D3)	D-VI-SOL	DROPS	N
cholecalciferol (vitamin D3)	D-VITA	DROPS	N
cholecalciferol (vitamin D3)	VITAMIN D3	DROPS	N
cholecalciferol (vitamin D3)	VITAMIN D3	TABLET	N
cholecalciferol (vitD3)/vit K2	DOSOQUIN	TABLET	N
ergocalciferol (vitamin D2)	CALCIDOL	DROPS	N
ergocalciferol (vitamin D2)	CALCIFEROL	DROPS	N
ergocalciferol (vitamin D2)	DRISDOL	DROPS	N
ergocalciferol (vitamin D2)	ERGOCALCIFEROL	DROPS	N
vitamin D3/folic acid	DERMACINRX PUREFOLIX	TABLET	N
calcium	HI-CAL	TABLET	
calcium carb/mag ox/zinc sulf	CALCIUM-MAGNESIUM-ZINC	TABLET	
calcium carb/vitamin D3/soyb	SOY FORMULA	TABLET	
calcium carbonate	CALCIUM CARBONATE	TABLET	
calcium carbonate/vitamin D2	LIQUID CALCIUM	CAPSULE	
calcium carbonate/vitamin D2	CALCIUM CARBONATE W/VITAMIN D	TABLET	

calcium carbonate/vitamin D2	OYSTER + D	TABLET
calcium carbonate/vitamin D2	OYSTER SHELL CALCIUM	TABLET
calcium carbonate/vitamin D2	OYSTER SHELL CALCIUM W/VIT D	TABLET
calcium carbonate/vitamin D2	OYSTER SHELL CALCIUM W-VIT D	TABLET
calcium/magnesium/zinc	CALCIUM-MAGNESIUM-ZINC	TABLET
dihydrotachysterol	DHT	TABLET

Appendix 2. Proposed Prior Authorization Criteria

Calcium and Vitamin D Supplements

Goal(s):

- Restrict use of calcium and vitamin D supplements to patients who are pregnant; have a documented nutritional deficiency; have a diagnosis of osteopenia or osteoporosis; infants 0-24 months or elderly patients at risk for falls.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred calcium and vitamin D 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. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Does the patient meet any of the following criteria: • Pregnancy; • Documented nutrient deficiency; • Diagnosis of osteopenia or osteoporosis; • Infants 0-24 months of age **OR** • Age 65 years or older and at risk for falls	**Yes:** Approve for up to 12 months. Request that a 90 day's supply be filled at a time.	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *3/19 (KS), 3/16 (KS)*
Implementation: *5/1/16*

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

Prior Authorization Criteria Update: Hydroxyprogesterone Caproate

Purpose of Update:

Evidence for hydroxyprogesterone products was last evaluated in January 2017. Currently all products require prior authorization (PA) to ensure they are used for Food and Drug Administration (FDA) approved conditions, and brand Makena® is the currently preferred product. Historically, only Makena® has been FDA approved for prevention of preterm birth. Generic formulations of hydroxyprogesterone caproate and Delalutin® (including its generics) are indicated for amenorrhea, adenocarcinoma of the uterus, and other endometrial disorders. However, in 2018 a generic version of Makena® indicated for prevention of preterm birth was FDA-approved. This update provides necessary PA changes to accommodate these new generic formulations.

Recommendation:

- Update PA criteria to accommodate new generics for Makena®

Appendix 1. Proposed Prior Authorization Criteria

Hydroxyprogesterone caproate

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which hydroxyprogesterone caproate injection has been shown to be effective and safe.

Length of Authorization:

- 20 weeks to 6 months (criteria-specific)

Requires PA:

- Hydroxyprogesterone caproate injection(physician administered and pharmacy claims)

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 OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the drug formulation to be used for an FDA-approved indication? Message: ~~Generic formulations of hydroxyprogesterone caproate are not~~Only Makena and its generics are approved for prevention of preterm birth	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
~~Is the request for generichydroxyprogesterone caproate?~~	~~**Yes:** Go to #5~~	~~**No:** Go to #6~~
4. Is the request for a non-preferred product and ~~W~~will the prescriber consider a change to a preferred product? Message: ~~Preferred products do not generally require a PA.~~ 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**: ~~Approve for 6 months~~Go to #5
5. Is the request for Delalutin® or its generic products?	**Yes:** Approve for 6 month	**No:** Go to #6
~~5.~~6. Is the request for Makena or its generics and is the patient between 16 weeks and 36 weeks 6 days gestation with a singleton pregnancy?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~7. Has the patient had a prior history of preterm delivery before 37 weeks gestation (spontaneous preterm singleton birth)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~7.~~8. Is treatment being initiated at 16 weeks, 0 days and to 20 weeks, 6 days of gestation?	**Yes:** Approve through week 37 of gestation or delivery, whichever occurs first (no more than 20 doses).	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *3/19 (SS); 1/17 (SS); 5/13*
Implementation: *TBD; 4/1/17, 1/1/14*

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

Prior Authorization Criteria Update: Benzodiazepines

Purpose of Update:

Benzodiazepines are FDA indicated for treatment of alcohol withdrawal, epilepsy, anxiety and panic disorder, and are often used off-label for other mental health conditions including bipolar disorder and schizophrenia. Despite lack of evidence supporting long-term use for mental health conditions, benzodiazepines are often utilized for long-term treatment. In an effort to prevent inappropriate long-term benzodiazepine use, a prior authorization (PA) is required for benzodiazepine durations exceeding 30 days over the last 120 days. Though benzodiazepines are often used for short-term treatment of alcohol withdrawal syndrome, current criteria does not specifically address this condition. However, a PA may be required for patients with recurrent episodes of alcohol withdrawal or patients with a history of recent benzodiazepine use. This update revises current criteria to include outpatient management of alcohol withdrawal syndrome.

Benzodiazepines, in combination with adequate monitoring, are the current standard of care for management of moderate to severe symptoms during acute alcohol withdrawal.[1] Other anticonvulsants such as carbamazepine, gabapentin or valproic acid may be considered as alternatives if adequate monitoring is not available, if potential abuse is likely, or for patients unable to tolerate benzodiazepines.[1]

Guidelines from the National Institute for Health and Care Excellence (NICE) recommend outpatient treatment of alcohol withdrawal syndrome for patients with mild to moderate alcohol dependence.[2] Similar recommendations from the Veterans Administration and Department of Defense (VA/DOD) allow for outpatient management in patients with mild to moderate symptoms.[1] Inpatient medically supervised alcohol withdrawal management is recommended in the following circumstances: [1]

- severe alcohol withdrawal
- inability to tolerate oral medications
- history of delirium tremens or withdrawal seizures
- risk of withdrawal from other substances in addition to alcohol
- presence of comorbid conditions which may complicate ambulatory withdrawal management such as severe coronary heart disease, liver cirrhosis, or congestive heart failure

Inpatient medically supervised withdrawal may also be considered with moderate severity withdrawal if there are indicators that the patient will not complete ambulatory withdrawal management (e.g., previous recurrent unsuccessful ambulatory withdrawal attempts or homelessness), or with presence of active psychosis, cognitive impairment, or other comorbid conditions which may complicate ambulatory withdrawal.[1]

Recommendation:

- Update PA criteria to include outpatient management of alcohol withdrawal syndrome.

References:

1. The Management of Substance Use Disorders Work Group. Veterans Administration/Department of Defense Clinical Practice Guideline for the Management of Substance Use Disorders. 2015; https://www.healthquality.va.gov/guidelines/MH/sud/. Accessed October 15, 2018.
2. National Collaborating Centre for Mental Health (UK). Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. National Clinical Practice Guideline 15. London: National Institute for Health and Care Excellence (UK). 2014; Available from https://www.nice.org.uk/guidance/cg115/evidence/full-guideline-pdf-136423405.

Appendix 1. Proposed Prior Authorization Criteria

Benzodiazepines

Goal(s):

- Approve only for OHP-funded diagnoses.
- Prevent inappropriate long-term benzodiazepine use beyond 4 weeks for new starts (no history within the last 120 days).
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:

- 6 months to 12 months (criteria-specific)

Requires PA:

- All benzodiazepines used beyond 4 weeks. Short-term use does not require PA.

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 malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Does the patient have a seizure disorder diagnosis or is the patient enrolled in a program for short-term outpatient management of alcohol withdrawal syndrome? Note: benzodiazepines are not indicated for alcohol dependence.	**Yes:** Approve for 12 months for seizure disorder or up to 1 month for alcohol withdrawal	**No:** Go to #5
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber evaluated the PDMP at least once in the past 3 months for this patient?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; ~~not funded by the OHP~~medical appropriateness.
6. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
7. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have a documented trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including antidepressants AND psychotherapy (e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing)? Note: An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
10. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #11	**No:** Go to #12
11. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have an adequate trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including second-generation antipsychotics AND psychotherapy (e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation)? Note: For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
12. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13

Approval Criteria		
13. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #2
2. Is the request for an increase in dose?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #4	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.

Renewal Criteria		
4. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.

P&T Review: *9/18(SS), 3/14*
Implementation: *11/1/2018; 5/1/16*

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

Prior Authorization Criteria Update: Cannabidiol

Purpose of Update:

- Some clinicians have been prescribing cannabidiol at 30 mg/kg/day, which is an investigational dose. This maximum dose outlined in the cannabidiol prescribing information is 20mg/kg/day.[1]

Recommendation:

- Update prior authorization criteria to include maximum dose limits.

References:

1.Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. June 2018.

Appendix 1. Proposed Prior Authorization Criteria

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

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/

Author: Deanna Moretz, PharmD, BCPS

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication? (Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older).	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication? AND Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 20mg/kg/day?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
~~5.~~6. Are baseline liver function tests on file (serum transaminases and total bilirubin levels)? LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver. Note: dosage adjustment is recommended for patients with moderate or severe hepatic impairment. See Table 1 for dosing recommendations.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent LFT's documented in patient records?	**Yes:** Go to # 2 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 20mg/kg/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4
~~3.~~4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment[1]

Hepatic Impairment	Starting Dosage	Maintenance Dosage	Maximum Recommended Dosage
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)

Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. June 2018.

P&T/DUR Review: 1/19 (DM)
Implementation: TBD; 3/1/19

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Oral Tetracyclines

Date of Review: March 2019
Generic Name: omadacycline
sarecycline

End Date of Literature Search: 11/26/2018
Brand Name (Manufacturer): Nuzyra™ (Paratek Pharmaceuticals, Inc.
Seysara™ (Allergan Pharmaceuticals, Inc.)
Dossier Received: Yes / No

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

Purpose for Class Update:
The tetracycline class has had two new drug approvals, omadacycline and sarecycline, since the last review in May of 2017. The purpose of this review is to evaluate the data related to the new tetracycline antibiotics and any additional new comparative efficacy or harms data published for the tetracycline class since the last review.

Research Questions:
1. Is there any new comparative evidence for antibiotics in the tetracycline class for clinically important outcomes such as mortality, hospitalizations, clinical clearance, and re-infection?
2. Is there any new comparative evidence evaluating harms for antibiotics in the tetracycline class?
3. Are there subpopulations of patients for which specific tetracycline antibiotics may be more effective or associated with less harm?
4. What is the evidence for efficacy and harms for the new tetracycline antibiotics, omadacycline and sarecycline?

Conclusions:
- Three guidelines, one systematic review and three randomized clinical trials provided evidence for the tetracycline class review.
- The National Institute of Health and Care Excellence (NICE) guideline recommendations are:
  - Doxycycline first-line for the treatment of an acute exacerbation of chronic obstructive pulmonary disease (COPD)[1]
  - Doxycycline as an alternative treatment option in patients requiring antibiotics for acute sinusitis[2]
  - Doxycycline as first-line treatment in patients 9 years and older with Lyme disease[3]

Efficacy
- Cochrane found moderate quality evidence of higher clinical cure rates with azithromycin compared to doxycycline for patients with mild to moderate pelvic inflammatory disease (PID), 85% versus 63%, (relative risk [RR] 1.35; 95% confidence interval [CI], 1.10 to 1.67; P<0.05/number needed to benefit [NNTB] 5).[4]

Author: Kathy Sentena, PharmD

- There is insufficient evidence to support superior efficacy or safety of the new tetracycline antibiotics, omadacycline and sarecycline, over currently preferred therapies.[5–7]
- There is insufficient evidence on the use of tetracycline antibiotics in specific subgroups of patients.

Safety
- There is insufficient evidence demonstrating differences in harms between antibiotics used for the treatment of acute COPD exacerbations.

Recommendations:
- No changes to the preferred drug list are recommended.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- There was no evidence of differences in comparative efficacy/effectiveness or safety between the antibiotics in the tetracycline class based on the previous review in May of 2017. A policy review at this time found insufficient evidence for the use of tetracyclines beyond 14 days, with the exception of the diagnosis of acne fulminans, severe cystic acne (coverage starting in 2020), and rosacea, which is unfunded. In response to the review, the use of tetracycline antibiotics beyond 14 days, for two separate claims, every 3 months requires prior authorization (Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes) to ensure use for an Oregon Health Plan (OHP) funded condition. Preferred drugs in the class include doxycycline and tetracycline.

Background:
The tetracycline class consists of five, broad spectrum antibiotics (**Table 1**).[8] Tetracyclines exhibit a bacteriostatic effect by inhibiting protein synthesis. The spectrum of activity for tetracyclines include aerobic-gram positive and gram-negative bacteria, as well as atypical pathogens. Doxycycline is most commonly used clinically due to twice daily dosing, tolerability, broad spectrum of activity and the availability of oral and intravenous (IV) dosage forms. Some of the common indications for tetracyclines include: acne, rosacea, sexually transmitted diseases, respiratory tract infections, acute bacterial skin structure infections (ABSS), and urinary tract infections (UTI).[8] In addition, doxycycline is indicated for the treatment of moderate to severe purulent skin infections for empiric treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). Tetracyclines are commonly given for short durations, up to 14 days, with the exception of treatment for vertebral osteomyelitis and bone and joint infections, and certain dermatological conditions (e.g., acne fulminans, severe cystic acne).[9]

Antibacterial resistance to tetracyclines has been demonstrated. Resistance develops by preventing accumulation of the drug inside the cell, and resistance to one drug in the class often confers resistance to the entire class. The newly approved omadacycline has been shown to have activity against some bacteria that are resistant to doxycycline and minocycline.[10]

Table 1. Tetracycline Antibiotics[8,10,11]

Drug	Route	Comments
Tetracycline	Oral	Twice daily to four-times daily dosing
Doxycycline	Oral/IV	Administer without regard to food; twice daily dosing
Minocycline	Oral	Used for acne, not usually first-line
Omadacycline	Oral/IV	Requires loading dose; available in IV and oral formulation

Sarecycline	Oral	Approved for non-nodular moderate to severe acne only

Abbreviations: IV = intravenous

Tetracyclines should not be administered with multivalent cations (e.g., calcium, aluminum, iron, magnesium) which have been shown to inhibit the absorption. Tetracyclines should not be given to children under the age of eight due to the potential of permanent tooth discoloration, with the exception of doxycycline which can be used in any age child if absolutely necessary for short durations.[8] The most common adverse effects of the tetracycline class are: gastrointestinal upset, photosensitivity and tooth discoloration (young children).

The main outcomes of importance in patients using tetracycline antibiotics are: mortality, hospitalization, re-infection, number of acne lesions and clinical cure. Reduction in exacerbations is an important outcome in patients with COPD receiving antibiotics (e.g., pneumonia).

Ninety-eight percent of tetracycline claims are for the preferred agent doxycycline. Overall the tetracycline class represents a small source of health care utilization for Oregon Health Plan (OHP) fee-for-service (FFS) patients.

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

<u>Cochrane – Antibiotic Therapy for Pelvic Inflammatory Disease</u>

A 2017 Cochrane review evaluated the comparative efficacy of antibiotics to treat PID among women.[4] Thirty-seven trials of women 14 years and older with a diagnosis of PID (based on Centers for Disease Control criteria) were identified and included the following antibiotics: clindamycin, doxycycline, azithromycin, quinolones, cephalosporins, nitroimidazoles, and aminoglycosides.[4] Many of the eligible studies had an unclear risk of bias, partly due to clinical trial completion before 2000 with inferior study designs. Selective reporting and unclear allocation concealment led to unclear risk of bias. Funnel plot analysis indicated some degree of publication bias. Women were divided into groups based on PID severity; mild-moderate (e.g., absence of tubo-ovarian abscess) and severe (e.g., systemically unwell, presence of tubo-ovarian abscess). Patients from inpatient and outpatient settings were included. Primary outcomes of interest were clinical cure (time to resolution of signs and symptoms of PID as determined by the provider) and adverse events.

In an analysis of two trials comparing azithromycin to doxycycline, there was no statistically significant difference in clinical cure rates for mild to moderate PID, 82% and 69% (RR 1.18; 95% CI, 0.89 to 1.55; p>0.05).[4] However, restricting the analysis to studies with low risk of bias found moderate strength of evidence (one

RCT) that azithromycin had a higher rate of clinical cure compared to doxycycline in patients with mild to moderate PID, 85% versus 63% (RR 1.35; 95% CI, 1.10 to 1.67; P<0.05; NNTB 5). For severe PID, doxycycline was similar to azithromycin based on low quality evidence (RR 1.0; 95% CI, 0.96 to 1.05). Adverse events were also similar between comparators.[4]

After review, four systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), insufficient or low quality evidence or outcome studied (e.g., non-clinical).[12–15]

New Guidelines:

NICE – Chronic Obstructive Pulmonary Disease (acute exacerbation): Antimicrobial Prescribing

A 2018 guideline on managing acute exacerbations of COPD as it relates to antimicrobial prescribing was published by NICE. Acute exacerbations can be triggered by multiple causes and approximately half have bacterial etiology. Evidence for recommendations were from a systematic review and meta-analysis of randomized controlled trials which included antibiotic treatment (including doxycycline) durations of 5 to 14 days.[1] Moderate quality evidence found antibiotic treatment in patients with an acute exacerbation of COPD reduced the number of patients with a subsequent exacerbation (didn't resolve or improve up to 1 month after treatment) compared to placebo, 29.4% versus 36.1% (NNT 15).[1] Patients with more severe infections, based on treatment setting, benefited the most from antibiotic treatment. Moderate quality evidence found no significant difference in all-cause mortality (1.0% vs. 1.6%; 95% CI, 0.27 to 1.63; p>0.05). Limitations to the evidence used for treatment recommendations is that studies often included patients with varying severity of acute exacerbations and the diagnosis of an acute exacerbation is variable from study to study.

When treating exacerbations, the following considerations should be taken: severity of symptoms, need for inpatient treatment, previous exacerbations/hospitalizations, previous sputum cultures and susceptibility results, and the risk of antimicrobial resistance with repeated courses of antibiotics.[1] Consideration should be taken to have susceptibility analysis done on sputum cultures and switch antibiotics if resistance is present and symptoms are not improving. Antibiotic treatment recommendations are presented in **Table 2**. Patients that are receiving prophylactic antibiotics should receive antibiotics for acute treatment from a different antibiotic class. Doxycycline is recommended as a first line treatment for COPD exacerbations.

Table 2. Antibiotic Treatment for Acute Exacerbations of COPD in Adults (18 years and older)[1]

Antibiotic	Dosage
*First Line Treatment**	
Amoxicillin	500 mg three times daily for 5 days
Doxycycline	200 mg on first day, then 100 mg once a day for 5-day course in total
Clarithromycin	500 mg twice a day for 5 days
Second-line Treatment	
Use alternative first-choice option from a different class	See above
*Second-line Treatment if Patient is at High Risk of Treatment Failure^*	
Amoxicillin/clavulanic acid	500/125 mg three times daily for 5 days
Levofloxacin	500 mg once a day for 5 days
Sulfamethoxazole and trimethoprim	960 mg twice a day for 5 days

First-line Intravenous Antibiotic†	
Amoxicillin	500 mg three times a day‡
Amoxicillin/clavulanic acid	1.2 grams three times daily‡
Clarithromycin	500 mg two times a day
Sulfamethoxazole and trimethoprim	960 mg twice a day (based on trimethoprim component)
Piperacillin with tazobactam	4.5 grams three times a day
Second-choice Intravenous Antibiotic	
Consult local microbiologist: guided by susceptibilities	
Key: * Empirical treatment or guided by sputum cultures, † Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible, ^ Patients considered at high risk of treatment failure if they have had repeated courses of antibiotics, a previous or current sputum culture with resistant bacteria or a higher risk of developing complications, ‡ Not available as an intravenous solution in the US	

Safety

Common adverse reaction for antibiotics in general include diarrhea in 2% to 25% of patients and low quality evidence found the incidence of adverse events was higher with antibiotics compared to placebo, 10.6% versus 7.4%.[1] There was no difference found between different antibiotics or classes of antibiotics in the risk of adverse events.

NICE – Sinusitis (acute): antimicrobial prescribing

NICE released guidance on the use of antibiotics in patients with sinusitis.[2] Often patients improve without the use of antibiotics and withholding antibiotics rarely leads to complications. Moderate quality of evidence found increased cure rates with antibiotics compared to placebo (NNT 7-21).[3] A back-up antibiotic prescription is recommended for patients if symptoms do not improve within 7 days or if symptoms worsen abruptly or increase in severity. Patients should be treated when presenting with symptoms if they are systemically unwell, have signs or symptoms of a more serious illness or are at high risk of complications. Doxycycline is recommended as an alternative first-line treatment for those patients with sinusitis and a penicillin allergy or intolerance, for both adults and those 12-17 years old.

Safety

Antibiotics are associated with more adverse reactions compared to placebo with a number needed to harm (NNH) of 8-11.[2] Diarrhea was found to more common with antibiotic therapy compared to placebo with a NNH of 18.

NICE – Lyme Disease

The National Institute for Health and Care Excellence released a guideline on the treatment of Lyme disease in 2018.[3] Antibiotics are recommended for patients who are diagnosed with Lyme disease. The route and type of antibiotic are symptom dependent. Oral doxycycline for 21 days is recommended first line in adults and in children over the age of 9 years. The exception is in patients that have Lyme disease affecting the central nervous system and for those with Lyme carditis and are hemodynamically unstable, in which intravenous ceftriaxone is recommended first line. Alternative treatment options include amoxicillin or azithromycin. For patients who are 12 and under the recommendations are divided by age: 9-12 years and under 9.[3] In children 9-12 years oral doxycycline is recommended for 21 days, with amoxicillin or azithromycin as alternatives. In patients under 9 years, amoxicillin is recommended with azithromycin as an

alternative. The exception is the same as for adults in that for those patients with Lyme disease affecting the central nervous system or those with Lyme carditis and are hemodynamically unstable, IV ceftriaxone is recommended regardless of age. A second course of antibiotics should be considered in patients with ongoing symptoms.

New Formulations or Indications:
Minocycline (Minolira®) – a new extended-release (ER) formulation of minocycline was approved in May of 2017 for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients in 12 years and older.[16] Minocycline ER was studied in two, 12 week, placebo-controlled studies which demonstrated mean improvement in inflammatory lesions compared to placebo by 11.4% more in study 1 and 15% more in study 2 (p-values not provided).[16]

Doxycycline (Xyrosa®) - a new formulation of doxycycline was approved for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients in April of 2017.[17] Prescribing information is not available.

Doxycycline (Lymepak®) – doxycycline is used off-label for the treatment of Lyme disease. A new packaging system containing doxycycline tablets has been approved for use in patients, eight years and older weighing 45 kg or more, with early Lyme disease (as evidenced by erythema migrans) due to *Borrelia burgdorferi*.[18] Clinical efficacy evidence was derived from previous trials evaluating doxycycline use in children and adults with Lyme disease. Lymepak is available in blister cards containing 14 tablets of doxycycline 100 mg, to be taken every 12 hours for a total of 21 days.[18]

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Doxycycline[19]	Acticlate	November 2017	Warnings and precautions	Severe skin reactions (e.g., exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic symptoms (DRESS). Discontinue doxycycline if skin reactions occur.
Doxycycline[19]	Acticlate	November 2017	Adverse reactions	Superficial discoloration of adult permanent dentition, reversible upon discontinuation. Permanent discoloration and enamel hypoplasia may occur when used during tooth development.

Randomized Controlled Trials:
A total of 20 citations were manually reviewed from the initial literature search. After further review, 17 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 included studies are available in Table 6 and 8.

NEW DRUG EVALUATION: Omadacycline

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Omadacycline is a tetracycline antibiotic indicated for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin structure infections (ABSSI) in adults that are infected with susceptible organisms.[10] Omadacycline is classified as an aminomethylcycline antibacterial within the tetracycline class which exhibits bacteriostatic activity, with the exception of having bactericidal activity against some isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae*, by binding to the 30S ribosomal subunit and inhibiting protein synthesis. Omadacycline is one of the few oral antibiotics with activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[20]

Three (1 in CABP and 2 in ABSSI), phase 3, double-blind, double-dummy randomized controlled, noninferiority trials provided evidence for approval (OPTIC, OASIS-1 and OASIS-2).[5,6,10,21] In two of the trials (OPTIC and OASIS-1), patients received intravenous (IV) loading doses followed with oral therapy, with the total treatment duration lasting 7-14 days in all trials. The primary endpoint for the CABP trial was early clinical response (ECR) (survival with improvement in at least 2 of 4 symptoms, which include cough, sputum production, chest pain, dyspnea without rescue antibiotics) at 72-120 hours following the first dose.[5] The primary endpoint for the studies evaluating omadacycline in ABSSI was early clinical response (ECR) (survival with a reduction in lesion size of at least 20% without rescue antibacterial therapy) at 48-72 hours after the first dose.[6,10] The noninferiority margin was set at 10% for all trials based on the modified intent to treat (mITT) population.

In the OPTIC trial, included patients had CABP, were hospitalized, mean age of 62 years old, 55% male, and Pneumonia Severity Index (PSI) risk II-IV.[5,19] The PSI is a I-V classification of risk of death, with higher numbers indicating more risk. Omadacycline 100 mg IV every 12 hours for 2 doses on day 1, followed by 100 mg IV daily for 3 days or more, then 300 mg orally once daily was compared to moxifloxacin 400 mg which was given IV for 3 or more days and then 400 mg orally.[5] Clinical success at the ECR time point occurred in 81.1% of patients treated with omadacycline and 82.7% treated with moxifloxacin (mean difference [MD] -1.6%; -7.1 to 3.8)(Table 6).[5] Patients with risk factors indicating a higher severity of illness (e.g., age 65 or older, chronic lung disease, diabetes) demonstrated lower clinical success rates when treated with omadacycline compared to moxifloxacin. At post therapy evaluations clinical response rates for omadacycline were the highest for the following organisms (baseline pathogen): *Streptococcus pneumonia* (86%), *Methicillin-susceptible Staphylococcus aureus* (MSSA) (72.7%), *Haemophilus influenzae* (81.3%), *Haemophilus parainfluenzae* (83.3*%), Klebsiella pneumonia* (76.9%), *Legionella pneumophila* (93.1%), *Mycoplasma pneumoniae* (88.6%), and *Chlamydophila pneumoniae* (93.3%).[5,19]

Patients included in the first ABSSSI trial, OASIS-1, were 44-47 years and a majority were male (63-65%). Patients were treated for 7-14 days of omadacycline or linezolid.[6] Pathogen diagnosis were as follows: cellulitis (38%), wound infection (33%), and major abscess (29%). Patients were randomized to omadacycline 100 mg IV every 12 hours for 2 doses then 100 mg IV daily for 3 or more days, then transitioned to oral omadacycline 300 mg daily if possible, or linezolid 600 mg IV every 12 hours for 3 or more days then switching to 600 mg every 12 hours orally if possible. Clinical success was 84.8% with omadacycline compared to 85.5% with linezolid (MD -0.7%; 95% CI, -6.3 to 4.9)(**Table 6**).[6] Clinical response at the post-treatment evaluation for baseline pathogens were as follows: *Staphylococcus aureus* (methicillin-susceptible) (84%), *Staphylococcus aureus* (methicillin-resistant) (83%), *Streptococcus anginosus group* (74%), *Streptococcus pyogenes* (73%) and *Enterococcus faecalis* (90%).[20] Pooled clinical response from both ABSSSI studies based on type of infection are presented in **Table 4**.[21]

In the second trial, OPTIC-2 (not published), patients with ABSSSI were given omadacycline 450 mg orally on day 1 and day 2 followed by 300 mg orally once daily was compared to linezolid 600 mg every 12 hours. Patients had the following infections: wound infections (58%), cellulitis (24%), and major abscess (18%). The clinical ECR was 87.3% in patients receiving omadacycline and 82.2% in patients receiving linezolid (MD 5.1%; 95% CI, -0.2 to 10.5).[10] Pooled clinical response from both ABSSSI studies based on type of infection are presented in **Table 4**.[21]

Table 4. Early Clinical Response based on Wound Infection Type Pooled for both ABSSI studies (mITT population)[21]

Clinical Success Rate	Omadacycline	Linezolid	Difference vs. Linezolid
Cellulitis/erysipelas	165 (78.9%)	164 (83.9%)	-2.2 (95% CI, -10.0 to 5.5)
Wound infection	278 (89.1%)	269 (88.5%)	4.5 (95% CI, -0.8 to 9.9)
Major Abscess	140 (90.3%)	130 (84.3%)	4.2 (95% CI, -3.1 to 11.8)

Noninferiority was demonstrated in all three trials.[5,6,10]

Limitations to the evidence include: lack of long-term trial data, analysis of mITT population in a trial with a noninferiority design which could bias the results to show no difference between treatments; however, post-hoc analysis of per-protocol population confirmed noninferiority of omadacycline to moxifloxacin and omadacycline to linezolid.[19,20] Evaluating the data based on the per protocol population is preferred for noninferiority trials. There is insufficient data to show superiority of omadacycline compared to moxifloxacin, and there may be an increased risk of mortality associated with therapy.

Clinical Safety:
Common adverse events associated with omadacycline include nausea, vomiting and infusion site reactions. Other adverse events occurring in 2% or greater patients include the following: alanine aminotransferase increases, aspartate aminotransferase increases, gamma-glutamyl transferase increases, hypertension, headache, diarrhea, insomnia, and constipation.[10] An imbalance in the mortality rates between omadacycline and moxifloxacin (2% versus 1%, respectively) was demonstrated in patients with CABP without a known etiology.[10,20] Use with caution in patients at increased risk of mortality. An additional trial will be required to further evaluate this finding. Use of omadacycline in pregnancy and childhood may cause tooth discoloration and enamel hypoplasia as well as inhibition of bone growth. Discontinue omadacycline if *Clostridium difficile* Associated Diarrhea (CAD) occurs. In the ABSSI trials discontinuations due to adverse events was 1.6% to 1.8% in the omadacycline group and 1.1% to 2.1% in the linezolid group.[21]

Table 5. Pharmacology and Pharmacokinetic Properties of Omadacycline[10]

Parameter	
Mechanism of Action	Aminomethylcycline antibacterial within the tetracycline class of antibacterial drugs
Oral Bioavailability	34.5% following single 300 mg dose
Distribution and Protein Binding	23.6 to 25.6 Liters 20% protein bound
Elimination	14.4% urine and 77.5% to 84.0% feces
Half-Life	8.1 to 10.7 hours oral and 21.7 hours IV
Metabolism	Not metabolized

Abbreviations: IV - intravenous

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Infection resolution
2) Mortality
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Early clinical response (see Table 6)

Table 6. Comparative Evidence Table for Omadacycline.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Stets, et al[5] Phase 3, DB, DD, RCT, NI (OPTIC)	1. Omadacycline 100 mg IV every 12 hours for 2 doses then 100 mg IV every 24 hours (O)* 2. Moxifloxacin 400 mg IV every 24 hours (M)* * A transition to oral omadacycline 300 mg every 24 hours or oral moxifloxacin 400 mg every 24 hours was allowed after 3 days Total treatment: 7-14 days	Demographics: Age (mean): 62 yrs Male: 55% Current smoker: 24% Mild to moderate COPD: 54% Asthma: 5% PSI score: 84 Key Inclusion Criteria: - 18 years or older - ≥ 3 of the following: cough, purulent sputum production, dyspnea, or pleuritic chest pain - ≥ 2 abnormal vital signs - ≥ 1 clinical sign or laboratory finding associated with CABP - radiologically confirmed pneumonia - Pneumonia severity index class II-IV Key Exclusion Criteria:	mITT: 1. 386 2. 388 PP: 1. 340 2. 345 Attrition: 1. 12% 2. 11%	Early Clinical Response (mITT population)†: O: 313 (81.1%) M: 321 (82.7%) MD -1.6% (95% CI, -7.1 to 3.8) *Noninferior to moxifloxacin* Early Clinical Response (per-protocol population/post-hoc analysis)†: O: 308 (86.5%) M: 314 (87.2%) MD -0.7 (95% CI, -5.7 to 4.3) Secondary Endpoints: Clinical response at post-treatment evaluation (5 to 10 days after last dose): O: 338 (87.6%) M: 330 (85.1%) MD 2.5% (95% CI, -2.4 to 7.4)	NA for all	ALT increased: O: 14 (3.7%) M: 18 (4.6%) Hypertension: O: 13 (3.4%) M: 11 (2.8%) Discontinuations due to adverse events: O: 21 (5.5%) M: 27 (7.0%) Serious Adverse Events: O: 23 (6%) M: 26 (6.7%) Death: O: 8 (2.1%) M: 4 (1.0%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized in a 1:1 ratio via an interactive voice response/interactive web response system. Performance Bias: (low) double-blind design and trial personal were blinded to treatment assignment. Detection Bias: (high) data analysis done by manufacturer. Attrition Bias: (high) Over 10% attrition in both groups. Analysis done on mITT population. Reporting Bias: (low) Outcomes reported as prespecified. Other Bias: (high) Industry funded. **Applicability**: Patient: In patients with community acquired bacterial pneumonia. More patients in the omadacycline group compared to moxifoxacin were current smokers, 27% vs. 21%, and more patients had COPD, 57% vs. 51%. Intervention: Omadacycline dose was appropriate. Comparator: Comparison to another first-line treatment for pneumonia would be more informative than a moxifloxacin comparison,

		- One or more doses of potentially effective systemic antibacterial treatment within 72 hours of the first dose - history of hospital-acquired pneumonia or empyema - clinically significant renal or hepatic insufficiency - immunocompromised patients						which is not recommended first or second line by guidelines. Outcomes: Clinical response to therapy is an appropriate outcome. Setting: Multi-center study in 86 sites in Europe, North America, South America, the Middle East, Africa and Asia.
O'Riordan, et al[6] (OASIS-1) Phase 3, DB, DD, RCT, NI	1. Omadacycline 100 mg IV every 12 hours for 2 doses then 100 mg IV every 24 hours (O)* 2. Linezolid 600 mg IV every 12 hours (L)* * A transition to oral omadacycline 300 mg every 24 hours or oral linezolid 600 mg every 12 hours was allowed after 3 days Total treatment: 7-14 days	Demographics: Age (mean): 47 yrs Male: 64% Infection type: Wound infection: 32% Cellulitis or erysipelas: 39% Major abscess: 28% Key Inclusion Criteria: - 18 years and older - qualifying skin infection, cellulitis, or erysipelas or major abscess - contiguous surface area of at least 75 cm^2 - evidence of erythema, edema, or induration Key Exclusion Criteria: - use of 1 or more potentially effective systemic antibacterial treatment or topical antibiotic within 72 hours of first dose	mITT: 1. 316 2. 311 PP: 1. 269 2. 260 Attrition: 1. 15% 2. 16%	Early Clinical Response (mITT population)‡: O: 268 (84.8%) L: 266 (85.5%) MD -0.7% (95% CI, -6.3 to 4.9) *Noninferior to linezolid* Early Clinical Response (per-protocol population/post-hoc analysis)‡: 14 days after last dose): O: 276 (92.6%) L: 278 (94.6%) MD -1.9% (95% CI, -6.1 to 2.1) Secondary Endpoints: Clinical response at post-treatment evaluation (7 to 14 days after last dose): O:272 (87.1%) L: 260 (83.6%) MD 2.5% (95% CI, -3.2 to 8.2)	NA for all	Discontinuations due to adverse events: O: 6 (1.9%) L: 7 (2.2%) Serious Adverse Events: O: 12 (3.7%) L: 8 (2.5%) Death: O: 1 (0.3%) L: 2 (0.6%) Nausea: O: 40 (12.4%) L: 32 (9.9%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized in a 1:1 ratio via an interactive voice response/interactive web response system. Performance Bias: (low) double-blind design and trial personal were blinded to treatment assignment. Detection Bias: (high) data analyses and interpretation done by manufacturer. Attrition Bias: (high) Over 10% attrition in both groups. Analysis was done on mITT population. Reporting Bias: (low) Outcomes reported as prespecified. Other Bias: (high) Industry funded. **Applicability**: Patient: In patients with median IV treatment of 4.4 days in both groups and an average of 5.5 days of oral therapy (88% of patients transitioned to oral therapy) with ABSSSI. Intervention: Omadacycline dose was appropriate. Comparator: Linezolid approved for uncomplicated skin and skin structure infections but not recommended first-line in most cases. Outcomes: Clinical response to therapy is an appropriate outcome.

		- only gram-negative pathogens identified (mITT population) - infections thought to require more than 14 days of treatment - chronic (> 3 months) skin lesions, ulcers or wounds - clinically significant liver or renal insufficiency - immunocompromised patients						Setting: Multi-center study in 86 sites in Europe, North America, South America, the Middle East, Africa and Asia.
Abbreviations: ABSSSI = acute bacterial skin or skin structure infection; CABP = community acquired bacterial pneumonia; COPD = chronic obstructive pulmonary disease; DB = double-blind; IV = intravenous; MD = mean difference; mITT = modified intent-to-treat analysis; NI = noninferiority; PSI = pneumonia severity index; PC = placebo-controlled; PG = parallel-group, RCT = randomized controlled trial Key: † early clinical response defined as survival with improvement in at least two of four symptoms (cough, sputum production, pleuritic chest pain and dyspnea) assessed 72 – 120 hours after the first dose; ‡ early clinical response defined as survival with a reduction in lesion size of at least 20% without rescue antibacterial therapy at 48 to 72 hours after first dose of trial drug								

NEW DRUG EVALUATION: Sarecycline

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Sarecycline is a narrow spectrum tetracycline antibiotic that is FDA approved for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients that are 9 and older.[11] Sarecycline has efficacy against *Propionibacterium Acnes*, including efficacy against erythromycin resistant isolates. Efficacy for the use of sarecycline for the treatment of infections or use beyond 12 weeks has not been evaluated; however, an open-label extension study lasting 40 weeks has been performed. Sarecycline was studied in two, 12-week, double-blind, placebo-controlled trials in a total of 2002 patients ages 9 to 45 years with moderate to severe acne vulgaris (mean Investigator's Global Assessment [IGA] score of 3)(**Table 8**). The IGA score is a non-validated assessment used in clinical trials to evaluate the signs associated with atopic dermatitis (e.g., erythema, lichenification, edema, exudation) based on a six-point scale from clear to severe.[22] The FDA considers a change of 2 grades to be indicative of a success in the treatment of acne.[23] Sarecycline 60 mg, 100 mg, or 150 mg capsules were dosed based on weight with ranges of 1.1 to 1.8 mg/kg once daily.[24] In both trials the co-primary endpoints were: percent of patients achieving IGA success (defined as a score of clear (0) or almost clear (1) and a 2-point decrease from baseline on IGA score at week 12 and absolute reduction from baseline in inflammatory lesions count at week 12) evaluated in the ITT population. The sarecycline trials evaluated inflammatory lesions and noninflammatory lesions; however, noninflammatory lesions were a prespecified secondary endpoint in the second trial only. The Skindex-16 patient reported questionnaire was used to measure patient's quality of life and evaluated patients' symptoms, emotions, and functioning. Scores ranged from 0 (never bothered) to 100 (always bothered).[24] No minimal clinically important change in the Skindex-16 has been described.

In both studies, sarecycline was more effective than placebo for both co-primary endpoints. In the first study, 21.9% of patients in the sarecycline group achieved an IGA score of 0 or 1 compared to 10.5% in the placebo group (ARR 11.4%/NNT 9; p<0.001).[24] The mean absolute reduction in inflammatory lesion count was higher with sarecycline compared to placebo, 15.3 versus 10.2, respectively (P<0.001).[17] Results for the second study were similar with 22.6% of patients in sarecycline group achieving an IGA score of 0 or 1 compared to 15.3% in the placebo group (ARR 7.3%/NNT 14; p=0.004).[17] The absolute change in the number of inflammatory lesions was higher for sarecycline compared to placebo, 15.5 versus 11.1 (p<0.001).[24]

Limitations to this study include a high or unclear risk of bias for selection, detection, reporting and attrition domains. The quality of this study was graded as low quality.

Clinical Safety:
A similar amount of patients experienced adverse events with sarecycline and placebo, 27.7% and 29.2%.[24] The most common adverse event associated with sarecycline is nausea.[11] Like other tetracycline antibiotics sarecycline should not be used in young children and in pregnant women in the second in third trimester. Sarecycline can cause photosensitivity and should be discontinued if signs of *C. diff* or intracranial hypertension.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Number of inflammatory lesions
2) Acne severity
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
2) IGA response and inflammatory lesions

Table 7. Pharmacology and Pharmacokinetic Properties of Sarecycline[11]

Parameter	
Mechanism of Action	Tetracycline antibiotic with unknown mechanism of action against acne
Oral Bioavailability	Not described
Distribution and Protein Binding	91.4 – 97.0 Liter 62.5-74.7% protein bound
Elimination	44.1% urine and 77.5% to 42.6% feces
Half-Life	21-22 hours
Metabolism	<15% from human liver microsomes

Table 8. Comparative Evidence Table for Sarecycline.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Moore, et al[7] Phase 3, DB, RCT, PC, PG (SC 1401)	1. Sarecycline 1.5 mg/kg/day dosed once daily (S) 2. Placebo tablets (P) 12 weeks	Demographics: Age (mean): 20 yrs Male: 45% IGA score of 3: 86% IGA score of 4: 14% Key Inclusion Criteria: - IGA score equal to or greater than 3 - 20-50 inflammatory lesions - 100 or less non-inflammatory lesions - 2 or less nodules Key Exclusion Criteria: - other dermatological condition or facial hair - chronic illness interfering with study evaluation - allergy or resistance to tetracycline antibiotics - drug-induced acne - other medications that could impact acne 12 weeks prior to initiation	ITT: 1. 483 2. 485 PP: 1. 463 2. 403 Attrition: 1. 4% 2. 16%	Co-primary Endpoints: IGA Success*: S: 106 (21.9%) P: 51 (10.5%) P<0.0001 CI not reported Mean absolute change in inflammatory lesions: S: 250 (-51.8%) P: 170 (-35%) P<0.0001 Secondary Endpoints: Skindex-16 total score†: MD -3.5 (95% CI, -6.0 to -1.1) P <0.05	11%/9 NA NA	Nausea: S: 22 (4.6%) P: 12 (2.5%) Nasopharyngitis S: 15 (3.1%) P: 8 (1.7%) Headache: S: 13 (2.7%) P: 13 (2.7%) Discontinuations due to adverse events: S: 3 (0.6%) P: 7 (1.4%) Serious Adverse Events: S: 4 (0.6) P: 5 (1.0) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomization procedures not described. Balanced baseline characteristics Performance Bias: (low) Matching tablets to prevent unblinding. Double-blind design but details not provided Detection Bias: (unclear) Outcome assessment not described. Attrition Bias: (high) Twelve percent difference in discontinuation rates between groups could bias results. Analysis was done on the ITT population with a multi-imputation approach for missing data Reporting Bias: (high) Outcomes reported as prespecified but lacked confidence intervals Other Bias: (high) Industry funded **Applicability**: Patient: In patients with inflammatory moderate to severe acne Intervention: Intervention appropriate Comparator: Active treatment comparison would helpful to determine comparative efficacy Outcomes: IGA scores and number of acne lesions are common outcomes used in studies evaluating efficacy of acne treatment Setting: Multi-center study in over 100 sites within the United States
2. Moore, et al[7] Phase 3, DB, RCT, PC, PG (SC 1402)	1. Sarecycline 1.5 mg/kg/day dosed orally once daily (S) 2. Placebo tablets (P) 12 weeks	Demographics: Age (mean): 20 years Male: 41% IGA score of 3: 85% IGA score of 4: 15% Key Inclusion Criteria: - IGA score equal to or greater than 3	ITT: 1. 519 2. 515 PP: 1. 427 2. 442 Attrition: 1. 17%	Co-primary Endpoints: IGA Success*: S: 117 (22.6%) P: 79 (15.3%) P=0.004 CI not reported Mean absolute change in inflammatory lesions: S: 259 (-49.9%)	7%/14	Nausea: S: 10 (1.9%) P: 5 (1.0%) Nasopharyngitis S: 13 (2.5%) P: 15 (2.9%) Headache: S: 15 (2.9%)	NA for all	**Risk of Bias (low/high/unclear)**: See above

		- 20-50 inflammatory lesions - 100 or less non-inflammatory lesions - 2 or less nodules <u>Key Exclusion Criteria</u>: - other dermatological condition or facial hair - chronic illness interfering with study evaluation - allergy or resistance to tetracycline antibiotics - drug-induced acne - other medications that could impact acne 12 weeks prior to initiation	2. 14%	P: 182 (-35.4%) P<0.0001 <u>Secondary Endpoints</u>: Absolute percent change of noninflammatory lesions (in patients with 20 or more inflammatory lesions at baseline): S: 84 (16.2%) P: 69 (13.4%) P<0.01 Skindex-16 total score†: MD -5.9 (95% CI, -8.1 to -3.6) P <0.05	NA NA NA	P: 25 (4.9%) <u>Discontinuations due to adverse events:</u> S: 11 (2.1%) P: 6 (1.2%) <u>Serious Adverse Events</u>: S: 4 (0.8) P: 1 (0.2) p-value not reported for all		
Key: * IGA – 2 or more grade improvement and score 0 (clear) or 1 (almost clear), † Individual group results not reported Abbreviations: DB = double-blind; IGA = Investigator's Global Assessment; MD = mean difference; NA = not applicable: PC = placebo-controlled; PG = parallel-group, RCT = randomized controlled trial								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
doxycycline hyclate	DOXYCYCLINE HYCLATE	TABLET	Y
doxycycline hyclate	DOXYCYCLINE HYCLATE	CAPSULE	Y
doxycycline hyclate	ED DOXY-CAPS	CAPSULE	Y
doxycycline hyclate	MORGIDOX	CAPSULE	Y
doxycycline hyclate	VIBRAMYCIN	CAPSULE	Y
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	CAPSULE	Y
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	SUSP RECON	Y
doxycycline monohydrate	VIBRAMYCIN	SUSP RECON	Y

tetracycline HCl	ALA-TET	CAPSULE	Y
tetracycline HCl	TETRACYCLINE HCL	CAPSULE	Y
doxycycline calcium	VIBRAMYCIN	SYRUP	N
doxycycline hyclate	DOXYCYCLINE HYCLATE	TABLET	N
doxycycline hyclate	LYMEPAK	TABLET	N
doxycycline hyclate	DORYX	TABLET DR	N
doxycycline hyclate	DORYX MPC	TABLET DR	N
doxycycline hyclate	DOXYCYCLINE HYCLATE	TABLET DR	N
doxycycline monohydrate	DOXYCYCLINE IR-DR	CAP IR DR	N
doxycycline monohydrate	ORACEA	CAP IR DR	N
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	CAPSULE	N
doxycycline monohydrate	ADOXA	TABLET	N
doxycycline monohydrate	ADOXA PAK	TABLET	N
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	TABLET	N
minocycline HCl	XIMINO	CAP ER 24H	N
minocycline HCl	DYNACIN	CAPSULE	N
minocycline HCl	MINOCIN	CAPSULE	N
minocycline HCl	MINOCYCLINE HCL	CAPSULE	N
minocycline HCl	MINOCYCLINE HCL ER	TAB ER 24H	N
minocycline HCl	SOLODYN	TAB ER 24H	N
minocycline HCl	MINOCYCLINE HCL	TABLET	N
demeclocycline HCl	DEMECLOCYCLINE HCL	TABLET	N
omadacycline	NUZYRA	TABLET/IV	N
sarecycline	SEYSARA	TABLET	N

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to November Week 5 2018
Search Strategy:

#	Searches	Results
1	doxyclycline.mp.	4
2	tetracycline.mp.	37597
3	minocycline.mp. or MINOCYCLINE/	7691
4	demeclocycline.mp. or DEMECLOCYCLINE/	988
5	omadacycline.mp.	29
6	1 or 2 or 3 or 4 or 5	44352
7	limit 6 to (structured abstracts and english language and humans and yr="2017 -Current")	319
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	23

Appendix 3: Prescribing Information Highlights

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

NUZYRA (omadacycline) for injection, for intravenous use
NUZYRA (omadacycline) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
NUZYRA is a tetracycline class antibacterial indicated for the treatment of adult patients with the following infections caused by susceptible microorganisms (1):

- Community-acquired bacterial pneumonia (CABP) (1.1)
- Acute bacterial skin and skin structure infections (ABSSSI) (1.2)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZYRA and other antibacterial drugs, NUZYRA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.3)

----------DOSAGE AND ADMINISTRATION----------
- Dosage of NUZYRA in CABP and ABSSSI Adult Patients (2.2, 2.3):

Infection	Loading Doses	Maintenance Dose
CABP	Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice (2.2)	100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily (2.2)
ABSSSI	Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice (2.3) OR	100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily (2.3)
ABSSSI (NUZYRA tablets only)	Day 1 and Day 2: 450 mg orally once daily (2.3)	300 mg orally once daily (2.3)

- CABP and ABSSSI: Treatment duration is 7 to 14 days. (2.2, 2.3)
- Fast for at least 4 hours and then take NUZYRA tablets with water. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours. (2.1)
- See full prescribing information for the preparation of NUZYRA IV and other administration instructions. (2.1, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- For Injection: 100 mg of omadacycline (equivalent to 131 mg omadacycline tosylate) as a lyophilized powder in a single dose vial for reconstitution and further dilution before intravenous infusion (3.1)
- Tablets: 150 mg omadacycline (equivalent to 196 mg omadacycline tosylate) (3.2)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to omadacycline, tetracycline-class antibacterial drugs or any of the excipients in NUZYRA (4)

----------WARNINGS AND PRECAUTIONS----------
- Mortality Imbalance in Patients with CABP: In the CABP trial, mortality rate of 2% was observed in NUZYRA-treated patients compared to 1% in moxifloxacin-treated patients. The cause of the mortality imbalance has not been established. Closely monitor clinical response to therapy in CABP patients, particularly in those at higher risk for mortality. (5.1, 6.1)
- Tooth Discoloration and Enamel Hypoplasia: The use of NUZYRA during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia. (5.2, 8.1, 8.4)
- Inhibition of Bone Growth: The use of NUZYRA during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth. (5.3, 8.1, 8.4).
- *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥2%) are nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Paratek Pharmaceuticals, Inc. at 1-833-727-2835 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage while taking NUZYRA. (7.1)
- Absorption of tetracyclines, including NUZYRA is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron containing preparations. (2.1, 7.2)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Breastfeeding is not recommended during treatment with NUZYRA. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2018

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

SEYSARA™ (sarecycline) tablets for oral use.
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
SEYSARA™ is a tetracycline-class drug indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. (*1*)

Limitations of Use
Efficacy of SEYSARA beyond 12 weeks and safety beyond 12 months have not been established. SEYSARA has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SEYSARA should be used only as indicated *[see Warnings and Precautions (5.6)]*.

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage of SEYSARA is once daily with or without food:
- 60 mg for patients who weigh 33-54 kg,
- 100 mg for patients who weigh 55-84 kg,
- 150 mg for patients who weigh 85-136 kg. (*2*)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 60 mg, 100 mg, 150 mg (*3*)

----------CONTRAINDICATIONS----------
SEYSARA is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (*4*)

----------WARNINGS AND PRECAUTIONS----------
- The use of SEYSARA during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (*5.1*)
- If Clostridium difficile Associated Diarrhea (antibiotic associated colitis) occurs, discontinue SEYSARA. (*5.2*)
- Central nervous system side effects, including light-headedness, dizziness or vertigo, have been reported with tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may disappear during therapy and may disappear when the drug is discontinued. (*5.3*)
- SEYSARA may cause intracranial hypertension. Discontinue SEYSARA if symptoms occur. (*5.4*)
- Photosensitivity can occur with SEYSARA. Patients should minimize or avoid exposure to natural or artificial sunlight. (*5.5*)

----------ADVERSE REACTIONS----------
Most common adverse reaction (incidence ≥ 1%) is nausea. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Oral retinoids: avoid coadministration. (*5.4, 7.1*)
- Antacids and iron preparations: separate dosing of SEYSARA. (*7.1*)
- Penicillin: avoid coadministration. (*7.2*)
- Anticoagulants: decrease anticoagulant dosage as appropriate. (*7.2*)
- P-glycoprotein substrates: monitor for toxicities of drugs that may require dosage reduction. (*7.2*)

----------USE IN SPECIFIC POPULATIONS----------
- Sarecycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. (*5.1, 8.1*)
- The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of teeth. (*5.1, 8.4*)
- Lactation: Breastfeeding is not recommended. (*8.2*)

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

Revised: 10/2018

Appendix 4: Key Inclusion Criteria

Population	Children and adults with an indication for tetracycline antibiotics
Intervention	Tetracycline therapy
Comparator	Placebo or active treatment
Outcomes	Clinical cure rate, reinfection, lesion reduction
Timing	Not applicable
Setting	Outpatient therapy

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review: Hereditary Angioedema

Date of Review: March 2019 **End Date of Literature Search:** 10/29/2018

Purpose for Class Review:
The purpose of this review is to evaluate evidence for efficacy and safety of pharmacological treatments for hereditary angioedema (HAE). The review was prompted by the Food and Drug Administration (FDA) approval of 2 therapies for prophylaxis in HAE: lanadelumab in 2018 and subcutaneous C1 esterase inhibitor (C1-INH-H; Hargarda®) in 2017. Therapies which are approved for treatment of HAE are listed in **Table 1**, and prior treatments included only acute therapies or intravenous (IV) formulations for prophylactic use.

Research Questions:
1. What is the evidence for efficacy and harms of prophylactic or acute treatment for HAE?
2. Is there any comparative evidence on efficacy of treatments for HAE pertaining to clinical outcomes (morbidity, mortality, hospitalization rate, reduction in HAE attacks, and quality of life)?
3. Is there any comparative evidence on the harms of therapy for HAE with prophylactic or acute use?
4. Are there subpopulations of patients with HAE for which treatment may be more effective or associated with more harms?

Conclusions:
- There is no direct comparative evidence evaluating prophylactic use or acute treatment of HAE.
- There is insufficient evidence to assess long-term efficacy or safety of C1 inhibitors, lanadelumab, ecallantide, or icatibant. While there are no long-term, randomized controlled data regarding efficacy and safety of these therapies, the first C1 inhibitors were initially FDA approved in 2008. A summary of warnings and precautions associated with each treatment is available in **Appendix 1**. Anaphylaxis has been documented in 3-4% of patients treated with ecallantide, 1% of patients treated with lanadelumab-flyo, and with C1 esterase inhibitors (incidence unknown).[1-4] It is recommended that epinephrine be immediately available with administration of all human-derived C1 esterase inhibitors (C1-INH-B, C1-INH-C, C1-INH-H) due to the risk of anaphylaxis.[5-7] C1 esterase inhibitors also have a risk of thrombotic events and upon long-term prophylactic use of C1-INH-C over 2.6 years, 5 patients (3%; n=146) had thrombotic events.[8]

Acute Treatment
- Compared to placebo during treatment of an acute HAE attack, time to symptom relief or resolution was improved by approximately 1-2 hours with human or recombinant C1 inhibitor (low quality evidence).[9-11] For specific C1 inhibitor products, the median time to symptom relief was 1.5 versus 2.5 hours for C1 esterase inhibitor (C1-INH-R; Ruconest®), 0.5 versus 1.5 hours for C1 esterase inhibitor (C1-INH-B; Berinert®), and 2 versus 4 hours for C1 esterase inhibitor (C1-INH-C; Cinryze®) compared to placebo, respectively.[9-11] The clinical benefit of a 1-2 hour improvement in symptoms in unclear, and there is insufficient evidence to evaluate efficacy in patients with laryngeal attacks.

- In clinical trials for treatment of acute attacks, symptom severity was statistically improved at 4 hours after treatment with ecallantide compared to placebo (difference in mean symptom complex score of 0.4 points and difference in treatment outcomes scale of 25.5 points; low quality evidence).[12,13] The clinical significance of this change is unclear. Mean symptom complex score provides an average score of various symptoms and improvement over time on a severity scale of 0-3 with lower scores indicating improved symptoms. The treatment outcomes scale evaluates severity of symptoms on a -100 to 100 range associated with significantly worse to significantly improved symptoms. Scores of 0 are associated with no change from baseline and 50 points are associated with improvement.
- In patients with type 1 or 2 HAE, there is inconsistent evidence from 2 trials that icatibant may be associated with improved time to symptom improvement during an acute attack (low quality evidence).[14-16] Compared to placebo, time to clinical symptom improvement was not statistically significant for a patient's primary symptom (median difference 2.1 hours; p=0.14, n=56), but a second study demonstrated a median time to 50% improvement in overall symptoms of 17.8 hours compared to placebo (19.8 vs. 2.0 hours; p<0.001; n=93).[14-16]

Prophylactic Treatment

- In patients with a frequent history of angioedema attacks (baseline rate of 3-4 per month), prophylactic use of C1 esterase inhibitors (C1-INH-H and C1-INH-C) was associated with a mean reduction of 2.1 to 3.5 attacks per month over 12 to 16 weeks compared to placebo (low to moderate quality evidence). [8]
- With prophylactic use of lanadelumab compared to placebo in patients with a baseline rate of 3-4 attacks per month, the average angioedema attack rate was reduced by 1.5 to 1.7 attacks per month compared to baseline (moderate quality evidence).[8]
- There is insufficient evidence that prophylactic use of HAE treatments affects mortality, hospitalization rate, quality of life, or long-term impacts on work, school, depression or anxiety.

Recommendations:

- Recommend implementation of prior authorization criteria to promote use for appropriate indications and ensure safe use.
- Recommend ecallantide be non-preferred due to concerns with anaphylaxis. Evaluate comparative costs in executive session.

Background:

Hereditary angioedema (HAE) is caused by a deficiency or lack of function of C1 inhibitor protein.[1,17] C1 inhibitor is an important regulator of the complement system and the kallikrein-kinin pathway which is involved in formation of bradykinin.[17] A lack of functional C1 inhibitor protein can result in an overproduction of bradykinin which is the primary cause of swelling in patients with hereditary angioedema. The deficiency is most commonly hereditary, though it may also be acquired via increased catabolism of C1 inhibitor protein, often as a result of malignancy or autoantibodies, thereby decreasing inhibitor function.[17] Diagnosis is based on laboratory analysis of complement C4 and C2 levels and C1 inhibitor antigenic levels.[1,17] There are 3 types of HAE. Type 1 and type 2 are clinically indistinguishable from each other and account for the majority of cases of C1 inhibitor deficiency. Approximately 75% of patients diagnosed with HAE have a family history of angioedema.[17]

Symptoms of the disease include angioedema without urticaria which typically occur in early childhood or adolescence. Attacks of angioedema worsen gradually and resolve slowly over 24-72 hours.[17] Attacks may also be preceded by a prodromal phase with symptoms such as fatigue, non-urticarial rash, or other flu-like symptoms. Attacks most commonly involve the extremities and abdomen, but can be life-threatening if they involve the oropharynx or larynx.[17] Severity and frequency of attacks is highly variable between patients.[17] Frequency of attacks may be affected by hormone levels and often occur with onset of puberty, menopause, use of contraceptives, pregnancy, or other changes in estrogen levels. Precipitating factors for attacks are often unclear though both stress and physical trauma have been correlated with onset of acute attacks.[1,17]

Current standard of care for treatment of acute attacks of angioedema include C1 inhibitors, ecallantide, or icatibant (**Table 1**). While no high quality guidelines met inclusion criteria for this review, guidelines from the World Allergy Organization recommend on-demand therapy be considered for treatment of acute attacks of angioedema, and that any attack affecting the upper airway be treated (based on expert consensus opinion).[1] Guidelines are limited by significant conflicts of interest and lack of details on guideline development methodology, with many recommendations based on expert consensus opinion. In general, early administration of medications is associated with better treatment response.[1] Recommended first-line prophylactic therapy includes a C1 inhibitor, though guidelines did not include evidence on lanadelumab-flyo which was recently FDA-approved.[1] No recommendations are made for a specific type of C1 inhibitor therapy. Administration of other anaphylactic therapy, such as epinephrine, antihistamines, and corticosteroids are only recommended if the cause of swelling and diagnosis of hereditary angioedema is unclear as these therapies do not improve symptoms of HAE attacks.[1]

Efficacy in acute attacks has been documented in short-term clinical trials, though the long-term effects of treatment are less clear, particularly for newer therapies. A summary of pivotal clinical trials completed for each agent is available in **Table 2** and warnings and precautions associated with each therapy are documented in **Appendix 1**. While plasma-derived products are screened extensively, there is still a risk for transmission of infectious disease (i.e., viruses) with plasma-derived C1 inhibitors.[5-7] Other major safety concerns include hypersensitivity reactions and thrombotic events which have been reported with both plasma-derived and recombinant C1 inhibitors.[5-7,18] Anaphylaxis is also a concern with ecallantide (reported in 3-4% of patients in clinical trials), lanadelumab-flyo (1% of patients), and with C1 esterase inhibitors (incidence unknown).[1-4] It is recommended that epinephrine be immediately available with administration of all human-derived C1 esterase inhibitors (C1-INH-B, C1-INH-C, C1-INH-H) due to the risk of anaphylaxis. After self-administration of treatment for laryngeal HAE attacks, patients should be instructed to seek immediate medical care due to the ongoing potential for airway obstruction during acute laryngeal attacks.[1-4]

Common outcomes evaluated in clinical trials include time to symptom resolution during an acute attack and reduction in number of attacks over time with prophylactic treatment. There is no established or validated measure to evaluate symptom improvement in patients with HAE attacks, and clinical trials have used a variety of scales to evaluate symptom severity. Examples of these scales include individual or composite visual analog scales evaluating overall symptom improvement or severity at multiple sites, the mean symptom complex score, and the treatment outcome score. The mean symptom complex score was developed during clinical trials for ecallantide and evaluates symptom severity at several locations on a 0 to 3 point scale. Scores at each site are averaged to achieve a total score. The treatment outcomes scale evaluates change in symptom severity over time. Lower scores are associated with worse symptoms from baseline and higher scores are associated with improved symptoms (range -100 to 100). Scores of 100 are associated significant improvement, 50 with improvement, 0 with no change, -50 with worsening, and -100 with significant worsening.[19] While the minimum clinically important difference for these scales has not been established, several thresholds have been proposed by manufacturers. Proposed minimum thresholds associated with clinically important differences are 20-30 points on the 0-100 visual analog scales, 30 points for treatment outcomes scale, and 0.3 point on the mean symptom complex score.[15,19]

Currently, in the fee-for-service (FFS) population, approximately 77 patients have a diagnosis indicating defects in the complement system (D84.1). This number is likely an overestimate of patients as this diagnosis includes conditions with other types of complement deficiencies. Administration of acute treatment may occur in the acute treatment setting (during hospitalization or an emergency department visit), and pharmacy utilization of acute or prophylactic treatments is limited with paid claims for 2 FFS members in the past year.

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

Table 1. FDA-approved Indications and Dosing[20]

Generic Name; Designation (Brand Name)	Indication(s)	Strength/Route	Dose and Frequency
Acute Treatment			
C1 esterase inhibitor; C1-INH-B (Berinert®)	Treatment of acute abdominal, facial, or laryngeal HAE attacks in adults and pediatric patients	500 units IV kit	20 units/kg as a single dose
C1 esterase inhibitor, recombinant ; C1-INH-R (Ruconest®)	Treatment of acute HAE attacks in adult and adolescent patients. Efficacy has not been established in laryngeal attacks	2100 units IV reconstituted solution	50 units/kg as a single dose; maximum dose: 4,200 units
Ecallantide (Kalbitor®)	Treatment of acute HAE attacks in patients 12 years and older	10 mg/mL SC solution	30 mg as a single dose; may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Treatment of acute HAE attacks	10 mg/mL SC solution	30 mg once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
Prophylactic Treatment			
C1 esterase inhibitor ; C1-INH-C (Cinryze®)	HAE prophylaxis in adults, adolescents, and pediatric patients ≥6 years of age	500 units IV reconstituted solution	1,000 units every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor; C1-INH-H (Haegarda®)	HAE prophylaxis in adults and adolescents	2000 and 3000 units SC reconstituted solution	60 units/kg every 3 to 4 days (twice weekly)
Lanadelumab-flyo (Takhzyro™)	HAE prophylaxis in patients ≥12 years of age	300 mg/2mL SC solution	300 mg every 2 weeks; may consider dosing every 4 weeks for patients who are well-controlled for > 6 months

Abbreviations: HAE = hereditary angioedema, IV = intravenous; SC = subcutaneous

Table 2. Summary of Pivotal Studies Completed

Study	Comparison	Population	Primary Outcome	Results
Acute Treatment				
Cicardi, et al.[15] FAST 1 and FAST 2 DB, MC, PC, RCT	FAST 1 1. Icatibant 30 mg SC 2. Placebo SC FAST 2 1. Icatibant 30 mg SC 2. Tranexamic acid 3 gm PO for 2 days	HAE type I or II presenting with an acute attack and ≥ 1 moderate to severe cutaneous symptom (defined as severity of >30 points on a 0-100 scale) FAST1: N= 56 FAST2: N=74	Time to clinically significant symptomatic relief in the prespecified primary symptom (decrease of 20-30 points). In patients with multiple symptoms (cutaneous swelling, cutaneous pain, or abdominal pain), a single symptom was chosen for assessment.	FAST 1: 1. Median 2.5 hours (IQR 1.1 to 6.0) 2. Median 4.6 hours (IQR 1.8 to 10.2) Difference = 2.1 hours; p=0.14 FAST 2: 1. Median 2.0 hours (IQR 1.0 to 3.5) 2. Median 12.0 hours (IQR 3.5 to 25.4) Difference = 10 hours; p<0.001

Lumry, et al.[16] FAST 3 DB, PC, MC, RCT, phase 3	1. Icatibant 30 mg SC 2. Placebo	HAE type 1 or II with acute angioedema (presenting within 6 hours of an acute attack) and with at least moderate abdominal or cutaneous symptoms or mild laryngeal symptoms N=93	Subject-assessed median time to 50% reduction in mean symptom severity (3 symptoms for cutaneous attacks: swelling, skin pain, abdominal pain OR 5 symptoms for laryngeal attacks including difficulty swallowing and voice change)	Non-laryngeal attacks; n=88 1. 2.0 hours (95% CI 1.5 to 3.0) 2. 19.8 hours (6.1 to 26.3) Difference = 17.8 hours; p<0.001 Laryngeal attacks; n=5 1. 2.5 hours (95% CI 1.3 to 3.0) 2. 3.2 hours (95% CI 1.0 to 5.4) Difference =0.7 hours; p value NR
Levy, et al.[13] EDEMA4 DB, PC, RCT, phase 3	1. Ecallantide 30 mg SC 2. Placebo	Type I or II HAE ≥10 years of age N=96	Change from baseline in MSCS score 4 hours after dosing (range 0-3)*	1. -0.8 (SD 0.6) 2. -0.4 (SD 0.8) Difference = 0.4 points; p=0.01
Cicardi, et al.[12] EDEMA3 DB, PC, MC, RCT, phase 3	1. Ecallantide 30 mg SC 2. Placebo	HAE ≥10 years of age with moderate to severe symptoms of angioedema N=72	Change from baseline in TOS at 4 hours (range -100 to 100)¥	1. 46.8 (SD 59.3) 2. 21.3 (SD 69.0) Difference = 25.5 points; p = 0.004
Riedl, et al.[10] DB, PC, MC, RCT, phase 3	1. C1-INH-R 50 IU/kg; maximum 4200 IU/treatment 2. Placebo	HAE ≥ 13 years of age with acute angioedema (presenting within 5 hours of an acute attack) and with symptom severity of ≥ 50 points N=75	Time to onset of sustained symptom relief evaluated as improved intensity and severity of symptoms (severity score of 5-7 corresponding with "a little" to "much" better on a 1-7 point scale from much worse to much better)	1. Median 90 minutes (95% CI 61-150) 2. Median 152 (95% CI 93 to --) Difference 62 minutes; p = 0.031
Craig, et al.[9] IMPACT1 MC, PG, PC, DB, RCT, phase 2/3	1. C1-INH-B 10 units/kg 2. C1-INH-B 20 units/kg 3. Placebo	HAE type I and II ≥6 years of age with moderate to severe abdominal or facial angioedema (presenting within 5 hours of an acute attack) N=125	Time to onset of symptom relief	Reported as mean (SD) and median (range). Time was calculated at 24 hours if any rescue, analgesic, or antiemetic therapy was given. 1. Mean 7.47 (10.51); median 1.17 (0.17 to 24) 2. Mean 3.89 (8.20); median 0.50 (0.17 to 24) 3. Mean 10.27 (11.48); median 1.50 (0.2 to 24) 1 vs. 3: median difference 0.33 hours; p=0.2731 2 vs. 3: median difference 1 hour; p=0.0048 1 vs. 2: median difference 0.67 hours; p=0.0025
Zuraw, et al.[11] DB, PC, RCT	1. C1-INH-C 1000 units 2. Placebo A second dose was given if symptoms had	HAE ≥ 6 years with moderate-severe abdominal, face or genital symptoms presenting	Time to unequivocal symptom relief at the defining site (site with the most severe symptoms at baseline)	1. 2 hours 2. >4 hours RR 2.41, 95% CI 1.17 to 4.95; p=0.02

	not improved at 60 minutes	within 4 hours of attack onset N=207 eligible; 71 had an attack and were enrolled		
Prophylactic Treatment				
Longhurst, et al.[21] COMPACT DB, MC, PC, RCT, cross-over, phase 3	1. C1-INH-H SC 40 IU/kg twice weekly 2. C1-INH-H SC 60 IU/kg twice weekly 3. Placebo Randomized 1:1:1:1 based on dose and treatment sequence	Type I or II HAE age ≥ 12 years with ≥ 4 attacks over 2 months prior to screening and ≥ 2 attacks during the 8 week run-in period N=90	Number of angioedema attacks over 16 weeks during treatment or placebo phases	Treatment sequence with 40 IU/kg - 40 IU/kg: 1.19 (95% CI 0.54 to 1.85) - Placebo: 3.61 (95% CI 2.96 to 4.26) MD -2.42 (95% CI -3.38 to -1.46); p<0.001 Treatment sequence with 60 IU/kg - 60 IU/kg: 0.52 (95 % CI 0.00 to 1.04) - Placebo: 4.03 (95% CI 3.51 to 4.55) MD -3.51 (95% CI -4.21 to -2.81); p<0.001 40 vs. 60 IU/kg: -0.64 (95% CI -1.43 to 0.16);p=0.11
Zuraw, et al.[11] DB, PC, cross-over, RCT	1. C1-INH-C 1000 units every 3-4 days 2. Placebo	HAE ≥ 6 years enrolled in acute treatment trial with history of ≥ 2 attacks per month N=24	Average number of angioedema attacks over 12 weeks	1. 6.26 attacks 2. 12.73 attacks MD 6.47 attacks (95% CI 4.21 to 8.73); p<0.001
Banerji, et al.[22] HELP3 DB, PC, PG, MC, RCT, phase 3	1. Lanadelumab 150 mg SC every 4 weeks 2. Lanadelumab 300 mg SC every 4 weeks 3. Lanadelumab 300 mg SC every 2 weeks 4. Placebo	HAE type I or II age ≥ 12 years with ≥ 1 attack during the 4-week run-in period N=125	Average monthly number of investigator-confirmed Angioedema attacks over 26 weeks	1. 0.48 (95% CI 0.31-0.73) 2. 0.53 (95%CI 0.36-0.77) 3. 0.26 (95% CI 0.14-0.46) 4. 1.97 (95% CI 1.64-2.36) 1 vs. 4: MD −1.49 (95% CI −1.90 to −1.08); p<0.001 2 vs. 4: MD −1.44 (95%CI −1.84 to −1.04); p<0.001 3 vs. 4: MD −1.71 (95% CI −2.09 to −1.33); p<0.001

* MSCS is a composite score evaluating symptom severity at various sites from mild to severe on a 1-3 scale. Decreases in score represent improvement in symptoms.
¥ TOS evaluates symptom severity on a 0-100 scale with larger scores representing more significant improvement
Abbreviations: CI = confidence interval; DB = double-blind; HAE = hereditary angioedema; IQR = interquartile range; MC = multicenter; MD = mean difference; MSCS = mean symptom complex score; NS = non-significant; PC = placebo-controlled; PG = parallel group; PO = oral; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; TOS = treatment outcome score

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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 2018, the Institute for Clinical and Economic Review evaluated prophylactic therapies for type 1 or 2 HAE.[8] The review included products approved by the Food and Drug Administration (FDA) for prophylaxis including C1 inhibitors (C1-INH-C and C1-INH-H) and lanadelumab. Both RCTs and observational single-arm or extension studies were included in the review. Baseline attack rate was typically 3-4 attacks per month for included trials. Evidence supported a mean reduction in HAE attacks per month compared to placebo.[8] The average reduction in attacks per month compared to placebo was 2.1 for C1-INH-C, 2.4 to 3.5 for C1-INH-H (40 and 60 IU/kg, respectively), and 1.5 to 1.7 attacks for lanadelumab.[8] Attack severity (assessed on a 1-3 point scale) was also statistically reduced with use of C1-INH-C compared to placebo (1.9 vs. 1.2, mean difference 0.7) and with C1-INH-H (1.6-1.8 vs. 1.9-2.0 points, mean difference 0.2-0.3).[8] More patients treated with lanadelumab (39-44%) were attack free over 6.5 months compared to placebo (2%).[8] There was no direct comparative data between treatments, no data on mortality, and only limited, inconsistent data on patient reported outcomes such as quality of life, or long-term impacts on work, school, depression or anxiety.[8] Use in pediatric patients was limited, but overall outcomes were similar in patients less than 18 years of age.[8] Serious adverse events were rare, and the most common adverse events reported in clinical trials included mild infections, headache, hypersensitivity, dizziness, and injection site reactions with subcutaneous administration.[8] Only one long-term safety study was identified evaluating use of C1-INH-C for up to 2.6 years.[8] Over this period 5 thrombotic events (3%; n=146) were observed in patients with underlying risk factors.[8] Two patients died of causes considered to be unrelated to C1-INH-C.[8] Overall the population evaluating long-term safety was small, and information on long-term safety of all prophylactic therapies remains limited.[8]

A series of 3 CADTH rapid response reports evaluated evidence of treatment and prophylactic therapies for HAE. For prophylactic treatment, an assessment of 8 studies evaluating efficacy and safety of C1 esterase inhibitors was included.[23] Study types included 1 randomized controlled trial and data from 7 long-term prospective and retrospective observational studies.[23] Authors concluded C1 esterase inhibitors were likely effective for the prevention of HAE attacks, but there was no high-quality data available.[23] Data were limited by small population sizes, unclear methods for randomization and blinding, presence of potential confounding factors (such as androgen therapy), lack of comparator data for non-randomized studies, and use of self-reported outcomes which have a higher risk of recall bias in retrospective studies.[23] Due to these significant limitations, discussion of evidence will primarily focus on significant safety-related signals observed in the observational studies, and these outcomes should be interpreted with caution. Adverse events reported in observational studies included gastrointestinal events, major depression, musculoskeletal chest pain, lightheadedness, fever, rash, infusion-site reactions, headache.[23] Serious adverse events included thrombotic events which were reported in 3 studies.[23] The exact incidence of these events is unknown.

Two CADTH drug reviews evaluated evidence of icatibant for treatment of acute HAE attacks. No high-quality evidence was found in Type 3 HAE; evidence included only one poor quality, single-arm cohort study, 3 case series and 3 case reports.[24] Evidence for icatibant in patients with Type 1 or 2 HAE included 2 placebo-controlled RCTs (FAST 1 and 3) and associated open-label extension studies. On average, patients experienced more cutaneous attacks (6.7 to 9.9) compared to abdominal (3.8 to 6.8) or laryngeal attacks (0.7 to 2.8) in the 6 months before enrollment.[14] Both trials were limited by small population sizes, potential unblinding due to injection-site reactions, and use of patient reported outcomes which may be subject to higher reporting bias.[14] Data on patients with laryngeal attacks were limited and patients with coronary artery disease were excluded from clinical trials as animal models showed bradykinin 2 inhibition may decrease coronary blood flow.[14] Symptom improvement was evaluated using visual analogue scales in each trial, reported as a composite of 3 symptoms (skin

swelling, skin pain, and abdominal pain) in FAST 3 and reported as individual symptoms in FAST 1.[14] Use of the composite score to evaluate symptoms has not been validated and the minimum clinically important difference has not been established. In one trial (FAST 3), median time to 50% reduction in symptoms improved with icatibant compared to placebo (2.0 vs. 19.8 hours; p<0.001), but time to symptom relief (reduction of 20-30 points on a 100 point scale) was not statistically significant in the second trial (FAST 1; 2.5 vs. 4.6 hours; p=0.142).[14] Of the patients enrolled in these clinical trials 4-11% required a second injection of icatibant to control symptoms.[14] Neither trial included data on quality of life, daily activities, physical or mental functioning.[14]

After review, 4 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[25-28]

Guidelines:

High Quality Guidelines:

No high-quality guidelines met inclusion criteria.

Additional Guidelines for Clinical Context:

In 2017, the World Allergy Organization in conjunction with the European Academy of Allergy and Clinical Immunology published an updated guideline for the management of HAE.[1] The guideline had the following limitation: more than half of members, including first authors, reported competing interests with industry, and details on the guideline development process including literature searches and process to address conflicts of interest were not available.[1] Due to the limited evidence available for the treatment of HAE the majority of guideline recommendations are based on trials with severe methodological limitations or adapted from consensus expert opinion.[1] Guideline recommendations based on GRADE A evidence (randomized, double-blind clinical trial of high quality) or GRADE B evidence (randomized, clinical trials of lesser quality or limited sample size) are discussed here. For each recommendation, the amount of agreement among guideline panel members was also documented.

- Acute HAE attacks should be treated with C1 inhibitors, ecallantide or icatibant (GRADE A, strong recommendation, 90% agreement)[1]
- Attacks should be treated as early as possible (GRADE B, strong recommendation, 100% agreement)[1]
- C1-inhibitors are recommended as first-line long-term prophylactic treatment in patients with HAE (GRADE A, strong recommendation, 50-75% agreement)[1]

After review, 4 guidelines were excluded due to poor quality.[29-32]

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Appendix 1: Specific Drug Information

Table A1. Clinical Pharmacology and Pharmacokinetics

Drug Name/Route	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
C1 esterase inhibitor (Berinert®) intravenous[5]	Serine protease inhibitor which inhibits several factors in the complement and coagulation cascades including complement component 1, coagulation factor XIIa, kallikrein, and coagulation factor XIa. Inhibition of these systems is thought to inhibit production of bradykinin.	NA	NA; inhibition of serine proteases results in inactivation and consumption of the C1 esterase inhibitor.	Adults • Half-life: 18.4 ± 3.5 hours • AUC: 12.8 ± 6.7 hr*IU/mL • Vd: 35.4 ± 10.5 mL/kg
C1 esterase inhibitor (Cinryze®) intravenous[6]	Serine protease inhibitor	NA	NA (see above)	Single dose of 1,000 units in adults • Half-life: 56 ± 36 hours • Cmax: 0.68 ± 0.08 U/mL • AUC: 74.5 ± 30.3 U*hr/mL
C1 esterase inhibitor (Haegarda®) subcutaneous[7]	Serine protease inhibitor	Percent bioavailability: 42.7%	NA (see above)	Twice weekly dosing • Half-life: median 69 hours • Cmax: 60.7 % • Vd: 0.05 L/kg
C1 esterase inhibitor, recombinant (Ruconest®) intravenous[18]	Serine protease inhibitor	NA	NA (see above)	Single dose of 100 U/kg • Half-life: 2.7 ± 0.3 hours • Cmax: 2.3 ± 0.2 U/mL • AUC: 10.6 ± 2.5 U*hr/mL • Vd:2.4 ± 0.5 L
Icatibant (Firazyr®) intravenous and subcutaneous[2]	Bradykinin B2 receptor antagonist	Bioavailability: 97%	Metabolized by proteolytic enzymes with <10% excreted unchanged in the urine	Single 30 mg subcutaneous dose • Half-life: 1.4 ± 0.4 hours • Cmax: 974 ± 280 ng/mL • AUC: 2165 ± 568 ng*hr/mL • Vd: 29.0 ± 8.7 L
Ecallantide (Kalbitor®) subcutaneous[3]	Selective, reversible inhibitor of plasma kallikrein	NA	Excreted in the urine	Single 30 mg subcutaneous dose • Half-life: 2.0 ± 0.5 hours • Cmax: 586 ± 106 ng/mL • AUC: 3017 ± 402 ng*hr/mL • Vd:26.4 ± 7.8 L
Lanadelumab (Takhzyro™) subcutaneous[4]	Plasma kallikrein inhibitor	NA	NA	300 mg every 2 weeks • Half-life: 15.0 ± 2.48 days • Cmax: 34.4 ± 11.2 µg/mL • AUC: 400 ± 138 µg*day/mL • Vd: 16.6 ± 4.79 L

Abbreviations: AUC = area under the curve; CI = confidence interval; Cmax = maximum plasma concentration; hrs = hours; NA = not applicable; Vd = volume of distribution

Use in Specific Populations:

Pregnancy:

- C1 esterase inhibitor, human: There are no data available in humans or and animal studies have not been conducted.
- C1 esterase inhibitor, recombinant: There are no adequate or well-controlled trials in pregnancy. Studies in rats and rabbits could not exclude an effect on embryofetal development.
- Icatibant: There are no adequate or well-controlled trials in pregnancy. Animal studies document delayed parturition, fetal death, pre-implantation loss, premature birth, and abortion in rats or rabbits. Only use icatibant if potential benefits outweigh risks.
- Ecallantide: There are no adequate or well-controlled trials in pregnancy. Developmental toxicity has been documented in rats but not rabbits. Ecallantide should only be used during pregnancy if clearly needed.
- Lanadelumab: There are no data available on use in pregnant women. Animal data indicate no evidence of harm to the developing fetus.

Lactation:

- C1 esterase inhibitor, human: No information available
- C1 esterase inhibitor, recombinant: No information available
- Icatibant: No information available in humans. Icatibant is excreted in the milk of rats and caution is advised for this population.
- Ecallantide: No information available
- Lanadelumab: There are no data available in presence of lanadelumab-flyo in human milk. Animal data indicate lanadelumab-flyo was detected in the milk at approximately 0.2% of the maternal plasma concentration.

Pediatric:

- C1 esterase inhibitor, human: Cinryze® has been studies in 12 pediatric patients, Haegarda® has been evaluated in 6 patients, and Berinert® has been evaluated in 20 pediatric patients. Results were overall consistent with an adult population.
- C1 esterase inhibitor, recombinant: Recombinant C1 esterase inhibitor has been evaluated in 17 adolescents 13 to 17 years of age. Eight (42%) of patients experienced adverse events (primarily abdominal pain, headache, and oropharyngeal pain), and none experienced severe adverse events.
- Icatibant: Safety and effectiveness in patients less than 18 years of age has not been established. Animal data indicate administration in juvenile rats delayed sexual maturation of male reproductive tissues, impaired fertility, and decreased reproductive performance. No effects were observed in females.
- Ecallantide: Ecallantide has been evaluated in patients 12-17 years of age. Data on efficacy in patients 12 to 15 years of age is extrapolated from an older population and pharmacokinetic analyses. Safety profile for adolescents is similar to the adult population. Safety and effectiveness in patients less than 12 years of age has not been established.
- Lanadelumab: Lanadelumab-flyo has been evaluated in 23 patients, 12-17 years of age. Results of the subgroup analysis by age (in 10 participants enrolled in a randomized trial) were consistent with the overall population. Safety and effectiveness in patients less than 12 years of age has not been established.

Geriatric:

- C1 esterase inhibitor, human: Patients over 65 years of age were not included in clinical trials. In general, conservative dosing is recommended to account for greater frequency of decreased hepatic, renal, or cardiac function.
- C1 esterase inhibitor, recombinant: No information available
- Icatibant: No information available in patients ≥ 65 years of age. Elderly patients are likely to have increased systemic exposure, but dose adjustment is not recommended.
- Ecallantide: No information available
- Lanadelumab: Lanadelumab-flyo has been evaluated in 5 patients ≥ 65 years of age. Overall results were consistent with other populations.

Drug Safety:

Boxed Warnings:

- Due to risk of anaphylaxis with ecallantide, it should be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.[3]

Risk Evaluation Mitigation Strategy Programs: None

Contraindications:

- Risk of hypersensitivity reactions with C1 esterase inhibitors and ecallantide. Do not use in patients with a history of hypersensitivity, including anaphylaxis, to these medications or their excipients.[3]
- Do not use recombinant C1 esterase inhibitor (Ruconest®) in patients with known or suspected allergy to rabbits or rabbit-derived products.[18]

Table A2. Summary of Warnings and Precautions.

Warning/Precaution	C1 esterase inhibitor, human	C1 esterase inhibitor, recombinant	Icatibant	Ecallantide	Lanadelumab-flyo
Severe hypersensitivity reactions	X	X		X	X
Thromboembolic events	X	X			
Risk of infection transmission	X				
Seek immediate medical attention after laryngeal HAE attacks	X (Berinert® only)		X		

Appendix 2: Medline Search Strategy

Ovid MEDLINE® 1946 to October Week 3 2018

1	exp Angioedemas, Hereditary/	936
2	exp complement c1 inactivator proteins/ or exp complement c1 inhibitor protein/	2579
3	exp Bradykinin Receptor Antagonists/	1289
4	ecallantide.mp.	138
5	icatibant.mp.	1262
6	lanadelumab.mp.	3
7	2 or 3 or 4 or 5 or 6	4420
8	1 and 7	653
9	limit 8 to (english language and humans)	607
10	limit 9 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	135

Appendix 3: Key Inclusion Criteria

Population	Patients with hereditary angioedema
Intervention	Pharmacotherapy listed in Appendix 1
Comparator	Pharmacotherapy listed in Appendix 1 or placebo
Outcomes	Symptom improvement including acute or recurrent attacks of angioedema Functional improvement Quality of life Morbidity Mortality
Setting	Outpatient

Hereditary Angioedema

Goal(s):

- To promote safe and effective use of hereditary angioedema treatments.

Length of Authorization:

Up to 12 months

Requires PA:

- All pharmacotherapy for hereditary angioedema (pharmacy and physician administered claims).

NOTE: This policy does not apply to hereditary angioedema treatments administered during emergency department visits or hospitalization.

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 a request for continuation of prophylactic therapy OR for treatment of a second acute attack previously approved through fee-for-service?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication? Note: medications may be indicated for prophylaxis in patients with hereditary angioedema or treatment of acute hereditary angioedema attacks.	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Has the provider documented discussion with the patient of risks (including thrombotic events and/or anaphylaxis) versus benefits of therapy?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Notify provider of potential serious adverse effects of therapy. See notes below.
7. Is the request for icatibant or lanadelumab-flyo?	**Yes:** Go to #9	**No:** Go to #8
8. Is the patient prescribed concurrent epinephrine or do they have epinephrine on hand?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the medication intended to be administered by a non-healthcare professional?	**Yes:** Go to #10	**No:** Go to #11
10. Has the member received training on identification of an acute attack?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the request for treatment of an acute hereditary angioedema attack?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack. Document attack severity if available	**No:** Go to #12

Approval Criteria		
12. Is the request for prophylactic use in a patient with hereditary angioedema in a patient with a history of attacks?	**Yes:** Go to #13 Document baseline number of attacks in the last 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
13. Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate?	**Yes:** Approve for up to 6 months or length of therapy, whichever is less.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for additional treatment for acute attacks?	**Yes:** Go to #2	**No:** Go to #5
2. Is there documented utilization and benefit of the initial approved dose?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack. Document attack severity if available	**No:** Go to #3
3. Does the patient currently already have at least one on-demand dose for an acute attack?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is there documentation from the prescriber that an on-demand dose is necessary and risks of therapy continue to outweigh the benefits?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack. Document attack severity if available	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
5. Since initiation of therapy, has the number or severity of hereditary angioedema attacks decreased?	**Yes:** Go to #6 Document change in attack frequency or severity	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been attack free for at least 6 months?	**Yes:** Go to #7	**No:** Approve for up to 12 months.
7. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Note on adverse effects of treatment:

C1 esterase inhibitors

- In clinical trials of patients with moderate to severe hereditary angioedema attacks, use of C1 esterase inhibitors improved the duration of symptoms by an average 1-2 hours compared to placebo. Prophylactic use has only been evaluated in patients with more than 2 attacks per month.
- Hypersensitivity reactions have been observed with C1 esterase inhibitors. Due to the risk of anaphylaxis, it is recommended that all patients prescribed human derived C1 esterase inhibitors have epinephrine immediately available.
- Serious arterial and venous thrombotic events have been reported with use of C1 esterase inhibitors, particularly in patients with pre-existing risk factors for thromboembolism. The exact incidence of thrombosis with C1 esterase inhibitors is unclear. In patients using prophylactic therapy with Cinryze®, over an average of 2.6 years, 3% of patients experienced thrombosis.

Ecallantide

- The average improvement in symptoms compared to placebo at 4 hours after treatment of an acute attack was 0.4 points on a 0-3 point scale.
- Ecallantide has a box warning for anaphylaxis. In clinical trials, 3-4% of patients treated with ecallantide experienced anaphylaxis. Risks of treatment should be weighed against the benefits.

Icatibant

- In clinical trials of icatibant for acute attacks, time to 50% overall symptom improvement was 17.8 hours better than placebo (19 vs. 2 hours). A second study demonstrated no difference from placebo in time to symptom improvement. There are no data available on quality of life, daily activities, physical or mental functioning with use of icatibant.

Lanadelumab-flyo

- Prophylactic use has only been evaluated in patients with more than 1 moderate-severe attack per month. Hypersensitivity reactions, including anaphylaxis, were observed in 1% of patients treated with C1 esterase inhibitors. Elevated liver enzymes were also observed more frequently with lanadelumab compared to placebo (2% vs. 0%), and the long-term safety is unknown.

P&T/DUR Review: 3/19 (SS)
Implementation: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Drugs for Endometriosis

Date of Review: March 2019

Date of Last Review: May 2015 (GnRH Agonists); Jan 2017 (Hormone Replacement); November 2018 (Elagolix)
Dates of Literature Search: 01/01/1996-12/14/18

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

Purpose for Class Update:
A comprehensive review of drugs used to manage moderate to severe pain associated with endometriosis has never been completed for Pharmacy and Therapeutics (P and T) Committee assessment. This drug class update examines comparative evidence for safety and efficacy of oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists, danazol, and GnRH antagonists for management of moderate to severe pain due to endometriosis.

Research Questions:
1. What is the comparative evidence assessing efficacy of oral contraceptives, progestins, GnRH agonists, danazol, and GnRH antagonists for the treatment of moderate to severe pain associated with endometriosis?
2. What is the comparative evidence assessing long term safety and harms of oral contraceptives, progestins, GnRH agonists, danazol, and GnRH antagonists when used to treatment of moderate to severe pain associated with endometriosis?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with oral contraceptives, progestins, GnRH agonists, danazol, or GnRH antagonists for pain associated with endometriosis?

Conclusions:
- There is insufficient evidence to support the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) in managing pain caused by endometriosis.[1] A high quality systematic review concluded there is insufficient evidence to support the effectiveness of oral contraceptives compared to placebo or goserelin in managing pain caused by endometriosis.[2]
- A high quality systematic review evaluated available evidence on the safety and efficacy of danazol in managing pelvic pain associated with endometriosis.[3] The authors concluded there is low quality evidence that treatment with danazol significantly reduces total pain scores (based on a 4-point scale) at six months in women with endometriosis pain compared to placebo-treated subjects (weighted mean difference (WMD) -5.7, 95% confidence interval (CI) -7.5 to -3.8).[4] The same trial evaluated adverse effects associated with danazol and found a significant increase in the following symptoms at six months compared to placebo: acne (Odds Ratio [OR] 10.8; 95% CI 2.7 to 42.8), muscle cramps (OR 9.7; 95% CI 1.7 to 55.3) and edema (OR 7.11; 95% CI 1.5 to 31.6).[4] Absolute values were not reported.

Author: Deanna Moretz, PharmD, BCPS

- A high quality systematic review concluded there is limited evidence to support the use of progestins for pain associated with endometriosis.[5] Low quality evidence demonstrates that when compared to placebo, medroxyprogesterone is more effective in reducing pelvic pain at 6 months (Mean Difference [MD] -1.3, 95% CI -1.63 to -0.97, p<0.00001) and reducing of all symptoms associated with endometriosis at 6 months (MD -5.20, 95% CI -6.8 to -3.6, p<0.00001).[5] There is no evidence to suggest a benefit in symptoms for depot or oral progestins compared with oral contraceptives or leuprolide.[5] In clinical studies, patients receiving progestins experienced significantly more cases of adverse effects compared with other medical treatments.[5]
- There is limited evidence from 3 small trials (n=135) that use of postoperative levonorgestrel-releasing intrauterine device (LNG-IUD) reduces the recurrence of painful periods in women with endometriosis.[6] Moderate quality evidence from 2 small trials demonstrates postoperative LNG-IUD was more effective than no treatment in reducing symptoms associated with endometriosis.[6] In addition, one trial provides moderate quality evidence postoperative LNG-IUD and goserelin have similar effects in reducing the intensity of pain associated with endometriosis.[6]
- One high quality systematic review reported low quality evidence of an overall benefit in symptom relief for women with endometriosis for GnRH agonists compared with placebo or no treatment.[7] There was no evidence of a difference in pain relief between GnRH agonists and danazol or leveonorgestrel.[7] However, significantly more women experienced vaginal dryness and hot flushes when treated with GnRH agonists whereas significantly more women experienced weight gain and acne when treated with danazol.[7]
- There is a lack of long-term data on safety and efficacy for elagolix compared to other treatments. Evidence on elagolix compared to GnRH agonists, hormonal contraceptives, and aromatase inhibitors was insufficient to judge the net health benefit.

Recommendations:

- Combine PA criteria for GnRH analogs and antagonists into one document entitled GnRH modifiers (**Appendix 3**). Retire previous criteria for these products (**Appendix 4**).
    - Revise step therapy for elagolix to remove requirement for trial of acetaminophen or a nonsteroidal anti-inflammatory agent prior to trial of elagolix
    - Add endometriosis diagnosis with step therapy for leuprolide, goserelin, and nafarelin
    - Reinforce warnings about bone mineral density (BMD) loss with use of GnRH modifiers
- Evaluate comparative costs of GNRH analogs and antagonists in executive session

Summary of Prior Reviews and Current Policy

Previous P and T Committee recommendations for drugs used to manage endometriosis were included in 2 separate reviews:

- January 2017 - Class Update: Hormone Replacement Therapy (Non-Contraceptive Uses)
    - Recommendation: 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 on utilization and comparative drug costs in the executive session add medroxyprogesterone acetate tablets, micronized progesterone capsules, norethindrone acetate tablets, and Depo-Provera injection to the PDL and make all other progestins non-preferred.
- November 2018 - New Drug Evaluation: Elagolix (Orilissa™): Moderate quality evidence from two phase 3 studies showed that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant difference in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia symptoms. However, the clinical significance of these differences is unclear. There is insufficient evidence to compare the safety and efficacy of elagolix to any other analgesics, oral contraceptives, GnRH analogs, danazol, or progestins for treatment of endometriosis-related pain in specific subpopulations.
    - Recommendation: Create a new preferred drug list (PDL) class for gonadotropin-releasing hormone (GnRH) receptor agonists.
    - Recommendation: Implement prior authorization criteria for elagolix for use in patients with moderate to severe pain associated with endometriosis.

- Prior authorization is currently required for utilization of GnRH agonists in pediatric patients under 18 years of age for medically appropriate conditions funded under the Oregon Health Plan (e.g., central precocious puberty or gender dysphoria).

There are more than 1500 women currently in Oregon Medicaid Fee-for-Service (FFS) with claims indicative of an endometriosis-related diagnosis between July 2016 and June 2017. The preferred progestin agents medroxyprogesterone acetate, micronized progesterone, and norethindrone are the most requested progestins in the Oregon Medicaid FFS population. Utilization of GnRH agonists is low, with only 2 pharmacy claims for leuprolide during the third and fourth quarters of 2018.

Background:

Endometriosis is a gynecological disorder identified by the presence of ectopic endometrial tissue outside the uterine cavity.[8] There are generally three distinct clinical presentations: endometrial implantation superficially on the peritoneum; endometrial lined ovarian cysts (chocolate cysts) or endometriomas; and endometriotic nodules (a complex, solid mass of endometrial, adipose, and fibromuscular tissue found between the rectum and vagina).[9] Three types of endometriotic lesions have been identified: white, red, and black lesions. The red lesions represent activity with a high level of vascularization, the whitish lesions are later phases of red lesions that have undergone a process of inflammation and fibrosis, and the black lesions are attributable to cyclic tissue decomposition and healing with the subsequent formation of scar tissue.[8] The most common sites of pelvic endometriosis are the ovaries, uterine ligaments, pouch of Douglas, and fallopian tubes.[8] Clinical manifestations of endometriosis include dyspareunia, cyclic menstrual pain, chronic pelvic pain, and dyschezia.[8] In 2017, the prevalence of endometriosis in the United States was estimated to be roughly 5 million women.[10] It is estimated that 1 in 10 women between the ages of 15-49 may experience endometriosis with the highest incidence among those between 25 and 29 years of age.[10] Quality of life and work productivity are negatively impacted by endometriosis pain.[11] Epidemiologic studies have concluded that women with early menarche (<10 years old), with more frequent menstrual cycles (<28 days), and longer menstrual flows (>5-6 days) are at higher risk for endometriosis.[10]

As the most common cause of unexplained pelvic pain, endometriosis may be suspected through ultrasound and confirmed by histologic confirmation of lesions through laparoscopy.[12] During menstruation, the endometriotic tissue responds to hormonal stimulation similarly to the endometrium itself with associated bleeding and inflammation.[13] Over time, the inflammation leads to fibrosis and adhesions which may result in pelvic anatomical changes that range from symptoms of slight discomfort to severe disabling pelvic pain and dyspareunia.[13] The type, duration, and magnitude of pain may vary greatly among individuals and often manifests independently of the menstrual cycle.[14] Up to 50% of women with endometriosis become infertile.[10] It is not uncommon for endometriosis patients to experience depression and other mental health issues because of this condition.[14]

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[8] Although available medical and surgical treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief.[8] Medical therapy for endometriosis is based on the observation that ectopic tissue is hormonally responsive.[15] Drugs that suppress ovulation have been found to be beneficial in managing the pain associated with endometriosis. Danazol, an anabolic steroid which inhibits gonadotropin secretion, was the first FDA-approved agent for endometriosis, but its usefulness has been undermined by a significant adverse effect profile.[16] Androgenic adverse effects, such as acne, hirsutism, and male pattern baldness, often limit the tolerability of danazol in women. Current first-line therapies to manage pain associated with endometriosis are continuous combined oral contraceptives (COCs) or progestin.[17] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[16,18] Most of the data supporting the use of COCs in managing endometriosis pain is observational.[17]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy or in combination with a levonorgestrel-releasing intrauterine device (LNG-IUD).[17] Gonadotropin-releasing hormones (i.e. goserelin, leuprolide, and nafarelin) initially stimulate the

release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), resulting in a temporary increase of ovarian steroidogenesis.[15] However, continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[16,18] Goserelin, leuprolide, and nafarelin are FDA-approved for six months of continuous use for treatment of pelvic pain caused by endometriosis.[16] The six-month treatment limitation is due to concern about the significant bone loss that occurs with GnRH agonist therapy. Add-back therapy or the simultaneous use of estrogen and progestin, progestin alone, or progestin plus a bisphosphonate may alleviate some of the GnRH agonist side effects including bone loss.[17] The FDA recommends the use of add-back therapy (estrogen, progestin, bisphosphonates) when a GnRH agonist is used for greater than 6 months.[17]

Elagolix is a GnRH antagonist recently approved to manage pain symptoms associated with endometriosis. Elagolix rapidly suppresses the pituitary-ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production.[19] Randomized controlled studies (RCTs) have compared elagolix to placebo, but there are no comparative trials that evaluate elagolix to other FDA-approved therapies for endometriosis. Another group of estrogen biosynthesis blockers under investigation are the aromatase inhibitors, which are currently used off-label for endometriosis treatment.[16] Surgical management, including laparoscopy for definitive diagnosis, lysis of adhesions, and removal of visible implants, is an option in women with endometriosis who do not respond to medical therapy, especially for those who are infertile.[16,18] Hysterectomy has also been recommended for women with severe, debilitating, and refractory endometriosis who do not wish to become pregnant and in whom other therapeutic measures have failed.[8] **Table 1** outlines the pharmacotherapies that are approved by the FDA for management of moderate to severe pain associated with endometriosis.

Table 1. FDA-Approved Medications for Management of Pain Associated with Endometriosis[20]

Drug Name (Brand Name)	Formulation	FDA-Approved Endometriosis Dose and Frequency	Safety Precautions (* Indicates a Boxed Warning)
Anabolic Steroid			
Danazol (Danocrine)	Oral Capsule: 50mg, 100 mg, 200 mg	Initial, mild disease: 200 to 400 mg PO given in 2 divided doses; adjust depending on clinical response Moderate to severe disease: 800 mg PO in 2 divided doses; titrate downward depending on clinical response Duration: 3-6 months, may be extended to 9 months if necessary	-Thrombotic events including strokes* -Peliosis hepatis and benign hepatic adenoma* -Intracranial hypertension* -Use in pregnancy is contraindicated* -Lipoprotein changes -Androgen effects
Gonadotropin Releasing Hormone Agonists			
Goserelin acetate (Zoladex)	Subcutaneous Implant: 3.6 mg	3.6 mg SC every 28 days Duration: 6 months maximum	-Hyperglycemia -Loss of BMD -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Leuprolide acetate (Lupron)	Intramuscular depot Injection: 1-month: 3.75 mg 3-month: 11.25 mg	3.75 mg IM monthly for 6 months OR 11.25 mg IM every 3 months for 1 or 2 doses Duration: 6 months maximum	-Loss of BMD -Worsening depression and memory disorders -Convulsions -Use in pregnancy is contraindicated
Drug Name (Brand Name)	**Formulation**	**FDA-Approved Endometriosis Dose and Frequency**	**Safety Precautions (* Indicates a Boxed Warning)**

Nafarelin acetate (Synarel)	Nasal Spray: 200 mcg/actuation	400 mcg/day intranasally by 1 spray (200 mcg) into 1 nostril in the morning and 1 spray (200 mcg) into the other nostril in the evening starting between days and 4 of the menstrual cycle (maximum daily dose = 800 mcg) Duration: 6 months	-Loss of BMD -Worsening depression -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Progestins			
Medroxyprogesterone acetate (Depo-SubQ Provera)	Subcutaneous Depot Injection: 104 mg	104 mg SC every 3 months during the first 5 days of menstrual period Duration: Do not use for longer than 2 years (boxed warning)	-Loss of BMD* -Ocular disorders -Ectopic pregnancy -Bleeding irregularities -Use in pregnancy is contraindicated
Norethindrone Acetate (Aygestin)	Oral Tablets: 5mg	5 mg PO once daily for 2 weeks; increase dose by 2.5 mg per day every 2 weeks until 15 mg once daily is achieved Duration: 6 to 9 months or until breakthrough bleeding demands temporary termination	-Ocular disorders -Worsening depression -Increased risk for thrombosis -Bleeding irregularities -Ectopic pregnancy -Adverse effects on lipid metabolism -Use in pregnancy is contraindicated
Gonadotropin-Releasing Hormone Antagonist			
Elagolix (Orilissa)	Oral Tablet: 150 mg, 200 mg	Initial: 150 mg PO once daily OR Concomitant dyspareunia: 200 mg PO twice daily Duration: 150 mg dose: 24 months 200 mg dose: 6 months	-Loss of BMD -Suicidal ideation -Hepatic transaminase elevations -Use in pregnancy is contraindicated

Abbreviations: BMD = bone mineral density; FDA = Food and Drug Administration; IM = intramuscular; mcg = microgram; mg = milligram; PO = oral; SC = subcutaneous

There are several non-specific assessment scales that have been used to measure patient response to medical treatment intervention. For pain assessment, the visual agonist or verbal rating scale is a numeric rating scale which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable).[21] The ease of administration and scoring allows this tool to be used in a variety of settings, however, it may not be appropriate for low literacy patients.[21] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[22] A specific tool known as the Biberoglu and Behrman (B & B) Scale is patient-reported symptom assessment tool for dysmenorrhea, chronic pelvic pain, dyspareunia, as well as pelvic tenderness and induration.[22] The B & B scale is graded on a scale from 0 to 3 (or 4 for dyspareunia) with higher scores representative of more symptoms.[22] However, several organizations including the National Institutes of Health have indicated that the B&B has never been validated nor administered consistently.[22]

In some trials, objective evaluation of improvement of endometriotic implants was assessed by the American Fertility Society (AFS) classification of endometriosis.[23] The AFS was renamed the American Society for Reproductive Medicine (ASRM) in 1995. The ASRM classification stratifies endometriosis into stages based on minimal (Stage I), mild (Stage II), moderate (Stage III), and severe (Stage IV) symptoms. The weighted point score ranges from 1-5 (Stage I); 6-15 (Stage II); 16-40 (Stage III); to greater than 40 points (Stage IV).[23] Assessment of the extent of endometriosis (in centimeters) and presence of adhesions in the peritoneum, ovaries, and tubes is included in the scoring.[23] One study evaluated 244 patients for the correlation between pain symptoms measured by using visual analog scale (VAS) and ARSM stage.[23] No correlation was found between stages I-II and III-IV and acyclic pelvic pain (VAS 5 vs. VAS 4; $p > 0.05$), deep dyspareunia (VAS 5 vs. VAS 1; $p > 0.05$), and dysmenorrhea (VAS 8 vs. VAS 8; $p > 0.05$).[23] Laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.[23] Validation of the AFS classifications as predictors of infertility has been limited to 3 trials.[23]

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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. 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:
After review, 3 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[24-26]

Nonsteroidal anti-inflammatory drugs
Nonsteroidal anti-inflammatory drugs are effective for treating primary dysmenorrhea, so they are often used as first line treatment for suspected endometriosis.[27] However, a 2017 Cochrane review found insufficient evidence that NSAIDs improve pain associated with endometriosis.[1] One low quality, small RCT (n=24) of short duration (2 menstrual cycles) compared naproxen versus placebo in women with pain due to endometriosis and found no difference in pain relief (odds ratio (OR) 3.27, 95% CI 0.61 to 17.69).[28] The overall risk of bias was unclear owing to lack of methodological detail with a high risk of bias due to imprecision (wide confidence interval and small sample size).[1] There is insufficient evidence to support the effectiveness of NSAIDs in managing pain caused by endometriosis.[1]

Danazol
A 2007 Cochrane review evaluated the effectiveness of danazol compared to placebo in the treatment of symptoms and signs of endometriosis in women of reproductive age.[3] All of the early literature recommending danazol for treatment of endometriosis referenced data from non-controlled, non-randomized clinical trials.[3] For the Cochrane review, literature was searched through April 2007. Two trials comparing danazol to placebo met the inclusion criteria. One study recorded improvement in symptoms as an outcome, while the other trial evaluated changes in fertility using the AFS score as the primary outcome.[3] Patients recorded occurrence and severe of pain on a four-point scale (0 = symptoms absent, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms). A significant decrease in the levels of pelvic pain, lower back pain, and defecation pain with danazol therapy compared to placebo was observed.[4] Total pain scores were

reduced at six months in those patients who received danazol compared to placebo (WMD -5.7; 95% CI -7.5 to -3.8).[4] Improvement in pain scores was still present six months after discontinuing danazol therapy.[3] However, no significant difference was found between the two groups in dysuria and dyspareunia.[3] The same study evaluated adverse effects and found a significant increase in the following symptoms associated with danazol therapy vs. placebo at six months: acne (OR 10.8; 95% CI 2.7 to 42.8), muscle cramps (OR 9.7; 95% CI 1.7 to 55.3) and edema (OR 7.11; 95% CI 1.5 to 31.6).[3] Absolute values were not reported. The method of randomization was not specified, therefore the results may not be valid as the method of randomization may not have been adequate.[3] The other trial examined changes in AFS scores at laparoscopy six months after stopping danazol and found no significant difference in total AFS score (WMD -0.4; 95% CI -1.5 to 0.7).[3] Neither of the trials was truly double blinded as women who received placebo tablets continued menstruating while women who received danazol became amenorrheic, making identification of therapy possible.[3] Furthermore, the measurement of pain was inadequate as none of the trials used visual analogue scales or other recognized methods for measuring pain.[3] For these reasons, the studies were graded as having a high risk of bias with low quality of evidence.[3]

Combination estrogen/progestin oral contraceptives

A 2018 Cochrane update included literature published through October 2017 to determine the effectiveness and safety of oral contraceptives in the treatment of painful symptoms associated with the diagnosis of laparoscopically proven endometriosis.[2] The other formulations of hormonal contraception such as the transdermal patch, vaginal ring or depot injections were not included in this review.[2] The primary outcome was self-reported pain (dysmenorrhea) at the end of treatment. Eights RCTs conducted in Japan, Italy, Egypt and the United States (U.S) met inclusion criteria. Five trials evaluated COCs versus placebo for durations ranging from 3 to 11 months. Three trials used a monophasic COC containing ethinyl estradiol 0.035 mg and norethindrone 1 mg, 1 trial used ethinyl estradiol 0.02 mg combined with desogestrel 0.15 mg, and the fifth trial used ethinyl estradiol 0.02 mg and drospirenone 3 mg. Three trials compared COCs to a GnRH agonist (leuprolide or goserelin). Four trials used the B & B verbal rating score or a modified version of it to assess pain at the end of treatment, as well as other visual or numerical pain ratings methods.[2]

Treatment with COCs was associated with a lower score on the B & B verbal rating scale (scale 0 to 3) compared with placebo (MD -1.30 points, 95% CI -1.84 to -0.76, 1 RCT, 96 women; very low quality evidence), a lower score on the dysmenorrhea visual analog rating score (no details of scale) compared with placebo (MD -23.68 points, 95% CI -28.75 to -18.62, 2 RCTs, 327 women; very low quality evidence) at the end of treatment and a greater reduction in menstrual pain from baseline to the end of treatment (MD 2.10 points, 95% CI 1.38 to 2.82, 1 RCT, 169 women; very low quality evidence).[2] The trials were assessed as having a high risk of bias due to unclear randomization methods, unclear concealment of allocation, unclear blinding, incomplete outcome data, and selective reporting.[2] Most of the trials were designed and executed by the pharmaceutical company funding the trial.[2] Three trials were at high risk of attrition bias and none of the trials had published protocols.[2]

One small trial (n=50) compared efficacy of COCs with subcutaneous goserelin over 6 months.[29] The study was at high risk of bias as the trial was unblinded and there was insufficient detail to judge allocation concealment and randomization.[2] At the end of treatment, the women in the goserelin group were amenorrheic, and therefore, no comparisons could be made between the groups for the primary outcome.[2] At six months' follow-up, there was no clear evidence of a difference between women treated with the COCs and women treated with goserelin for measures of dysmenorrhea on a visual analogue scale (scale 1 to 10) [MD -0.10, 95% CI -1.28 to 1.08; very low quality evidence] or a verbal rating scale (scale 0 to 3) [MD -0.10, 95% CI -0.99 to 0.79; very low quality evidence].[2] At six months follow-up, there was no clear evidence of a difference between the COCs and goserelin groups in complete absence of pain as measured by the visual agonist scale (risk ratio (RR) 0.36, 95% CI 0.02 to 8.43; very low quality evidence) or the verbal rating scale (RR 1.00, 95% CI 0.93 to 1.08; low quality evidence).[2] In this trial, the power calculation became invalid as a result of a higher than expected recurrence rate of pain in the goserelin group (77% recurrence rather than the 35% that was used in the power calculation), rendering the study underpowered.[2] It is possible the study may have failed to detect a difference in efficacy between COC

and goserelin.[2] This study, which was conducted in Italy, is also unlikely to be generalizable to other settings.[2] The 2 trials that compared COCs with leuprolide did not provide sufficient data that could be included in a meta-analysis.[2]

Based on the limited evidence from 5 trials at high risk of bias with limited data for the prespecified outcomes, there is insufficient evidence to make a judgement on the effectiveness of the COCs compared with placebo and the findings cannot be generalized.[2] In addition, based on the limited evidence from one small trial with high risk of bias, there is insufficient evidence to make a judgement on the effectiveness of the COCs compared with goserelin.[2] Despite limited evidence of effectiveness, hormonal contraceptives are widely used as treatment for pain in women with endometriosis, which could be due to some practical advantages, including contraceptive protection, long-term safety, and control of menstrual cycle.[30]

Progestins

A 2012 Cochrane review focused on identifying evidence for the effectiveness of progestins in the treatment of painful symptoms associated with endometriosis.[5] Twenty studies were identified in which progestins were compared with placebo, danazol, oral contraceptives, or a GnRH agonist. Depo medroxyprogesterone acetate (DMPA), dydrogesterone, cyproterone acetate, medroxyprogesterone acetate (MPA), gestagen and dienogest were the different progestins evaluated in clinical trials for treatment of endometriosis.[5] The 2 progestins available on the U.S. market are DMPA and MPA therefore, only the evidence focused on these products will be presented. The primary outcome was relief of any or all symptoms of endometriosis using qualitative measures such as visual agonist scales.[5] Resolution of endometriotic implants assessed by either the revised AFS score was evaluated in some trials as an objective outcome. Although this is neither a direct or indirect measure of pain, it is an independent assessment of disease resolution.[5]

One small (n=51), low-quality trial compared continuous oral MPA 100 mg or placebo.[4] This trial had an unclear risk of bias due to incomplete information about randomization, concealment of allocation, and blinding, a small sample size, and a high attrition rate (31% of patients withdrew from the trial). When compared to placebo, MPA was more effective in reduction of pelvic pain at 6 months (MD -1.3, 95% CI -1.63 to -0.97, p<0.00001) and reduction of all symptoms at 6 months (MD -5.20, 95% CI -6.8 to -3.6, p<0.00001).[5] Reduction in pelvic pain and all symptoms was sustained after 12 months of follow-up (MD -0.85, 95% CI -1.19 to -0.51, p<0.00001 and MD -7.0, 95% CI -8.61 to -5.39, p<0.00001; respectively).[5] No improvement in AFS scores at 12 months of follow-up (MD -0.58, 95% CI -1.41 to 0.25; p=0.17) was observed.[5] There were more cases of acne (6 vs. 1; OR 9.6; 95% CI 1.00 to 91.96) and edema (11 vs. 1; OR 35.20; 95% CI 3.60 to 344.19) reported in the medroxyprogesterone group than the placebo group.[31]

Two trials reported on the use of depot progestins compared with other treatments. One study compared intramuscular DMPA 150 mg every 3 months with a low dose oral contraceptive pill and 50 mg danazol.[32] A significant reduction was observed in all symptom scores for both the visual analogue score and verbal rating scale in both study groups.[5] The only difference was that dysmenorrhoea was improved in the progesterone only arm at 12 months follow-up.[5] Seventy-two percent of patients in the DMPA group were satisfied after 1 year of therapy compared with 57.5% in the oral contraceptive plus danazol group (p=0.24, OR 1.95, 95% CI 0.76 to 4.97).[32] The other trial compared the efficacy of subcutaneous DMPA 104 mg every 3 months versus intramuscular leuprolide acetate 11.25 mg every 3 months over a 6 month study period.[33] Symptoms of dysmenorrhea were significantly reduced in the DMPA group at six months compared with the leuprolide acetate group (OR 0.19, 95% CI 0.05 to 0.69; p=0.01), but this effect was not sustained at the 12 month follow-up (OR 0.63, 95% CI 0.37 to 1.08).[33] Absolute values were not reported. There was no evidence of a difference between groups for dyspareunia at six months.[33] At 12 months, significantly fewer women in the leuprolide group appeared to report dyspareunia (OR 4.83, 95% CI 2.14 to 10.93; p=0.0002).[33] In the Cochrane meta-analysis, patients receiving depot DMPA experienced more bloating (OR 4.39, 95% CI 1.71 to 11.30; p=0.002), intermenstrual bleeding (OR 20.56, 95% CI 6.44 to 65.56; p<0.00001), weight gain (OR 2.58, 95% CI 1.03 to 6.46; p=0.04), amenorrhea (OR 21.18, 95% CI 1.18 to 380.9; p=0.04), and nausea (OR 3.86, 95% CI 1.12, 13.26; p=0.03) compared with other treatments.[33] Absolute values were not reported.

Three trials compared oral progestins with other treatments. One study compared oral medroxyprogesterone with danazol[34] and another compared dienogest with leuprolide.[35] The Cochrane meta-analysis shows that in comparison to other treatments, there was no significant difference in self-reported pain (MD 0.10, 95% CI -0.26 to 0.46, NS) at six months, but at 12 months of follow-up, medroxyprogesterone was more effective than danazol in subjective reduction of the sum of all symptoms (MD -3.4, 95% CI -4.83 to -1.97, p<0.00001).[5] Another trial compared the efficacy of oral MPA 15 mg twice daily versus intranasal nafarelin 200 mcg twice daily.[36] Although there was a significant reduction in bleeding, dysmenorrhea, dyspareunia and pelvic pain in the total study group, there was no difference demonstrated between groups at 6 months of treatment or at 12 months of follow-up.[5] Twelve patients given MPA and 6 subjects in the nafarelin group did not complete treatment. Data could not be included in the meta-analysis as it was presented as mean ranks and not raw scores.[5]

In summary, in one trial comparing oral MPA with placebo, low quality evidence identified a benefit for reduction of symptoms in favor of medroxyprogesterone.[5] There was no evidence to suggest a benefit in symptoms for depot or oral administration of progestins compared with other medical treatments and the progestin groups experienced significantly more cases of adverse effects compared with other medical treatments.[5]

Levonorgestrel-releasing intrauterine device

A 2013 Cochrane review focused on the evidence for postoperative LNG-IUD insertion in women with endometriosis to improve pain and reduce recurrence of symptoms.[6] Three small, randomised controlled trials met inclusion criteria. The total number of subjects enrolled in all 3 trials was 135 women with a 12 month duration of follow-up.[6] In two trials, there was a statistically significant reduction in the recurrence of painful periods in the LNG-IUD group compared with the control group that received no treatment (OR 0.14, 95% CI 0.04 to 0.47, 95 women, moderate strength of evidence).[6] Absolute values were not reported. The proportion of women who were satisfied with their treatment was also higher in the LNG-IUD group compared to the control group, but did not reach statistical significance (OR 3.00, 95% CI 0.79 to 11.44, 95 women, 2 trials).[6] The number of women reporting a change in menstruation was significantly higher in the LNG-IUD group versus control group (RR 37.80, 95% CI 5.40 to 264.6).[6] One trial (n=40), showed comparable effectiveness in reducing pain associated with endometriosis between women receiving postoperative LNG-IUD versus women receiving goserelin via injection every 4 weeks for 24 weeks (MD -0.16, 95% CI -2.02 to 1.70).[6] Patients in the LNG-IUD group experienced more irregular bleeding and abdominal pain while patients administered the GnRH agonist experienced more vasomotor symptoms and amenorrhea.[37]

In summary, there is limited evidence of benefit for LNG-IUD in reducing pain associated with endometriosis after surgery for endometriosis.[6] Moderate quality evidence from 2 small trials demonstrates postoperative LNG-IUD was more effective than no treatment in reducing symptoms associated with endometriosis.[6] In addition, one trial provides moderate quality evidence postoperative LNG-IUD and goserelin have similar effects in reducing the intensity of pain associated with endometriosis.[6]

Gonadotrophin Releasing Hormone Agonists

A 2010 Cochrane review and meta-analysis evaluated the safety and efficacy of GnRH agonists in the treatment of painful symptoms associated with endometriosis.[7] Forty-one randomized controlled trials (RCTs) met inclusion criteria encompassing a total of 4,935 pre-menopausal women.[7] The primary outcome was pain relief defined by using both quantitative measures such as the visual analogue scale or categorical outcomes at the end of treatment.[7] Six trials compared GnRH agonists with no treatment or placebo. The evidence suggests that GnRH agonists were more effective at pain relief of dysmenorrhea associated with endometriosis than no treatment/placebo (RR 3.93, 95% CI 1.37 to 11.28).[7] Absolute values were not reported.Twenty-seven trials compared a GnRH with danazol, and no statistically significant difference was observed between GnRH agonists and danazol for relief of dysmenorrhea (RR 0.98, 95%CI 0.92 to 1.04, p=0.53).[7] There was a benefit in overall pain resolution for GnRH agonists (RR 1.10, 95% CI 1.01 to 1.21, p=0.03) compared with danazol.[7] Five of the most commonly reported side effects were vaginal dryness, hot flushes, headaches, weight gain, and acne.[7] Vaginal dryness was compared in 16 studies, and

occurrence was more frequent with GnRH agonists versus danazol (RR 1.96, 95% CI 1.68 to 2.30, p<0.00001).[7] Nineteen studies looked at hot flushes and found significantly more patients experienced hot flushes with GnRH agonists versus danazol (RR 1.55, 95% CI 1.47 to 1.65, p<0.00001).[7] Headaches were compared in 16 studies, and a statistically significant benefit was found in favor of danazol compared to GnRH agonists (RR 1.40, 95% CI 1.22 to 1.61, P<0.00001).[7] Weight gain was reported in 12 studies that found evidence to suggest a statistically significant increase in danazol-treated patients compared to GnRH agonists (RR 0.20, 95% CI 0.16 to 0.26, p<0.00001).[7] Acne was reported by 13 studies and evidence suggested a statistically significant increase in danazol-treated patients compared to GnRH agonists (RR 0.55, 95% CI 0.47 to 0.65).[7] Three trials compared GnRH agonists with levonorgestrel. There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel (Standardized Mean Difference [SMD] -0.25; 95%CI -0.60 to 0.10; p=0.46).[7] Evidence was limited on optimal dosage or duration of treatment for GnRH agonists.[7] No route of administration appeared superior to another.[7]

In summary, low quality evidence shows an overall benefit for GnRH agonists in relieving pain associated with endometriosis compared with placebo or no treatment.[7] There was no evidence of a difference in pain relief between GnRH agonists and danazol.[7] However, the side-effect profile of these two drugs were different, with significantly more women experiencing vaginal dryness and hot flushes when treated with GNRH agonists whereas significantly more women experienced weight gain and acne when treated with danazol.[7] There was no evidence of a difference in pain relief between GnRH agonists and levonorgestrel.[7] There is limited evidence to draw conclusions regarding the benefit of varying doses or length of treatment.[7] The route of administration does not appear to be an important factor in attaining benefit.[7]

Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence

In 2017, the National Institute for Health and Care Excellence (NICE) updated guidance documents for management of endometriosis with various treatments including diagnostic recommendations, pharmacotherapy options for pain, and surgery.[38] It is recommended that endometriosis be diagnosed through abdominal and pelvic examination, magnetic resonance imaging (MRI) or ultrasound, and diagnostic laparoscopy with biopsy when needed.[38] NICE recommends that pain from endometriosis be treated with a short trial (i.e. 3 months) of NSAIDs and/or acetaminophen as first-line management.[38] The committee recognized there is insufficient evidence to support using NSAIDs in pain associated with endometriosis. However, according to the World Health Organization pain guidelines, NSAIDs are recommended first line to manage acute or chronic non-malignant pain.[38] For these reasons, the NICE committee concluded a short trial of analgesics for first-line management of endometriosis-related pain is appropriate.[38] For women with suspected, confirmed, or recurrent endometriosis, hormonal treatment with an oral contraceptive or progestin can be initiated.[38] This recommendation was supported by a network meta-analysis completed by the NICE authors.[38] Surgical management is recommended for women with suspected or confirmed endometriosis with bowel, bladder, or ureter involvement.[38] GnRH agonists may be considered as adjunct treatment 3 months prior to surgery for deep endometriosis.[38] NICE recommends a hysterectomy with or without oophorectomy for women with endometriotic complications unresponsive to other treatments.[38]

European Society of Human Reproduction and Embryology

The European Society of Human Reproduction and Embryology (ESHRE) updated recommendations for the management of women with endometriosis in 2013.[30] The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the implementation of the guideline. The guideline group members did not receive payment. All guideline group members disclosed any relevant conflicts of interest.[30] Literature was searched through January 2012. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method was used to assess published evidence.[39] Grade A recommendations were based on high quality meta-analyses or multiple RCTs.[30] Grade B recommendations were

based on moderate quality evidence from meta-analyses or multiple RCTs.[30] Most of the cited evidence is from the Cochrane reviews on different medical treatments for pain associated with endometriosis.[30] The grade A and B recommendations regarding pharmacotherapy are as follows:

- Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Grade of Recommendation B).[30]
- Clinicians are recommended to use medroxyprogesterone acetate (oral or depot), norethindrone or danazol as one of the options, to reduce endometriosis-associated pain (Grade of Recommendation A).[30]
- Clinicians can consider prescribing a levonorgestrel-releasing intrauterine system (LNG-IUS) as one of the options to reduce endometriosis-associated pain (Grade of Recommendation B).[30]
- Clinicians are recommended to use GnRH agonists (nafarelin, leuprolide, or goserelin), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Grade of Recommendation A).[30]
- Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment. This is not known to reduce the effect of treatment on pain relief (Grade of Recommendation A).[30]

Additional Guidelines for Clinical Context:

After review, 2 guidelines were excluded due to poor quality. The American Society for Reproductive Medicine (ASRM) published recommendations for the treatment of pelvic pain associated with endometriosis in 2014.[40] However, the guideline recommendations did not meet the quality standards outlined in the Appraisal of Guidelines for Research and Evaluation (AGREE) guidance.[41] The publication did not state how the systematic review of the evidence was developed by the ASRM Practice Committee. American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin on the management of endometriosis in 2010.[42] However, the recommendations were not based on a systematic review or grading of the evidence. Stakeholder involvement, method of consensus, and search terms were not reported. Finally, detailed search strategy and inclusion/exclusion criteria not were reported.

Randomized Controlled Trials:

A total of 178 citations were manually reviewed from the initial literature search. After further review, all other 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

GNRH agonists and antagonists

Generic	Brand	Formulation	Route	PDL
goserelin acetate	ZOLADEX	IMPLANT	SQ	
leuprolide acetate	ELIGARD	SYRINGE	SQ	
leuprolide acetate	LEUPROLIDE ACETATE	KIT	SQ	
leuprolide acetate	LEUPROLIDE ACETATE	VIAL	SQ	
leuprolide/norethindrone acet	LUPANETA PACK	KT SYR TAB	MC	
leuprolide acetate	LUPRON DEPOT	SYRINGEKIT	IM	
leuprolide acetate	LUPRON DEPOT (LUPANETA)	SYRINGEKIT	IM	
leuprolide acetate	LUPRON DEPOT-PED	KIT	IM	
leuprolide acetate	LUPRON DEPOT-PED	SYRINGEKIT	IM	
nafarelin acetate	SYNAREL	SPRAY	NS	
elagolix sodium	ORILISSA	TABLET	PO	

Progestational Agents

Generic	Brand	Formulation	Route	PDL
medroxyprogesterone acetate	DEPO-PROVERA	VIAL	IM	Y
medroxyprogesterone acetate	MEDROXYPROGESTERONE ACETATE	TABLET	PO	Y
medroxyprogesterone acetate	PROVERA	TABLET	PO	Y
norethindrone acetate	AYGESTIN	TABLET	PO	Y
norethindrone acetate	NORETHINDRONE AC (LUPANETA)	TABLET	PO	Y
norethindrone acetate	NORETHINDRONE ACETATE	TABLET	PO	Y

Other Hormone Therapies

Generic	Brand	Formulation	Route	PDL
danazol	DANAZOL	CAPSULE	PO	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2018; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 12, 2018

1. Exp ENDOMETRIOSIS/	11944
2. Exp GOSERELIN/	982
3. Exp LEUPROLIDE/	1912
4. NAFARELIN/	124
5. Elagolix.mp.	32
6. Exp MEDROXYPROGESTERONE ACETATE/	2819
7. NORETHINDRONE/	1025
8. DANAZOL/	791
9. 2 or 3 or 4 or 5 or 6 or 7 or 8	7160
10. 1 and 9	570

11. limit 10 to (english language and humans and (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 consensus development conference or controlled clinical trial or equivalence trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 178

Gonadotropin-Releasing Hormone Modifiers

Goal(s):

- Restrict pediatric use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan (eg, central precocious puberty or gender dysphoria).
- Promote safe use of elagolix in women with endometriosis-associated pain.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative treatment period not to exceed 24 months.

Requires PA:

- GnRH agonists (i.e., goserelin, histrelin, leuprolide, nafarelin, triptorelin) prescribed for pediatric patients less than 18 years of age.
- Non-preferred GnRH agonist (i.e., goserelin, leuprolide, nafarelin) or antagonist (i.e. elagolix).

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 OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of elagolix therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the prescriber a pediatric endocrinologist?	**Yes:** Go to #5	**No:** Go to #9

Approval Criteria		
5. What diagnosis is being treated and what is the age and gender of the patient assigned at birth?	Record ICD10 code. Record age and gender assigned at birth	
6. Is the diagnosis central precocious puberty (ICD10 E301, E308) or other endocrine disorder (E34.9)?	**Yes:** Approve for up to 6 months	**No:** Go to #7
7. Is the diagnosis gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #8	**No:** Go to #9
8. Does the request meet **all** of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience in gender dysphoria. • Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2. • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.* • *From Guideline Note 127: To qualify for cross-sex hormone therapy, the patient must:A) have persistent, well-documented gender dysphoria B) have the capacity to make a fully informed decision and to give consent for treatment C) have any significant medical or mental health concerns reasonably well controlled D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh; deny for medical appropriateness
9. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #10
10. Is this request for leuprolide for the management of preoperative anemia due to uterine leiomyoma?	**Yes:** Approve for up to 3 months	**No:** Go to #11

Approval Criteria		
11. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the request for goserelin, leuprolide, nafarelin or elagolix?	**Yes:** Go to # 13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Has the patient tried and failed an adequate trial of preferred first line therapy options including continuous administration of combined hormonal contraceptives or progestins alone? -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as hormonal contraceptives or progestins do not require PA
15. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? *Note: In women with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH modifiers may pose an additional risk, and the risks and benefits should be weighed carefully	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #16
16. Is the request for elagolix?	**Yes:** Go to #17	**No:** Approve for up to 6 months

Approval Criteria		
17. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors? (e.g. cyclosporine, gemfibrozil, etc.)	**Yes:** Deny; medical appropriateness	**No:** Go to #18
18. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #19
19. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #20	**No:** Approve for 6 months
20. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
21. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.		

Renewal Criteria		
1. Has the patient been receiving therapy with elagolix 150 mg once daily?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)

Renewal Criteria		
2. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #3
3. Has the patient's condition improved as assessed and documented by the prescriber?	**Yes:** Approve for up to 6 months. Total cumulative treatment period not to exceed 24 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T / DUR Review: *1/19 (DM)*
Implementation: *TBD*

Gonadotropin-Releasing Hormone (GnRH) Analogs

Goal(s):

- Restrict pediatric use to medically appropriate conditions funded under the Oregon Health Plan (eg, central precocious puberty or gender dysphoria)

Length of Authorization:

- Up to 6 months

Requires PA:

- GnRH analogs (i.e., goserelin, histrelin, leuprolide, nafarelin, triptorelin) prescribed for pediatric patients less than 18 years of age.

Approval Criteria		
1. What diagnosis is being treated and what is the age and gender of the patient assigned at birth?	Record ICD10 code. Record age and gender assigned at birth	
2. Is the prescriber a pediatric endocrinologist?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Is the diagnosis central precocious puberty (ICD10 E301, E308) or other endocrine disorder (E34.9)?	**Yes:** Approve for up to 6 months	**No:** Go to #4
4. Is the diagnosis gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #5	**No:** Pass to RPh; go to #6
5. Does the request meet **all** of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience in gender dysphoria. • Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2. • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria
6. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.

P&T / DUR Review: *11/15 (KS); 7/15; 5/15; 9/07*
Implementation: *1/1/16; 7/1/15; 11/07; 7/09*

Elagolix

Goal(s):
- Promote safe use of elagolix in women with endometriosis-associated pain.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:
- Initial: Up to 6 months
- Renewal: Up to 6 months for 150 mg daily dose with total cumulative treatment period not to exceed 24 months.

Requires PA:
- Elagolix

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		
7. What diagnosis is being treated?	Record ICD10 code.	
8. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
9. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
10. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
12. Has the patient tried and failed an adequate trial of preferred first line therapy options including continuous administration of combined hormonal contraceptives or progestins alone +/- acetaminophen +/- non-steroidal anti-inflammatory drugs (NSAIDs) -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as hormonal contraceptives or progestins do not require PA
13. Does the patient have a diagnosis of osteoporosis or related bone-loss condition?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
14. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors? (e.g. cyclosporine, gemfibrozil, etc.)	**Yes:** Deny; medical appropriateness	**No:** Go to #9
15. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
16. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #11	**No:** Approve for 6 months
17. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Has the patient been receiving therapy with elagolix 150 mg once daily?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
5. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #3
6. Has the patient's condition improved as assessed and documented by the prescriber?	**Yes:** Approve for up to 6 months. Total cumulative treatment period not to exceed 24 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

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 Use Evaluation: Antipsychotics Utilization in Schizophrenia Patients

Research Questions:

1. How many schizophrenia patients are prescribed recommended first-line second-generation treatments for schizophrenia?
2. How many schizophrenia patients switch to an injectable antipsychotic after stabilization on an oral antipsychotic?
3. How many schizophrenia patients are prescribed 2 or more concomitant antipsychotics?
4. Are claims for long-acting injectable antipsychotics primarily billed as pharmacy or physician administered claims?
5. Does adherence to antipsychotic therapy differ between patients with claims for different routes of administration (oral vs. long-acting injectable)?

Conclusions:

- In total, 4663 schizophrenia patients met inclusion criteria, and approximately 14% of patients (n=685) were identified as treatment naïve without claims for antipsychotics in the year before their first antipsychotic prescription. Approximately 45% of patients identified as treatment naïve had a history of remote antipsychotic use, but it is unclear if antipsychotics were historically prescribed for schizophrenia.
- Oral second-generation antipsychotics which are recommended as first-line treatment in the MHCAG schizophrenia algorithm were prescribed as initial treatment in 37% of treatment naive patients and 28% of all schizophrenia patients. Recommended agents include risperidone, paliperidone, and aripiprazole.
- Utilization of parenteral antipsychotics was limited in patients with schizophrenia. Overall only 8% of patients switched from an oral to an injectable therapy within 6 months of their first claim. Approximately, 60% of all schizophrenia patients (n=2512) had claims for a single antipsychotic for at least 12 continuous weeks and may be eligible to transition to a long-acting injectable antipsychotic. Only 710 of these patients were on continuous therapy with a recommended first-line therapy (aripiprazole, paliperidone, or risperidone) for which there is a recommended injectable formulation.
- Only 10% of treatment naïve schizophrenia patients were prescribed concomitant antipsychotics for more than 8 weeks. Utilization of concomitant medications was slightly higher in all schizophrenia patients with approximately 17% of patients prescribed combination antipsychotic therapy.
- The vast majority of claims for long-acting injectable antipsychotics are billed through pharmacy for members enrolled in a coordinated care organization (CCO) whereas approximately 72% of fee-for-service (FFS) claims are billed as medical claims by providers after administration to the patient.
- Adherence to therapy was similar in patients with schizophrenia and did not differ between oral and injectable antipsychotic formulations. In the 6 months following the first claims, approximately 9-11% of patients had less than 25% of days covered (corresponding to less than 45 days) and 62-64% of patient had more than 75% of days covered (corresponding to >135 days).

Recommendations:

- Explore opportunities to increase access to recommended therapies for schizophrenia patients through discussion of provider educational opportunities and retrospective drug use review.

Background:
In order to improve care for patients with mental health conditions, the Mental Health Clinical Advisory Group (MHCAG), a subcommittee of the Pharmacy and Therapeutics Committee, has developed treatment algorithms for patients with schizophrenia. This is the first treatment algorithm developed by MHCAG, and full treatment algorithms are undergoing publication. Medication algorithms include the following recommendations:

- Initial treatment: In treatment naïve patients, recommend use of aripiprazole, risperidone, or paliperidone as a first-line treatment
    - If the patient has an inadequate response after dose optimization over 2-6 weeks, recommend trial of another first-line treatment
    - With adequate response after 2-4 weeks, recommend transition to a long-acting injectable formulation to promote adherence to treatment
    - If first-line treatment options are not successful, consider switching to clozapine as a second or third-line agent
- Alternative treatment: If patient has an inadequate response to clozapine or partial response to 2 oral antipsychotic monotherapies, consider obtaining a second opinion with referral to a specialist. Recommended options for treatment include 1) switching to a different second-generation antipsychotic or a first-generation antipsychotic with a cross-taper to avoid dual therapy OR 2) augmentation of antipsychotic therapy if patient has a partial response to monotherapy
    - If the patient has inadequate response to one of these treatment options, recommend trial of the second treatment option
    - If both regimens are unsuccessful, reassess patient for clozapine treatment
    - If clozapine treatment is unsuccessful, consider augmentation with a first-generation, second-generation antipsychotic or electroconvulsive therapy.

Currently in the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and prior authorization (PA) requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine and pimavanserin. The majority of antipsychotic use is for second generation antipsychotics. The goal of this analysis is to assess current utilization patterns and identify opportunities for provider education and retrospective drug use review.

Methods:
The patient population included current Medicaid patients (enrolled in FFS and CCOs) with an index event from 6/1/2017 to 5/31/2018. The index event was defined as the first paid FFS pharmacy claim for an oral first or second generation antipsychotic or paid pharmacy or medical claims for injectable antipsychotics. Patients were included if they had a diagnosis of schizophrenia identified based on ICD-10 diagnosis codes in the 1.5 years before or 6 months after the index event (ICD-10 codes F20.0-F20.9). Data in the most recent 6 months may not capture all patients with a diagnosis of schizophrenia as medical claims may be incomplete. Patients were excluded if they had Medicare part D coverage or had ≤75% eligibility in the year prior to the index event in order to ensure complete medical records for diagnoses.

Treatment naïve patients were defined as patients without any claims for antipsychotics within the prior year based on medical and pharmacy claims. In some cases, patients may have a remote history of antipsychotic use and are not truly treatment naïve for their condition. A remote history of antipsychotic use was defined as patients with paid claims for antipsychotics at greater than 12 months before the index event. This data may be incomplete as many patients may not have a history of Medicaid eligibility. In addition, these patients may have been prescribed antipsychotics for conditions other than schizophrenia.

If patients had not transitioned to a parenteral antipsychotic within 6 months of an initial paid index event, they were categorized based on duration of treatment. Current treatment algorithms recommend transition of patients to a parenteral antipsychotic if patients have an adequate response after 2-4 weeks. Assessment of treatment response is difficult based on claims data, but patients would likely be eligible for transition to a parenteral antipsychotic if they are on

the same medication for ≥ 12 continuous weeks. Continuous therapy was defined as claims for the same drug (based on HICL sequence number [HSN]) for at least 12 weeks with a gap in therapy of no more than 2 weeks. If patients had claims for more than one antipsychotic and discontinued or started another antipsychotic drug (based on HSN) during this timeframe, patients were considered to be on non-optimal therapy and were excluded from this subgroup.

The number of patients prescribed at least 2 concomitant antipsychotics was evaluated in the 6 months following the index event. Utilization of concomitant antipsychotic therapy was defined as paid claims for at least 2 distinct drugs (based on HSN) with a duration of ≥ 8 weeks continuous treatment, ≥ 8 weeks of overlapping therapy, and no more than a 1 week gap in concomitant therapy.

Utilization of long-acting injectable antipsychotics in all patients with a diagnosis of schizophrenia was also evaluated. Claims were classified based on patient enrollment (either FFS or CCO) at the time of the pharmacy or medical claim for a long-acting injectable antipsychotic. A single member may have claims paid by multiple CCOs or FFS and a CCO if their enrollment status changed over the course of the assessment period.

Adherence to long-acting injectable formulations compared to oral formulations was assessed for all patients with a schizophrenia diagnosis. All adherence data was assessed in the 6 months following the index event. Days of coverage were defined according to **Table A3** for medical claims and defined based on days' supply submitted on pharmacy claims. If submitted days' supply for pharmacy claims of an injectable antipsychotic was less than 7 days, then **Table A3** was used to approximate days of coverage. In some cases (e.g., aripiprazole lauroxil or paliperidone palmitate) duration of coverage is dependent on the units given or dose administered. The proportion of days covered (PDC) may give an estimate of the number of patients who are adherent to their antipsychotic therapy. As defined here, short-term therapy over a period of 6 months would correspond to a PDC of up to 25% (≤45 days), intermittent therapy corresponds to PDC of 25-75%, and long-term therapy corresponds to a PDC of 75% or more (>135 days). The number of subsequent paid claims for injectable vs. oral antipsychotic therapy was also used as a measure of patient adherence.

Results:

In total, over 4,600 schizophrenia patients met inclusion criteria, and approximately 14% of patients were identified as treatment naïve without claims for antipsychotics in the year prior to the index event. Baseline characteristics for this population are shown in **Table 1**. Patients were most commonly adult males with a diagnosis of unspecified schizophrenia. Only a few patients had a history of schizophrenia diagnosis for more than one year and the majority of schizophrenia diagnoses were noted in the 6 month before or after the first claim for an antipsychotic. However, because diagnoses are based on medical claims, the patient's history of diagnoses may be incomplete, and Medicaid enrollment status may account for the limited number of patients with diagnoses prior to 1 year.

Table 1. Baseline demographics for schizophrenia patients

	All Schizophrenia		Treatment Naïve	
N=	**4,663**	**%**	**653**	**%**
Age				
Average (min - max)	40.5	(7-77)	34.4	(8-73)
<13	13	0.3%	2	0.3%
13-18	169	3.6%	50	7.7%
18-59	4,067	87.2%	575	88.1%
≥ 60	414	8.9%	26	4.0%

Female	1,784	38.3%	215	32.9%
White	3,008	64.5%	318	48.7%
Native American	269	5.8%	40	6.1%
Average time between first diagnosis and index event				
≥1 year	284	6.1%	34	5.2%
≥6 months	405	8.7%	30	4.6%
<6 months	3,974	85.2%	589	90.2%
Type of schizophrenia				
Paranoid (F20.0)	827	17.7%	93	14.2%
Disorganized (F20.1)	87	1.9%	17	2.6%
Catatonic (F20.2)	36	0.8%	13	2.0%
Undifferentiated (F20.3)	244	5.2%	37	5.7%
Residual (F20.5)	32	0.7%	2	0.3%
Other (F20.8)	366	7.8%	69	10.6%
Unspecified (F20.9)	3,071	65.9%	422	64.6%

Antipsychotic utilization by drug is shown in **Table 2** for all schizophrenia patients and treatment naïve patients. Approximately half of the patients defined as treatment naïve also had a remote history of antipsychotic use at least 1 year before their first antipsychotic claim. Because diagnoses are not available on prescriptions, it is unclear if patients with a remote history of antipsychotic use were prescribed these medications for schizophrenia or for other mental health conditions. Overall, there was no difference in prescribing patterns for patients with a remote history of antipsychotic use and those without prior antipsychotic use.

Oral second-generation antipsychotics which are recommended as first-line treatment in the MHCAG schizophrenia algorithm (aripiprazole, risperidone, or paliperidone) were prescribed as initial treatment in only 38% of treatment naïve patients. Approximately 4-6% of the treatment naive were initially prescribed parenteral antipsychotics and 6-7% were prescribed a first-generation antipsychotic. Parenteral antipsychotics may be initially prescribed for patients who transition from inpatient treatment. Of the second generation antipsychotics which are not recommended as first-line treatments, olanzapine and quetiapine were most commonly prescribed. Utilization of first generation antipsychotics, parenteral antipsychotics, and other second generation antipsychotics which are not recommended as first-line treatment were slightly more common in all patients with schizophrenia. Increased use of these medications in a broader population including treatment-experienced schizophrenia patients is not unexpected, as these treatments are more likely to be used for patients who have tried and failed other therapies.

Table 2. Antipsychotic utilization based on treatment regimen. Utilization presented for all patients, treatment naïve patients, and treatment naïve patients with remote history of antipsychotic use. Treatment naïve was defined as patients with no antipsychotic use in the 12 months before the index event. Remote antipsychotic use was defined as patients with a history of any antipsychotic use at >12 months before the index event.

	All Schizophrenia		Treatment Naïve			
			All treatment naïve		History of remote antipsychotic use	
Index Drug Event	**4,663**	**%**	**653**	**%**	**300**	**%**
1st generation antipsychotic	**514**	**11.0%**	**39**	**6.0%**	**22**	**7.3%**
2nd generation antipsychotic	**3,685**	**79.0%**	**585**	**89.6%**	**259**	**86.3%**
Recommended 1st line regimen	*1,307*	*28.0%*	*248*	*38.0%*	*101*	*33.7%*
aripiprazole	572	12.3%	119	18.2%	43	14.3%
paliperidone	153	3.3%	20	3.1%	7	2.3%
risperidone	582	12.5%	109	16.7%	51	17.0%
Other regimens	*2,378*	*51.0%*	*337*	*51.6%*	*158*	*52.7%*
asenapine	41	0.9%	5	0.8%	2	0.7%
clozapine	309	6.6%	8	1.2%	3	1.0%
olanzapine	967	20.7%	159	24.3%	73	24.3%
quetiapine	628	13.5%	117	17.9%	57	19.0%
IE dose =< 50 mg/day	76	1.6%	33	5.1%	18	6.0%
ziprasidone	177	3.8%	8	1.2%	6	2.0%
lurasidone	187	4.0%	25	3.8%	11	3.7%
brexpiprazole	29	0.6%	11	1.7%	4	1.3%
cariprazine	32	0.7%	2	0.3%	1	0.3%
iloperidone	7	0.2%	2	0.3%	1	0.3%
pimavanserin	1	0.0%	0	0.0%	0	0.0%
Parenteral antipsychotic	**464**	**10.0%**	**29**	**4.4%**	**19**	**6.3%**
Recommended regimens	*350*	*7.5%*	*11*	*1.7%*	*8*	*2.7%*
aripiprazole (all formulations)	89	1.9%	2	0.3%	0	0.0%
paliperidone palmitate	211	4.5%	9	1.4%	8	2.7%
risperidone (all formulations)	50	1.1%	0	0.0%	0	0.0%
Non-recommended regimens (all other parenteral)	*114*	*2.4%*	*18*	*2.8%*	*11*	*3.7%*

Current MCHAG algorithms for patients with schizophrenia recommend transition to an injectable antipsychotic if the patient has an adequate response after 2-4 weeks. Only 58 patients (9.3% of all treatment naïve patients) had a claim for a long-acting injectable antipsychotic within the 6 months following the index

event. Approximately, 25% of treatment naïve patients prescribed oral therapy (n=155) had claims for a single antipsychotic for at least 12 weeks and would likely be eligible to transition to a long-acting injectable antipsychotic. Similar trends were observed in all schizophrenia patients. Overall, only 8% of patients transition to a long-acting injectable antipsychotic within 6 months, but approximately 60% of patients have claims for continuous treatment for at least 12 weeks and may be eligible for LAI therapy. More patients who were prescribed a recommended first-line treatment option transitioned to a long-acting injectable antipsychotic in the 6 months following the index event (84% vs. 46% for all schizophrenia patients).

Table 3. Number and proportion of schizophrenia patients who switch to a parenteral or long-acting injectable (LAI) antipsychotic within 6 months after the index event (based on pharmacy and medical claims).

	Treatment Naïve				**All Schizophrenia**			
	Patients with LAI use		Patients without LAI use AND with ≥ 12 weeks of continuous therapy		Patients with LAI use		Patients without LAI use AND with ≥ 12 weeks of continuous therapy	
Index Drug Event	**58**		**155**		**342**		**2,512**	
1st generation antipsychotic	**2**	**3.4%**	**7**	**4.5%**	**56**	**16.4%**	**305**	**12.1%**
2nd generation antipsychotic	**56**	**96.6%**	**148**	**95.5%**	**286**	**83.6%**	**2,206**	**87.8%**
Recommended 1st line regimen	*31*	*53.4%*	*60*	*38.7%*	*129*	*37.7%*	*710*	*28.3%*
aripiprazole	11	19.0%	33	21.3%	50	14.6%	302	12.0%
paliperidone	7	12.1%	1	0.6%	33	9.6%	73	2.9%
risperidone	13	22.4%	26	16.8%	46	13.5%	335	13.3%
Other regimens	*25*	*43.1%*	*88*	*56.8%*	*157*	*45.9%*	*1,496*	*59.6%*
asenapine		0.0%	1	0.6%	2	0.6%	21	0.8%
clozapine		0.0%	4	2.6%	5	1.5%	287	11.4%
olanzapine	12	20.7%	34	21.9%	78	22.8%	552	22.0%
quetiapine	8	13.8%	33	21.3%	47	13.7%	359	14.3%
ziprasidone		0.0%	1	0.6%	8	2.3%	123	4.9%
lurasidone	4	6.9%	7	4.5%	11	3.2%	114	4.5%
brexpiprazole	1	1.7%	5	3.2%	3	0.9%	12	0.5%
cariprazine		0.0%	1	0.6%	2	0.6%	22	0.9%
iloperidone		0.0%	2	1.3%	1	0.3%	6	0.2%
pimavanserin		0.0%		0.0%		0.0%	1	0.0%

Overall, 795 schizophrenia patients (17% of the entire population) had claims for 2 or more concomitant antipsychotic medications in the 6 months following the index event**.** Of the patients with dual antipsychotic therapy, few patients (10%) had claims for more than 2 antipsychotics at a time and dual antipsychotic use was infrequent in treatment naïve patients. The most commonly prescribed combinations of antipsychotic medications are listed in **Table 4** and commonly included olanzapine, quetiapine, aripiprazole, and risperidone.

Table 4. Concomitant antipsychotic therapy in patients with ≥ 2 antipsychotic medications (duration of overlap ≥ 8 weeks) in the 6 months after the index event.

			All Schizophrenia		Treatment Naïve	
N=			**795**	**%**	**24**	**%**
Duration of overlap						
8-12 weeks			295	37.1%	13	54.2%
13-24 weeks			350	44.0%	9	37.5%
>24 weeks			264	33.2%	3	12.5%
Number of drugs						
2			719	90.4%	24	100.0%
3			71	8.9%	0	0.0%
4			4	0.5%	0	0.0%
5			1	0.1%	0	0.0%
Most commonly prescribed concomitant antipsychotics						
1	risperidone	quetiapine fumarate	45	5.7%	1	4.2%
2	haloperidol	olanzapine	43	5.4%	3	12.5%
3	aripiprazole	quetiapine fumarate	40	5.0%	2	8.3%
4	aripiprazole	olanzapine	36	4.5%	2	8.3%
5	risperidone	olanzapine	31	3.9%	1	4.2%
6	clozapine	haloperidol	30	3.8%	1	4.2%
7	olanzapine	quetiapine fumarate	28	3.5%		0.0%
8	paliperidone palmitate	olanzapine	25	3.1%	1	4.2%
9	clozapine	olanzapine	24	3.0%		0.0%
10	risperidone	aripiprazole	23	2.9%	1	4.2%
11	paliperidone	olanzapine	21	2.6%	2	8.3%
12	clozapine	aripiprazole	20	2.5%		0.0%
13	aripiprazole	haloperidol	20	2.5%		0.0%
14	perphenazine	olanzapine	18	2.3%	2	8.3%
15	olanzapine	lurasidone HCl	17	2.1%		0.0%
16	clozapine	risperidone	17	2.1%	1	4.2%
17	paliperidone palmitate	quetiapine fumarate	16	2.0%		0.0%
18	paliperidone	quetiapine fumarate	16	2.0%	1	4.2%
19	haloperidol	quetiapine fumarate	16	2.0%		0.0%
20	clozapine	quetiapine fumarate	15	1.9%	1	4.2%

Table 5 describes how claims for injectable antipsychotics are billed for FFS and CCO members. Mental health medications, including antipsychotics, are carved out of the CCO budget and paid for by FFS when they are billed as a pharmacy claim. However, these medications are administered by providers and may be billed by as provider administered medical claims. Any medical claims for injectable antipsychotics administered to members enrolled in a CCO are billed to the

CCO. As a result, the vast majority of claims for CCO members are billed through pharmacy whereas approximately 72% of FFS claims are billed by providers after administration rather than through a pharmacy.

Table 5. Evaluation of long-acting injectable antipsychotic use by billing method (pharmacy vs. medical claims) in all schizophrenia patients. Claims are categorized based on CCO or FFS member enrollment at the time of the claim.

	Pharmacy claims		Medical claims		Total paid claims
	#	%	#	%	#
FFS enrollment	11	27.5%	29	72.5%	40
CCO enrollment	221	98.7%	3	1.3%	224
HEALTH SHARE OF OREGON	62	100.0%		0.0%	62
EASTERN OREGON CCO, LLC	41	100.0%		0.0%	41
WILLAMETTE VALLEY COMM. HEALTH	34	100.0%		0.0%	34
TRILLIUM COMMUNITY HEALTH PLAN	30	100.0%		0.0%	30
PACIFICSOURCE COMMUNITY SOL INC	11	100.0%		0.0%	11
ALLCARE CCO, INC.	9	100.0%		0.0%	9
COLUMBIA PACIFIC CCO LLC	8	80.0%	2	20.0%	10
FAMILYCARE, CCO	5	100.0%		0.0%	5
JACKSON CARE CONNECT	5	100.0%		0.0%	5
CAPITOL DENTAL CARE INC	4	100.0%		0.0%	4
INTERCOMMUNITY HEALTH NETWORK	4	100.0%		0.0%	4
ADVANTAGE DENTAL	3	75.0%	1	25.0%	4
PRIMARYHEALTH JOSEPHINE CO CCO	2	100.0%		0.0%	2
UMPQUA HEALTH ALLIANCE, DCIPA	2	100.0%		0.0%	2
OREGON DENTAL SERVICES	1	100.0%		0.0%	1

Adherence was evaluated for all schizophrenia patients using the proportion of covered days in the 6 months following the index event for patients prescribed oral or injectable therapy (**Table 6**). Overall there were no large differences in days of coverage for patients prescribed injectable versus oral therapy or in the numbers of subsequent prescriptions filled in the 6 months after the first claim (**Table 6**). In the 6 months following the first claims, approximately 9-11% of patients had less than 25% of days covered (corresponding to less than 45 days) and 62-64% of patient had more than 75% of days covered (corresponding to >135 days). Because covered days may be inaccurate, particularly for injectable claims, the number of subsequent filled claims was also evaluated for each patient. Overall, results were similar to the proportion of covered days, assuming the majority of patients received claims for 30 days' supply. Approximately 8% of patients in each group never receive another prescription for an antipsychotic and 55-65% of patients had at least 5 claims paid over 6 months.

A significant proportion of patients (46%) who were on injectable antipsychotics, transition back to oral therapy and only 8% of patients initially prescribed oral therapy had a subsequent claim for a long-acting injectable antipsychotic. There are multiple reasons patients may transition between therapies. For example, if patients are late receiving a routine antipsychotic injection they may briefly need oral therapy until they achieve therapeutic levels with an injectable formulation.

Table 6. Adherence information for patients with injectable or oral therapy in the 6 months following the Index Event (IE) (all schizophrenia patients).

	Patients with IE for a long-acting injectable antipsychotic		Patients with IE for oral therapy	
N=	**464**	**%**	**4,199**	**%**
Days of coverage				
<= 30 days	31	6.7%	384	9.1%
31-90 days	53	11.4%	664	15.8%
91-180 days	294	63.4%	2,349	55.9%
>= 181 days	86	18.5%	802	19.1%
Proportion of days covered				
<=25%	41	8.8%	482	11.5%
26-75%	122	26.3%	1,096	26.1%
>75%	301	64.9%	2,621	62.4%
Number of paid claims with the same route of administration (oral vs. injectable)				
0 (only the IE)	39	8.4%	343	8.2%
1-4	168	36.2%	1121	26.7%
5-6	169	36.4%	1150	27.4%
>6	88	19.0%	1585	37.8%
Number of patients with claims for the alternative route of administration (oral or injectable)				
	212	45.7%	342	8.1%

The most common prescribers of antipsychotics in schizophrenia patients are shown in **Table 7**. Physician and nurse practitioner psychiatric and mental health specialists account for the majority of prescribing in both treatment naïve patients and the general schizophrenia population (55% for treatment naïve and 66% for all schizophrenia patients). Family physicians and nurse practitioners prescribe antipsychotic medications in approximately 13% of patients with schizophrenia.

Table 7. Prescribing rates stratified by primary provider taxonomy for the top 20 providers prescribing antipsychotics to schizophrenia patients

		All Schizophrenia		Treatment Naïve	
	N=	**4,663**		**653**	
1	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	1,594	34.2%	217	33.2%
2	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	1,510	32.4%	144	22.1%
3	PHYSICIAN-FAMILY MEDICINE	340	7.3%	61	9.3%
4	NURSE PRACTITIONER - FAMILY	305	6.5%	49	7.5%
5	PHYSICIAN-INTERNAL MEDICINE	140	3.0%	25	3.8%

6	PHYSICIAN ASSISTANT	118	2.5%	18	2.8%
7	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	98	2.1%	21	3.2%
8	PHYSICIAN ASSISTANT - MEDICAL	96	2.1%	15	2.3%
9	PHYSICIAN-EMERGENCY MEDICINE	60	1.3%	23	3.5%
10	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH	56	1.2%	4	0.6%
11	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY	41	0.9%	4	0.6%
12	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	40	0.9%	4	0.6%
13	STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	33	0.7%	8	1.2%
14	NURSE PRACTITIONER	31	0.7%	7	1.1%
15	PHYSICIAN-HOSPITALIST	20	0.4%	9	1.4%
16	HOSPITALS: GENERAL ACUTE CARE HOSPITAL	19	0.4%	12	1.8%
17	NATUROPATH	16	0.3%	3	0.5%
18	PHYSICIAN-GENERAL PRACTICE	16	0.3%	0	0.0%
19	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY	15	0.3%	3	0.5%
20	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY	14	0.3%	6	0.9%

Discussion and Limitations:

Data presented in this report is based on Medicaid claims history and has several inherent limitations. For example, we depend on providers to submit accurate diagnostic information for their patients, though it may not be accurate in all circumstances and it is likely that delays in billing for medical claims resulted in some patients who have schizophrenia being excluded from this analysis since they did not have a recent schizophrenia diagnosis based on medical claims. Similarly, information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers, and prescribers with multiple specialties or designations may not be identified. In addition, 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 and patients may not always be categorized appropriately. We rely on pharmacies to submit accurate duration of therapy, but duration is likely to vary (especially for injectable medications) making estimates of PDC less reliable. Medical claims are not submitted with a days' supply and while attempts were made to estimate the duration of coverage for medical claims based on standard dosing regimens, these estimates may not reflect the true duration of coverage.

In the Oregon Health Plan, antipsychotic medications are primarily carved-out of CCOs and are paid for by FFS. However, billing mechanisms should be taken into account for any educational initiatives or proposed projects. For patients enrolled in a CCO, injectable antipsychotics are primarily only covered through the pharmacy and paid for by FFS. Comparatively, for FFS patients, injectable antipsychotics can be billed as either a pharmacy or medical claim if the injectable antipsychotics is bought by and administered in a provider's office. When physician administered medications (i.e., long-acting injectable antipsychotics) are billed through the pharmacy rather than a medical facility, there are several factors to consider. First, paying for injectable antipsychotics through the pharmacy may be associated with a significant amount of waste if the drug is never administered to the patient. Medical claims may only be billed after administered to the patient, and in this circumstance, we are certain the patient actually received the drug. When injectable antipsychotics are billed as a pharmacy claim, in some circumstances, they may never be administered to the patient if, for example, the patient misses their appointment with their provider.

When claims were evaluated for administration of an intramuscular or subcutaneous injection following a paid pharmacy claim for an injectable antipsychotic, there were no patients who had claims associated with medication administration. There could be several possible explanations for this:

1) Providers are not billing for costs associated with administering the antipsychotic

2) Providers are not billing *correctly* for costs associated with administration of the antipsychotic
3) There is no easy way to distinguish administration of medication from other medical claims
4) There is a significant time difference between a paid antipsychotic pharmacy claim and patient administration (> 3 weeks)
5) Patients are not being administered the long-acting injectable antipsychotic even though it was paid for by Medicaid

In the Oregon Health Plan (OHP), antipsychotic medications are exempt from traditional preferred drug list (PDL) and PA requirements. While OHP uses a voluntary preferred drug list, non-preferred medications do not currently stop for prior authorization. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Historical initiatives for mental health medications have focused on provider education surrounding monitoring recommendations for antipsychotics and dose consolidation initiatives. For example, a target population of patients is identified and faxes are sent to providers which include a summary of the initiative and request for a voluntary change to the less expensive agent or consolidated dose. Depending on the initiative, initiatives have had limited success in changing prescriber behavior. The following are a few examples of provider educational opportunities and retrospective drug use review initiatives which may be worth considering to increase awareness of MHCAG recommendations for patients with schizophrenia:

1) Broad educational initiative (e.g., newsletter) on MHCAG schizophrenia recommendations
2) Targeted intervention identifying patients who are non-adherent to current therapy or patients with a history of previous emergency room admissions or hospitalizations. Notify these prescribers of the MHCAG algorithm for schizophrenia and request they consider trial of a preferred product or long-acting injectable.
3) Targeted intervention identifying treatment naïve schizophrenia patients and patients with no recent use of recommended regimens for schizophrenia (paliperidone, risperidone, or aripiprazole). Notify these prescribers of the MHCAG algorithm for schizophrenia and request they consider trial of a product recommended by the OHA and MHCAG.
4) Targeted intervention identifying patients on combination antipsychotic treatment and provide education to these prescribers on the MHCAG algorithm and resources available in Oregon for additional provider consultation services.
5) Explore opportunities to increase access to injectable antipsychotic medication in provider offices through replenishment models.

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339	Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	
Bipolar Mania	F3010; F339; F3110-F3113; F312	
Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

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

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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		
5. What diagnosis is being treated?	Record ICD10 code	
6. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
7. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
8. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
9. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
10. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

Appendix 2. Coding Information

Table A1. Drug codes

Class	HSN	Generic
Antipsychotics, 2nd Gen	024551	aripiprazole
Antipsychotics, 2nd Gen	036576	asenapine maleate
Antipsychotics, 2nd Gen	042283	brexpiprazole
Antipsychotics, 2nd Gen	042552	cariprazine HCl
Antipsychotics, 2nd Gen	004834	clozapine
Antipsychotics, 2nd Gen	037321	lurasidone HCl
Antipsychotics, 2nd Gen	011814	olanzapine
Antipsychotics, 2nd Gen	034343	paliperidone
Antipsychotics, 2nd Gen	043373	pimavanserin tartrate
Antipsychotics, 2nd Gen	014015	quetiapine fumarate
Antipsychotics, 2nd Gen	008721	risperidone
Antipsychotics, 2nd Gen	021974	ziprasidone HCl
Antipsychotics, Parenteral	024551	aripiprazole
Antipsychotics, Parenteral	042595	aripiprazole lauroxil
Antipsychotics, Parenteral	045050	aripiprazole lauroxil,submicr.
Antipsychotics, Parenteral	001621	chlorpromazine HCl
Antipsychotics, Parenteral	001624	fluphenazine decanoate
Antipsychotics, Parenteral	001626	fluphenazine HCl
Antipsychotics, Parenteral	001660	haloperidol decanoate
Antipsychotics, Parenteral	001661	haloperidol lactate
Antipsychotics, Parenteral	011814	olanzapine
Antipsychotics, Parenteral	036716	olanzapine pamoate
Antipsychotics, Parenteral	036479	paliperidone palmitate
Antipsychotics, Parenteral	008721	risperidone
Antipsychotics, Parenteral	025509	risperidone microspheres
Antipsychotics, Parenteral	001630	trifluoperazine HCl
Antipsychotics, Parenteral	023379	ziprasidone mesylate
Antipsychotics, 1st Gen	001621	chlorpromazine HCl
Antipsychotics, 1st Gen	001626	fluphenazine HCl
Antipsychotics, 1st Gen	001627	perphenazine
Antipsychotics, 1st Gen	001630	trifluoperazine HCl
Antipsychotics, 1st Gen	001631	thioridazine HCl
Antipsychotics, 1st Gen	001661	haloperidol lactate
Antipsychotics, 1st Gen	001662	haloperidol
Antipsychotics, 1st Gen	001667	thiothixene HCl

Antipsychotics, 1st Gen	001668	thiothixene
Antipsychotics, 1st Gen	001637	pimozide
Antipsychotics, 1st Gen	001664	loxapine succinate
Antipsychotics, 1st Gen	039886	loxapine

Table A2. Administration Codes for Long-acting Injectables

Code	Short Description	Long Description
G0351	Therapeutic/Diagnostic Injec	Therapeutic Or Diagnostic Injection (Specify Substance Or Drug); Subcutaneous Or Intramuscular
T1502	Medication Admin Visit	Administration of oral, intramuscular and/or subcutaneous medication by health care agency/professional, per visit
90772	Ther/proph/diag inj, sc/im	Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

Table A3. Days of coverage associated with injectable antipsychotic prescriptions

ProcCode	NameDrugGen	NAMEPROCLONG	Days of coverage
C9035	aripiprazole lauroxil,submicr.	Injection, Aripiprazole Lauroxil (Aristada Initio), 1 Mg	10 days
C9037	risperidone	Injection, Risperidone (Perseris), 0.5 Mg	28 days
C9470 J1942	aripiprazole lauroxil aripiprazole lauroxil,submicr.	Injection, Aripiprazole Lauroxil, 1 Mg	28 days (<700 mg or units) 42 days (700-900 mg or units) 56 days (>900 mg or units)
J0400	aripiprazole	Injection, Aripiprazole, Intramuscular, 0.25 Mg	28 days
J0401	aripiprazole	Injection, Aripiprazole, Extended Release, 1 Mg	28 days
J1630	haloperidol lactate	Injection, Haloperidol, Up To 5 Mg	1 day (acute use)
J1631	haloperidol decanoate	Injection, Haloperidol Decanoate, Per 50 Mg	28 days
J2358	olanzapine pamoate	Injection, Olanzapine, Long-Acting, 1 Mg	28 days
J2426	paliperidone palmitate	Injection, Paliperidone Palmitate Extended Release, 1 Mg	28 days (<250 mg or units) 84 days (>=250 mg or units)
J2680	fluphenazine decanoate	Injection, Fluphenazine Decanoate, Up To 25 Mg	28 days
J2794	risperidone microspheres	Injection, Risperidone, Long Acting, 0.5 Mg	14 days
J3230	chlorpromazine HCl	Injection, Chlorpromazine Hcl, Up To 50 Mg	1 day (daily injection)
J3486	ziprasidone mesylate	Injection, Ziprasidone Mesylate, 10 Mg	1 day (acute use)
S0166	olanzapine	Injection, Olanzapine, 2.5 Mg	28 days

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Antipsychotics

Date of Review: March 2019

Date of Last Review: September 2018
Literature Search: 01/01/2018 – 01/8/2019

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

Conclusions:

- Two systematic reviews are included in this literature scan of recent evidence for antipsychotic safety and efficacy.
- The Agency for Healthcare Research and Quality (AHRQ) published a systematic review to assess the effectiveness of drug and non-drug therapies for treating acute mania or depression symptoms and preventing relapse in adults with bipolar disorder (BD) diagnoses.[1] No high- or moderate-strength evidence was identified for any intervention to effectively treat any phase or type of BD versus placebo or an active comparator.[1] When compared to placebo, pooled data from low strength evidence showed asenapine, cariprazine, olanzapine, and quetiapine improved acute mania symptoms in Bipolar Disorder Type I (BD-I).[1] Data from the specific trials is outlined in **Table 2**. Lithium was the only mood stabilizer that improved acute mania in the short-term and prolonged time to relapse in the long term compared to placebo (low-strength evidence).[1] Evidence was largely insufficient to draw conclusions for all other non-approved FDA drugs for BD-I for the primary outcomes of interest (response, symptom scores, and function).[1]
- A 2018 Cochrane review evaluated the evidence to support the efficacy and safety of oral olanzapine when used as an antiemetic in the prevention and treatment of nausea and vomiting related to cancer in adults.[2] Currently the use of olanzapine to mitigate nausea and vomiting associated with chemotherapy is off-label, as olanzapine is not FDA-approved for this indication. There is moderate-quality evidence that oral olanzapine increases the likelihood of nausea or vomiting during chemotherapy from 25% to 50% in adults with solid tumors, in addition to standard therapy, compared to placebo or no treatment.[2] Number needed to treat for additional beneficial outcome (NNTB) was 5 (95% CI 3.3 to 6.6).[2] It is uncertain if olanzapine increases the risk of serious adverse events (absolute risk difference 0.7% more, 95% CI 0.2 to 5.2; relative risk (RR) 2.46, 95% CI 0.48 to 12.55, low-quality evidence).[2]
- The FDA published a new safety alert for ziprasidone advising against use in elderly patients with dementia due to the increased risk of death in these patients when administered ziprasidone.[3]
- Warnings about dosing errors were added to Aristada Initio® extended-release injection labeling. Aristada Initio® is for single administration in contrast to Aristada® which is administered monthly, every 6 weeks, or every 8 weeks.[4]

Recommendations:

- No further review or research needed at this time.
- No changes to the PDL are recommended for oral or parenteral antipsychotics based on efficacy or safety data.
- Evaluate costs in executive session.

Author: Deanna Moretz, PharmD, BCPS

Summary of Prior Reviews and Current Policy

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and PA requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The PA criteria for these safety edits are outlined in **Appendix 5**. Injectable formulations of aripiprazole, haloperidol, chlorpromazine, fluphenazine, trifluoperazine, paliperidone palmitate, and risperidone are preferred on the Preferred Drug List (PDL). Oral antipsychotics that are preferred on the PDL include chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, and risperidone. The majority of antipsychotic use in the Oregon Medicaid population is for oral second generation antipsychotics (SGA) including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 10% of antipsychotic medication claims are for parenteral formulations. Paliperidone, aripiprazole, and haloperidol are the most frequently prescribed injectable agents in this class. The antipsychotics included on the Oregon PDL are presented in **Appendix 1**.

Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy, effectiveness, or harms between antipsychotic agents for schizophrenia, bipolar mania or major depressive disorder (MDD). There is insufficient evidence from randomized controlled trials or high quality systematic reviews to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

After review, 4 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[5-8]

<u>Agency for Healthcare Research and Quality</u>

In 2018, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review completed by the Minnesota Evidence-based Practice Center.[1] The purpose of the review was to assess the effectiveness of drug and non-drug therapies for treating acute mania or depression symptoms and preventing relapse in adults with bipolar disorder (BD) diagnoses.[1] The literature search evaluated trials published from 1994 through May 2017. Eligible studies included randomized controlled trials and prospective cohort studies with comparator arms in adults with BD of any type with 3 weeks follow up for acute mania, 3 months for depression, and 6 months for maintenance treatments.[1] One hundred fifty-seven studies were included in the review; 108 studies for 28 drugs and 49 studies for

non-drug interventions.[1] Trials with greater than 50 percent attrition rates were excluded from the systematic review because of potential systematic differences between patients who complete a study and those who do not.[1] Study findings were interpreted using published minimally important differences (MIDs) for the Young Mania Rating Scale (YMRS) (MID=6) and the Clinical Global Impressions (CGI) scale (MID=1).[9] Drug treatments approved by the Food and Drug Administration (FDA) for bipolar treatment are summarized in **Table 1**. No high- or moderate-strength evidence was identified for any intervention to effectively treat any phase or type of BD versus placebo or an active comparator.[1] Evidence was largely insufficient to draw conclusions regarding the effects of drug treatments for depression in adults with BD for the primary outcomes of interest (relapse, symptom scores, and function).[1]

Table 1. FDA-approved medications for bipolar disorder[1]

Drug Type	Generic Name (Date Approved)	Brand Name	Manic	Mixed (Mania/Depression)	Maintenance	Depression
Salts	Lithium (1970)	Lithobid®	X	X	X	
Atypical Antipsychotics	Aripiprazole (2004)	Abilify®	X	X	X	
	Asenapine (2015)	Saphris®	X	X	X	
	Cariprazine (2015)	Vraylar®	X	X		
	Lurasidone (2013)	Latuda®				X
	Olanzapine (2000)	Zyprexa®	X	X	X	
	Quetiapine (2004)	Seroquel®	X		X	X
	Risperidone (2003)	Risperdal®	X	X	X	
	Ziprasidone (2004)	Geodon®	X	X	X	
Anticonvulsants	Carbamazepine (2004)	Equetro®	X	X		
	Lamotrigine (2003)	Lamictal®			X	
	Divalproex Sodium (1995)	Depakote®	X	X		

Antipsychotics to treat acute mania in bipolar disorder

When compared to placebo, pooled data showed asenapine, cariprazine, olanzapine, and quetiapine improved acute mania symptoms (low-strength evidence).[1] However, improvements were of modest clinical significance, with values that were less than the MID, but still large enough that a reasonable proportion of participants likely received a benefit.[1] Unpooled evidence indicated an overall beneficial effect of risperidone and ziprasidone on acute mania symptoms compared to placebo (low-strength evidence).[1] Specific findings for the atypical antipsychotics in managing acute mania are summarized in **Table 2.** Evidence was insufficient for all outcomes to address whether aripiprazole or haloperidol was better than placebo for acute mania in adults with BD-I, due to high study limitations and imprecise data.[1] Participants using atypical antipsychotics, except quetiapine, reported more extrapyramidal symptoms compared to placebo (specific rates not specified by the authors).[1] Patients using olanzapine reported more clinically significant weight gain (at least a 7 percent increase) compared to placebo.[1]

Table 2. Summary of findings with at least low-strength evidence for antipsychotic drug treatments for acute mania[1]

Intervention	Number of Studies (number of patients) Timing	Findings	Strength of Evidence
Asenapine vs. placebo	3 RCTs (n=936) 3 weeks	Response/Remission Rates: No difference YMRS: Favors Asenapine, MD 4.37 (95% CI 1.27, 7.47; MID 6) CGI-BP-S: Favors Asenapine, MD 0.5 (95% CI 0.29, 0.71; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference	Low (moderate study limitations, imprecise)
Cariprazine vs. placebo	3 RCTs (n=1,047) 3 weeks	Response Rate: Favors Cariprazine, OR 2.14 (95% CI 1.08, 4.23); NNT 6 Remission Rate: Favors Cariprazine, OR 1.95 (95% CI 1.45, 2.63); NNT 7 YMRS: Favors Cariprazine, MD 5.38 (95% CI 1.84, 8.92; MID 6) CGI-BP-S: Favors Cariprazine, MD 0.54 (95% CI 0.35, 0.73; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference	Low (moderate study limitations, imprecise)
Olanzapine vs. placebo	5 RCTs (n=1,199) 3 weeks	Response Rate: Favors Olanzapine, OR 1.99 (95% CI 1.29, 3.08); NNT 6 Remission Rate: Favors Olanzapine, OR 1.75 (95% CI 1.19, 2.58); NNT 8 YMRS: Favors Olanzapine, MD 4.9 (95% CI 2.34, 7.45; MID 6) Withdrawal (Lack of Efficacy, Overall): Favors Olanzapine, MD 0.42 (95% CI 0.29, 0.61); NNH 2	Low (moderate study limitations, imprecise)
Quetiapine vs. placebo	4 RCTs (n=1,007) 3 weeks 5 RCTs (n=699) 3 weeks	Response Rate: Favors Quetiapine, OR 2.07 (95% CI 1.39, 3.09); NNT 7 Withdrawal (Lack of Efficacy): Favors Quetiapine, MD 0.38 (95% CI 0.23, 0.63); NNH 2 YMRS: Favors Quetiapine, MD 4.92 (95% CI 0.31, 9.53; MID 6)	Low (moderate study limitations, imprecise)
Risperidone vs. placebo	2 RCT (n=584) 3 weeks	Response Rate, YMRS, and CGI: Favors Risperidone (not pooled)	Low (moderate study limitations, imprecise)
Ziprasidone vs. placebo	2 RCT (n=402) 3 weeks	Response Rate, YMRS, and CGI: Favors Ziprasidone (not pooled)	Low (moderate study limitations, imprecise)

Abbreviations: AE=adverse events; CGI =Clinical global impression; CGI-BP=Clinical global impression scale, bipolar edition; CI=confidence interval; MD=mean difference; MID=minimally important difference; n=number; NNH = Number needed to harm; NNT=number needed to treat; OR=odds ratio; RCT=randomized controlled trial; YMRS=Young mania rating scale

Mood stabilizers to treat acute mania in bipolar disorder

Four mood stabilizers, all FDA approved for use in patients with bipolar disorder experiencing mania, were evaluated as single drugs: carbamazepine, divalproex/valproate, lamotrigine, and lithium. All studies enrolled adults with BD-I. Only one study (for lithium) also included adults with BD Type II (BD-II). Low-strength evidence showed lithium increased response rates, remission rates, and manic symptom improvement in BD-I participants with acute mania compared to placebo.[1] The data from these trials is summarized in **Table 3**. Lithium improved acute mania in the short-term and prolonged time to relapse in the long-term

compared to placebo (low-strength evidence).[1] All other drug comparisons to placebo or active controls had insufficient evidence for acute mania, depression, and maintenance treatment outcomes.[1] No difference was found between olanzapine and divalproex/valproate for acute mania (low-strength evidence).[1]

Table 3. Summary of findings with at least low-strength evidence for lithium for acute mania[1]

Intervention	Number of Studies (number of patients) Timing	Findings	Strength of Evidence
Lithium vs. placebo	1 RCT + 1 IPD (n=325) 3 weeks 3 RCTs (n=325) 3 weeks	Remission and Response Rates: Favors Lithium (not pooled) YMRS: Favors Lithium, MD 5.81 (95% CI 2.21, 9.4; MID=6) Withdrawal (Overall): No difference	Low (moderate study limitations, imprecise)

Abbreviations: AE=adverse events; CI=confidence interval; IPD=Individual patient data; MD=mean difference; MID=minimally important difference; n=number; RCT=randomized controlled trial; YMRS=Young mania rating scale

Drugs Not FDA-approved for acute mania in bipolar disorder

Ten drugs not FDA approved for BD were examined for acute mania: allopurinol, celecoxib, donepezil, dipyridamole, endoxifen, gabapentin, paliperidone, tamoxifen, topiramate, and oxcarbazepine, some in combination with mood stabilizers.[1] Low-strength evidence showed paliperidone improved manic symptoms over placebo in adults with BD-I, although the improvement was not a clinically important difference (n=763).[1] Low-strength evidence showed topiramate was not significantly different from placebo for symptom improvement, and participants using placebo withdrew less for adverse events (n=876) in adults with BD-I.[1] Low-strength evidence showed allopurinol plus mood stabilizers/other psychotropic medications did not differ significantly from mood stabilizers alone for manic symptom, CGI improvement, or overall withdrawals (n=355) in adults with BD-I.[1] Evidence was largely insufficient to draw conclusions for all other non-approved FDA drugs for BD-I for the primary outcomes of interest (response, symptom scores, and function).[1]

Non-drug studies examined eight therapy approaches, seven of which were psychosocial intervention types: 1) psychoeducation, 2) cognitive behavioral therapy (CBT), 3) systematic/collaborative care, 4) family/partner interventions, 5) interpersonal and social rhythm therapy (IPSRT), 6) combination treatments (treatments that combined two or more psychosocial interventions, and 7) other psychosocial treatments (e.g. self-management via phone application support).[1] For psychosocial interventions, CBT was no better for depression or mania symptoms than psychoeducation or other active psychosocial comparators (low-strength evidence).[1] Systematic/collaborative care had no effect on relapse compared to inactive comparators (low-strength evidence).[1] Evidence for other non-drug interventions was insufficient.[1]

Cochrane Collaborative

A 2018 Cochrane review evaluated the evidence to support the efficacy and safety of oral olanzapine when used as an antiemetic in the prevention and treatment of cancer-related nausea and vomiting in adults.[2] Currently the use of olanzapine to mitigate nausea and vomiting associated with chemotherapy is off-label, as olanzapine is not FDA-approved for this indication. Thirteen RCTs at high risk of bias due to inadequate blinding were included in the Cochrane systematic review. Most of the RCTs enrolled less than 50 subjects per treatment arm and compared olanzapine to placebo. Olanzapine may double the likelihood of no nausea or vomiting during chemotherapy from 25% to 50% (risk ratio (RR) 1.98,95% confidence interval (CI) 1.59 to 2.47; 561 participants; 3 studies; moderate-quality evidence) when added to standard therapy.[2] Number needed to treat for additional beneficial outcome was 5 (95% CI 3.3 to 6.6).[2] It is uncertain if olanzapine

increases the risk of serious adverse events (absolute risk difference 0.7% more, 95% CI 0.2 to 5.2; RR2.46, 95% CI 0.48 to 12.55; 7 studies, 889 participants, low-quality evidence).[2]

One study (20 participants) compared olanzapine versus neurokinin 1 (NK1) antagonists and no difference in any reported outcomes was observed.[2] One study (112 participants) compared olanzapine versus metoclopramide and reported that olanzapine may increase freedom from overall nausea (RR 2.95, 95% CI 1.73 to 5.02) and overall vomiting (RR 3.03, 95% CI 1.78 to 5.14).[2] Absolute risk reduction was not reported for this trial. Another study (62 participants) examined olanzapine versus 5-hydroxytryptamine (5-HT3) antagonists, reporting olanzapine may increase the likelihood of 50% or greater reduction in nausea or vomiting at 48 hours (RR 1.82, 95% CI 1.11 to 2.97), but not at 24 hours (RR 1.36, 95% CI 0.80 to 2.34).[2] One study (229 participants) compared olanzapine versus dexamethasone, reporting that olanzapine may reduce overall nausea (RR 1.73, 95% CI 1.37 to 2.18), overall vomiting (RR 1.27, 95% CI 1.10 to 1.48), delayed nausea (RR 1.66, 95% CI 1.33 to 2.08), and delayed vomiting (RR 1.25, 95% CI 1.07 to 1.45).[2] All of the data comparing olanzapine to an active comparator was rated as low quality or very low quality evidence.[2]

In summary, there is moderate-quality evidence that oral olanzapine may increase the likelihood of not being nauseous or vomiting during chemotherapy from 25% to 50% in adults with solid tumors, in addition to standard therapy, compared to placebo or no treatment.[2] There is uncertainty whether it increases serious adverse events.[2]

New Guidelines: No new guidelines have been published since the last literature scan.

New Formulations: No new formulations have been FDA-approved since the last literature scan.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ziprasidone	Geodon	11/2018	Boxed Warning and Warnings/Precautions	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Geodon® is not approved for elderly patients with dementia related psychosis.[3]
Aripiprazole Extended Release Injection	Aristada	11/2018	Dosage and Administration and Warnings/Precautions	Medication errors, including substitution and dispensing errors, between Aristada® and Aristada Initio® could occur. Aristada Initio is for single administration in contrast to Aristada® which is administered monthly, every 6 weeks, or every 8 weeks.[4] Do not substitute Aristada Initio® for Aristada® because of differing pharmacokinetic profiles.[4]

References:

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3. Geodon (ziprasidone) Prescribing Information. New York, NY; Pfizer. 11/2018.
4. Aristada (aripiprazole lauroxil) Extended Release Injectable Prescribing Information. Waltham, MA; Alkermes, Inc. 11/2018.
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10. Nicol GE, Yingling MD, Flavin KS, et al. Metabolic Effects of Antipsychotics on Adiposity and Insulin Sensitivity in Youths: A Randomized Clinical Trial. JAMA psychiatry. 2018; 75(8):788-796.
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Appendix 1: Current Preferred Drug List

Second Generation Antipsychotics

Generic	Brand	Form	PDL
asenapine maleate	SAPHRIS	TAB SUBL	Y
cariprazine HCl	VRAYLAR	CAP DS PK	Y
cariprazine HCl	VRAYLAR	CAPSULE	Y
clozapine	CLOZAPINE	TABLET	Y
clozapine	CLOZARIL	TABLET	Y
lurasidone HCl	LATUDA	TABLET	Y
olanzapine	OLANZAPINE	TABLET	Y
olanzapine	ZYPREXA	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE	TABLET	Y
quetiapine fumarate	SEROQUEL	TABLET	Y
risperidone	RISPERDAL	SOLUTION	Y
risperidone	RISPERIDONE	SOLUTION	Y
risperidone	RISPERDAL	TABLET	Y
risperidone	RISPERIDONE	TABLET	Y
aripiprazole	ARIPIPRAZOLE	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	TAB SENSPT	V
aripiprazole	ABILIFY	TABLET	V
aripiprazole	ARIPIPRAZOLE	TABLET	V
brexpiprazole	REXULTI	TABLET	V
clozapine	VERSACLOZ	ORAL SUSP	V
clozapine	CLOZAPINE ODT	TAB RAPDIS	V
clozapine	FAZACLO	TAB RAPDIS	V
olanzapine	OLANZAPINE ODT	TAB RAPDIS	V
olanzapine	ZYPREXA ZYDIS	TAB RAPDIS	V
paliperidone	INVEGA	TAB ER 24	V
paliperidone	PALIPERIDONE ER	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	CAPSULE	V
pimavanserin tartrate	NUPLAZID	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE ER	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	TAB24HDSPK	V
risperidone	RISPERIDONE ODT	TAB RAPDIS	V
ziprasidone HCl	GEODON	CAPSULE	V
ziprasidone HCl	ZIPRASIDONE HCL	CAPSULE	V

First Generation Antipsychotics

Generic	Brand	Form	PDL
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ELIXIR	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	TABLET	Y
fluphenazine HCl	PROLIXIN	TABLET	Y
haloperidol	HALOPERIDOL	TABLET	Y
haloperidol lactate	HALOPERIDOL LACTATE	ORAL CONC	Y
loxapine succinate	LOXAPINE	CAPSULE	Y
perphenazine	PERPHENAZINE	TABLET	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL CONC	Y
thioridazine HCl	THIORIDAZINE HCL	TABLET	Y
thiothixene	THIOTHIXENE	CAPSULE	Y
thiothixene HCl	THIOTHIXENE HCL	ORAL CONC	Y
trifluoperazine HCl	STELAZINE	TABLET	Y
trifluoperazine HCl	TRIFLUOPERAZINE HCL	TABLET	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	TABLET	V
chlorpromazine HCl	THORAZINE	TABLET	V
loxapine	ADASUVE	AER POW BA	V
pimozide	ORAP	TABLET	V
pimozide	PIMOZIDE	TABLET	V

Parenteral Antipsychotics

Generic	Brand	Form	PDL
aripiprazole	ABILIFY MAINTENA	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	SUSER VIAL	Y
aripiprazole lauroxil	ARISTADA	SUSER SYR	Y
aripiprazole lauroxil,submicr.	ARISTADA INITIO	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	AMPUL	Y
chlorpromazine HCl	THORAZINE	AMPUL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALDOL DECANOATE 50	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	VIAL	Y
haloperidol lactate	HALDOL	AMPUL	Y
haloperidol lactate	HALOPERIDOL LACTATE	AMPUL	Y

haloperidol lactate	HALOPERIDOL LACTATE	SYRINGE	Y
haloperidol lactate	HALOPERIDOL LACTATE	VIAL	Y
risperidone	PERSERIS	SUSER SYKT	Y
risperidone microspheres	RISPERDAL CONSTA	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	SYRINGE	Y
trifluoperazine HCl	STELAZINE	VIAL	Y
olanzapine	OLANZAPINE	VIAL	V
olanzapine	ZYPREXA	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	VIAL	V
ziprasidone mesylate	GEODON	VIAL	V

Appendix 2: New Comparative Clinical Trials

A total of 70 citations were manually reviewed from the initial literature search. After further review, 68 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Nicol et al.[10]	Oral aripiprazole vs. oral olanzapine vs. oral risperidone	Anti-psychotic-naïve youths aged 6 to 18 years diagnosed with 1 or more psychiatric disorders and clinically significant aggression n=144	Percentage of total body fat measured by DXA and insulin sensitivity in muscle measured via hyperinsulinemic clamps with stable isotopically labeled tracers over 12 weeks.	From baseline to week 12, DXA percentage total body fat increased by 1.81% (95% CI 0.91 to 2.71; p <0.001) for risperidone, 4.12% (95% CI 3.16 to 5.08; p<0.001) for olanzapine, and 1.66% (95% CI 0.86 to 2.46; p <0.001) for aripiprazole. Increased in total body fat was significantly greater for olanzapine than risperidone or aripiprazole. From baseline to week 12, insulin-stimulated change in glucose rate of disappearance increased by 2.30% (95% CI -24.04 to 28.64; p=0.87) for risperidone and decreased by 29.34% for olanzapine (95% CI -58.53 to -0.15; p=0.06) and 30.26% (95% CI -50.55 to -9.97; p=0.006) for aripiprazole, with no significant difference across medications.
Calabrese et al.[11]	Aripiprazole 400mg IM once monthly vs. placebo	Adults with bipolar I disorder stabilized on oral aripiprazole N=266	Time to recurrence of any hospitalization over 52 weeks.	AOM 400 significantly delayed the time to hospitalization for any mood episode compared with placebo (log-rank test, P=0.0002) with a recurrence rate of 2.3% (n=3) for the AOM 400 group versus 13.5% (n=18) for placebo. AOM 400 treatment led to more than 85% reduction in risk of recurrence defined by hospitalization over 1 year compared with placebo (HR 0.14; 95% CI 0.04–0.47; p=0.0002).

Abbreviations: AOM = Aripiprazole once a month; CI = Confidence Interval; DXA= dual-energy x-ray absorptiometry; HR = hazard ratio

Appendix 3: Abstracts of Comparative Clinical Trials

Nicol GE, Yingling MD, Flavin KS, et al. Metabolic Effects of Antipsychotics on Adiposity and Insulin Sensitivity in Youths: A Randomized Clinical Trial. JAMA psychiatry. 2018;75(8):788-796.

Objective: To characterize the metabolic effects of first exposure to antipsychotics in youths using criterion standard assessments of body composition and insulin sensitivity.
Design, Setting, and Participants: This randomized clinical trial recruited antipsychotic-naive youths aged 6 to 18 years in the St Louis, Missouri, metropolitan area who were diagnosed with 1 or more psychiatric disorders and clinically significant aggression and in whom antipsychotic treatment was considered. Participants were enrolled from June 12, 2006, through November 10, 2010. Enrolled participants were randomized (1:1:1) to 1 of 3 antipsychotics commonly used in children with disruptive behavioral disorders and evaluated for 12 weeks. Data were analyzed from January 17, 2011, through August 9, 2017.
Interventions: Twelve weeks of treatment with oral aripiprazole (n = 49), olanzapine (n = 46), or risperidone (n = 49).
Main Outcomes and Measures: Primary outcomes included percentage total body fat measured by dual-energy x-ray absorptiometry (DXA) and insulin sensitivity in muscle measured via hyperinsulinemic clamps with stable isotopically labeled tracers. Secondary outcomes included abdominal adiposity measured by magnetic resonance imaging (MRI) and adipose and hepatic tissue insulin sensitivity measured via clamps with tracers.
Results: The intention-to-treat sample included 144 participants (98 males [68.1%]; mean [SD] age, 11.3 [2.8] years); 74 (51.4%) were African American, and 43 (29.9%) were overweight or obese at baseline. For the primary outcomes, from baseline to week 12, DXA percentage total body fat increased by 1.18% for risperidone, 4.12% for olanzapine, and 1.66% for aripiprazole and was significantly greater for olanzapine than risperidone or aripiprazole (time by treatment interaction $P < .001$). From baseline to week 12, insulin-stimulated change in glucose rate of disappearance increased by 2.30% for risperidone and decreased by 29.34% for olanzapine and 30.26% for aripiprazole, with no significant difference across medications (time by treatment interaction, $P < .07$). This primary measure of insulin sensitivity decreased significantly during 12 weeks in the pooled study sample (effect of time, $F = 17.38$; $P < .001$). For the secondary outcomes from baseline to week 12, MRI measured abdominal fat increased, with subcutaneous fat increase significantly greater for olanzapine than risperidone or aripiprazole (time by treatment, $P = .003$). Behavioral improvements occurred with all treatments.
Conclusions and Relevance: Adverse changes in adiposity and insulin sensitivity were observed during 12 weeks of antipsychotic treatment in youths, with the greatest fat increases on olanzapine. Such changes, likely attributable to treatment, may be associated with risk for premature cardiometabolic morbidity and mortality. The results inform risk-benefit considerations for antipsychotic use in youths.

Calabrese JR, Sanchez R, Jin N, et al. Symptoms and functioning with aripiprazole once-monthly injection as maintenance treatment for bipolar I disorder. Journal of Affective Disorders.227:649-656.

Background: Effects of maintenance treatment with aripiprazole once-monthly 400 mg (AOM 400) on symptoms and functioning were assessed in adults with bipolar I disorder (BP-I) after a manic episode.
Methods: Patients were stabilized on oral aripiprazole, cross-titrated to AOM 400, then randomized in a 52-week, double-blind, placebo-controlled, withdrawal phase. Prespecified secondary outcomes are reported: time to hospitalization for mood episode, Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression–Bipolar scale, Functioning Assessment Short Test (FAST), and Brief Quality of Life in Bipolar Disorder questionnaire. Time to hospitalization for mood episode was analyzed using log-rank test and changes from baseline using mixed model for repeated measures or analysis of covariance.
Results: AOM 400 significantly increased time to hospitalization for any mood episode versus placebo (P=0.0002). YMRS total scores decreased with oral aripiprazole; improvements were maintained with AOM 400. After randomization, YMRS scores changed little with AOM 400 but worsened with placebo (P=0.0016), and MADRS scores, already low at trial initiation, did not differ between groups. FAST score improvements were maintained with AOM 400 but not placebo (P=0.0287).
Limitations: Results are generalizable to patients with BP-I stabilized on aripiprazole following a manic episode.
Conclusions: Patients with BP-I experiencing an acute manic episode exhibited symptomatic and functional improvements during stabilization with oral aripiprazole and AOM 400 that were maintained with continued AOM 400 treatment but not placebo. AOM 400 is the first once-monthly long-acting injectable antipsychotic to demonstrate efficacy in maintenance treatment of the manic phase of BP-I.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 4 2018 & Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 8, 2019

1 exp CHLORPROMAZINE/	1567
2 exp HALOPERIDOL/	5577
3 exp FLUPHENAZINE/	285
4 exp ARIPIPRAZOLE/	1984
5 exp Paliperidone Palmitate/	663
6 exp RISPERIDONE/	5334
7 olanzapine.mp.	7991
8 exp PERPHENAZINE/	243
9 exp Trifluoperazine/	573
10 exp Thioridazine/	392
11 exp THIOTHIXENE/	17
12 exp LOXAPINE/	188
13 exp PIMOZIDE/	271
14 exp CLOZAPINE/	5533
15 exp Quetiapine Fumarate/	2435
16 asenapine maleate.mp.	15
17 exp Lurasidone Hydrochloride/	170
18 ziprasidone HCl.mp.	6
19 brexpiprazole.mp.	101
20 cariprazine.mp.	118
21 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	26144
22 limit 21 to (English language and full text and last year)	237
23 limit 22 to 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 guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	70

Appendix 5: Prior Authorization Criteria

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339	~~For Seroquel XR® only,~~ Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	
Bipolar Mania	F3010; F339; F3110-F3113; F312	
Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

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

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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		
5. What diagnosis is being treated?	Record ICD10 code	
6. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
7. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
8. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
9. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
10. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *9/18 (DM); 3/18; 01/17*
Implementation: *4/1/17*