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, February 2, 2023 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
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 in accordance with Oregon Revised Statute 183.333.

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Election of Chair and Vice Chair	R. Citron (OSU)
	D. Approval of Agenda and Minutes	R. Citron (OSU)
	E. Department Update	A. Gibler (OHA)
	F. Legislative Update	D. Weston (OHA)
1:25 PM	II. CONSENT AGENDA TOPICS	TBD (Chair)
	A. PDL Old Business: Inhaled Anticholinergics	
	B. Pharmacy and Therapeutics Evidence Methods	
	C. Pharmacy and Therapeutics Policy and Procedures	
	D. Oncology Prior Authorization Updates	
	E. Orphan Drug Policy Updates	
	1. Public Comment	
1:30 PM	III. DUR ACTIVITIES	
	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	L. Starkweather (Gainwell)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Review	K. Sentena (OSU)
	1. Antimicrobial Stewardship	
	2. An Update in Lipid Lowering Therapies	
	3. COVID-19 Vaccine Bivalent Boosters	

IV. PREFERRED DRUG LIST NEW BUSINESS

2:00 PM	A. GnRH Antagonists PA Update	D. Moretz (OSU)
	1. Prior Authorization Criteria	

2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:05 PM B. Antidepressant Class Update
1. Class Update/Prior Authorization Criteria — K. Sentena (OSU)
2. MHCAG Treatment Algorithms for Depression — A. Gibler (OHA)
3. Public Comment
4. Discussion and Clinical Recommendations to OHA

2:25 PM C. Spinal Muscular Atrophy DERP report — D. Moretz (OSU)
1. DERP report/Prior Authorization Criteria
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:45 PM BREAK

3:00 PM D. Medications for Substance Use Disorders, Opioid & Alcohol
1. SUD Literature Scan/Prior Authorization Criteria — D. Moretz (OSU)
2. Buprenorphine for Pain Indication Review — S. Servid (OSU)
3. Public Comment
4. Discussion and Clinical Recommendations to OHA

3:25 PM E. Biologics for Rare Conditions Class Update — D. Moretz (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

3:55 PM V. EXECUTIVE SESSION

4:50 PM VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

Drug Use Research & Management Program
OHA Health Policy & Analytics
Office of Delivery System Innovation
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Dental3	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2025
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2025
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2025

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, December 1st, 2022 1:00 - 5:00 PM

Via Zoom webinar

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 in accordance with Oregon Revised Statute 183.333

Members Present: Stacy Ramirez, PharmD; Bill Origer, MD; Mark Helm, MD; Cat Livingston, MD; Tim Langford, PharmD; Robin Moody, MPH; Russ Huffman, PMHNP; Eddie Saito, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Kathy Sentena, PharmD; Lan Starkweather, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH; Deborah Weston, JD; Jessica Ickes, MPA; Liz Stuart, MPH

Audience: Amy Burns, AllCare CCO; Brandie Feger, Advanced Health CCO; Georgette Dzwilewsk, Indivior; Janine Fournier, Jason Kniffin; Jim Slater, CareOregon; Kevin Gallagher, Fennec Pharmaceuticals; Lori McDermott, Viking HCS; Marc Rueckert, Argenx; Mark Kantor, AllCare CCO; Matt Metcalf, CSL Vifor; Melissa Snider, Gilead; Michael Foster, BMS; Norm Navarro, Providence Health Plan; Rick Frees, Vertex Pharmaceutical; Rochelle Yang, Teva; Saghi Maleki, Takeda Pharmaceuticals; Sydney Thomas, AllCare/APPE student; Tiffany Jones, Pacificsource; Tiina Andrews, UHA; Tom Telly, Supernus; Andrea Willcuts; Idorsia

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I. CALL TO ORDER

A. Roll Call & Introductions
   - Called to order at approx. 1:05 p.m., introductions by Committee and staff
B. Conflict of Interest Declaration – no new conflicts of interest were declared
C. Approval of Agenda and October 2022 Minutes presented by Roger Citron
   ACTION: Motion to approve, 2nd, all in favor with one abstention
D. Department Update provided by Andrew Gibler, PharmD

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E. Recognition of Dr. Helm provided by Trevor Douglass, DC

II. CONSENT AGENDA TOPICS

A. **Quarterly Utilization Report**
B. **Oncology Prior Authorization (PA) Updates**
Recommendation:
- Add: Lytgobi® (futibatinib); Tecvayli™ (teclistamab-cqyv); and Imjudo® (tremelimumab) to Table 1 in the Oncology Agents prior authorization (PA) criteria
C. **Orphan Drug Policy Updates**
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Pedmark® (sodium thiosulfate) based on FDA-approved labeling
ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVITIES

A. **ProDUR Report**: Lan Starkweather, PharmD
B. **RetroDUR Report**: Dave Engen, PharmD
C. **Oregon State Drug Review**: Kathy Sentena, PharmD
- **Asthma Guidance Update with a Focus on Changes for Managing Patients with Mild Asthma**
- **Population Trends in the Use of Migraine Preventative Treatments**

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

IV. DUR NEW BUSINESS

A. **Polypharmacy Drug Utilization Evaluation:** Dave Engen, PharmD
Recommendation:
- No policy changes are recommended
ACTION: Motion to approve, 2nd, all in favor

B. **Early Periodic Screening, Diagnostic and Treatment (EPSDT) Program PA Criteria Update:** Sara Fletcher, PharmD; Jessica Ickes, MPA; Liz Stuart, MPH
Recommendations:

- Update all PA criteria to support individualized review for members younger than 21 years of age who have an unfunded diagnosis, to evaluate whether medically appropriate and necessary
- In the absence of more specific criteria already approved by P&T, standard definitions for medically appropriate and necessary use will include:
  - FDA-approved or compendia-supported indication;
  - Trial and failure, contraindication, or intolerance to at least 2 preferred products (when available in the class);
  - and Documentation that the disease is of sufficient severity that it impact's the patient's health

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

V. DUR OLD BUSINESS

A. **Sedatives PA Criteria Update:** Sarah Servid, PharmD

Recommendations:

- Update PA criteria to limit sedative use to 30 days and encourage use of cognitive behavioral therapy for insomnia.

ACTION: The Committee recommended adding language regarding the member being unable to access such therapy and to explore options to auto-approve a short-term supply

Motion to approve, 2nd, all in favor

VI. PREFERRED DRUG LIST NEW BUSINESS

A. **Growth Hormone PA Criteria Update:** Dave Engen, PharmD

Recommendations:

- Update the growth hormone PA criteria to align with HERC coverage guidance and FDA-approved indications
- Evaluate costs in executive session

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

B. **Drugs for Asthma/COPD Class Update:** Kathy Sentena, PharmD

Recommendations:

- No Preferred Drug List (PDL) changes recommended based on review of recently published evidence
- Update PA criteria to align with current guidelines

- Retire ICS/LABA specific criteria and subject non-preferred therapies to general PA criteria for non-preferred products
- Evaluate costs in executive session

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

C. **Influenza Class Update:** Sara Fletcher, PharmD

Recommendations:

- No PDL changes recommended based on review of recently published evidence
- Update PA criteria with expanded indications and age ranges for peramivir and baloxavir
- Evaluate costs in executive session

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

D. **Topical Products for Inflammatory Skin Conditions Class Update and New Drug Evaluations**: Deanna Moretz, PharmD

Recommendations:

- Update PA criteria to include use of ruxolitinib in patients 12 years and older, meeting HERC guidance for severe nonsegmental vitiligo, or having hand, foot, face, or mucous membrane involvement
- Designate roflumilast and tapinarof non-preferred on the PDL and subject to the PA criteria limiting use to:
  - Individuals meeting HERC guidance for severe plaque psoriasis or those having hand, foot, face, or mucous membrane involvement and,
  - FDA-approved ages and,
  - History of inadequate response to at least 2 moderate-to-high potency topical corticosteroids for at least 4 weeks
- Update PA criteria to remove PA for preferred products and accommodate individual review under EPSDT
- Combine the "Topical Anti-Psoriatic" class in with the "Topical Agents for Inflammatory Skin Conditions" class
- Evaluate costs in Executive Session

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

VII. EXECUTIVE SESSION

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Members Present: Stacy Ramirez, PharmD; Bill Origer, MD; Mark Helm, MD; Tim Langford, PharmD; Robin Moody, MPH; Russ Huffman, PMHNP; Eddie Saito, PharmD

Staff Present: Sarah Servid, PharmD; Deanna Moretz, PharmD; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Lan Starkweather, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD

VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Growth Hormone PA Criteria Update
Recommendation: Make Nutropin AQ® Nuspin non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. Drugs for Asthma/COPD Class Update
Recommendations: Make Combivent Respimat® non-preferred and Spiriva Respimat® preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

C. Influenza Class Update
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

D. Topical Products for Inflammatory Skin Conditions Class Update and New Drug Evaluations
Recommendations: Make tazarotene gel non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

VIII. ADJOURN

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Drug Class Update: Inhalers for Asthma/COPD

Date of Review: December 2022

Date of Last Review: Inhaled anticholinergics (Oct 2021)
Short-acting beta agonists (July 2019)
Other inhalers (Oct 2020)

Dates of Literature Search: 01/01/2020 - 10/03/2022

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

Plain Language Summary:

- This review looks at new evidence for medicines that are inhaled to treat people that have lung diseases called asthma and chronic obstructive pulmonary disease (COPD). These medicines work in several different ways. Groups of medicines that work the same way are put into the same category that are called classes. Classes include:
  - Medicines that help to quickly open up the lungs (called fast-acting beta-agonists [FABA])
  - Medicines that help to reduce swelling to open up the lungs (called an inhaled corticosteroid [ICS])
- New evidence shows that people who used both a FABA and ICS were able to breathe normaly, needed less additional medication to treat their asthma, and went to the hospital or urgent care for treatment less frequently than when people used placebo or other asthma treatments.
- In people with COPD, an inhaled medicine that combines three classes of medicines helped people breathe better than inhalers that contained only two classes of medicines. The product with 3 classes includes the medicines budesonide, glycopyrronium and formoterol fumarate compared to inhalers with only two of these medicines.
- New evidence shows that people with mild COVID-19 symptoms who were not vaccinated and used an ICS inhaler needed to go to the hospital less often than people who did not use an ICS.
- A new study compared 2 different FABA and ICS combination inhalers called formoterol/ICS and salmeterol/ICS. People who took these medicines had similar risk of severe side effects.
- The National Asthma Education Prevention Program Coordinating Committee (NAEPPCC) recommends that people with asthma use the combination of ICS-formoterol if they:
  - require medicine occasionally when they have trouble breathing or
  - have symptoms more often and require daily treatment with medicine.
- The Drug Use Research and Management Group (DURM) recommends no changes to our current policy for inhaled therapies used for people with asthma and COPD.

Author: Kathy Sentena, PharmD

Purpose for Class Update:
The purpose of this update is to review new literature on effectiveness and safety of asthma and COPD inhaled therapies published since the last reviews.

Research Questions:
1. What is the comparative efficacy for asthma and COPD maintenance medications for important outcomes such as symptoms, lung function, hospitalizations and mortality?
2. What is the evidence for harms associated with asthma and COPD maintenance medications?
3. Are there subpopulations of patients based on demographics (e.g., age, racial groups, gender), comorbidities (drug-disease interactions), or other medications (drug-drug interactions) for which treatments for asthma or COPD are better tolerated or more effective?

Conclusions:
- There were 4 high-quality systematic reviews, 3 new guidelines, 2 randomized controlled trials (RCTs) and 4 new formulations identified for this review.
- Evidence for the use of budesonide 182 mcg plus glycopyrronium 8.2 mcg plus formoterol fumarate 5.8 mcg (BGF) in people with COPD was evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH). There was moderate quality of evidence that BGF reduced the rate of moderate to severe COPD exacerbations compared with glycopyrronium 14.4 mcg plus formoterol fumarate 9.6 mcg (GFF) and budesonide 320 mcg plus formoterol fumarate 9.6 mcg (BFF) at 52 weeks and improved FEV_1 at 24 weeks when compared to GFF and BFF. The changes were Results were not clinically significant for this comparison.[1] There is insufficient direct evidence which compares this product to other triple therapy inhalers; however, indirect comparison suggest similar efficacy and safety.
- A high quality systematic review and meta-analysis evaluated the use of FABA and ICS inhalation in patients with mild asthma. The single combination inhaler of FABA/ICS reduced asthma exacerbations requiring steroids (high quality evidence), hospital admissions or unscheduled healthcare visits (low quality of evidenced), and exposure to systemic corticosteroids compared to FABA, taken as needed (low quality evidence). When compared to ICS, the use of FABA/ICS demonstrated reductions in asthma-related hospital admissions or unscheduled heath care visits (low quality of evidence).[2]
- Patients with mild COVID-19 treated with ICS, in addition to standard of care (e.g., antipyretics and antibiotics if bacterial pneumonia was suspected), had a reduced risk of hospital admission or death up to day 30.[3] Incidence of admission or death was 57 per 1000 people treated with ICS compared to standard of care (incidence 79 per 1000 people treated; relative risk [RR] 0.72; 95% confidence intervals [CI], 0.51 to 0.99) based on moderate quality evidence.[3]
- A high quality systematic review and meta-analysis evaluated risk of death and severe adverse reactions associated with formoterol/ICS compared to salmeterol/ICS.[4] There was insufficient evidence to make conclusions on mortality outcomes due to low incidence of events. Based on data for all-cause non-fatal serious events, there is probably no difference in safety profiles between formoterol/ICS compared to salmeterol/ICS (moderate quality evidence).
- New guidance from the National Asthma Education Prevention Program Coordinating Committee (NAEPPCC) recommends the use of single-inhaler ICS-formoterol both daily and as needed for individuals 4 years and older with moderate persistent asthma.[5] This single inhaler regimen is referred to as "single maintenance and reliever therapy (SMART)". Long acting muscarinic antagonists (LAMAs) are recommended in addition to an ICS in people 12 years and older who have uncontrolled persistent asthma who cannot tolerate ICS-long-acting beta-agonist (LABA).[5] The addition of LAMA is also indicated in individuals using ICS-LABA and still experiencing symptoms.[5]
- The Global Initiative for Asthma (GINA), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 and US Preventative Services Task Force (USPSTF) updates support current policy.[6,7,8]
- There is insufficient evidence for the use of inhaled therapies for asthma and COPD in non-white people and in Medicaid populations.

Recommendations:

- No changes recommended based on the review of the current evidence.
- The prior authorization (PA) criteria will be updated to align with current guideline recommendations. Recommend retiring the ICS/LABA specific criteria and making non-preferred therapies subject to general PA for non-preferred products.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- Literature for inhaled anticholinergics was last evaluated in October 2021. At the time, the NAEPPCC Expert Panel recommended the use of LAMAs in patients with asthma and conditionally recommended adding LAMA to ICS controller therapy instead of continuing the same dose of ICS alone (conditional recommendation; moderate certainty of evidence). After executive session Combivent®, Respimat®, and Incruse Ellipta® were made preferred.
- Evidence for short acting beta agonists (SABA) was reviewed July of 2019. In certain groups with asthma, the use of SABA with anticholinergics may reduce hospitalization rates when presenting to an emergency room compared to SABA use alone. No changes in policy were made.
- A list of preferred therapies are available in **Appendix 1**. All classes have PA criteria for non-preffered therapies. The LABAs require step-therapy prior to coverage of non-preferred LABA and LABA/ICS products for patients with asthma and COPD. There is PA criteria for all LAMA/LABA and LAMA/LABA/ICS products.
- The inhaled therapies for asthma and COPD are comprised of 7 classes: anticholinergics, SABAs, LABAs, ICS, ICS/LABAs, and LAMA/LABA combinations. The inhaled therapies account for a significant cost to the Oregon Health Authortiy. Compliane to the PDL ranges from a low of 25% for the LABA class to 100% for SABAs.

Background:

ASTHMA

Asthma is a chronic inflammatory condition of the lungs resulting in airway obstruction, bronchial hyperresponsiveness and airway edema. Genetics and environmental factors are thought to contribute to asthma development. Centers for Disease Control and Prevention data from 2018 reports the burden of asthma in Oregon to be over 11%.[9] Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis is confirmed by spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after SABA use), airway obstruction that is at least partially reversible and exclusion of other potential diagnoses.[6] Asthma is characterized as being intermittent or persistent (and further divided into mild, moderate or severe). The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma. In particular, those patients with eosinophil asthma Type 2 (T2)-high, which indicates high levels of T-helper type 2 lymphocytes, respond well to ICS therapy and biologic therapy if asthma remains uncontrolled. Patients with eosinophilic asthma also have high levels of sputum eosinophils, and while a correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines typically diagnose eosinophilic asthma when blood eosinophils are greater than or equal to 150 cells/µL.[6] Studies of biologic therapies have evaluated use in patients with eosinophil levels of at least 150 cells/µL to more than 400 cells/µL.

Asthma treatment can be categorized as quick-relief medication and long-term control medications. Asthma treatment is inititated in a stepwise manner based on the severity of asthma symptoms.[6] Evidence demonstrates that even people with mild asthma can be at risk of exacerbations; therefore, several guidelines recommend the use of ICS-formoterol as a controller and reliever therapy, also referred to as SMART (single maintenance and reliever therapy) or MART (maintenance and reliever therapy).[5] ICS, alone or in combination, are the preferred maintenance therapy for all patients with persistent asthma.[5] If additional therapy is required to control asthma symptoms, LABAs are recommended in combination with ICS.[6] Other maintenance therapy options include leukotriene

inhibitors, methylxanthines, cromolyn sodium and nedocromil. Fast-acting beta-agonists, ICS-formoterol, anticholinergics and systemic corticosteroids are recommended for acute symptom management. Biologic asthma treatments are recommended for those patients with severe asthma that is unresponsive to controller-drug therapy.[6]

Outcome measures used in asthma trials are forced expiratory volume in one minute (FEV_1), asthma exacerbations, hospitalization, emergency room visits, and need for oral corticosteroids. Change from baseline in FEV_1 is a common surrogate endpoint used in clinical trials and clinical practice since it is highly reproducible. Research in COPD patients suggest that minimally important FEV_1 changes range from 100-140 mL.[6] Moderate-quality evidence suggests that targeting interventions for asthma based on sputum eosinophil levels in people with severe asthma that is difficult to treat may reduce the number and severity of asthma attacks in adults; however, additional research is needed.[6] The Asthma Control Questionnaire (ACQ) is used to determine symptom control. Scores range from 0-6 with higher scores indicative of worse asthma. The ACQ-5 consists of 5 questions that are averaged for a score. MCID for the ACQ-5 is a change of 0.5 points.[6]

COPD

Chronic obstructive pulmonary disease is a chronic respiratory disorder characterized by reduced expiratory flow due to irreversible airway inflammation. Airway narrowing, hyperinflation and impaired gas exchange are pathological changes associated with COPD. Chronic bronchitis and emphysema are often associated with COPD.[1] The most common cause of COPD is airway irritation, usually from cigarette smoking. In rare cases, alpha-1 antitrypsin (AAT) deficiency has been implicated in the development of early onset COPD.

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of $FEV_1/FVC < 0.70$), symptom severity, risk of exacerbations and comorbidities.[1] COPD is classified into four stages based on spirometric measurements of FEV_1/FVC: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (very severe). The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines recommend therapeutic approaches based on disease burden (e.g., breathlessness, exercise limitations, health status and risk of exacerbations) as well as FEV_1. Patients are classified into groups A-D (low to high risk of symptoms and exacerbations).[1] This type of classification system shifts the focus from only FEV_1 measurements as these are not always indicative of COPD status.[7]

Common treatment options for patients with COPD are bronchodilators and antimuscarinic drugs (LABAs and LAMAs). For patients who require additional therapy, the combination of a LABA and LAMA is often used.[1] Triple therapy with a LABA, LAMA and ICS is recommended for those with COPD and sustained symptoms despite dual therapy.[1] Bronchodilators (short and long-acting) have demonstrated improvements in FEV_1 and symptom improvement. Long-acting bronchodilators (LAMAs and LABAs) improve lung function, dyspnea, health status and reduce exacerbation rates. Inhaled corticosteroids/LABAs have been shown to improve health status, reduce exacerbations and improve lung function compared to ICS monotherapy. Conclusive evidence of benefit has not been demonstrated with ICS alone in patients with COPD. Phosphodiesterase-4 inhibitors have a role in COPD management by minimizing airway narrowing and damage due to inflammation. Phosphodiesterase-4 inhibitors are used as add-on therapy for patients with COPD who have persistent symptoms or exacerbations despite optimal treatment with other COPD therapies. There is a lack of conclusive benefit for improved survival rates with any of the inhaled respiratory medications used in the management of COPD, and no medications have shown a preventative effect in the decline of lung function.[7]

Goals of therapy for COPD management are to improve symptoms, reduce frequency of exacerbations, improve exercise tolerance and daily activities and reduce mortality.[1] Important outcomes to access the effectiveness of therapies include: lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, mortality and adverse events. FEV_1 is the most common surrogate outcome used in studies to determine therapy effectiveness. The minimal clinically

important difference (MCID) in FEV_1 values for COPD changes have not been clearly defined, but Cochrane reviews recommend a change of 100 mL.[7] Other sources suggest a change in percent predicted FEV_1 of 10.38% or more would correlate with a MCID.[7] The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on quality of life with scores ranging from 0-100 and higher scores indicative of more limitations. The MCID for the SGRQ is a change of 4 units.[7] The transitional dyspnea index (TDI) is a measurement of breathlessness in people with COPD. A score change of 1 unit has been shown to be clinically meaningful. Symptom are also accessed by the Modified British Medical Reasearch Council (mMRC) questionnaire which is a scale measuring dyspnea and the COPD Assessment Test (CAT) which evaluates a range of symptoms from cough to energy.[10] Smoking cessation is the only intervention shown to reduce the rate of lung function decline.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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:
<u>CADTH- Budesonide-Glycopyrronium-Formoterol Fumarate Reimbursement Review</u>
CADTH evaluated the clinical efficacy of the combination product budesonide, glycopyrronium and formoterol fumarate (BGF) for long-term maintenance treatment of patients with COPD.[1] A systematic review of the clinical benefits and adverse events of BGF identified 2 RCTs for evaluation (ETHOS and KRONOS).[11,12] Relevant outcomes of significance were COPD exacerbations, symptom relief, and incidence of chronic bronchitis and/or emphysema. Results for exacerbation outcomes are presented in **Table 1**. In the KRONOS study, the primary outcome was FEV_1 area under the curve (AUC) from 0-4 hours for BGF versus BFF, GFF or versus BUD-FOR comparisons. Change from baseline in morning pre-dose trough FEV_1 was higher for BGF compared to GFF and for BGF compared to BUD/FORM.[1] For the secondary outcome of use of rescue medications, the difference was not statistically different in KRONOS between groups but was reduced with the use of BGF in ETHOS when compared to GFF and BFF. Between group difference in SGRQ scores were not clinically significant. In ETHOS, there was a reduced risk of mortality with BGF compared to GFF (HR 0.51; 95% CI, 0.330 to 0.80) with no differences compared to BFF.[1] Mortality was not measured in KRONOS. Adverse events were similar between groups. The most common events were nasopharyngitis, and upper respiratory tract infection. Serious adverse events were reported in approximately 20% of patients treated in ETHOS and 9% treated in KRONOS.[1]

Both studies had high rates of discontinuations due to adverse events (6.1% in ETHOS and 4.25% in KRONOS) and missing data.[1] Additional limitations were under enrollment of females and lower use than expected of the LAMA-LABA combination inhaler (14%) at baseline and the overall magnitude of benefit was small for the use of triple inhalation combination therapy.

Table 1. Description of Randomized Comparative Clinical Trials.[1,11,12]

Study	Comparison	Population	Outcome	Results	Notes/Limitations
ETHOS DB, MC, PG	1. BGF MDI 2. GFF MDI 3. BFF MDI 52 week duration	Patients with moderate to very severe COPD and at least 1 exacerbation in the last year N=8,588	Moderate to severe COPD exacerbations*	Adjusted rate: 1. 1.08 2. 1.42 3. 1.24 <u>BGF vs. GFF</u> RR 0.76 (95% CI, 0.69 to 0.83) <u>BGF vs. BFF</u> RR 0.87 (95% CI, 0.79 to 0.95)	- BGF was more effective than GFF and GFF at reducing COPD exacerbations
			Lung function (FEV_1 AUC_{0-4h} mL)‡	<u>BGF vs. GFF</u> LSM 22 mL (95% CI, 4 to 39)	- Differences between groups were not clinically meaningful
			Symptoms (based on TDI focal score)	<u>BGF vs. GFF</u> 0.40 units (95% CI, 0.24 to 0.55) <u>BGF vs. BFF</u> 0.31 units (95% CI, 0.15 to 0.46)	- Symptom improvement was higher with BGF compared to GFF and BFF but the difference was not considered clinically meaningful
KRONOS DB, MC, PG	1. BGF MDI 2. GFF MDI 3. BFF MDI 4. BUD-FOR DPI (400 mcg-12 mcg active control) open-label 24 week duration	Symptomatic patients with moderate to very severe COPD N=1,902	Moderate to severe COPD exacerbations	Adjusted rate: 1. 0.46 2. 0.95 3. 0.56 4. 0.55 <u>BGF vs. GFF</u> RR 0.48 (95% CI, 0.37 to 0.64); P<0.0001 <u>BGF vs. BFF</u> RR 0.82 (95% CI, 0.58 to 1.17); P=0.2792 <u>BGF vs. BUD-FOR</u> RR 0.83 (95% CI, 0.59 to 1.18); P=0<0.0001 <u>BGF vs. BUD-FOR</u> RR 0.83 (95% CI, 0.59 to 1.18); P=0.3120	- All comparisons were prespecified superiority analysis with the exception of BFF MDI vs. BUD/FORM DPI which was prespecified as a non-inferiority analysis

			Lung function* (FEV_1 $AUC_{0\text{-}4h}$ mL)	1. 305 mL 2. 288 mL 3. 201 mL 4. 214 mL <u>BGF vs. GFF</u> LSM 16 mL (95% CI, -6 to 38); P=0.1448 <u>BGF vs. BFF</u> LSM 104 mL (95% CI, 77 to 131); P<0.0001 <u>BGF vs. BUD-FORM</u> LSM 91 mL (95% CI, 64 to 117); P<0.0001	- MCID for FEV_1 $AUC_{0\text{-}4h}$ mL is 0.10 L to 0.14 L so results are clinically significant for BGF vs BFF comparison BGF vs. BUD-FORM
			Change from baseline in morning pre-dose trough FEV_1*	1. 293 mL 2. 125 mL 3. 73 mL 4. 88 mL <u>BGF vs. GFF</u> LSM 22 mL (95% CI, 4 to 39); P=0.0139 <u>BGF vs. BFF</u> LSM 74 mL (95% CI, 52 to 95)†; P<0.0001 <u>BGF vs. BUD-FORM</u> LSM -10 mL (95% CI, -36 to 16); P=0.4390	- BGF increased morning pre-dose trough FEV_1 more than GFF and BFF but not more than BUD-FORM
			Symptoms (based on TDI focal score)	<u>BGF vs. GFF</u> 0.177 units (95% CI, -0.071 to 0.426) <u>BGF vs. BFF</u> 0.237 units (95% CI, -0.068 to 0.542) <u>BGF vs. BUD-FOR</u> 0.461 units (95% CI, 0.156 to 0.766)	- None of the comparison differences were clinically significant.

Key: * Primary outcome; † Prespecified secondary endpoint; ‡ Prespecified substudy population

Abbreviations: $AUC_{0\text{-}4h}$ – area under the curve in 0 to 4 hours; BFF – budesonide 320 mcg plus formoterol fumarate 9.6 mcg; BGF – budesonide 182 mcg plus glycopyrronium 8.2 mcg plus formoterol fumarate 5.8 mcg; FEV_1 – forced expiratory flow in 1 second; GFF – glycopyrronium 14.4 mcg plus formoterol fumarate 9.6 mcg; MCID – minimal clinically important difference; MDI – meter-dose inhaler; RR – rate ratio; TDI – Transitional Dyspnea Index (TDI)

Cochrane – Combination Fixed-dose Beta Agonist and Steroid Inhaler as Required for Adults or Children with Mild Asthma

The efficacy and safety of using a single combination therapy inhaler consisting of a FABA plus ICS for the treatment of mild asthma, as needed for symptoms, was evaluated by Cochrane in 2021. Studies that were at least 12 weeks in duration were included.[2] Single fixed-dose FABA/ICS inhaler as needed was compared to placebo, SABA as needed, ICS with SABA as needed, fixed-dose combination ICS/LABA, or fixed-dose combination ICS/FABA with as needed ICS/FABA. Six studies (n=9,656) were included and all studies used budesonide (200 mcg or 320 mcg) and formoterol (6 or 9 mcg) in a single dry powder inhaler.[2] Two-studies were open-label. Active comparators contained fast-acting bronchodilators terbutaline (0.5 mg per puff or 500 mcg) and formoterol (4.5 mcg per puff) or salbutamol (2 puffs of 100 mcg each/not available in the United States). Four studies included adults and 2 studies included people at least 12 years of age. The mean age of enrolled patients was 36 to 43 years. Overall, the studies were found to be at low risk of bias even with the inclusion of 2 open-label studies.

Results for the comparisons are available in **Table 2**. Combination therapy of FABA/ICS demonstrated reductions in asthma exacerbations requiring steroids, hospital admissions or unscheduled healthcare visits, and exposure to systemic corticosteroids in patients with mild asthma compared to FABA as needed. When compared to ICS the use of FABA/ICS demonstrated reductions in asthma-related hospital admissions or unscheduled heath care visits.[2] There were no clinically meaningful changes in perceived symptom control by patients, as measured by the ACQ-5, for any comparison.

Table 2. Results for Comparison of FABA/ICS to Active Comparators in Patients with Mild Asthma[2]

Treatment	Comparator	Outcome	Result	Strength of Evidence	Comments
FABA/ICS as needed (2 RCTs)	FABA as needed	Exacerbations requiring systemic steroids	OR 0.45 (95% CI, 0.34 to 0.60)	High	Equates to 109 people out of 1000 in the FABA group experiencing an exacerbation compared to 52 out of 1000 people taking FABA/ICS
		Asthma-related hospital admission or emergency-department or urgent care visit	OR 0.35 (95% CI, 0.20 to 0.60)	Low	Results favored FABA/ICS
		Asthma control (based on ACQ-5)*	MD -0.15 points (95% CI, -0.20 to -0.10)	Moderate	Results favored FABA/ICS but did not meet the MCID threshold of a difference of 0.5.
		Inhaled steroid dose	MD 76.50 mcg beclomethasone (the mean ICS dose was 18.7 mcg in the FABA as needed group)	Moderate	Patients treated with a combined therapy containing ICS have a higher daily inhaled steroid dose than those treated with FABA alone
		Total systemic steroid dose	MD 9.90 mg prednisolone lower in FABA/ICS group (the mean total dose in the FABA as needed group was 17.4 mg prednisolone)	Low	Similar between groups since both groups utilized small doses of systemic steroids

		Adverse Events	OR 0.82 (95% CI, 0.71 to 0.95)	Moderate	Fewer adverse events in those taking FABA/ICS as needed
FABA/ICS as needed (4 RCTs)	Maintenance ICS plus as needed FABA	Exacerbations requiring systemic steroids	OR 0.79 (95% CI, 0.59 to 1.07)	Low	Results favored as needed FABA/ICS but was not statistically significant
		Asthma-related hospital admission or emergency-department or urgent care visit	OR 0.63 (95% CI, 0.44 to 0.91)	Low	Results favored as needed FABA/ICS
		Asthma control (based on ACQ-5)*	MD 0.12 points higher	High	Results favored maintenance ICS but change from baseline was not clinically significant
		Inhaled steroid dose	MD 154.51 mcg lower in FABA/ICS group	Moderate	Results favored lower inhaled steroid doses in FABA/ICS group
		Total systemic steroid dose	MD 7 mg prednisolone lower in FABA/ICS group (the mean total dose in the FABA as needed group was 20.97 mg prednisolone)	Moderate	Similar between groups since both groups utilized small doses of systemic steroids
		Adverse Events	OR 0.96 (0.82 to 1.14)	Moderate	Incidence was similar between groups

Key: * Lower scores indicate better asthma control

Abbreviations: ACQ-5 – asthma control questionnaire-5; CI – confidence interval; FABA – fast-acting beta-agonist; ICS – inhaled corticosteroid; MD – mean difference; OR – odds ratio; RCTs – randomized controlled trials

Cochrane – Inhaled Corticosteroids for the Treatment of COVID-19

A 2022 Cochrane review evaluated the safety and efficacy of ICS use for the treatment of COVID-19.[3] Three RCTs, including 3,607 participants, evaluated people with confirmed mild COVID-19. The majority of participants were adults and those over 50 years of age had comorbidities such as hypertension, diabetes, or lung disease. Inhaled corticosteroids studied were budesonide (1600 mcg/day) and ciclesonide (640 mcg/day) and given in addition to usual care. Comparisons were made to standard of care (e.g., antipyretics and antibiotics if bacterial pneumonia was suspected).[3]

The most robust evidence was for the outcomes of hospital admission or death and symptom reduction (all initial symptoms resolved). The use of ICS resulted in a reduced risk of admission to the hospital or death up to day 30 by 57 per 1000 people treated compared to standard of care with 79 per 1000 people treated (RR 0.72; 95% CI, 0.51 to 0.99; moderate-quality evidence).[3] There was moderate-quality evidence that symptom resolution (all initial syptoms resolved) at day 14 occurred in 553 people per 1000 in those using an ICS compared to 465 per 1000 people treated with standard of care (RR 1.19; 95% CI, 1.09 to 1.30).[3] There was low-quality evidence that there was little difference in all-cause mortality and in duration (time) to symptom resolution upon comparison of ICS and standard of care.[3]

Results are mostly applicable to people with mild COVID-19. Studies were completed before the introduction of COVID vaccines so applicability of these results to vaccinated populations is unclear. There is insufficient evidence on adverse reactions, quality of life, and use in people with moderate to severe COVID.

Cochrane – Regular Treatment with Formoterol and an Inhaled Corticosteroid versus Regular Treatment with Salmeterol and an Inhaled Corticosteroid for Chronic Asthma: Serious Adverse Events

A systematic review and meta-analysis published in 2021 evaluated 11,572 adults and 723 children and adolescents with chronic asthma to evaluate formoterol or salmeterol, with an ICS, on mortality and non-fatal serious adverse events.[4] Included studies were at least 12 weeks in duration and randomized patients to either formoterol/budesonide, salmeterol/fluticasone, formoterol/extra-fine beclomethasone, formoterol/mometasone, or salmeterol/budesonide. Most of the included studies had low risk of bias.

There was insufficient evidence to make conclusions on mortality, as the rate of death was low in all studies. Forty-six adults experienced asthma-related severe adverse events.[4] Moderate quality evidence demonstrated no difference between formoterol/ICS versus salmeterol/ICS for the outcomes of all-cause non-fatal serious events in studies lasting 18 to 26 weeks.[4] The specific findings for all-cause non-fatal serious adverse events comparison were:

- formoterol/budesonide versus salmeterol/fluticasone odds ratio (OR) 1.14 (95% CI, 0.82 to 1.59);
- formoterol/beclomethasone versus salmeterol/fluticasone OR 0.94 (95% CI, 0.43 to 2.08) and
- formoterol/mometasone versus formoterol/salmeterol OR 1.02 (95% CI, 0.47 to 2.20).[4]

Limitations include a low number of serious adverse events related to asthma, making it difficult to have high confidence in comparative findings for patients treated with formoterol/ICS and salmeterol/ICS.

After review, nine systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[13–21]

New Guidelines:

High Quality Guidelines:

NAEPPCC – Update on the Asthma Management Guidelines

Guidance for the management of asthma was updated in 2020 by the NAEPPCC.[5] Recommendations were formulated by an Expert Panel using the GRADE framework in conjunction with a methodology team. A systematic review was completed by the Agency for Healthcare Research and Quality Evidence-Based Practice Center. Conflicts of interest (COI) were disclosed and those with a high level of COI were excluded from the Expert Panel. Priority topics were identified and those pertaining to inhaled treatments will be presented.[5]

The intermittent use of ICS and LAMAs for asthma was one of the priority topics included in this update.[5] Recommendations are presented in **Table 3**. A change from previous guidance is the use of ICS-formoterol as a controller and reliever therapy, based on evidence that the combination therapy reduces asthma exacerbations.[5]

Table 3. NAEPP Recommendations for Asthma Management Inhaled Therapies[5]

Recommendation	Age Group	Strength of Recommendation
Recommendations for use of Intermittent ICS for Asthma		
Children that have recurrent wheezing triggered by respiratory tract infections and no wheezing between infections should receive a short course of daily ICS at the onset of a respiratory tract	0-4 years of age	Conditional recommendation, high strength of evidence

infection with an as-needed SABA for quick-relief therapy compared to an as needed SABA only for quick-relief therapy		
Individuals with mild persistent asthma should receive either of the following treatments as part of Step 2 therapy for worsening asthma: 1. Daily low-dose ICS and as-needed SABA for quick-relief therapy OR 2. Intermittent* as-needed SABA and an ICS used concomitantly	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
Individuals with mild to moderate persistent asthma who are likely to be adherent to daily ICS, short-term increases in the ICS dose for increased symptoms or decreased peak flow are NOT recommended	Ages 4 years and older	Conditional recommendation, low strength of evidence
Individuals with moderate to severe persistent asthma should receive ICS-formoterol in a single inhaler‡ used as both daily controller and reliever therapy† compared to either a higher-dose ICS as daily controller therapy and SABA for quick-relief therapy or the same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy	Ages 4 years and older	High certainty of evidence for ages 12 years and older, moderate certainty of evidence for ages 4 to 11 years
Individuals with moderate to severe persistent asthma should receive ICS-formoterol‡ in a single inhaler used as both daily controller and reliever therapy compared to higher-dose ICS-LABA as daily controller therapy and SABA for quick relief therapy	Ages 12 years and older	Conditional recommendation, high strength of evidence
Recommendations for the use of LAMAs for Asthma		
In individuals with uncontrolled persistent asthma, it is not recommended to add LAMA to ICS compared to adding LABA to ICS	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
In individuals not using LABA for uncontrolled persistent asthma, adding a LAMA to ICS controller therapy is recommended over continuing the same dose of ICS	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
In individuals with uncontrolled persistent asthma, adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA is recommended	Ages 12 years and older	Conditional recommendation, moderate certainty of evidence

Key: * intermittent therapy is defined as temporary use of ICS in those not regularly using ICS controller therapy; † Single-inhaler ICS-formoterol both daily and as needed is referred to as "single maintenance and reliever therapy (SMART)"; ‡ The maximum recommended formoterol dose is 12 puffs (54 mcgs) for those 12 years and older and 8 puffs (36 mcgs) for children 4 to 11 years.

GINA – Global Strategy for Asthma Management and Prevention

The Global Initiative for Asthma published an update in 2022 for the management of asthma. GINA updates their recommendations on an annual basis to guide diagnosis and management of asthma in adults and adolescents.[6] Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D (**Table 4**) .[6] Guideline limitations included to the guidelines were lack of reporting for conflicts of interest and limited discussion on barriers to implementing ecommendations.[6]

Table 4. GINA Guidance Levels of Evidence[6]

Evidence Categories	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs)	Evidence from well designed RCTs

	• High quality evidence without significant limitations	
B	• Randomized controlled trials with important limitations • Limited body of evidence	Evidence from RCTs that include only a limited number of patients, post-hoc, or subgroup analyses of RCTs or meta-analyses of RCTs
C	• Non-randomized trials • Observational studies	Evidence is from outcomes of uncontrolled or non-randomized tirlas or from observational studies
D	• Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature on the subject matter is insufficient

Pharmacotherapy used to treat people with asthma is based off of asthma severity (**Table 5**). A substantial change in treatment recommendations is that monotherapy with SABAs in adults and adolescents is no longer recommended for asthma management. GINA guidelines recommend that all adults and adolescents with asthma receive an ICS-containing controller treatment.[6] Therapy can be given as a regular daily treatment for people with persistent symptoms or as-needed in people with mild asthma for symptom relief. Recommendations are divided into treatment tracks based on *the choice of reliever therapy*: Track 1 and Track 2.

- Track 1: Low dose ICS -formoterol. Preferred option due to exacerbation reduction compared to SABA monotherapy.
- Track 2: SABA for reliever therapy

Initial treatment recommendations for adults and adolescents with asthma are presented in **Table 6**. Track 1 is the preferred treatment option. Recommendations for children 6-11 years old are in **Table 7**.

Table 5. Asthma Severity Directing Therapy[6]

Mild Asthma	*Step 1* – Symptoms less than twice a month
	Step 2 – Symptoms twice a month or more, but less than daily
Moderate Asthma	*Step 3* – Symptoms most days or waking with asthma once a week or more
Severe Asthma	*Step 4* – Symptoms most days or waking with asthma once a week or more or low lung function
	Step 5 – Severely uncontrolled asthma

Table 6. GINA Recommendations for Starting Treatment in Adults and Adolescents with Asthma[6]

STEP	Treatment Recommendation Track 1*	Treatment Recommendation Track 2†
STEP 1	-As-needed low dose ICS-formoterol	-Low dose ICS whenever a SABA is taken
STEP 2	-As-needed low dose ICS-formoterol	-Low dose maintenance ICS
STEP 3	-Low dose maintenance ICS-formoterol (MART)	-Low dose maintenance ICS/LABA
STEP 4	-Medium dose maintenance ICS-formoterol (MART)	-Medium/high dose maintenance ICS/LABA
STEP 5	-Add-on LAMA -Refer for phonotypic assessment -Consider high dose maintenance ICS-formoterol +/- other pharmacotherapy	-Add-on LAMA -Refer for phonotypic assessment -Consider high dose maintenance ICS-LABA +/- other pharmacotherapy

Key: * Reliever is as-needed low-dose ICS-formoterol; † Reliever is as-needed SABA
Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MART – maintenance and reliever therapy with ICS-formoterol; SABA – short-acting beta agonist

Table 7. GINA Recommendations for Starting Treatment in Children 6-11 years with Asthma[6]

STEP	Preferred Controller Therapy *	Alternate Controller Therapy Options*
STEP 1	- Low dose ICS whenever a SABA is taken	- Consider low dose daily ICS
STEP 2	- Daily low dose ICS	- Daily LTRA *or* - Low dose ICS taken whenever a SABA is used
STEP 3	- Low dose ICS-LABA *or* - Medium dose ICS *or* - Very low dose ICS-formoterol maintenance and reliever (MART)	- Low dose ICS + LTRA
STEP 4	- Medium dose ICS-LABA *or* - Low dose ICS-formoterol maintenance and reliever therapy (MART)	- Add tiotropium *or* - Add LTRA
STEP 5	- Refer for phonotypic assessment *+/-* - Higher dose ICS-LABA *or* - Other add-on pharmacotherapy	- Add-on anti-IL5 *or* - As a last resort, consider add-on low dose OCS but consider side effects
Key: *As-needed SABA (or low dose ICS-formoterol reliever for MART) Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; IL-5 – interleukin 5; LTRA - leukotriene receptor antagonist; MART – maintenance and reliever therapy with ICS-formoterol; OCS – oral corticosticosteroids; SABA – short-acting beta agonist		

GOLD – Global Strategy for Diagnosis, Management, and Prevention of COPD

The Global Initiative for Chronic Obstructive Lung Disease updated recommendations for managing COPD in 2022.[7] A systematic review was undertaken to evaluate new literature. Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D (**Table 8**) . Conflict of interest were documented for 76% of the committee. Other limitations include no discussion on resource implications/barriers to implementation of recommendations.

Table 8. GOLD Guidance Levels of Evidence

Evidence Categories	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs) • High quality evidence without significant limitations	Evidence from well designed RCTs
B	• Randomized controlled trials with important limitations • Limited body of evidence	Evidence from RCTs that include only a limited number of patients, post-hoc, or subgroup analyses of RCTs or meta-analyses of RCTs
C	• Non-randomized trials • Observational studies	Evidence is from outcomes of uncontrolled or non-randomized tirlas or from observational studies
D	• Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature on thee subject matter is insufficient

COPD is classified based on FEV_1 and symptoms/risk of exacerbations as described in **Table 9 and Table 10**.[7] Exacerbations are also an important component of managing symptoms in people that have COPD. Exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy. Mild exacerbations are those that require treatment with SABA only, moderate require treatment with SABA and antibiotics and/or oral corticosteroids, and severe exacerbations are those that require the patient be hospitalized or visits the ER. The combination of symptomatic assessment, spirometry, and risk of exacerbations helps to determine the impact of COPD on the patient.

Table 9. Classification of Airflow Limitation for Patients wit COPD Based on 2022 GOLD Guidelines*[7]

Classification	Severity	Post-Bronchodilator FEV_1
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

* For patients with a FEV1/FVC < 0.70

Table 10. Classification of Symptoms/Exacerbation Risk for Patients wit COPD Based on 2022 GOLD Guidelines[7]

Classification	Assessment Test	Exacerbations
GOLD Category A	mMRC 0-1 or CAT <10	History of 0-1 moderate to severe exacerbations*
GOLD Category B	mMRC ≥2 or CAT ≥10	History of 0-1 moderate to severe exacerbations*
GOLD Category C	mMRC 0-1 or CAT <10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)
GOLD Category D	mMRC ≥2 or CAT ≥10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)

Key: * Not leading to hospital admission
Abbreviations: CAT – COPD Assessment Test; MRC – modified Medical Research Counsel questionnaire

Inhaled bronchodilators are recommended for regular use in people with COPD for the prevention and reduction of symptoms. Specific evidence related to their use is presented in **Table 11**.[7] Generally long-acting bronchodilators are preferred to short-acting therapies. Inhaled anti-inflammatory use is also an important component in the management of COPD (**Table 12**).[7] The use of ICS is not recommended in patients with COPD that have repeated pneumonia, blood eosinophils <100 cells/microliter or history of mycobacterial infection. Long-term ICS monotherapy is not recommended; however, long-term ICS with LABAs may be appropriate in people with a history of exacerbations despite appropriate treatment with long-acting bronchodilators.[7] There is some evidence to suggest the use of LABA/LAMA combination may have beneficial mortality effect in people with symptomatic COPD and a history of frequent or severe exacerbations.

Table 11. Evidence for the Use of Bronchodilators in COPD[7]

Recommendation	Evidence level
Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms	A
Combination of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms	A
LABAs and LAMAs significantly improve lung function, dyspnea, health status and reduce exacerbations rates	A
LAMAs have greater effect on exacerbation reduction* and decreased hospitalizations† compared with LABAs	A* and B†
Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy	A
Combination treatment with LABA/LAMA reduces exacerbations compared to monotherapy	B
Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance	B

Table 12. Evidence for the Use of Inhaled Anti-inflammatory Therapies in COPD[7]

Recommendation	Evidence level
The combination of an ICS and LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to severe COPD	A
Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease	A
Triple inhaled therapy of LABA/LAMA/ICS improves lung function symptoms, improves health status, and reduces exacerbations compared to LABA/ICS, LABA/LAMA, or LAMA monotherapy	A

Treatments for COPD should be initiated in people based on symptoms and exacerbation risk. There is no high quality evidence to guide initial therapy; however, **Figure 1** recommends treatment options based on available evidence.

Figure 1. Initial Pharmacological Management of COPD[7]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** * Consider if highly symptomatic (e.g., CAT > 20) ** Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator (short or long-acting) mMRC 0-1 CAT <10	**Group B** A Long Acting Bronchodilator (LABA or LAMA) mMRC ≥ 2 CAT ≥ 10

Abbreviations: EOS = blood eosinophil count in cells per microliter; mMRC = modified Medical Research Council dyspnea questionnaire; CAT = COPD assessment test

US Preventative Services Task Force – COPD Updated Evidence Report and Systematic Review

In 2022 the USPSTF updated treatment recommendations for the screening and management of COPD.[8] The guidance was based off of a systematic review and meta-analysis done by the Agency for Heatlhcare Research and Quality (AHRQ).[10] There were 3 new trials (n=20,058) included in the updated analysis on the use of pharmacological therapies for the treatment of COPD.[8]

There was moderate quality of evidence that the use of LABA, LAMA, ICS or LABA/ICS reduces the risk of exacerbations in people with moderate COPD.[8] Tiotropium demonstrated reduction in deterioration in people with moderate COPD and exacerbations in people with minimally symptoms and moderate airflow obstruction. Harms data from new evidence is consistent with previous findings from trials that show no serious adverse reactions from the use of LAMA, LABAs or ICS.[8] Data from observations trials suggest that there may be a increased risk of cardiovascular disease with LABA use and long-term use of ICS may affect bone health negatively.

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

Breztri Aerosphere (budesonide 160 mcg, glycopyrrolate 9 mcg, and formoterol fumarate 4.8 mcg inhalation aerosol) – In July of 2020 a triple combination product of budesonide, glycopyrrolate, and formoterol was approved for the maintenance treatment of patients with COPD.[22] The approved dose is 2 inhalations twice daily. Two studies evaluated the use of Breztri in patients with COPD and history of previous LAMA, LABA and ICS use. Breztri reduced COPD exacerbation more than combination therapy with 2 agents over 52 weeks in trial 1 and over 24 weeks in trial 2 (**Table 13**).[22]

Table 13. Rate of Moderate to Severe Exacerbations[22]

Treatment	Mean Annual Rate	Rate Ratio vs. Comparator
Trial 1 (52 weeks, n=6388)		
Breztri Aerosphere*	1.08	N/A
GFF MDI	1.42	RR 0.76 (95% CI, 0.69 to 0.83); p<0.0001
BFF MDI	1.24	RR 0.87 (95% CI, 0.79 to 0.95); p=0.0027
Trial 2 (24 weeks, n=1,896)		
Breztri Aerosphere	NR	
GFF MDI	NR	RR 0.48 (95% CI, 0.37 to 0.64); p<0.05
BFF MDI	NR	RR 0.82 (95% CI, 0.58 to 1.17); p>0.05

Key: * budesonide 320 mcg/glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg

Abbreviations: BFF – budesonide/formoterol fumarate 320 mcg/9.6 mcg; GFF – glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg; MDI – meter dose inhaler; NR – not reported; RR – rate ratio.

ArmonAir Respiclick (fluticasone propionate) – Prescribing information for Armonair Respiclick® formulation of fluticasone was updated in April of 2022 to include the addition of a new 30 mcg strength.[23]

ArmonAir Respiclick (fluticasone propionate) – In July of 2021, ArmonAir Respiclick® received the approval for use as maintenance treatment for asthma as prophylactic therapy in pediatric patients ages 4 to 11 years.[23]

Trelegy Ellipta (fluticasone furoate-umeclidinium-vilanterol) – In September of 2022, Trelegy Ellipta® received an expanded indication from the FDA for maintenance treatment in people 18 years and older with asthma. A new dosage form of fluticasone furoate 200 mcg-umeclidinium 62.5 mcg-vilanterol 25 mcg was approved.[24]

New FDA Safety Alerts:
No new FDA safety alerts identified.

Randomized Controlled Trials:
A total of 160 citations were manually reviewed from the initial literature search. After further review, 158 citations were excluded because of wrong study design (e.g., observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining two trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 14. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Papi, et al[25] DB, MC, Phase 3, RCT	1. Albuterol 180 mcg -budesonide 160 mcg as needed 2. Albuterol 180 mcg -budesonide 80 mcg as needed 3. Albuterol 180 mcg as needed	Patients (4 years and older) with uncontrolled moderate to severe asthma receiving inhaled glucocorticoid-containing maintenance therapy N=3132	The first event of severe asthma exacerbation in a time-to-event analysis	Annualized Rate Ratio: 1. 0.43 2. 0.48 3. 0.59 Albuterol 180 mcg/budesonide 160 mcg vs. Albuterol 180 mcg: HR 0.74 (95% CI, 0.62 to 0.89); P=0.001 Albuterol 180 mcg/budesonide 80 mcg vs. Albuterol 180 mcg: HR 0.84 (95% CI, 0.71 to 1.0); P=0.052	As needed albuterol 180 mcg/budesonide 160 mcg was more effective than albuterol 180 mcg in reducing the risk of severe asthma exacerbations. A majority of patients were white (81.1%) and 25.9% were Latinx or Hispanic.
Clemency, et al[26] DB, MC, Phase 3, RCT	1. Ciclesonide 320 mcg 2. Placebo 30 days	Non-hospitalized participants with symptomatic COVID-19 infection N=413	Time to alleviation of all COVID-19-related symptoms by day 30	1. 19.0 days 2. 19.0 days OR 1.28 days (95% CI, 0.84 to 1.97)	There was no difference between ciclesonide and placebo in reducing symptoms of COVID-19

Abbreviations: CI = confidence intervals; DB = double-blind; HR = hazard ratio; MC = multicenter; OR = odds ratio; RCT = randomized clinical trial.

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Appendix 1: Current Preferred Drug List

Anticholinergics, Inhaled

Generic	Brand	Form	PDL
ipratropium bromide	ATROVENT HFA	HFA AER AD	Y
ipratropium bromide	IPRATROPIUM BROMIDE	SOLUTION	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	AMPUL-NEB	Y
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	MIST INHAL	Y
tiotropium bromide	SPIRIVA HANDIHALER	CAP W/DEV	Y
umeclidinium bromide	INCRUSE ELLIPTA	BLST W/DEV	Y
aclidinium bromide	TUDORZA PRESSAIR	AER POW BA	N
glycopyrrol/nebulizer/accessor	LONHALA MAGNAIR STARTER	VIAL-NEB	N
glycopyrrolate/neb.accessories	LONHALA MAGNAIR REFILL	VIAL-NEB	N
revefenacin	YUPELRI	VIAL-NEB	N
tiotropium bromide	SPIRIVA RESPIMAT	MIST INHAL	N

Beta agonists, Inhaled Long-acting

Generic	Brand	Form	PDL
salmeterol xinafoate	SEREVENT DISKUS	BLST W/DEV	Y
arformoterol tartrate	ARFORMOTEROL TARTRATE	VIAL-NEB	N
arformoterol tartrate	BROVANA	VIAL-NEB	N
formoterol fumarate	FORMOTEROL FUMARATE	VIAL-NEB	N
formoterol fumarate	PERFOROMIST	VIAL-NEB	N
olodaterol HCl	STRIVERDI RESPIMAT	MIST INHAL	N

Beta-agonists, Inhaled Short-acting

Generic	Brand	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	SOLUTION	Y

albuterol sulfate	ALBUTEROL SULFATE	VIAL-NEB	Y
albuterol	ALBUTEROL	AER REFILL	N
albuterol sulfate	PROAIR RESPICLICK	AER POW BA	N
albuterol sulfate	PROAIR DIGIHALER	AER PW BAS	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	VIAL-NEB	N
levalbuterol HCl	XOPENEX	VIAL-NEB	N
levalbuterol HCl	XOPENEX CONCENTRATE	VIAL-NEB	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	HFA AER AD	N

Corticosteroids, Inhaled

Generic	Brand	Form	PDL
budesonide	PULMICORT FLEXHALER	AER POW BA	Y
fluticasone propionate	FLOVENT HFA	AER W/ADAP	Y
fluticasone propionate	FLUTICASONE PROPIONATE HFA	AER W/ADAP	Y
fluticasone propionate	FLOVENT DISKUS	BLST W/DEV	Y
mometasone furoate	ASMANEX	AER POW BA	Y
beclomethasone dipropionate	QVAR REDIHALER	HFA AEROBA	N
budesonide	BUDESONIDE	AMPUL-NEB	N
budesonide	PULMICORT	AMPUL-NEB	N
ciclesonide	ALVESCO	HFA AER AD	N
fluticasone furoate	ARNUITY ELLIPTA	BLST W/DEV	N
fluticasone propionate	ARMONAIR DIGIHALER	AER PW BAS	N
mometasone furoate	ASMANEX HFA	HFA AER AD	N

Corticosteroid/LABA Combination Inhalers

Generic	Brand	Form	PDL
budesonide/formoterol fumarate	BUDESONIDE-FORMOTEROL FUMARATE	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO RESPICLICK	AER POW BA	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	AER POW BA	Y
fluticasone propion/salmeterol	ADVAIR DISKUS	BLST W/DEV	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	BLST W/DEV	Y
fluticasone propion/salmeterol	WIXELA INHUB	BLST W/DEV	Y
fluticasone propion/salmeterol	ADVAIR HFA	HFA AER AD	Y
mometasone/formoterol	DULERA	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO DIGIHALER	AER PW BAS	N
fluticasone/vilanterol	BREO ELLIPTA	BLST W/DEV	N
fluticasone/vilanterol	FLUTICASONE-VILANTEROL	BLST W/DEV	N

LAMA/LABA Combination Inhalers

Generic	Brand	Form	PDL
tiotropium Br/olodaterol HCl	STIOLTO RESPIMAT	MIST INHAL	Y
umeclidinium brm/vilanterol tr	ANORO ELLIPTA	BLST W/DEV	Y
aclidinium brom/formoterol fum	DUAKLIR PRESSAIR	AER POW BA	N
budesonide/glycopyr/formoterol	BREZTRI AEROSPHERE	HFA AER AD	N
fluticasone/umeclidin/vilanter	TRELEGY ELLIPTA	BLST W/DEV	N
glycopyrrolate/formoterol fum	BEVESPI AEROSPHERE	HFA AER AD	N

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial

Objective: To determine the efficacy of the inhaled steroid ciclesonide in reducing the time to alleviation of all COVID-19-related symptoms among nonhospitalized participants with symptomatic COVID-19 infection.

Design, setting, and participants: This phase 3, multicenter, double-blind, randomized clinical trial was conducted at 10 centers throughout the US and assessed the safety and efficacy of a ciclesonide metered-dose inhaler (MDI) for treating nonhospitalized participants with symptomatic COVID-19 infection who were screened from June 11, 2020, to November 3, 2020.

Interventions: Participants were randomly assigned to receive ciclesonide MDI, 160 µg per actuation, for a total of 2 actuations twice a day (total daily dose, 640 µg) or placebo for 30 days.

Main outcomes and measures: The primary end point was time to alleviation of all COVID-19-related symptoms (cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell) by day 30. Secondary end points included subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19.

Results: A total of 413 participants were screened and 400 (96.9%) were enrolled and randomized (197 [49.3%] in the ciclesonide arm and 203 [50.7%] in the placebo arm; mean [SD] age, 43.3 [16.9] years; 221 [55.3%] female; 2 [0.5%] Asian, 47 [11.8%] Black or African American, 3 [0.8%] Native Hawaiian or other Pacific Islander, 345 [86.3%] White, and 1 multiracial individuals [0.3%]; 172 Hispanic or Latino individuals [43.0%]). The median time to alleviation of all COVID-19-related symptoms was 19.0 days (95% CI, 14.0-21.0) in the ciclesonide arm and 19.0 days (95% CI, 16.0-23.0) in the placebo arm. There was no difference in resolution of all symptoms by day 30 (odds ratio, 1.28; 95% CI, 0.84-1.97). Participants who were treated with ciclesonide had fewer subsequent emergency department visits or hospital admissions for reasons related to COVID-19 (odds ratio, 0.18; 95% CI, 0.04-0.85). No participants died during the study.

Conclusions and relevance: The results of this randomized clinical trial demonstrated that ciclesonide did not achieve the primary efficacy end point of reduced time to alleviation of all COVID-19-related symptoms.

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi , Bradley E Chipps , Richard Beasley, Reynold A Panettieri Jr, Elliot Israel , Mark Cooper , Lynn Dunsire , Allison Jeynes-Ellis , Eva Johnsson , Robert Rees , Christy Cappelletti , Frank C Albers

Background: As asthma symptoms worsen, patients typically rely on short-acting β_2-agonist (SABA) rescue therapy, but SABAs do not address worsening inflammation, which leaves patients at risk for severe asthma exacerbations. The use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, as rescue medication might reduce the risk of severe asthma exacerbation.
Methods: We conducted a multinational, phase 3, double-blind, randomized, event-driven trial to evaluate the efficacy and safety of albuterol-budesonide, as compared with albuterol alone, as rescue medication in patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid-containing maintenance therapies, which were continued throughout the trial. Adults and adolescents (≥12 years of age) were randomly assigned in a 1:1:1 ratio to one of three trial groups: a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide (with each dose consisting of two actuations of 90 µg and 80 µg, respectively [the higher-dose combination group]), a fixed-dose combination of 180 µg of albuterol and 80 µg of budesonide (with each dose consisting of two actuations of 90 µg and 40 µg, respectively [the lower-dose combination group]), or 180 µg of albuterol (with each dose consisting of two actuations of 90 µg [the albuterol-alone group]). Children 4 to 11 years of age were randomly assigned to only the lower-dose combination group or the albuterol-alone group. The primary efficacy end point was the first event of severe asthma exacerbation in a time-to-event analysis, which was performed in the intention-to-treat population.
Results: A total of 3132 patients underwent randomization, among whom 97% were 12 years of age or older. The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P = 0.001). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P = 0.052). The incidence of adverse events was similar in the three trial groups.
Conclusions: The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies. (Funded by Avillion; MANDALA ClinicalTrials.gov number, NCT03769090.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 03, 2022
Search Strategy:

#	Searches	Results
1	Ipratropium/ or ipratropium.mp.	2660
2	tiotropium.mp. or Tiotropium Bromide/	1986
3	umeclidinium.mp.	309
4	glycopyrrolate.mp. or Glycopyrrolate/	1674
5	revefenacin.mp.	41
6	salmeterol.mp. or Salmeterol Xinafoate/	3153
7	arformoterol.mp. or Formoterol Fumarate/	1910
8	formoterol.mp. or Formoterol Fumarate/	2878
9	olodaterol.mp.	252
10	albuterol.mp. or Albuterol/	11071
11	levalbuterol.mp. or Levalbuterol/	156
12	Budesonide/ or budesonide.mp.	6988
13	Fluticasone/ or fluticasone.mp.	5025
14	mometasone.mp. or Mometasone Furoate/	1309
15	beclomethasone.mp. or Beclomethasone/	3952
16	Budesonide/ or budesonide.mp.	6988
17	ciclesonide.mp.	458
18	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	30459
19	limit 18 to (english language and humans and yr="2020 -Current")	1721
20	limit 19 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	160

Appendix 4: Key Inclusion Criteria

Population	People with asthma and chronic obstructive pulmonary disease (COPD)
Intervention	Inhaled therapies for people with asthma or COPD
Comparator	Active therapies or placebo
Outcomes	Lung function, symptoms, hospitalizations and mortality
Timing	NA
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Long-acting Beta-agonists (LABA)

Goals:
- To optimize the safe and effective use of LABA therapy in patients with asthma and COPD.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred LABA 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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are 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 #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded
5. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/22 (KS), 10/20 (KS), 5/19 (KS); 1/18; 9/16; 9/15); 5/12; 9/09; 5/09*
Implementation: *3/1/18; 10/9/15; 8/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist (LAMA/LABA) and LAMA/LABA/Inhaled Corticosteroid (LAMA/LABA/ICS) Combinations

Goals:
- To optimize the safe and effective use of LAMA/LABA/ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma and COPD: short-acting bronchodilator and previous trial of two drug combination therapy (ICS/LABA, LABA/LAMA or ICS/LAMA). Preferred monotherapy inhaler LAMA and LABA products do NOT require prior authorization.

Length of Authorization:
- Up to 12 months

Requires PA:
- All LAMA/LABA and LAMA/LABA/ICS 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. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #8	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Is the request for a LAMA/LABA combination product?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Go to #6
6. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is there documentation that the prescriber is willing to stop coverage of all other LAMA, LABA, and ICS inhaler combination products?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
8. Does the patient have an active prescription for an on-demand short-acting acting beta-agonist (SABA) and/or for ICS-formoterol?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the request for Trelegy Ellipta (ICS/LAMA/LABA) combination product and is there a documented trial of an ICS/LABA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers (with the exception of ICS-formoterol which may be continued)	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *10/22 (KS), 10/21 (SF); 12/20 (KS), 10/20, 5/19; 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/1/21; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Inhaled Corticosteroids (ICS)

Goals:
- To optimize the safe and effective use of ICS therapy in patients with asthma and COPD.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred ICS 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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are 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 #3
3. Is the request for treatment of asthma or reactive airway disease?	**Yes:** Go to #6	**No:** Go to #4
4. Is the request for treatment of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *10/22 (KS), 10/20 (KS), 5/19 (KS), 1/18; 9/16; 9/15*
Implementation: *3/1/18; 10/13/16; 10/9/15*

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Review Standards and Methods for Quality Assessment of Evidence

Updated: February 2023

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the preferred drug list (PDL) and clinical prior authorization (PA) criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices.

2. The types of reviews may include, but are not limited to, the following:

Type of Review	Rationale for Review
Abbreviated Drug Review	New drug with evidence only for non-funded condition(s)
Class Literature Scan	Used when limited literature is found which would affect clinical changes in PDL status or PA criteria based on efficacy or safety data (may include new drug formulations or expanded indications if available literature would not change PDL status or PA criteria). Provides a summary of new or available literature, and outcomes are not evaluated via the GRADE methodology listed in **Appendix D**.
New Drug Evaluation (NDE)	Single new drug identified and the PDL class was recently reviewed, or the drug is not assigned to a PDL drug class
Class Review	New PDL class
Class Update	New systematic review(s) and clinical trials identified that may inform change in PDL status or clinical PA criteria in an established PDL class
Class Update with New Drug Evaluation	New drugs(s) or indication(s) also identified (excludes new formulations, expanded indications, biosimilars, or drugs for unfunded indications)
DERP Summary Report	New DERP report which evaluates comparative evidence
Drug Use Evaluation	Analysis of utilization trends in FFS population in order to identify safety issues or inform future policy decisions
Policy Evaluation	Evaluation safety, efficacy, and utilization trends after implementation of a policy to identify areas for improvement

3. The P&T Committee will rely primarily on high quality systematic reviews and randomized controlled trials in making its evidence summary recommendations. High quality clinical practice guidelines and relevant clinical trials are also used as supplementary evidence.

4. Emphasis will be placed on the highest quality evidence available. Poor quality trials, systematic reviews or guidelines are excluded if higher quality literature is available and results offer no additional value. Unless the trial evaluates an outcome or comparison of high clinical importance, individual RCTs with the following study types will be excluded from class updates, class reviews, and literature scans:
    a. Non-comparative, placebo-controlled trials
    b. Non-inferiority trials
    c. Extension studies
    d. Poor quality studies (as assessed in **Appendix A**)

5. Individual drug evaluations rely primarily on high quality RCTs or clinical trials used for FDA approval. Evidence from poor quality RCTs may be included if there is no higher quality evidence available.

6. Phase 2 trials may be considered if there is a compelling reason to include, such as use for FDA approval. Preference will be given for inclusion of applicable phase 3 and 4 trials over earlier phase studies. If fully published, of adequate duration, and with appropriate clinical outcome measures, authors may include phase 2 studies if phase 3 or 4 trials are inadequate or when direct comparative evidence and/or dose response are reported in a comparable population to available phase 3 or 4 studies.

7. The following are preferred sources that provide high quality evidence at this time:

    a. Drug Effectiveness Review Project at Oregon Health & Science University (OHSU)
    b. U.S. Department of Veterans Affairs/Department of Defense
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. National Institute for Clinical Excellence (NICE)
    ~~e.~~f. Scottish Intercollegiate Guidelines Network (SIGN)

8. The following types of evidence are preferred and will be considered only if they are of high methodological quality as evaluated by the quality assessment criteria below:

    a. Systematic reviews of randomized controlled trials
    b. Direct comparative randomized controlled trials (RCTs) evaluating clinically relevant outcomes; placebo-controlled studies not related to initial FDA-drug approval or new indications may be considered if likely to impact current policy
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

9. The following types of literature are considered unreliable sources of evidence and will rarely be reviewed by the P&T Committee:

a. Observational studies, case reports, case series
    i. However, observational studies and systematic reviews of observational studies will be included to evaluate significant safety data beyond the FDA labeling information. Observational studies will only be included when there is not adequate data from higher quality literature.
b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents
c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality compared to other relevant literature, or duplicate information in other materials under review.
d. Studies not designed to investigate clinically relevant outcomes
e. Systematic reviews identified with the following characteristics:
    i. Evidence is of poor or very poor quality
    ii. Evidence is of limited applicability to a US population
    iii. Systematic review does not meet defined applicability criteria (PICOTS criteria) for the topic
    iv. Systematic review is of poor methodological quality as evaluated by AMSTAR II criteria (see **Appendix B**)
    v. Evidence is based on indirect comparisons from network meta-analyses
    vi. Conflicts of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)
f. Guidelines identified with the following characteristics:
    i. There is no systematic guideline development method described
    ii. Strength of evidence for guideline recommendations are not provided
    iii. Recommendations are largely based on expert opinion
    iv. Poor methodological quality as assessed in **Appendix C** (AGREE II score is less than 113 points OR modified AGREE II-GRS score is less than 30 points)
    v. Conflict of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)

QUALITY ASSESSMENT

1. The standard methods used by the DURM faculty to assess quality of evidence incorporated into the evidence summaries for the OHP Pharmacy and Therapeutics Committee are described in detail in **Appendix A-C**.

2. The Cochrane Risk of Bias tool (modified) described in **Appendix A** is used to assess risk of bias (i.e., internal validity) of randomized controlled trials. The quality of non-inferiority trials will be also assessed using the additional criteria for non-inferiority trials in **Appendix A**. Internal validity of clinical trials are graded as poor, fair, or good quality.

3. The AMSTAR II measurement tool is used to assess for methodological quality of systematic reviews and is provided in **Appendix B**. Systematic reviews, meta-analyses or guidance identified from 'best sources' listed in **Appendix B** undergo methodological rigor and are considered to be high quality and are not scored for quality using the AMSTAR II tool.

4. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**. If there are concerns regarding applicability of guidelines to the Medicaid population, the AGREE-REX tool is available for use (https://www.agreetrust.org/resource-centre/agree-rex-recommendation-excellence/).

5. The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability, or directness, of randomized controlled trials to the OHP population. Detailed guidance is provided in **Appendix A**. Only randomized controlled trials with applicability to the OHP population, as assessed by the PICOS framework, are included in evidence summaries.

6. Emphasis of the review will be on clinically relevant outcomes. The following clinically relevant outcomes are graded for quality: mortality, morbidity outcomes, symptom relief, quality of life, functioning (physical, mental, or emotional), early discontinuation due to adverse events, and severe adverse effects. Surrogate outcomes are considered if directly linked to mortality or a morbidity outcome. Clinically meaningful changes in these outcomes are emphasized.

7. The overall quality of evidence is graded for clinically relevant outcomes of efficacy and harm using the GRADE methodology listed in **Appendix D**. Evaluation of evidence for each outcome of interest is graded as **high**, **moderate**, **low**, or **insufficient**. Final evidence summary recommendations account for the availability and quality of evidence for relevant outcomes and perceived clinical impact on the OHP population.

    a. Evidence grades are defined as follows:
        i. High quality evidence: High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
        ii. Moderate quality evidence: Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.
        iii. Low quality evidence: Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.
        iv. Insufficient evidence: Evidence is not available or too limited to permit any level of confidence in the estimated effect.

8. Conflict of Interest
    a. Conflict of interest is a critical component of quality assessment. A conflict of interest is "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a second interest." Conflict of interest includes any relationships or activities that could be perceived to have influenced or give the appearance of potentially influencing the literature.
        i. Reference: IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice*. Washington, DC: The National Academies Press.

    b. Conflict of interest analysis for DURM reviews:
        1. Sources will be excluded due to conflict of interest concerns if they contain one of the "fatal flaws" in **Table 1** below.
        2. If no "fatal flaws" exist, an analysis of the conflicts of interest will be completed and any limitations (examples in **Table 1** below) will be first and foremost discussed in the evidence review.
        3. Conflict of interest is also assessed through the Cochrane risk of bias, AMSTAR II, and AGREE tools (**Appendix A, B, and C**).

Table 1. DURM Conflict of Interest Analysis

Type of literature	"Fatal flaws"	If no "fatal flaws" exist, potential limitations to discuss when including the piece of literature	Other considerations- specific to the type of literature
Randomized controlled trial	• Conflict of interest not documented	• Authors or committee members have significant conflicts of interest • Concerning high dollar amounts of conflicts of interest are documented • Mitigation strategies (described in the article or journal/organization policies) are documented but could be more robust	• Higher risk of bias when the study sponsor is the pharmaceutical manufacturer and is included in data analysis and manuscript writing
Systematic review	• Conflict of interest not documented • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* persons with potential conflicts of interest are excluded from the assessment or review process, independent second review of articles considered for inclusion in SR that are reviewed first by their own author who is on the SR team		• May consider funding sources or conflicts of interest for both the systematic review and the included studies
Guideline	• Conflict of interest not documented • Chair has a conflict of interest • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* excluding persons with significant conflict of interest from the review process, recusing members with significant conflict of interest from voting on recommendations or having them leave the room during the discussion		• Guidelines with "fatal flaws" which are commonly used in practice may be included for clinical context but will not be considered when creating conclusions or recommendations

APPENDIX A. Methods to Assess Quality of Studies.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	Selection bias refers to **systematic differences** between **baseline characteristics of the groups** that were compared. The unique strength of proper ***randomization*** is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants. Successful randomization depends on fulfilling several interrelated processes. A rule for allocating patients to groups must be specified, based on some chance (random) process. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process if often termed ***allocation concealment***.
Performance Bias	Performance bias refers to **systematic differences** between groups in the **care provided**, or in exposure to factors other than the interventions of interest. After enrolment, ***blinding participants and investigators/care givers*** will reduce the risk that knowledge of which intervention was received affected the outcomes, rather than the intervention itself. Effective blinding ensures that all groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. Therefore, risk of differences in intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations and study duration between study groups are minimized.
Detection Bias	Detection bias refers to **systematic differences** between groups in how **outcomes were assessed**. ***Blinding of outcome assessors*** will reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affected outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes (eg, degree of post-operative pain).
Attrition Bias	Attrition bias refers to **systematic differences** between groups in **withdrawals** (exclusions and attrition) from a study. ***Withdrawals*** from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. ***Exclusions*** refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to assessors. ***Attrition*** refers to situations in which outcome data are not available.
Reporting Bias	Reporting bias refers to the **selective reporting of pre-specified outcomes**, on the basis of the results. Of particular concern is that statistically non-significant (negative) primary endpoints might be selectively reported while select positive secondary endpoints are over-emphasized. Selective reporting of outcomes may arise in several ways: 1) there can be selective omission of pre-specified outcomes (ie, only some of the pre-specified outcomes are reported); 2) there can also be selection of choice data for an outcome that differs from what was pre-specified (eg, there may be different time points chosen to be reported for an outcome, or different methods used to measure an outcome at the same time point); and 3) there can be selective analyses of the same data that differs from what was pre-specified (eg, use of continuous vs. dichotomous outcomes for A1c lowering, selection from multiple cut-points, or analysis of between endpoint scores vs. change from baseline).
Other Bias	Other sources of bias may be present depending on conflict of interests and funding sources, trial design, or other specific circumstances not covered in the categories above. Of particular concern is how conflicts of interest and funding sources may potentially bias results. Inappropriate influence of funders (or, more generally, of people with a vested interest in the results) is often regarded as an important risk of bias. Information about vested interests should be collected and presented when relevant, with specific regard for methodology that might be been influenced by vested interests and which may lead directly to a risk of bias. Additional sources of bias may result from trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the experimental and control interventions get 'mixed', for example if participants pool their drugs).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Assess each domain separately to determine if risk of each bias is likely **LOW**, **HIGH** or **UNCLEAR** (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix D**).

Conflicts of interest should also be assessed when determining risk of bias. This may be considered part of risk of reporting bias. Funding sources for the trial, conflicts of interest of the authors, and role the study sponsor played in the trial should be considered in this domain.

The quality of each trial will be graded as **good, fair,** or **poor** based on the following thresholds for converting the Cochrane Risk of Bias Tool to AHRQ Standards. A good quality trial will have low risk of bias for all domains. A fair quality trial will have one domain with high risk of bias or 2 domains with unclear bias, with the assessment that the one or more biases are unlikely to influence the outcome, and there are no known limitations which could invalidate results. A poor quality trial will have high risk of bias for one or more domains or have 2 criteria with unknown bias for which there may be important limitations which could invalidate the results or likely bias the outcome. Trials of poor quality will be excluded from review if higher quality sources of evidence are available.

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table • Coin toss	Sequence generated by: • Odd or even date of birth • Rule based on date or admission date • Hospital or clinic number • Alternating numbers	Method of randomization not described or sequence generation process not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Participants or investigators could not foresee assignment because: • Central allocation (telephone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Participants or investigators could possibly foresee assignment because: • Open random allocation • Envelopes without appropriate safeguards (eg, unsealed or not opaque) • Allocation based on date of birth or case record number • Alternating allocation	Method of concealment not described or not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate sequence generation, allocation concealment, or failed randomization. *Statistical tests of baseline imbalance are not helpful for randomized trials.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, other medications, medical/surgical history, etc.)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Systematic differences in how care was provided between groups due to un-blinding of participants or investigators/care providers or because of standard of care was not consistent across all sites.	• Study participants could not identify study assignment because blinding of participants was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Study participants could possibly identify study assignment because there was no blinding or incomplete blinding • Blinding potentially broken, which likely influenced effect estimate (eg, differences easily observed in appearance, taste/smell or adverse effects between groups) • Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	Not described or insufficient information to permit definitive judgment

DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Outcome assessors un-blinded	Outcome assessors could not identify study assignment because: • Blinding of assessors was ensured and unlikely broken • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding (ie, objective outcomes)	• Outcome data assessors could possibly identify study assignment because no blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, large differences in efficacy or safety outcomes between groups)	Not described or insufficient information to permit definitive judgment
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High Drop-out rate or loss to follow-up (eg, >10% for short-term studies; >20% for longer-term studies) • Differential drop-out or loss to follow-up >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed where appropriate (eg, superiority trials) • Intention-to-treat and per-protocol analyses performed and compared where appropriate (eg, non-inferiority trials) • Reasons for missing outcome data unlikely to influence effect estimates • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.)	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of selective outcome reporting	• Study protocol is available and was followed and all pre-specified primary and secondary outcomes are reported • Study protocol is not available, but it is clear that all expected outcomes are reported	• Not all pre-specified primary and secondary outcomes reported • Primary outcome(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary outcome(s) not pre-specified (unless clear justification provided) • Failure or incomplete reporting of other outcomes of interest • Inappropriate over-emphasis of positive secondary outcomes in study with negative primary outcome	Insufficient information to make determination
OTHER BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**

Evidence of other biases not described in the categories above	• No conflicts of interest present or study sponsor was not involved in trial design, data analysis or publication • No other potential sources of bias identified	• Conflicts of interest are present based on funding source or conflicting interests of authors • Study sponsor is involved in trial design, data analysis, and publication of data • There is a run-in period with pre-randomization administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention • Recruitment bias in cluster-randomized trials with differential participant recruitment in clusters for different interventions • Cross-over trials in which the crossover design is not suitable, there is significant carry-over effects, or incompletely reported data (data reported only for first period) • Conduct of the study is affected by interim results ((e.g. recruiting additional participants from a subgroup showing more benefit) • Deviation from the study protocol in a way that does not reflect clinical practice (e.g. post hoc stepping-up of doses to exaggerated levels).	• Conflicts of interest for authors or funding sources are not reported or not described • Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (ie, directness) of the evidence to the OHP population (**Table 3**).

Table 3. PICOS Domains that Affect Applicability.

PICOS Domain	Conditions that Limit Applicability
Patient	• Narrow eligibility criteria and broad exclusion criteria of those with comorbidities • Large differences between the demographic characteristics between the study population and patients in the OHP • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in OHP population
Intervention	• Doses, frequency schedule, formulations or duration of intervention used in study not reflective of clinical practice • Intensity/delivery of behavioral interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparator	• Inadequate dose or frequency schedule of comparator • Use of inferior or substandard comparator relative to alternative comparators that could be used
Outcomes	• Short-term or surrogate outcomes assessed • Composite outcomes used that mix outcomes of different significance
Setting	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care from highly trained/proficient practitioners in trial not reflective of typical clinical practice where intervention likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Non-inferiority (NI) trials are designed to prove a new treatment is not worse than the control treatment by a pre-determined difference, with a given degree of confidence. The pre-determined margin of difference in non-inferiority trials is defined as delta. Correctly determining this margin is a challenge in the design and interpretation of NI trials. The greatest challenge in use of NI trials is recognizing inappropriate use.

Non-inferiority trials will only be included in evidence summaries when there is a compelling reason to include them, and higher quality evidence is not available. The compelling reason for inclusion will be clearly stated as an introduction to the reporting of the NI trial.

The following template was developed using CONSORT and FDA guidance[1,2] and will be used as a guideline to evaluate non-inferiority studies included in DURM evidence summaries. Unless the trial evaluates an outcome or comparison of high clinical importance, individual non-inferiority trials will be excluded from class updates, class reviews, and literature scans. Evidence from poor quality RCTs may be included in individual drug evaluations if there is no higher quality evidence available. Items in bold (#1-5) are essential to conducting a non-inferiority trial with good methodological rigor. In general, a non-inferiority trial with high quality methods will score a "yes" on most of the components listed below.

Table 4. Non-inferiority Trial Quality Scoring Template

Developed using CONSORT and FDA guidance[1,2] **Use Template to evaluate trials supporting New Drug Evaluations and Class Update Reports** **A high-quality trial will meet all bolded assessments below**	
1. Rationale for choosing comparator with historical study results confirming efficacy (or safety) of this comparator is provided.	□ **Yes** □ **No** □ **Can't answer**
2. Active control (or comparator) represents current standard of care.	□ **Yes** □ **No** □ **Can't answer**
3. Non-inferiority margin was specified a priori and based on statistical reasoning and clinical considerations regarding benefit, risk, and cost.	□ **Yes** □ **No** □ **Can't answer**
4. Noninferiority margin is not larger than the expected difference between active control (or comparator) and placebo.	□ **Yes** □ **No** □ **Can't answer**
5. If a superiority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, the justification for switching is provided and superiority analysis was defined a priori.	□ **Yes** □ **No** □ **Can't answer**
6. Investigator reported both ITT and per-protocol analysis in detail and the results of both analyses demonstrate noninferiority. (If only one analysis is provided, per protocol is subject to less bias than ITT analysis in noninferiority trials.)	□ **Yes** □ **No** □ **Can't answer**
7. Rationale for using a noninferiority design is included (or why it would likely be unethical to conduct a placebo-controlled superiority trial of the new therapy).	□ Yes □ No □ Can't answer
8. Study hypothesis is stated in terms of noninferiority.	□ Yes □ No □ Can't answer
9.Eligibility criteria for participants and the settings in which the data were collected are similar to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
10. Trial is designed to be consistent with historical placebo-controlled trials.	□ Yes □ No □ Can't answer
11. The reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy (or safety).	□ Yes □ No □ Can't answer
12. The outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
13. The lower bound of that CI is clinically significant.	□ Yes □ No □ Can't answer
14. For the outcome(s) for which noninferiority was hypothesized, a figure showing confidence intervals and the noninferiority margin is included.	□ Yes □ No □ Can't answer
15. Results are interpreted in relation to the noninferiority hypothesis.	□ Yes □ No □ Can't answer

References:
1. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *Jama.* 2012;308(24):2594-2604.
2. FDA Industry Guidance for Noninferiority Trials. November 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

APPENDIX B. Methods to Assess Methodological Quality of Systematic Reviews.

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR II) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the measurement tool below, and questions can be scored in one of four ways: "Yes", "Partial Yes", "No", or "Not Applicable". The AMSTAR II is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies were not assessed or considered when conclusions were formulated (#9 and #13)). Other areas identified as important domains in the AMSTAR II criteria include registration of a protocol (#2); justification for excluding individual studies (#7); appropriateness of meta-analysis methods (#11); and assessment of publication bias (#15). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Ref. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include, but are not limited to: Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center; Agency for Healthcare Research and Quality (AHRQ); National Institute for Health and Care Excellence (NICE); U.S. Department of Veterans Affairs (VA); and Canadian Agency for Drugs and Technologies in Health (CADTH); and BMJ Clinical Evidence.

AMSTAR II Quality Scoring Template

1) Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- □ Population
- □ Intervention
- □ Comparator group
- □ Outcome

Optional (recommended)

- □ Timeframe for follow-up

□ Yes
□ No

2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:

- □ review question(s)
- □ a search strategy
- □ inclusion/exclusion criteria
- □ a risk of bias assessment

For Yes: As for partial yes, plus the protocol should be registered and should also have specified:

- □ a meta-analysis/synthesis plan, if appropriate, and
- □ a plan for investigating causes of heterogeneity
- □ justification for any deviations from the protocol

□ Yes
□ Partial Yes
□ No

3) Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- □ Explanation for including only RCTs
- □ OR Explanation for including only NRSI
- □ OR Explanation for including both RCTs and NRSI

□ Yes
□ No

4) Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5) Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- No

6) Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- No

7) Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study

- Yes
- Partial Yes
- No

8) Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:
- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- Yes
- Partial Yes
- No

9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from:
- unconcealed allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- from confounding, and
- from selection bias

For Yes, must also have assessed RoB:
- methods used to ascertain exposures and outcomes, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10) Did the review authors report on the sources of funding for the studies included in the review?

For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- Yes
- No

11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- AND investigated the causes of any heterogeneity

- Yes
- No
- No meta-analysis conducted

NRSI	**For Yes:** □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	□ Yes □ No □ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** **For Yes:** □ included only low risk of bias RCTs □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	□ Yes □ No □ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?** **For Yes:** □ included only low risk of bias RCTs □ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	□ Yes □ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** **For Yes:** □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	□ Yes □ No
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** **For Yes:** □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	□ Yes □ No □ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** **For Yes:** □ The authors reported no competing interests OR □ The authors described their funding sources and how they managed potential conflicts of interest	□ Yes □ No

APPENDIX C. Methods to Assess Methodological Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The AGREE II is an updated instrument that has been validated. It consists of 23 items in 6 domains (scope, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence) to rate (**Table 1**). Because it is time-consuming to administer, a consolidated global rating scale (GRS) was developed, and is generally a reasonable alternative to AGREE II if resources are limited. The AGREE II-GRS instrument consists of only 4 items (**Table 2**). As the AGREE II-GRS does not take into account conflicts of interest, questions 22 and 23 regarding "Editorial Independence" will also be evaluated in conjunction with the AGREE II-GRS. With both instruments, each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. High quality clinical practice guidelines are eligible for inclusion in DURM evidence summaries. These guidelines will score 6-7 points for each component on rigor of development. In general, a high quality clinical practice guideline will score 5-7 points on most components presented in the AGREE II and each component of the AGREE II-GRS.

Table 1. AGREE II Instrument.

	ITEM	DESCRIPTION
SCOPE AND PURPOSE		
1	The overall objective(s) of the guideline is (are) specifically described.	The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem or health topic. **[SCORE:]**
2	The health question(s) covered by the guideline is (are) specifically described.	A detailed description of the health questions covered by the guideline should be provided, particularly for key recommendations, although they need not be phrased as questions. **[SCORE:]**
3	The population to whom the guideline is meant to apply is specifically described.	A clear description of the population (ie, patients, public, etc.) covered by a guideline should be provided. The age range, sex, clinical description, and comorbidities may be provided. **[SCORE:]**
STAKEHOLDER INVOLVEMENT		
4	The guideline development group includes individuals from all relevant professional groups.	This may include members of the steering group, the research team involved in selection and review of the evidence and individuals involved in formulation of the final recommendations. **[SCORE:]**
5	The views and preferences of the target population have been sought.	Information about target population experiences and expectations of health care should inform the development of guidelines. There should be evidence that some process has taken place and that stakeholders' views have been considered. For example, the public was formally consulted to determine priority topics, participation of these stakeholders on the guideline development group, or external review by these stakeholders on draft documents. Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of patient/public values, preferences or experiences. **[SCORE:]**
6	The target users of the guideline are clearly defined.	The target users should be clearly defined in the guideline so the reader can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopedic surgeons, rheumatologists, and physiotherapists. **[SCORE:]**
RIGOR OF DEVELOPMENT		
7	Systematic methods were used to search for evidence.	Details of the strategy used to search for evidence should be provided, which include search terms used, sources consulted, and dates of the literature covered. The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated. **[SCORE:]**
8	The criteria for selecting the evidence are clearly described.	Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. **[SCORE:]**

9	The strengths and limitations of the body of evidence are clearly described.	Statements that highlight the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions, using informal or formal tools/methods, to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. **[SCORE:]**
10	The methods for formulating the recommendations are clearly described.	A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, or formal consensus techniques (eg, Delphi, Glaser techniques). **[SCORE:]**
11	The health benefits, adverse effects, and risks have been considered in formulating the recommendations.	The guideline should consider both effectiveness/efficacy and safety when recommendations are formulated. **[SCORE:]**
12	There is an explicit link between the recommendations and the supporting evidence.	An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. **[SCORE:]**
13	The guideline has been externally reviewed by experts prior to its publication.	A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include both clinical and methodological experts. **[SCORE:]**
14	A procedure for updating the guideline is provided.	A clear statement about the procedure for updating the guideline should be provided. **[SCORE:]**
CLARITY OF PRESENTATION		
15	The recommendations are specific and unambiguous.	A recommendation should provide a precise description of which option is appropriate in which situation and in what population. It is important to note that in some instances, evidence is not always clear and there may be uncertainty about the best practice. In this case, the uncertainty should be stated in the guideline. **[SCORE:]**
16	The different options for management of the condition or health issue are clearly presented.	A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. **[SCORE:]**
17	Key recommendations are easily identifiable	Users should be able to find the most relevant recommendations easily. **[SCORE:]**
APPLICABILITY		
18	The guideline describes facilitators and barriers to its application.	There may be existing facilitators and barriers that will impact the application of guideline recommendations. **[SCORE:]**
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	For a guideline to be effective, it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer/online support. **[SCORE:]**
20	The potential resource implications of applying the recommendations have been considered.	The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff or expensive drug treatment. These may have cost implications on health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources. **[SCORE:]**
21	The guideline presents monitoring and/or auditing criteria	Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline (eg, HbA1c <7%, DBP <95 mm Hg). **[SCORE:]**
EDITORIAL INDEPENDENCE		
22	The views of the funding body have not influenced the content of the guideline.	Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. **[SCORE:]**
23	Competing interests of guideline development group members have been recorded and addressed	There should be an explicit statement that all group members have declared whether they have any competing interests. **[SCORE:]**

Table 2. AGREE II Global Rating Scale (modified).

	ITEM	DESCRIPTION
1	Rate the guideline development methods. **[SCORE:]**	• Appropriate stakeholders were involved in the development of the guideline. • The evidentiary base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs was made.
2	Rate the guideline presentation. **[SCORE:]**	• The guideline was well organized. • The recommendations were easy to find.
3	Rate the guideline recommendations. **[SCORE:]**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
4	Rate the completeness of reporting, editorial independence. **[SCORE:]**	• The information is complete to inform decision making. • The guideline development process is transparent and reproducible.
5	The views of the funding body have not influenced the content of the guideline. **[SCORE:]**	• Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.
6	Competing interests of guideline development group members have been recorded and addressed. **[SCORE:]**	• There should be an explicit statement that all group members have declared whether they have any competing interests. • All competing interests should be listed • There should be no significant competing interests

APPENDIX D. GRADE Quality of Evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a framework to assess quality of evidence for an *outcome* that emphasizes transparency of how evidence judgments are made, though it does not necessarily guarantee consistency in assessment. Quality assessment in GRADE is 'outcome-centric' and distinct from quality assessment of an individual study. Information on risk of bias (internal validity), indirectness (applicability), imprecision, inconsistency, and publication bias is necessary to assess quality of evidence and overall confidence in the estimated effect size. The GRADE framework provides an assessment for each outcome.

DURM evidence summaries, unless a single drug is evaluated, depend on the whole body of available evidence. Evidence from high quality systematic reviews is the primary basis for recommendations in the evidence summaries. High quality evidence-based clinical practice guidelines and relevant randomized controlled trials are used to supplement the whole body of evidence.

High quality systematic reviews and clinical practice guidelines often use the GRADE framework to assess overall quality of evidence for a given outcome. In such cases, the grade of evidence provided in the respective report can be directly transferred to the DURM evidence summary. When an evidence summary includes relevant clinical trials, or when high quality systematic reviews or clinical practice guidelines that did not use the GRADE framework were identified, quality of evidence will be graded based on hierarchy of available evidence, homogeneity of results for a given outcome, and methodological flaws identified in the available evidence (**Table 1**).

Table 1. Evidence Grades for Benefit and Harm Outcomes When a Body of Evidence is Evaluated.

GRADE	TYPE OF EVIDENCE
High	• Evidence is based on data derived from multiple randomized controlled trials with homogeneity with regard to the direction of effect between studies AND • Evidence is based on multiple, well-done randomized controlled trials that involved large numbers of patients.
Moderate	• Evidence is based on data derived from randomized controlled trials with some conflicting conclusions with regard to the direction of effect between studies OR • Evidence is based on data derived from randomized controlled trials that involved small numbers of patients but showed homogeneity with regard to the direction of effect between studies OR • Some evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.)
Low	• Most evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.) OR • Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with homogeneity with regard to the direction of effect between studies
Insufficient	• Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with some conflicting conclusions with regard to direction of effect between studies OR • Evidence is based on data derived from expert opinion/panel consensus, case reports or case series OR • Evidence is not available

New Drug Evaluations cannot depend on evidence from systematic reviews and clinical practice guidelines. A body of evidence that solely consists of one or more clinical trials is initially assigned 4 points. For every relevant limitation, points are deducted; but points are added for consistently large effect sizes between studies or for a consistent dose-response observed in the studies (**Table 2**). The quality of evidence is subsequently graded as shown:

QUALITY OF EVIDENCE GRADES:

- ≥4 points = **HIGH**
- 3 points = **MODERATE**
- 2 points = **LOW**
- ≤1 point = **INSUFFICIENT**

Table 2. Domains to Grade Evidence for Benefit and Harm Outcomes from Clinical Trials: Cochrane Evidence Grades (modified).

DOMAIN	DESCRIPTION	SCORE DEMOTION/PROMOTION (start with 4 points)
Risk of Bias (internal validity)	Risk of bias is the likelihood to which the included studies for a given comparison and outcome has an inadequate protection against bias that affects the internal validity of the study. • *Did any studies have important limitations that degrade your confidence in estimates of effectiveness or safety?*	• No serious limitation: all studies have low risk of bias: **(0)** • Serious limitations: ≥1 trial has high or unclear risk of bias: **(-1)** • Very serious limitations: most studies have high risk of bias: **(-2)**
Indirectness (applicability)	Directness (applicability) relates to evidence that adequately compares 2 or more reasonable interventions that can be directly linked to a clinically relevant outcome in a population of interest. • *Do studies directly compare interventions of interest in populations of interest using outcomes of interest (use of clinically relevant outcomes)?*	• Direct: clinically relevant outcomes of important comparisons in relevant populations studied: **(0)** • Indirect: important comparisons missing; surrogate outcome(s) used; or population not relevant: **(-1)**
Inconsistency	Inconsistency (heterogeneity) is the degree to which reported effect sizes from included studies appear to differ in direction of effect. Effect sizes have the same sign (ie, are on the same side of ''no effect'') and the range of effect sizes is narrow. • *Did trials have similar or widely varying results? Can heterogeneity be explained by differences in trial design and execution?*	• Large magnitude of effect consistent between studies: **(+1)** • Dose-response observed: **(+1)** • Small magnitude of effect consistent between studies: **(0)** • 1 study with large magnitude of effect: **(0)** • 1 study with small magnitude of effect: **(-1)** • Inconsistent direction of effect across studies that cannot be explained: **(-1)**
Imprecision	Imprecision is the degree of uncertainty surrounding an effect estimate with respect to a given outcome (ie, the confidence interval for each outcome is too wide to rule out no effect). • *Are confidence intervals for treatment effect sufficiently narrow to rule out no effect?*	• Precise: all studies have 95% confidence intervals that rule out no effect: **(0)** • Imprecise: ≥1 study demonstrated 95% confidence interval fails to rule out no effect: **(-1)**
Publication Bias	Publication bias is the degree in which completed trials are not published or represented. Unpublished studies may have negative outcomes that would otherwise change our confidence in the body of evidence for a particular comparison and outcome. • *Is there evidence that important trials are not represented?*	• No publication bias: all important trials published or represented: **(0)** • Serious publication bias: ≥1 important trial(s) completed but not published: **(-1)**

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: February 2023

MISSION:

To encourage safe, effective, and innovative drug policies that promote high value medications for patients served by the Oregon Health Plan (OHP) and other health care programs under the Oregon Health Authority (OHA) by evidence-based committee review of drug use research, clinical guidance and education.

DUTIES:

As defined by Oregon Revised Statutes (Chapter 414) the Pharmacy and Therapeutics (P&T) Committee was established to perform functions previously fulfilled by the Drug Use Review Board and Health Resources Commission. Responsibilities of the P&T committee include:

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.
2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
3. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.
4. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs.
5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
6. Consider input from Mental Health Clinical Advisory Group (MHCAG) on topics involving mental health. The Mental Health Clinical Advisory Group can make recommendations to both the Oregon Health Authority and the Pharmacy and Therapeutics Committee for:
    a. Implementation of evidence-based algorithms.
    b. Any changes needed to any preferred drug list used by the authority.
    c. Practice guidelines for the treatment of mental health disorders with mental health drugs.
    d. Coordinating the work of the group with an entity that offers a psychiatric advice hotline.
7. Guide and approve meeting agendas.
8. Periodically review and update operating procedures and evidence grading methods as needed.

AD-HOC EXPERT INVOLVEMENT:

1. The Director shall appoint an ad hoc expert to the P&T Committee when:
    a. The P&T Committee determines it lacks current clinical or treatment expertise with respect to a particular therapeutic class; or
    b. An interested outside party requests appointment and demonstrates to the satisfaction of the Director that the P&T Committee lacks necessary clinical knowledge or treatment expertise with respect to a particular therapeutic class. All such requests must be made at least 21 calendar days before the P&T Committee meeting at which the class will be discussed.

2. The medical experts shall have full voting rights with respect to the PDL drugs for which they have been selected and appointed including all utilization controls, prior authorization requirements, review of confidential pricing information or other conditions for the inclusion of a drug on the PDL. The medical experts may participate but may not vote in any other activities of the committee.

3. P&T staff also may engage relevant health care professionals with clinical specialty to serve as expert reviewers, in addition to the ad-hoc experts, if needed.

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.
2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings. Elections shall be held the first meeting of the calendar year.
3. Quorum consists of 6 permanent members of the P&T Committee. Quorum is required for any official vote or action to take place throughout a meeting.
4. All official actions must be taken by a public vote. Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.
5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual prescribers or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug lists adopted by the OHA.
6. Meetings will be held at least quarterly but the Committee may be asked to convene up to monthly by the call of the OHA Director or a majority of the members of the Committee. DUR programs will be the focus of the meeting quarterly.
7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.
    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

CONFLICT OF INTEREST POLICY:

The P&T Committee will function in a way that ensures the objectivity and credibility of its recommendations.

1. All potential initial committee members, staff members and consultants, future applicants, expert or peer reviewers, and ad-hoc medical experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and are required to submit a completed disclosure form as part of the appointment process which must be updated promptly with any changes in status.

2. Staff members are required to have no financial conflicts related to any pharmaceutical industry business for duration of work on P&T projects.

3. All disclosed conflicts will be considered before an offer of appointment is made.

4. If any material conflict of interest is not disclosed by a member of the P&T Committee on his or her application or prior to participation in consideration of an affected drug or drug class or other action of the Committee, that person will not be able to participate in voting decisions of the affected drug or drug class and may be subject to dismissal. Circumstances in which conflicts of interest not fully disclosed for peer reviewers, ad-hoc experts, or persons providing public comment will be addressed on a case by case basis.

5. Any person providing public testimony are also requested to disclose all conflicts of interest including, but not limited to, industry funded research prior to any testimony pertaining to issues before the P&T Committee. This includes any relationships or activities which could be perceived to have influenced, or that would give the appearance of potentially influencing testimony.

PUBLIC COMMENT:

1. The P&T Committee meetings will be open to the public.

2. The P&T Committee shall provide appropriate opportunity for public testimony at each meeting.

    a. Testimony can be submitted in writing or provided in-person. Persons planning to provide oral testimony during the meeting are requested to sign up and submit a conflict of interest form no later than 24 hours prior to the start of the meeting.

    b. Maximum of 3 minutes per speaker/institution per agenda item

        i. Information that is most helpful to the Committee is evidence-based and comparative research, limited to new information not already being reviewed by the Committee.
        ii. Oral presentation of information from FDA-approved labeling (i.e., Prescribing Information or “package insert”) is not helpful to the Committee.

    c. Please address written testimony related to final posted documents to the P&T Committee. Interested parties may submit written testimony on agenda items being considered by the P&T committee through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management). Written testimony that includes clinical information should be submitted at least 2 weeks prior to the scheduled meeting to allow staff and Committee members time to review the information.

d. Written documents provided during scheduled public testimony time of P&T Committee meetings will be limited to 2 pages of new information that was not included in previous reviews. Prescribing Information is not considered new information; only clinically relevant changes made to Prescribing Information should be submitted.

e. If committee members have additional questions or request input from public members during deliberations after the public comment period, members of the public may be recognized at the discretion of the committee chair to answer questions of the committee or provide additional commentary.

3. Written public comment is welcome from all interested parties on draft documents posted prior to the meeting.
    a. Written public comments submitted during the draft comment period are only considered by staff in order to prepare final documents. Only written public comment submitted based on final documents will be submitted to the P&T Committee for consideration.
    b. Interested parties may submit written testimony on posted draft documents through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the PDL and clinical prior authorization criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices. For detailed description of review standards, preferred sources of evidence, and evidence grading methods, see Quality Assessment Tool and Evidence Grading Methods.

2. Final documents as outlined in Chapter 414 of the Oregon Revised Statutes shall be made publicly available at least 30 days prior to review by the P&T Committee. Posted documents will include the agenda for the meeting, a list of drug classes to be considered, and background materials and supporting documentation which have been provided to committee members with respect to drugs and drug classes that are before the committee for review.

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews and New Drug Evaluations:

    a. The P&T Committee will review drugs and drug classes that have not been previously reviewed for PDL inclusion or for clinical PA criteria and will be prioritized based on:
        i. Potential benefit or risk
        ii. Use or potential use in covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.

b. The P&T Committee will make a reasonable effort to perform a timely review of new FDA-approved drug products following their market release, when they are a new molecular entity and are candidates for coverage under the pharmacy benefit.
    i. Until new drugs are reviewed by the P&T Committee, drugs meeting the following criteria will be reviewed to ensure they are used appropriately for an FDA-approved or compendia-supported indication, with FDA-approved dosing, and that the indication is funded by the OHP:
        a. A new drug in a drug class with clinical prior authorization criteria.
        b. A new drug used for a non-funded condition on the HERC Prioritized List of Health Services.
        c. A new drug not in a PDL class with existing PA criteria identified by the reviewing pharmacist during the weekly claim processing drug file load costing more than $5,000 per claim or $5,000 per month.

c. Line Extension and Combination Product Policy
    i. Line extensions include new strengths or new formulations of an existing drug.
        1. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
        2. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
    ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, the product will be designated a non-preferred drug until the P&T Committee reviews the combination product.
    iii. When a product becomes available that is a biosimilar for one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee reviews the product. A complete list of biological products and biosimilar products can be accessed at the FDA's Purple Book website.

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

    a. Literature of drug classes that have previously been reviewed for the PDL will be scanned and evaluated as needed to assess the need to update drug policies based on clinically relevant information and significant changes in costs published since the last review.
    b. Abbreviated drug reviews will evaluate drugs for unfunded conditions. Evidence supporting these reports is derived primarily from information in the product labeling.

Drug Use Research & Management Program
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Prior Authorization Criteria Update: Oncology

Purpose of the Update:
This update identifies antineoplastic drugs recently approved by the FDA to add to the oncology policy (see **Table 1**).

Table 1. New oncology drugs

Generic Name	Brand Name
adagrasib	KRAZATI
olutasidenib	REZLIDHIA
mirvetuximab soravtansive-gynx	ELAHERE

Recommendation:

- Update prior authorization criteria to include new, recently approved antineoplastic drugs.

Oncology Agents

Goal(s):

- To ensure appropriate use for oncology medications based on FDA-approved and compendia-recommended (i.e., National Comprehensive Cancer Network® [NCCN]) indications.

Length of Authorization:

- Up to 1 year

Requires PA:

- Initiation of therapy for drugs listed in **Table 1** (applies to both pharmacy and physician administered claims). This does not apply to oncologic emergencies administered in an emergency department or during inpatient admission to a hospital.

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 request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5.

Approval Criteria		
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.
6. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #8
8. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	**No:** Go to #9
9. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria
10. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Table 1. Oncology agents which apply to this policy (Updated 12/28/2022)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
adagrasib	KRAZATI
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
futibatinib	LYTGOBI
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA

Generic Name	Brand Name
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mirvetuximab soravtansive-gynx	ELAHERE
mobecertinib	EXKIVITY
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
nivolumab; relatlimab-rmbw	OPDUALAG
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/20

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Prior Authorization Criteria Update: Orphan Drug

Purpose of the Update:
This update identifies orphan drugs recently approved by the FDA to add to the orphan drug policy **(Table 1)**.

Table 1. New orphan drugs

Generic Name	Brand Name
Oplipudase alfa-rpcp	XENPOZYME
Trientine tetrahydrochloride	CUVRIOR

Recommendation:

- PA was modified to include new, recently approved orphan drugs.

Author: Sara Fletcher, PharmD, MPH, BCPS

February 2023

Orphan Drugs

Goal(s):
- To support medically appropriate use of orphan drugs (as designated by the FDA) which are indicated for rare conditions
- To limit off-label use of orphan drugs

Length of Authorization:
- Up to 6 months

Requires PA:
- See Table 1 (pharmacy and physician administered 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/

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
Alpelisib (VIJOICE)	PIK3CA-Related Overgrowth Spectrum (PROS) in those who require systemic therapy	≥ 2 yrs	Pediatric 2 to <18 yrs: • 50 mg once daily • May consider increase to 125 mg once daily if ≥6 years after 24 weeks of treatment • May gradually increase to 250 mg once daily once patient turns 18 Adult: • 250 mg once daily	Baseline Monitoring • Fasting BG, HbA1c Ongoing Monitoring • Fasting BG weekly x 2 weeks, then at least once every 4 weeks, then as clinically indicated • HbA1c every 3 months and as clinically indicated
Avacopan (TAVNEOS)	Severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with glucocorticoids.	≥18 yrs	30 mg (three 10 mg capsules) twice daily, with food	Baseline Monitoring • Liver function tests ALT, AST, ALP, and total bilirubin • Hepatitis B (HBsAg and anti-HBc) Ongoing Monitoring • Liver function tests every 4 wks for 6 months, then as clinically indicated
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH)	XLH ≥ 6 mo TIO	Pediatric <18 yrs: Initial (administered SC every 2 wks): XLH	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated

	FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	≥ 2 yrs	• <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 mg for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max dose 2 mg/kg or 180mg every 2 wks)	• Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Belumosudil (REZUROCK)	Treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	≥ 12 yrs	200 mg orally once daily with food 200 mg twice daily when coadministered with strong CYP3A inducers or proton pump inhibitors	Baseline & Ongoing Monitoring • Total bilirubin, AST, ALT at least monthly • Pregnancy test (if childbearing potential)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 yrs	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks)	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.

	cofactor deficiency (MoCD) Type A		Initial: 0.4mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary and plasma oxalate levels	N/A	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months **≥ 20 kg** Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months	N/A

			All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	<u>Baseline Monitoring/Documentation</u> • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure <u>Ongoing Monitoring</u> • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 1 yr	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 390 mcg/kg once daily after 1 week on initial dose, as tolerated	<u>Baseline/Ongoing Monitoring</u> • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily. Max dose: 50 mg twice daily Discontinuation should include down-titration.	<u>Baseline/Ongoing Monitoring</u> • Hgb, transfusion requirement
Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments	<u>Baseline/Ongoing Monitoring</u> • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K

	patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)		Max dose: 120 mcg/kg once daily; not to exceed 6 mg	
Trientine tetrahydrochloride (XENPOZYME)	Non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD)	N/A	Initial: Age based dose escalation table per Package insert Maintenance: 3 mg/kg via IV infusion every 2 weeks Weight: • If BMI ≤ 30, use actual body weight • If BMI > 30, use adjusted body weight Adjusted body weight (kg) = (actual height in M)^2 x 30	Baseline Monitoring • Liver function tests (ALT, AST) within 1 month • Pregnancy test (if childbearing potential) Ongoing Monitoring • Liver function tests (ALT, AST) within 72 hours of infusions during dose escalation, then during routine clinical management once at maintenance dose
Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given IV every 2 to 4 days	Baseline Monitoring • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) Ongoing Monitoring • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
Sodium thiosulfate (PEDMARK)	Decrease ototoxicity associated with cisplatin infusions lasting ≤ 6 hours. Not approved for use with longer infusions.	≥ 1 mo to ≤18 yr	< 5 kg: 10 g/m^2 5-10 kg: 15 g/m^2 >10 kg: 20 g/m^2	Baseline Monitoring • Serum potassium and sodium
Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg** 6500 mg **≥75 kg** 7500 mg	Baseline Monitoring • Vaccination against encapsulated bacteria (*Neisseria meningititides* (any serogroup), *Streptococcus pneumonia,* and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed

Trientine tetrahydrochloride (CUVRIOR)	Stable Wilson's disease who are de-coppered and tolerant to penicillamine	≥ 18 yr	Total daily dose in transition from penicillamine per table in package insert.	Baseline/Ongoing Monitoring • Serum NCC levels at baseline, 3 months, then roughly every 6 months serum levels or 6 to 12 months with urinary copper excretion

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BG = blood glucose; BSA = body surface area; CBC = complete blood count; CrCL = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycalated hemoglobin; Hgb = hemoglobin; INR = international normalized ratio; IV = intravenously; mo = months; NCC = non-ceruloplasmin copper; RBC = red blood cells; SC = subcutaneously; wks = weeks; yrs = years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	**Yes**: Approve for up to 6 months Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23; 12/22; 6/22; 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: 1/1/23; 7/1/22; 5/1/22; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: July 2021 - June 2022

Eligibility	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Total Members (FFS & Encounter)	1,212,729	1,222,901	1,230,474	1,238,036	1,249,056	1,258,864	1,270,424	1,276,063	1,284,291	1,291,200	1,296,769	1,303,371	1,261,182
FFS Members	109,457	112,375	108,825	111,347	109,132	112,664	117,322	110,548	109,789	112,522	113,945	111,881	111,651
OHP Basic with Medicare	8,110	8,273	8,141	8,429	8,051	8,195	8,488	8,161	8,271	8,510	8,597	8,424	8,304
OHP Basic without Medicare	10,947	11,003	10,811	10,888	10,718	10,697	10,889	10,579	10,500	10,595	10,601	10,503	10,728
ACA	90,400	93,099	89,873	92,030	90,363	93,772	97,945	91,808	91,018	93,417	94,747	92,954	92,619
Encounter Members	1,103,272	1,110,526	1,121,649	1,126,689	1,139,924	1,146,200	1,153,102	1,165,515	1,174,502	1,178,678	1,182,824	1,191,490	1,149,531
OHP Basic with Medicare	82,240	83,030	83,993	84,715	86,139	86,570	87,412	88,084	89,468	90,661	92,068	93,206	87,299
OHP Basic without Medicare	67,639	67,674	68,041	67,983	68,260	68,173	68,310	68,509	68,469	68,580	68,801	68,956	68,283
ACA	953,393	959,822	969,615	973,991	985,525	991,457	997,380	1,008,922	1,016,565	1,019,437	1,021,955	1,029,328	993,949

Gross Cost Figures for Drugs	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	YTD Sum
Total Amount Paid (FFS & Encounter)	$100,601,357	$104,031,441	$105,632,250	$97,594,488	$100,704,249	$103,213,832	$102,369,242	$98,629,300	$115,692,121	$106,268,650	$111,294,848	$112,845,085	$1,258,876,863
Mental Health Carve-Out Drugs	$11,634,301	$11,839,832	$11,283,569	$10,847,208	$11,008,403	$11,204,713	$11,274,059	$10,873,451	$12,323,136	$11,643,252	$12,142,938	$11,942,002	$138,016,864
OHP Basic with Medicare	$2,855	$5,699	$4,725	$8,509	$5,705	$2,848	$317	$11,314	$7,893	$11,471	$9,259	$10,001	$80,598
OHP Basic without Medicare	$4,468,778	$4,505,507	$4,324,752	$4,007,152	$4,054,014	$4,178,135	$4,088,556	$3,906,687	$4,431,152	$4,146,994	$4,342,389	$4,417,471	$50,871,588
ACA	$7,074,292	$7,240,075	$6,876,632	$6,749,876	$6,865,912	$6,936,149	$7,092,783	$6,865,375	$7,785,315	$7,397,043	$7,695,741	$7,436,315	$86,015,508
FFS Physical Health Drugs	$4,615,975	$4,679,918	$4,547,061	$4,525,063	$4,488,343	$4,568,580	$4,988,149	$4,507,668	$5,039,724	$5,256,497	$5,491,174	$5,198,354	$57,906,505
OHP Basic with Medicare	$167,274	$169,504	$164,733	$165,578	$171,115	$158,438	$187,759	$178,628	$203,099	$196,522	$205,439	$230,602	$2,198,690
OHP Basic without Medicare	$1,156,152	$1,203,299	$1,138,809	$1,201,436	$1,027,631	$1,116,766	$1,132,715	$990,058	$1,095,328	$1,162,800	$1,223,311	$1,193,739	$13,642,045
ACA	$3,159,504	$3,144,462	$3,051,649	$3,001,923	$3,125,516	$3,193,326	$3,519,663	$3,228,150	$3,625,735	$3,742,697	$3,910,664	$3,643,803	$40,347,089
FFS Physician Administered Drugs	$1,271,810	$1,252,463	$1,104,205	$1,455,392	$1,230,853	$1,092,575	$1,149,041	$1,567,355	$1,645,144	$1,318,463	$1,310,705	$1,658,584	$16,056,590
OHP Basic with Medicare	$109,361	$126,279	$104,609	$78,875	$155,381	$170,498	$181,660	$153,895	$128,029	$153,120	$124,869	$127,466	$1,614,042
OHP Basic without Medicare	$279,746	$209,919	$221,646	$584,257	$413,340	$236,106	$201,139	$525,783	$499,909	$255,292	$315,408	$566,923	$4,309,468
ACA	$512,495	$471,309	$445,795	$429,638	$369,302	$425,045	$387,337	$560,564	$585,650	$550,597	$504,671	$536,355	$5,778,757
Encounter Physical Health Drugs	$64,707,136	$65,517,545	$64,361,407	$63,575,908	$66,090,938	$68,070,202	$67,366,640	$64,531,840	$73,983,976	$69,205,260	$72,414,113	$71,988,031	$811,812,996
OHP Basic with Medicare	$424,894	$398,784	$416,252	$399,460	$446,477	$473,201	$426,508	$393,351	$443,278	$410,101	$426,556	$397,272	$5,056,134
OHP Basic without Medicare	$15,562,693	$16,284,282	$15,447,771	$15,475,998	$16,311,201	$16,377,133	$16,514,791	$16,149,682	$17,632,999	$17,054,716	$17,075,817	$17,288,472	$197,175,555
ACA	$47,565,868	$47,803,923	$47,639,868	$46,945,237	$48,574,675	$50,327,212	$49,559,613	$47,138,746	$54,874,624	$50,705,527	$53,879,595	$53,230,704	$598,245,591
Encounter Physician Administered Drugs	$18,372,135	$20,741,683	$24,336,009	$17,190,918	$17,885,711	$18,277,762	$17,591,354	$17,148,986	$22,700,141	$18,845,179	$19,935,919	$22,058,114	$235,083,909
OHP Basic with Medicare	$837,923	$939,339	$903,191	$1,018,565	$957,323	$921,145	$1,067,696	$879,855	$1,079,868	$965,403	$988,330	$1,104,356	$11,662,994
OHP Basic without Medicare	$4,013,080	$3,998,476	$10,735,628	$3,844,313	$4,269,013	$4,366,648	$3,829,479	$4,087,296	$5,552,461	$4,450,577	$5,710,590	$4,587,404	$59,444,965
ACA	$12,941,333	$15,437,701	$12,364,436	$12,156,098	$12,383,920	$12,785,256	$12,439,727	$11,919,514	$15,842,473	$13,260,717	$13,054,427	$16,016,056	$160,601,658

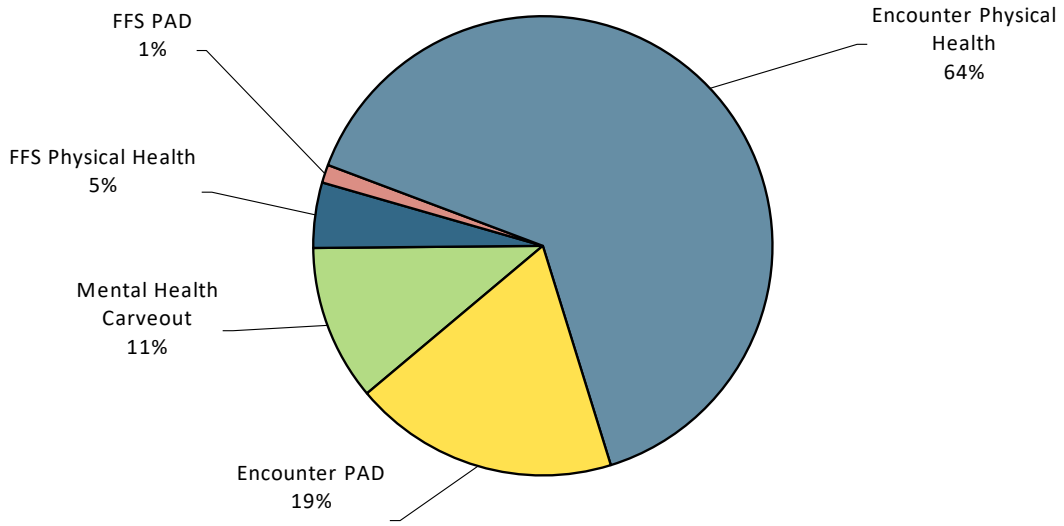
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

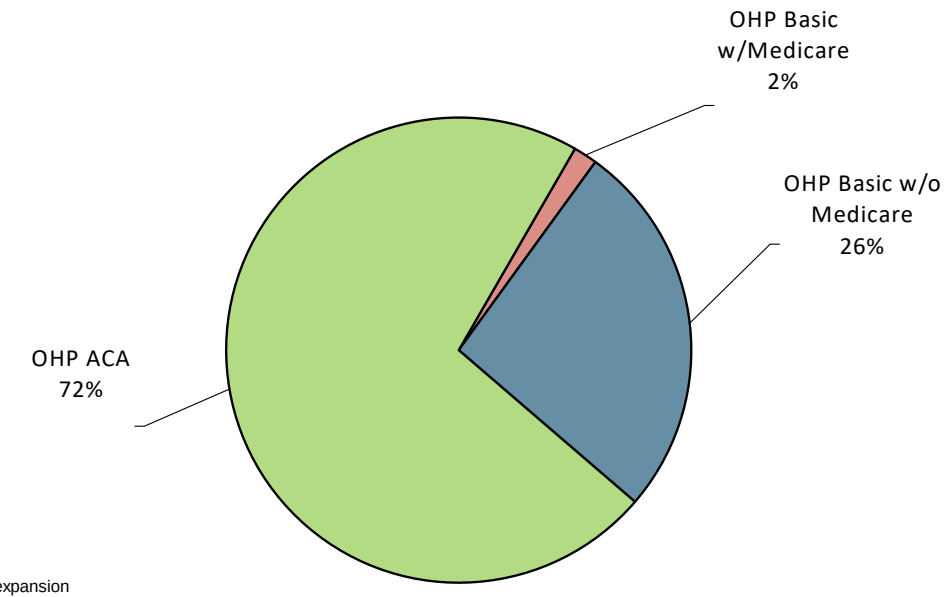
Last Updated: January 19, 2023

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 2021 - June 2022

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 ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: January 19, 2023

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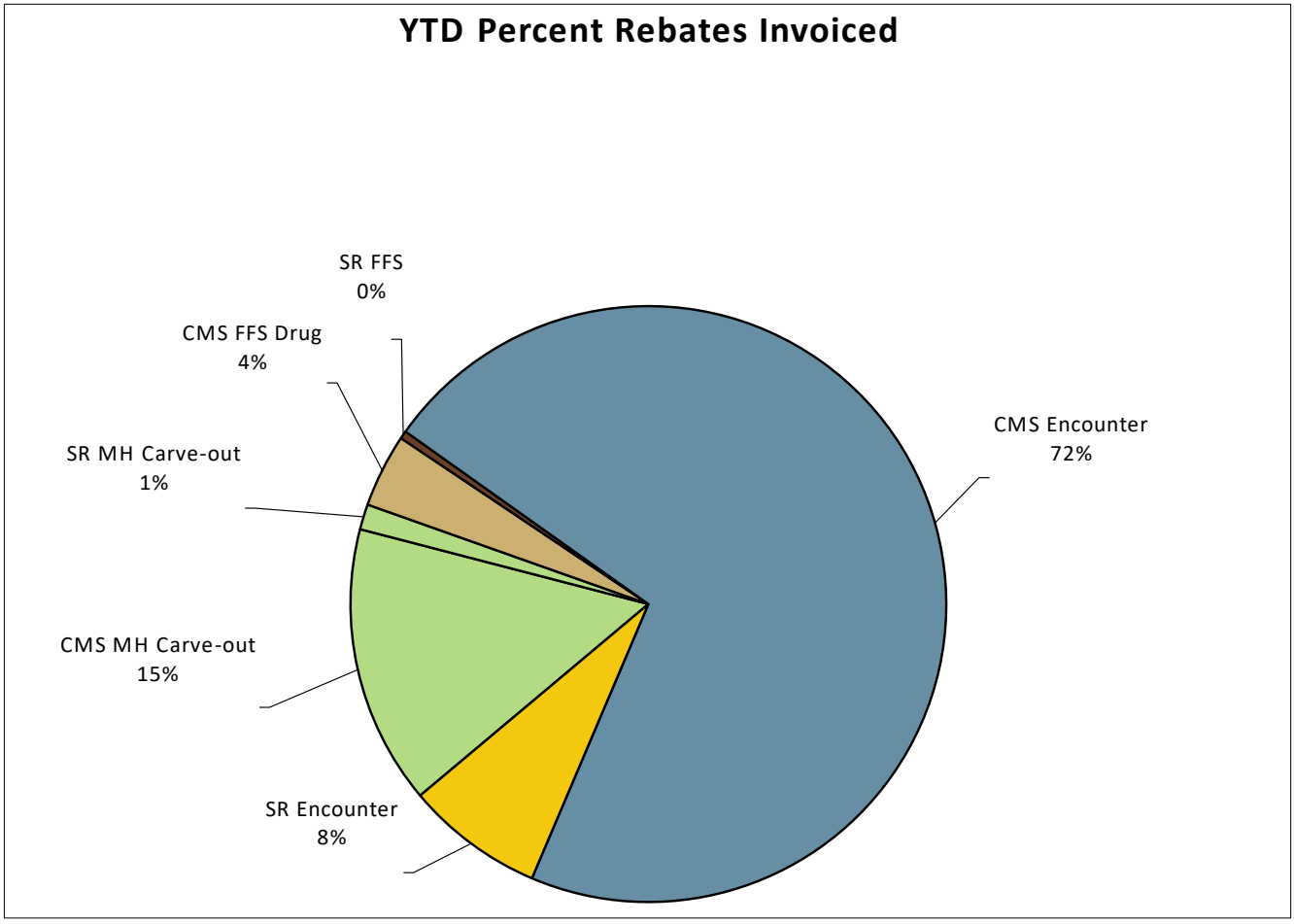
Pharmacy Utilization Summary Report: July 2021 - June 2022

Quarterly Rebates Invoiced	2021-Q3	2021-Q4	2022-Q1	2022-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$115,469,222	$112,672,501	$120,412,672	$122,705,833	$471,260,228
CMS MH Carve-out	$18,517,757	$17,613,738	$17,099,442	$18,192,637	$71,423,574
SR MH Carve-out	$1,615,634	$1,794,878	$1,341,151	$1,717,058	$6,468,720
CMS FFS Drug	$4,611,064	$4,769,712	$4,803,103	$4,585,725	$18,769,604
SR FFS	$453,749	$553,362	$503,150	$508,343	$2,018,605
CMS Encounter	$81,248,806	$79,112,861	$88,307,235	$88,589,036	$337,257,938
SR Encounter	$9,022,212	$8,827,950	$8,358,591	$9,113,034	$35,321,787

Quaterly Net Drug Costs	2021-Q3	2021-Q4	2022-Q1	2022-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$194,795,826	$188,840,067	$196,277,991	$207,702,751	$787,616,635
Mental Health Carve-Out Drugs	$14,624,311	$13,651,709	$16,030,053	$15,818,497	$60,124,570
FFS Phys Health + PAD	$12,406,618	$12,037,731	$13,590,828	$15,139,709	$53,174,886
Encounter Phys Health + PAD	$167,764,896	$163,150,627	$166,657,111	$176,744,545	$674,317,179



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

Last Updated: January 19, 2023

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: July 2021 - June 2022

Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$82.95	$85.07	$85.85	$78.83	$80.62	$81.99	$80.58	$77.29	$90.08	$82.30	$85.82	$86.58	$83.16
Mental Health Carve-Out Drugs	$9.59	$9.68	$9.17	$8.76	$8.81	$8.90	$8.87	$8.52	$9.60	$9.02	$9.36	$9.16	$9.12
FFS Physical Health Drugs	$42.17	$41.65	$41.78	$40.64	$41.13	$40.55	$42.52	$40.78	$45.90	$46.72	$48.19	$46.46	$43.21
FFS Physician Administered Drugs	$11.62	$11.15	$10.15	$13.07	$11.28	$9.70	$9.79	$14.18	$14.98	$11.72	$11.50	$14.82	$12.00
Encounter Physical Health Drugs	$58.65	$59.00	$57.38	$56.43	$57.98	$59.39	$58.42	$55.37	$62.99	$58.71	$61.22	$60.42	$58.83
Encounter Physician Administered Drugs	$16.65	$18.68	$21.70	$15.26	$15.69	$15.95	$15.26	$14.71	$19.33	$15.99	$16.85	$18.51	$17.05

Claim Counts	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Total Claim Count (FFS & Encounter)	1,130,587	1,128,715	1,095,814	1,096,769	1,097,333	1,110,529	1,123,308	1,048,625	1,199,366	1,146,357	1,181,936	1,172,956	1,127,691
Mental Health Carve-Out Drugs	188,047	190,954	185,225	183,233	185,490	188,463	190,990	179,945	204,504	193,220	199,624	197,883	190,632
FFS Physical Health Drugs	38,323	38,661	36,754	35,415	35,162	35,897	38,033	34,924	38,399	36,485	37,551	36,587	36,849
FFS Physician Administered Drugs	9,967	9,336	9,083	9,493	8,937	9,241	10,573	9,486	11,305	10,024	10,144	9,895	9,790
Encounter Physical Health Drugs	770,817	772,719	754,720	751,433	751,114	765,440	773,118	717,798	819,816	787,291	813,529	810,914	774,059
Encounter Physician Administered Drugs	123,433	117,045	110,032	117,195	116,630	111,488	110,594	106,472	125,342	119,337	121,088	117,677	116,361

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$88.98	$92.17	$96.40	$88.98	$91.77	$92.94	$91.13	$94.06	$96.46	$92.70	$94.16	$96.21	$93.00
Mental Health Carve-Out Drugs	$61.87	$62.00	$60.92	$59.20	$59.35	$59.45	$59.03	$60.43	$60.26	$60.26	$60.83	$60.35	$60.33
FFS Physical Health Drugs	$120.45	$121.05	$123.72	$127.77	$127.65	$127.27	$131.15	$129.07	$131.25	$144.07	$146.23	$142.08	$130.98
FFS Physician Administered Drugs	$127.60	$134.15	$121.57	$153.31	$137.73	$118.23	$108.68	$165.23	$145.52	$131.53	$129.21	$167.62	$136.70
Encounter Physical Health Drugs	$83.95	$84.79	$85.28	$84.61	$87.99	$88.93	$87.14	$89.90	$90.24	$87.90	$89.01	$88.77	$87.38
Encounter Physician Administered Drugs	$148.84	$177.21	$221.17	$146.69	$153.35	$163.94	$159.06	$161.07	$181.11	$157.92	$164.64	$187.45	$168.54

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.20	$22.40	$21.83	$22.02	$22.59	$22.85	$23.10	$23.25	$23.57	$23.98	$24.01	$24.48	$23.02
Mental Health Carve-Out Drugs	$17.01	$16.68	$16.14	$16.23	$16.45	$16.36	$16.49	$16.42	$16.30	$16.64	$16.81	$17.06	$16.55
FFS Physical Health Drugs	$78.01	$78.26	$77.72	$78.01	$81.31	$81.06	$84.30	$84.20	$86.86	$97.11	$99.47	$99.48	$85.48
Encounter Physical Health Drugs	$21.11	$21.48	$20.96	$21.15	$21.80	$22.22	$22.25	$22.39	$22.75	$22.76	$22.66	$23.28	$22.07

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$527.35	$512.72	$505.17	$517.67	$547.47	$535.57	$538.62	$607.10	$648.16	$641.44	$654.31	$665.87	$575.12
Mental Health Carve-Out Drugs	$1,012.91	$1,019.27	$1,005.24	$964.65	$932.32	$950.89	$946.63	$965.69	$963.50	$962.40	$964.47	$1,020.71	$975.72
FFS Physical Health Drugs	$270.46	$261.83	$273.16	$319.51	$290.47	$272.83	$281.78	$315.17	$345.71	$372.90	$375.53	$350.21	$310.80
Encounter Physical Health Drugs	$507.84	$492.39	$484.30	$495.16	$533.66	$522.47	$526.11	$595.15	$637.05	$627.39	$641.66	$653.22	$559.70

Generic Drug Use Percentage	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Generic Drug Use Percentage	88.3%	87.9%	87.5%	88.0%	88.3%	87.9%	88.3%	89.3%	90.0%	90.2%	90.2%	90.5%	88.9%
Mental Health Carve-Out Drugs	95.5%	95.5%	95.5%	95.5%	95.3%	95.4%	95.4%	95.4%	95.4%	95.4%	95.4%	95.7%	95.4%
FFS Physical Health Drugs	77.9%	76.7%	76.5%	79.4%	77.8%	75.9%	76.3%	80.6%	82.9%	83.0%	83.1%	83.0%	79.4%
Encounter Physical Health Drugs	87.1%	86.6%	86.1%	86.6%	87.1%	86.7%	87.1%	88.2%	89.0%	89.2%	89.3%	89.6%	87.7%

Preferred Drug Use Percentage	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Avg Monthly
Preferred Drug Use Percentage	90.04%	89.98%	89.89%	89.88%	89.82%	89.75%	89.84%	89.81%	89.89%	89.88%	89.89%	89.82%	89.9%
Mental Health Carve-Out Drugs	93.46%	93.42%	93.36%	93.47%	93.34%	93.35%	93.31%	93.29%	93.31%	93.34%	93.31%	93.27%	93.4%
FFS Physical Health Drugs	94.68%	94.90%	94.70%	94.80%	94.96%	94.98%	94.52%	94.43%	94.53%	94.65%	94.80%	94.89%	94.7%
Encounter Physical Health Drugs	89.00%	88.91%	88.82%	88.78%	88.73%	88.65%	88.77%	88.73%	88.84%	88.85%	88.86%	88.79%	88.8%

Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: January 19, 2023

Drug Use Research & Management Program
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA*	Antipsychotics, 2nd Gen	$6,938,985	16.6%	5,538	$1,253	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$4,037,891	9.6%	1,721	$2,346	Y
3	VRAYLAR*	Antipsychotics, 2nd Gen	$3,359,389	8.0%	2,865	$1,173	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,123,747	5.1%	959	$2,215	Y
5	REXULTI*	Antipsychotics, 2nd Gen	$2,015,722	4.8%	1,691	$1,192	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$972,535	2.3%	135	$7,204	Y
7	ARISTADA	Antipsychotics, Parenteral	$858,146	2.0%	353	$2,431	Y
8	TRINTELLIX	Antidepressants	$797,636	1.9%	1,909	$418	V
9	Epoetin Beta Esrd Use	Physican Administered Drug	$578,846	1.4%	42	$13,782	
10	SERTRALINE HCL	Antidepressants	$568,246	1.4%	58,731	$10	Y
11	BUPROPION XL	Antidepressants	$538,021	1.3%	42,231	$13	Y
12	DULOXETINE HCL	Antidepressants	$525,497	1.3%	36,815	$14	Y
13	CAPLYTA*	Antipsychotics, 2nd Gen	$493,185	1.2%	364	$1,355	V
14	TRAZODONE HCL	Antidepressants	$480,517	1.1%	47,222	$10	
15	FLUOXETINE HCL	Antidepressants	$475,045	1.1%	42,662	$11	Y
16	ESCITALOPRAM OXALATE	Antidepressants	$411,501	1.0%	41,416	$10	Y
17	LYBALVI*	Antipsychotics, 2nd Gen	$354,046	0.8%	273	$1,297	V
18	ATOMOXETINE HCL*	ADHD Drugs	$347,820	0.8%	7,276	$48	Y
19	INVEGA*	Antipsychotics, 2nd Gen	$329,049	0.8%	852	$386	
20	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$322,777	0.8%	26,495	$12	
21	LAMOTRIGINE	Antiepileptics, Outpatient	$316,682	0.8%	28,987	$11	Y
22	SPRAVATO*	Antidepressants	$306,094	0.7%	234	$1,308	V
23	CHOLBAM*	Bile Therapy	$298,829	0.7%	3	$99,610	N
24	LAMOTRIGINE ER	Antiepileptics, Outpatient	$260,175	0.6%	3,254	$80	V
25	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$256,070	0.6%	19,722	$13	Y
26	BIKTARVY	HIV	$253,153	0.6%	100	$2,532	Y
27	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$235,017	0.6%	234	$1,004	Y
28	VENLAFAXINE HCL ER	Antidepressants	$230,066	0.5%	18,630	$12	Y
29	BUPROPION XL	Antidepressants	$228,294	0.5%	1,265	$180	V
30	TRIKAFTA*	Cystic Fibrosis	$223,282	0.5%	24	$9,303	N
31	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$218,301	0.5%	19,862	$11	Y
32	Elosulfase Alfa, Injection	Physican Administered Drug	$204,710	0.5%	13	$15,747	
33	INVEGA*	Antipsychotics, 2nd Gen	$204,101	0.5%	547	$373	Y
34	CONCERTA*	ADHD Drugs	$187,076	0.4%	516	$363	Y
35	CITALOPRAM HBR	Antidepressants	$171,684	0.4%	19,883	$9	Y
36	VENLAFAXINE HCL ER	Antidepressants	$168,475	0.4%	2,433	$69	V
37	AMITRIPTYLINE HCL*	Antidepressants	$164,004	0.4%	13,917	$12	Y
38	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$163,075	0.4%	16	$10,192	Y
39	MIRTAZAPINE	Antidepressants	$162,083	0.4%	11,762	$14	Y
40	OLANZAPINE*	Antipsychotics, 2nd Gen	$159,896	0.4%	12,548	$13	Y
		Top 40 Aggregate:	**$30,939,669**		**473,500**	**$4,401**	
		All FFS Drugs Totals:	**$41,873,572**		**702,904**	**$604**	

*** 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 ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Epoetin Beta Esrd Use	Physican Administered Drug	$578,846	6.4%	42	$13,782	
2	CHOLBAM*	Bile Therapy	$298,829	3.3%	3	$99,610	N
3	BIKTARVY	HIV	$253,153	2.8%	100	$2,532	Y
4	TRIKAFTA*	Cystic Fibrosis	$223,282	2.5%	24	$9,303	N
5	Elosulfase Alfa, Injection	Physican Administered Drug	$204,710	2.3%	13	$15,747	
6	CONCERTA*	ADHD Drugs	$187,076	2.1%	516	$363	Y
7	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$163,075	1.8%	16	$10,192	Y
8	SABRIL	Antiepileptics, Outpatient	$138,421	1.5%	3	$46,140	N
9	STELARA*	Targeted Immune Modulators	$124,419	1.4%	22	$5,655	N
10	LANTUS SOLOSTAR*	Diabetes, Insulins	$122,384	1.4%	358	$342	Y
11	HUMIRA(CF) PEN*	Targeted Immune Modulators	$108,561	1.2%	41	$2,648	Y
12	ELIQUIS	Anticoagulants, Oral and SQ	$108,500	1.2%	295	$368	Y
13	Iron Sucrose Injection	Physican Administered Drug	$108,394	1.2%	255	$425	
14	Etonogestrel Implant System	Physican Administered Drug	$106,411	1.2%	148	$719	
15	VYVANSE*	ADHD Drugs	$103,574	1.2%	657	$158	Y
16	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$99,097	1.1%	176	$563	Y
17	IBRANCE*	Antineoplastics, Newer	$97,899	1.1%	7	$13,986	
18	EPIDIOLEX*	Antiepileptics, Outpatient	$88,563	1.0%	57	$1,554	N
19	Aflibercept Injection	Physican Administered Drug	$87,727	1.0%	176	$498	
20	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$85,905	1.0%	2,778	$31	Y
21	Inj Ivig Privigen 500 Mg	Physican Administered Drug	$84,946	0.9%	32	$2,655	
22	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$80,589	0.9%	1,297	$62	Y
23	Supprelin La Implant	Physican Administered Drug	$73,602	0.8%	1	$73,602	
24	Mirena, 52 Mg	Physican Administered Drug	$72,939	0.8%	103	$708	
25	COSENTYX PEN (2 PENS)*	Targeted Immune Modulators	$69,109	0.8%	14	$4,936	Y
26	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$67,323	0.7%	6	$11,221	
27	XYWAV	STC 47 - Sedative Non-barbiturate	$66,519	0.7%	4	$16,630	N
28	CREON	Pancreatic Enzymes	$65,229	0.7%	55	$1,186	Y
29	LENVIMA*	Antineoplastics, Newer	$63,968	0.7%	3	$21,323	
30	LENALIDOMIDE	STC 30 - Antineoplastic	$60,501	0.7%	3	$20,167	
31	METYROSINE	STC 71 - Other Hypotensives	$58,534	0.7%	2	$29,267	
32	PROMACTA	Thrombocytopenia Drugs	$57,294	0.6%	7	$8,185	Y
33	AFINITOR DISPERZ*	Antineoplastics, Newer	$56,546	0.6%	8	$7,068	
34	Injection, Nivolumab	Physican Administered Drug	$56,354	0.6%	21	$2,684	
35	Inj Pembrolizumab	Physican Administered Drug	$51,657	0.6%	32	$1,614	
36	Octreotide Injection, Depot	Physican Administered Drug	$51,152	0.6%	8	$6,394	
37	Mifepristone, Oral, 200 Mg	Physican Administered Drug	$50,630	0.6%	634	$80	
38	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists	$50,516	0.6%	114	$443	N
39	VOSEVI*	Hepatitis C, Direct-Acting Antivirals	$49,869	0.6%	2	$24,934	Y
40	VOTRIENT*	Antineoplastics, Newer	$48,824	0.5%	4	$12,206	
		Top 40 Aggregate:	**$4,524,932**		**8,037**	**$11,750**	
		All FFS Drugs Totals:	**$8,982,922**		**110,545**	**$614**	

*** 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 ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lo wer, pay Billed Amount, 2) - TPL amount

Last updated: January 19, 2023

ProDUR Report for October through December 2022
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	8	5	0	3	0.0%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	1,751	429	1	1,321	1.2%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	7,782	2,135	2	5,634	5.4%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	92,675	17,543	79	75,047	64.4%	**18.9%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	30,138	8,033	4	22,080	21.0%	**N/A**
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	826	162	0	664	0.5%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	8	8	0	0	0.0%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	809	216	0	590	0.5%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	425	119	0	306	0.3%	**N/A**
PA (Drug/Age Precaution)	Products containing Codeine or Tramadol being billed and patient is less than 18 years of age	Set alert/Pay claim	4	1	0	3	0.0%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	30	29	0	1	0.0%	**96.7%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	9,282	2,668	0	6,600	6.3%	**N/A**
		Totals	**143,738**					

ProDUR Report for October through December 2022
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	7,458	1,288	6,170	77,641	9.6%	17.3%
ER	Prozac (Fluoxetine)	5,667	993	4,493	56,877	10.0%	17.5%
ER	Lexapro (Escitalopram)	5,276	885	4,391	56,537	9.3%	16.8%
ER	Celexa (Citalopram)	2,103	321	1,781	25,730	8.2%	15.3%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Trazodone	6,525	1,169	5,356	60,718	10.7%	17.9%
ER	Wellbutrin (Bupropion)	6,181	1,194	5,986	75,802	8.2%	19.3%
ER	Cymbalta (Duloxetine)	4,939	898	4,168	50,300	9.8%	18.2%
ER	Effexor (Venlafaxine)	2,831	449	2,382	30,267	9.4%	15.9%
ER	Remeron (Mirtazapine)	1,726	260	1,466	15,088	11.4%	15.1%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	4,405	999	3,405	31,593	13.9%	22.7%
ER	Abilify (Aripiprazole)	3,585	550	3,035	28,471	12.6%	15.3%
ER	Zyprexa (Olanzapine)	2,479	556	1,923	19,626	12.6%	22.4%
ER	Risperdal (Risperidone)	1,917	411	1,506	13,710	14.0%	21.4%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	3,465	597	2,867	35,521	9.8%	17.2%
ER	Lorazepam	324	90	234	12,236	2.6%	27.8%
ER	Alprazolam	216	45	171	7,598	2.8%	20.8%
ER	Diazepam	132	34	98	4,247	3.1%	25.8%
							24.8%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,106	1,202	4,902	46,591	13.1%	19.7%
ER	Intuniv (Guanfacine ER)	1,708	266	1,441	12,534	13.6%	15.6%
ER	Suboxone (Buprenorphine/Naloxone)	101	33	68	1,941	5.2%	32.7%

ProDUR Report for October through December 2022

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-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	October	4,315	116	253	700	3	3,036	65	3	139
ER	November	4,221	214	227	691	2	2,895	61	0	131
ER	December	3,435	137	233	546	7	2,304	72	0	136
	Total =	**11,971**	**467**	**713**	**1,937**	**12**	**8,235**	**198**	**3**	**406**
	Percentage of total overrides =		**3.9%**	**6.0%**	**16.2%**	**0.1%**	**68.8%**	**1.7%**	**0.0%**	**3.4%**

ProDUR Report for October through December 2022			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
October	DD	24	$2,269.33
	ER	20	$8,026.37
	ID	5	$1,015.93
		October Savings =	**$11,311.63**
November	DD	20	$9,433.84
	ER	44	$10,040.05
	ID	20	$6,964.25
	MC	1	$54.99
	TD	6	$1,699.57
		November Savings =	**$28,192.70**
December	DC	11	$2,364.50
	DD	29	$2,775.55
	ER	204	$46,156.23
	HD	6	$1,508.94
	ID	28	$5,577.85
	PG	1	$444.20
	TD	17	$10,649.51
		December Savings =	**$69,476.78**
		Total 4Q2022 Savings =	**$108,981.11**

Drug Use Research & Management Program
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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	18	1		
		Unique Patients Identified	18	1		
		Total Faxes Successfully Sent	12	1		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	3			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$1,610			
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	119	7		
		Unique Patients Identified	120	7		
		Total Faxes Successfully Sent	76	6		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	36			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$14,995			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	109	4		
		Unique Patients Identified	110	4		
		Total Faxes Successfully Sent	69	2		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	27			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$2,169			

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	2	1		
		Total Faxes Successfully Sent	1			
		Safety Monitoring Profiles Identified	2			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	1064			
		High risk patients identified	6			
		Prescribers successfully notified	3			
		Patients with continued antipsychotic therapy in the following 90 days	3			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	55	11		
		Total prescribers identified	55	11		
		Prescribers successfully notified	53	7		
		Patients with claims for the same antipsychotic within the next 90 days	29	1		
		Patients with claims for a different antipsychotic within the next 90 days	2			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	80			
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	56			
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	207			
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	39			
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	3			
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	1			
		Letters Sent To Providers	1			
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	8			
		Letters Sent To Providers	4			
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	31			
		Letters Sent To Providers	5			
	Polypharmacy	RetroDUR Profiles Reviewed	18			
		Letters Sent To Providers	1			

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	16	1		
		Total prescribers identified	15	1		
		Prescribers successfully notified	15	1		
		Patients with paid claims within next 60 days	11			
		Patients with denied claim within next 60 days	8			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	83	17		
		Total prescribers identified	82	17		
		Prescribers successfully notified	61	12		
		Patients with discontinuation of therapy within next 90 days	29	14		
		Patients with new prescription for naloxone within next 90 days	3			
		Average number of sedative drugs dispensed within next 90 days	15	0		
		Average number of sedative prescribers writing prescriptions in next 90 days	15	0		
	Oncology Denials	Total patients identified	1			
		Total prescribers identified	1			
		Prescribers successfully notified	1			
	TCAs in Children	TCA Denials in Children	26	1		
		Total patients identified	12	2		
		Total prescribers identified	12	2		
		Prescribers successfully notified	8			
		Patients with claims for a TCA within the next 90 days	3			

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AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
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Antimicrobial Stewardship

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Antimicrobial stewardship originated out of the need to systematically provide guidance to providers on appropriate antibiotic use. In 2013 there were more than 260 million antibiotic prescriptions dispensed in the outpatient setting, with 30% or more of these deemed unnecessary.[1] Reducing the overuse of antibiotics and optimizing selection of correct antibiotics plays a large role in reducing antibiotic resistance. Antibiotic resistance is a major health concern, leading to 35,000 deaths a year in the United States (US).[2] Additionally, inappropriate antibiotic use has been shown to cause millions of dollars of excess healthcare expenditures.[3] Antibiotic stewardship programs are an important component of providing valuable direction on antibiotic use. This newsletter will discuss common areas of inappropriate prescribing and programs designed to facilitate best practices of antimicrobial use, with a focus on the outpatient setting.

Inappropriate Antimicrobial Prescribing

Inappropriate prescribing of antimicrobials is directly linked to antibiotic resistance. More than 2.8 million people annually in the US get infected with bacteria that are resistant to antibiotics.[2] Antibiotic selection, dosing, and duration all contribute to rising resistance rates. A study evaluating inappropriate antibiotic use in the outpatient setting found antibiotics were most commonly prescribed for sinusitis, suppurative otitis media, and pharyngitis.[4] The use of antibiotics for sinusitis and suppurative otitis media is not always warranted. An analysis of the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) data estimated half of the prescriptions written for these conditions were appropriate.[4] The Centers for Disease Control (CDC) recommends treatment of pharyngitis only for patients testing positive with a Rapid Antigen Detection Test (RADT) for streptococcal pharyngitis.[5,6] First-line treatment recommendations are amoxicillin or penicillin V for adults and children.[6,5] Penicillin-allergic adult antibiotic recommendations are cephalexin, cefadroxil, clindamycin, or macrolides and for children the recommendations are cephalexin, cefadroxil, clindamycin, clarithromycin, or azithromycin.[5,6] Children with acute otitis media should be treated if they have middle ear effusion. First line recommendations are for the use of amoxicillin or amoxicillin/clavulanate if recent amoxicillin use.[6] For children with a non-type I hypersensitivity to penicillin, the use of cefdinir, cefuroxime, cefpodoxime, or ceftriaxone is recommended.[6]

Adverse drug reactions are also a common consequence of antibiotic overuse. One out of every 5 emergency department (ED) visits is due to an adverse drug event related to antibiotics.[7] This is especially true in children, as adverse drug events due to antibiotics are the most common cause of ED visits in children under the age of 18 years.[7] A study of pediatric patients found that 31% to 36% of bacterial infections and 4% to 70% of viral infections were prescribed antibiotics inappropriately. An adverse event of these inappropriately prescribed antibiotics was an increase in *Clostridioides difficile* infection rates in children treated for otitis media (hazard ratio [HR] 6.23; 95% confidence interval [CI] 2.24 to 17.32).[8] There was also an increased rate of severe allergic reactions.

Antimicrobial Use During the COVID-19 Pandemic

Coronavirus disease (COVID-19) brought about additional concerns because antibiotics were frequently prescribed early in the pandemic. There were more resistant infections, increased antibiotic use, and less data and prevention actions compared to pre-pandemic years.[9(p19)] There were 15% more deaths and infections due to antimicrobial-resistance in 2020.[9(p19)] Increased resistance among specific pathogens are presented in **Table 1**. A meta-analysis found bacteria co-infection in patients with COVID-19 was generally low, with an incidence of 6.9%, but antibiotics were prescribed in 71.9% of cases.[10] The use of azithromycin was higher than expected across all healthcare settings during the COVID-19 pandemic (outpatient numbers based on retail prescriptions and Medicare carrier claims), partly due to initial thoughts that it could be used as a treatment for COVID .[11] In contrast, other outpatient antibiotic prescriptions decreased in 2020 which was thought to be due to COVID-19 pandemic mitigation measures.[11]

Table 1. Specific Pathogens with an 15% Increase in Resistance from 2019 to 2020[9]

Pathogen	Infection Rate Increase
Carbapenem-resistant *Acinetobacter*	78%
Multidrug-resistant *Pseudomonas aeruginosa*	32%
Vancomycin-resistant *Enterococcus* (VRE)	14%
Methicillin-resistant *Staphylococcus*	13%

Following national treatment guidelines for the management of COVID-19 is recommended.[12] If antibiotics are used in patients with COVID, utilization should be guided by laboratory diagnostics once available and de-escalating therapy if no bacterial infection is present.[9] The watchful waiting and symptom relief approach should be used when there is no clear diagnosis related to a bacterial etiology. Providing patients with guidance and education on managing symptoms related to viral illness can improve safe and appropriate antibiotic use.[12]

Fundamentals of Antimicrobial Stewardship

Identifying high-priority conditions and barriers to appropriate antibiotic prescribing are an important initial step in an antibiotic stewardship program. The Centers for Disease Control published guidance on the core elements of an antimicrobial stewardship program in the outpatient setting. The focus of the program is to measure and improve how antibiotics are prescribed by providers and used. The core elements of antimicrobial stewardship are[1]:

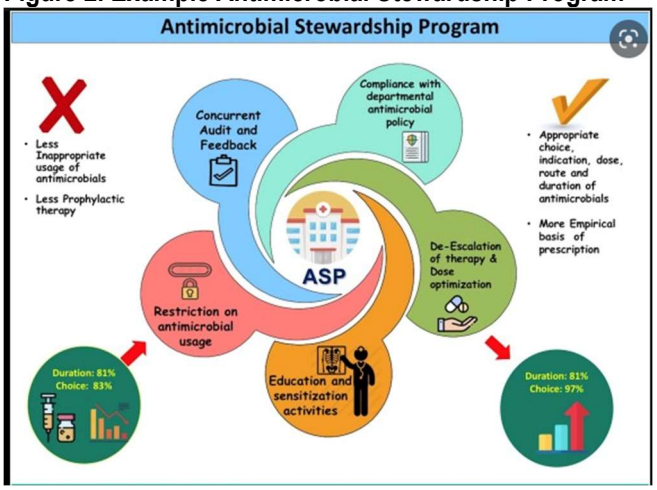
1) Commitment
2) Action for policy and practice
3) Tracking and reporting
4) Education and expertise

Goals of antimicrobial stewardship programs and an example of an antibiotic stewardship program are presented in **Figure 1 and Figure 2**.[1,13]

Figure 1. Goals of Antimicrobial Stewardship Programs

1. Measure antibiotic prescribing
2. Improve antibiotic prescribing by clinicians and use by patients so that antibiotics are only prescribed and used when needed
3. Minimize misdiagnoses or delayed diagnosis leading to underuse of antibiotics
4. Ensure the correct drug, dose, and duration are selected when an antibiotic is needed

Figure 2. Example Antimicrobial Stewardship Program[13]



- Duration percents represent inappropriate duration and choice percents represent wrong antibiotic selection

Circumstances that lend themselves to being targets for antimicrobial stewardship interventions include:

- Conditions in which antibiotics are commonly overprescribed or not indicated (e.g., acute bronchitis, nonspecific upper respiratory tract infection, viral pharyngitis or asymptomatic bactereiura)[1,14]
- Conditions in which antibiotics are indicated but the wrong agent, dose, or duration is often selected[1]
- Conditions for which watchful waiting or delayed prescribing is appropriate but often not utilized (e.g., acute otitis media or acute uncomplicated sinusitis)[1]
- Conditions in which antibiotics are underused or the need for timely antibiotics is not recognized (e.g., missed diagnoses of sexually transmitted infections or severe bacterial infection such as sepsis)[1]

Promotion of appropriate antibiotic prescribing practices can be accomplished through use of evidence-based diagnostic criteria and treatment recommendations. Important resources include clinical practice guidelines and knowledge of local pathogen susceptibilities. Health System antibiograms, which detail antibiotic resistance patterns, are a helpful resource to guide empiric antibiotic selection. Antibiograms need to be continually updated and applied to the health care setting in which they originated, as they vary by institution and region. In some cases, pathogens may be initially susceptible but become resistant such as with the ampC beta-lactamase producing organisms, in particular *Enterobacter cloacae, Klebsiella aerogenes,* and *Citrobacter freundii*. Therefore, patient clinical response should be

monitored and repeat testing may be needed. Pathogen susceptibility varies between health systems, patient treatment settings and demographic locations.[15]

Oregon Metrics on Antibiotic Prescribing

The state of Oregon tracks several areas to evaluate antibiotic stewardship. For example, the number of outpatient antibiotic prescriptions per 1000 people is less in Oregon compared to the nation as a whole (475 vs. 625, respectively - 2020 data).[1] In addition, antibiotic prescriptions in Oregon, compared to the national average, are consistently lower across all major antibiotic classes including: cephalosporins, fluoroquinolones, macrolides and penicillins.[1]

The CDC also publishes state-specific information on antibiotic prescribing and resistance patterns. Certain pathogens of particular interest are specifically tracked and reported.

- The rates hospital-associated carbapenem-resistant *Enterobacteriaceae* was 1.7% in 2019 in Oregon, compared to 2.4% for the US.
- The standardized infection ratio (SIR) was 0.51 for *C.difficile* in Oregon.[1] The SIR is a statistic used to track healthcare associated infections (HAIs) over time, at a national, state, or facility level. The SIR compares the actual number of HAIs at each hospital, to the predicted number of infections. *C.difficile* is the single most common pathogen responsible for healthcare-associated infections.[1]

Conclusion

Antibiotics are life-saving treatment options for susceptible organisms. Appropriate antibiotic use will ensure effective therapies are available and resistance rates are kept low. Inpatient and outpatient antimicrobial stewardship programs should be utilized to encourage appropriate antibiotic use. There are many resources available to assist providers in developing antibiotic stewardship programs and to inform best antibiotic prescribing practices (**Figure 3**).

Figure 3. Resources for Appropriate Antibiotic Use

- Antibiotic Resistance and Patient Safety Portal: https://arpsp.cdc.gov/
- Core Elements of Antibiotic Stewardship Programs: https://www.cdc.gov/antibiotic-use/core-elements/index.html
- CDC National Healthcare Safety Network (national infection tracking system): https://www.cdc.gov/nhsn/index.html
- Oregon Health Authority Treatment Algorithms: https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/ANTIBIOTICRESISTANCE//provider.aspx
- Society of Infectious Disease Pharmacists: https://sidp.org/Clinician-Education

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An Update in Lipid Lowering Therapies

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Hypercholesterolemia is a chronic condition characterized by high levels of low-density lipoprotein cholesterol (LDL-C), leading to an increased risk of atherosclerotic cardiovascular disease (ASCVD).[1] In the United States (U.S.), 47 million adults receive lipid lowering medications and 94 million have been diagnosed with hypercholesterolemia.[2] According to the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guideline, lifestyle modifications are prioritized for all individuals and statins remain the cornerstone of medication therapy due to strong and consistent evidence of ASCVD risk lowering.[1] The purpose of this newsletter is to summarize the evidence which supports the use of current lipid lowering therapies and describe the evidence and place in therapy of newer drugs.

Current Therapies for Lipid Lowering

Moderate- or high-intensity statins are recommended for specific patient populations with ASCVD risk (**Table 1**). High-intensity statins typically lower LDL-C levels at least 50% while moderate-intensity statins can lower LDL-C levels by 30%–49% (**Table 2**).[1]

Table 1: Patient Management Groups.[1]

Statin Benefit Group	Recommended Treatment
Secondary ASCVD Prevention	High-intensity statin
Severe Hypercholesterolemia (LDL-C ≥190 mg/dL)	High-intensity statin
Diabetes age 40-75 y and LDL-C ≥70 mg/dL	Moderate-to high-intensity statin (based on ASCVD risk assessment)
Primary Prevention (ASCVD risk ≥7.5%)	Moderate-to high-intensity statin (based on 10-year ASCVD risk, risk discussion, and ASCVD risk enhancers)
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipid lipoprotein cholesterol; y = years.	

Table 2: Statin Dosing.[1]

Moderate Intensity	High intensity
Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

A non-statin add-on therapy that has evidence for ASCVD risk reduction is recommended for patients who have very high ASCVD risk when LDL-C levels remain 70 mg/dL or higher despite maximally tolerated statin therapy.[1] Patients at very high-risk for future ASCVD events include those who have a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.[1] Ezetimibe is recommended as first-line add-on therapy to maximally tolerated statin therapy followed by a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (e.g., evolocumab or alirocumab) if LDL-C remain higher than 70 mg/dL. These add-on medications have demonstrated a modest reduction in ASCVD risk in very high-risk patients.[1] Additionally, icosapent ethyl may be added to a statin to prevent cardiovascular (CV) events in patients with hypertriglyceridemia (≥150 mg/dL) and ASCVD or in patients with diabetes plus other CV risks.[3,4] Currently, there is no evidence for reduction in CV outcomes for other LDL-C lowering agents like fibrates, bile acid sequestrants, and omega-3 fatty acids.

Newer Lipid Lowering Therapies

Since 2020, three new lipid lowering agents have been approved by the U.S. Food and Drug Administration (FDA) (**Table 3**). Clinical guidelines have yet to be updated to include these medications.

Table 3: New Lipid Lowering Agents.[4,8,12]

Generic Name	Dose/ Route	Indication	LDL-C Lowering (%)*	Population studied
Bempedoic Acid	180 mg PO once daily	Adults with HeFH or ASCVD	-17.4% to -18.1%	95% ASCVD 5% HeFH Mean LDL-C: 103-120 mg/dL 50% on high-intensity statin
Evinacumab	15 mg/kg IV every 4 weeks	Age ≥12 years with HoFH	-49%	Mean LDL-C: 255 mg/dl 77% on PCSK9 inhibitor 75% on ezetimibe 94% on statin
Inclisiran	284 mg SubQ at 0 and 3 mo., then every 6 mo.	Adults with HeFH or ASCVD	-47.9% to -52.3%	Mean LDL-C: 105-153 mg/dL 90% on statin PCSK9 inhibitors excluded
*Difference between treatment and placebo from baseline				
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CV: Cardiovascular; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; IV: intravenously; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type; mo: months; PO: by mouth; SubQ: subcutaneously				

Bempedoic Acid

Bempedoic acid is an oral adenosine triphosphate-citrate lyase (ACL) inhibitor approved by the FDA in February 2020 as adjunct therapy to lower LDL-C in adults with heterozygous familial hypercholesterolemia (HeFH) or in adults with established ASCVD on maximally tolerated statin therapy.[5] It lowers LDL-C by inhibition of cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the primary site of action for statins.[5] Bempedoic acid approval was based on two secondary prevention trials in high-risk patients with clinical ASCVD or HeFH.[6,7] Both were 52-week randomized, double-blind, placebo-controlled trials in patients on baseline lipid-modifying therapy with LDL-C of 70 mg/dL or higher. Both studies included adults with ASCVD or high CV risk who were on maximally tolerated lipid-lowering therapy.[6,7] Most patients in both trials had established ASCVD (~95%); data in those with HeFH was limited to less than 5% of patients. While most patients were on statin therapy, only half of patients were on a high intensity statin. Both trials resulted in a significant, but modest, reduction in LDL-C from baseline at week 12 compared to placebo (treatment difference -18.1%; 95% CI, -20 to -16.1% and -17.4%; 95% CI, -21 to -13.9%),with greater reductions seen in those not on statins.[6,7] The magnitude of LDL lowering is similar to observations of ezetimibe when added to statin therapy (-13 to -20%) but not as low as what is observed with PCSK9 inhibitors (-47% to -63%). Bempedoic acid is also available in combination with ezetimibe. The drug includes warnings and precautions for hyperuricemia and tendon rupture.[4] Bempedoic acid competes for the same renal transporters as uric acid and therefore can increase uric acid levels. Compared to placebo, more patients on bempedoic experienced gout (1.5% vs. 0.4%), increases in serum uric acid (3.5% vs. 1.1%), and tendon rupture/injury (0.5% vs. 0%).[6,7]

Both trials had significant exclusion criteria and a high percentage of participants screened failed to qualify for the study (34.3% and 66.1%), limiting generalizability of the results.[6,7] Neither trial was designed or powered to evaluate the effects of bempedoic acid on CV outcomes. Until further data is available on clinically important outcomes, statin therapy and ezetimibe should be optimized in patients with CV disease or HeFH. Bempedoic acid may be considered in high-risk patients on maximally tolerated statin and ezetimibe who prefer an oral medication over an injectable PCSK9 inhibitor or in statin intolerant patients. However, it's lipid lowering effects are modest and smaller than other therapies. It should be avoided in patients with a history of tendon problems and used cautiously in patients with gout. Lastly, it can increase concentrations of certain statins and should be avoided with daily doses of simvastatin higher than 20 mg or pravastatin higher than 40 mg.[5]

Evinacumab

Evinacumab is an angiopoietin-like 3 (ANGPTL3) inhibitor and monoclonal antibody that was approved by the FDA in February 2021 and is indicated as an add-on therapy to other LDL-C lowering medications for people aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).[8] ANGPTL3 proteins are secreted by the liver and bind with LDL receptors to inhibit LDL activity alone or as a functional complex with angiopoietin-like 8 (ANGPTL8) proteins.[9] This results in a reduction in LDL-C independent of the LDL-C receptor.

There remains no data evaluating evinacumab on clinical outcomes, including CV and all-cause mortality. Evinacumab approval was based on a single 24-week study including 65 patients who either received evinacumab 15 mg/kg intravenously (IV) every 4 weeks (n=43) or placebo (n=22) for a total of 24 weeks.[10] The study population included patients 12 years of age and older diagnosed with functional HoFH, who had LDL-C 70 mg/dL or higher despite being on a maximally tolerated lipid lowering therapy. Patients treated with evinacumab experienced a 47% reduction in LDL-C compared to an increase by 2% in the placebo group (treatment difference -49%; 95% CI, -65 to 33.1%).[10]

Evinacumab was generally well tolerated in the short-term study. Evinacumab is associated with hypersensitivity, including higher rates infusion reactions (7% vs. 4%) and anaphylaxis (1% vs. 0%) compared to placebo.[10] There were no reports of rhabdomyolysis, significant creatine kinase (CK) elevations, or hepatic dysfunction. However, there is not enough safety data or sample size to detect risk of uncommon but serious adverse events. Drug label warnings and precautions include risk of teratogenicity based on nonclinical data.[8]

HoFH is a rare genetic disease with mutations in both alleles of the LDL-receptor, affecting only 1 in 300,000 individuals.[11] The onset is usually during childhood, and patients often have LDL-C levels higher than 400 mg/dL and are at high risk of premature CV events. The small study population and narrow indication limits the applicability of this data. Efficacy and safety have not been established in patients with HeFH or established ASCVD who require additional LDL-C lowering, and it should not be used off-label for these indications at this time.

Inclisiran

Inclisiran is a small interfering ribonucleic acid (siRNA) directed at PCSK9 mRNA. It was approved in December 2021 as an add-on to maximally tolerated statin therapy for adults with HeFH or clinical ASCVD who require additional lowering of LDL-C.[12] Due to the mechanism of action of this medication, individuals who are on a PSCK9 inhibitor were excluded from clinical trials. Approval was based on 3 similarly designed randomized controlled trials (RCTs) (ORION-9, -10, and -11) evaluating the efficacy of four subcutaneous injections of inclisiran over 18 months in patients with HeFH, clinical ASCVD or high risk for ASCVD (**Table 4**).[13,14] The primary outcome of all three trials was the percent change in LDL-C from baseline to Day 510 compared to placebo.

Table 4: Inclisiran Trials[13,14]

Study	Study Population	% On High-Intensity Statin	Change in LDL-C from Baseline
ORION 9	HeFH, LDL-C ≥100 mg/dL*	76.4%	-48%
ORION N10	ASCVD and LDL-C ≥70 mg/dL*	67.2%	-52%
ORION 11	ASCVD or ASCVD risk equivalent, LDL-C ≥70 mg/dL*	79%	-50%
* On background lipid lowering therapy			
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; HeFH: heterozygous familial hypercholesterolemia; LDL: low-density lipoprotein cholesterol.			

From the 3,655 patients studied in these trials, very few discontinued due to adverse events in the inclisiran (5.6%) and placebo (7.2%) groups, and inclisiran was generally well tolerated in the short-term.[13,14] Injection site reactions were the most common adverse drug reaction. Long-term safety beyond 18 months remains unknown.

The LDL-lowering ability of inclisiran is similar to PCSK9 inhibitors when added on to a statin in high-risk CV patients. However, data demonstrating CV benefit with inclisiran is ongoing (ORION-4) and PCSK9 inhibitors are preferred until those data are available. PCSK9 inhibitors were excluded from trials, and they should not be used in combination with inclisiran. Additionally, this injectable agent has to be administered in a healthcare setting.

Figure 1: Cost Comparison for 30-Day Supply. *

*The average actual acquisition cost (AAAC) included for statins, ezetimibe, and evolocumab. The monthly average wholesale price (AWP) used for newer therapies. Price of inclisiran is calculated based on the injection schedule of every 6 months. Evinacumab is calculated based on a 80 kg person.

Current Policies

Overall, costs remain a barrier to use for these newer medications, particularly the injectable agents (**Figure 1**). Current policies in the Oregon fee-for-service Medicaid program are included in **Figure 2**. For most patients, the focus should remain to optimize diet and lifestyle choices, achieve maximally tolerated statin doses, and add on therapies with evidence of CV benefit when indicated.

Figure 2: Current Oregon Health Plan Fee-For-Service Policies for New Lipid Lowering Medications

- Bempedoic acid is non-preferred and includes prior authorization criteria requiring:
  - Very high-risk clinical ASCVD or diagnosis of HoFH or HeFH;
  - On high-intensity statin and ezetimibe OR contraindication (i.e., history of rhabdomyolysis or CK levels >10-times upper limit caused by statins); and
  - LDL-C of ≥70mg/dL
- Evinacumab is non-preferred and includes prior authorization criteria requiring:
  - Age 12 years or older with a diagnosis of HoFH;
  - LDL-C of ≥ 100 mg/dL while on a maximally tolerated dose of statin, ezetimibe, and a PCSK9 inhibitor for 12 weeks; and
  - Documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant
- Inclisiran is non-preferred and includes prior authorization criteria requiring:
  - Very high-risk clinical ASCVD or diagnosis of HoFH or HeFH;
  - On high-intensity statin and ezetimibe OR contraindication (i.e., history of rhabdomyolysis or CK levels >10-times upper limit caused by statins);
  - LDL-C of ≥70mg/dL;
  - Tried and failed a PCSK9 inhibitor; and
  - Not concurrently on a PCSK9 inhibitor

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CK: creatinine kinase; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; LDL: low-density lipoprotein

Conclusion

Currently, there is a limited place in therapy for the three newer lipid-lowering medications. They do improve lipid levels, but CV benefits are unknown. Current evidence suggests they may be used in specialized circumstances for very high-risk CV patients or patients with familial disease who require additional LDL-lowering or who do not tolerate current recommended therapies.

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COVID-19 Vaccine Bivalent Boosters

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Introduction

As the United States (U.S.) moves into the next phase of the coronavirus disease-2019 (COVID-19) pandemic, some individuals may question the need for COVID-19 booster vaccines during the upcoming fall and winter influenza season. Challenges to adequate immunization include inequitable vaccine distribution, lack of vaccine confidence, waning immunity, and the emergence of viral variants.[1] This newsletter will discuss the new COVID-19 bivalent booster vaccines, barriers to immunization, and tips for improving vaccine confidence.

Benefits of COVID-19 Vaccination:

- Reduce severity of illness
- Reduce risk of hospitalization
- Decrease risk of death

COVID-19 Primary Monovalent Vaccine Recommendations

Four COVID-19 vaccines are U.S. Food and Drug Administration (FDA)-approved to prevent COVID-19: Pfizer-BioNTech, Moderna, Novavax, and Johnson & Johnson's Janssen (J&J/Janssen). The Centers for Disease Control and Prevention (CDC) recommends the J&J/Janssen COVID-19 vaccine only be considered in certain situations due to the risk of serious, but rare adverse events, including thrombocytopenia and Guillain-Barre syndromes.[2] Individuals who are candidates for the J&J/Janssen vaccine include those who have had a severe reaction to an ingredient of the Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines); who would otherwise remain unvaccinated due to limited access to mRNA COVID-9 or Novavax vaccines; or who want to receive the J&J/Janssen COVID-19 vaccine despite safety concerns.[2]

The CDC recommends COVID-19 monovalent primary series vaccines for individuals ages 6 months and older, and COVID-19 monovalent boosters for individuals ages 5 years and older.[3] The monovalent vaccines only target the original SARS-CoV-2 alpha strain of the virus. Getting a COVID-19 vaccine after recovering from COVID-19 infection provides added protection against COVID-19.[3] CDC has stated the next vaccination can be delayed for 3 months from when symptoms started or, if individuals did not have symptoms, when they received a positive test.[4] Moderately or severely immunocompromised individuals have different recommendations for COVID-19 vaccines, including boosters.[3] This guidance can be accessed at the CDC website. Unless there are specific contraindications, vaccine providers should also offer to administer any other vaccines to eligible individuals at the time of the healthcare visit.[3]

COVID-19 Bivalent Booster Vaccine Recommendations

The initial monovalent mRNA Pfizer and Moderna vaccines induce short-term neutralizing antibody responses and protective efficacy.[1] However, the high initial serum neutralizing antibody titers induced by mRNA vaccines begin to wane by 3 to 6 months and decline further by 8 months, with a half-life of about 60 days.[1] The waning of immunity with mRNA vaccines is correlated with increased breakthrough infections in vaccinated persons.[1] In late 2021, the highly transmissible omicron (B.1.1.529) variant emerged and became the most prevalent virus globally.[1] In contrast to the 4 mutations in delta, omicron has more than 50 mutations, including more than 30 mutations in the spike protein, which result in substantial escape from neutralizing antibody responses elicited by vaccination or prior infection with a non-omicron variant.[1] Original monovalent vaccines may not provide robust protection against infection or transmission of currently circulating omicron subvariants.[1] The most important goal of COVID-19 immunization is to provide long-term protection against severe disease, including hospitalization and death.[3]

The FDA recently issued Emergency Use Authorization (EUA) for two new bivalent COVID-19 booster vaccines from Moderna and Pfizer-BioNTech that combine spike proteins from the original alpha variant and the omicron BA.4 and BA.5 subvariants, which match the virus strains currently circulating.[5,6] Pfizer-BioNTech's bivalent booster is authorized for individuals 12 years and older,[6] whereas Moderna's bivalent booster is authorized for individuals 18 years and older.[5] Dosing parameters for both vaccines are presented in **Table 1**. In late September 2022, Pfizer requested the FDA to expand use of its updated COVID-19 booster vaccine to children ages 5 to 11. Moderna also submitted a request for FDA authorization of its booster to children and adolescents aged 6 years and older. Both vaccines may be administered at least 2 months since the last COVID-19 primary vaccination or monovalent booster, regardless of the number of booster doses previously received.[5,6] Pfizer-BioNTech and Moderna monovalent vaccines are no longer authorized for use as a booster dose in individuals 12 years of age and older.[5,6] With the arrival of the updated boosters, CDC is reframing what it means to be up-to-date with COVID-19 vaccination. If individuals have completed the primary series and the most recent booster recommended by the CDC, they have completed the immunization series for COVID-19.

Table 1. COVID-19 Bivalent Booster Dosing (as of 9/22)

Manufacturer	Dose	Age
Pfizer-BioNTech	30 mcg/0.3 mL	≥ 12 years
Moderna	50 mcg/0.5 mL	≥ 18 years

The FDA based its decision for EUA of these bivalent vaccines on extensive safety and effectiveness data for each of the monovalent mRNA COVID-19 vaccines.[5,6] Clinical trials of both bivalent vaccines are ongoing. Influenza vaccines have long used a similar process that omits requirements for new clinical trials because the influenza virus mutates from year to year. As with all vaccines, safety monitoring will continue to be ongoing process through the FDA and CDC.

Of concern is whether individuals will choose to receive the bivalent booster dose. As of September 2022, CDC data show that while more than 262 million individuals within the U.S. (79% of the total population) have received their original primary vaccine series, only 109 million individuals, or half of those eligible, have received their booster vaccine.[7] There are disparities in first and second booster coverage by age group, sex, race and ethnicity; urban-rural classification; and primary series vaccine product.[8]
Booster and second booster dose vaccination coverage rates were lowest among the youngest age groups; males; Black, Hispanic, and multiracial persons; residents of rural counties; and Janssen primary series recipients.[8] Among age groups, the lowest booster dose coverage was among children aged 5–11 years (15.6%), followed by that among adolescents aged 12–17 years (33.4%).[8] Children aged 5–11 years were recommended to receive a booster dose most recently, which might partially explain the low coverage in this group.[8]
Understanding the factors contributing to low booster and second booster dose coverage among Black, Hispanic, and multiracial populations, and designing interventions to address these factors, is crucial to ensuring equitable access to COVID-19 vaccination.[8]

COVID-19 booster vaccines are fully covered under the Oregon Health Plan.

Find COVID-19 Vaccine Administration Sites

Vaccination Barriers

Children may face barriers in getting vaccinated not only for COVID-19 but for routine childhood vaccines, including:

- Children who are unable to establish routine care with a pediatrician — such as those who are experiencing limited access to housing or those who live in remote areas.[9]
- Children living in congregate settings — such as those who are incarcerated or detained or those who live in group homes.[9]
- Children historically and currently marginalized when it comes to healthcare — such as those in racial and ethnic minority groups or households with lower incomes.[9]
- Children who are non-English speakers, immigrants, or with undocumented status.[9]
- Children with developmental disabilities — such as cerebral palsy, autism spectrum disorder, or an intellectual disability.[9]
- Children who have special healthcare needs — such as lung, heart, or kidney disease, an immune system problem, malignancy, diabetes, some blood diseases, or conditions of the muscular or central nervous system.[9]

Improving immunization begins with taking a complete vaccination history from every patient.[10] Oregon's ALERT Immunization Information System is the best place to find immunization records for people who were vaccinated in Oregon. Individuals of all ages who are not up-to-date with their immunizations should be vaccinated, if eligible.[10] Pharmacists in Oregon can administer any vaccine to adults and children aged 7 years and older approved by the CDC Advisory Committee on Immunization Practices (ACIP) when done in accordance with current pharmacy immunization protocols.[11]

Vaccine Confidence

Increasing vaccine confidence is critical to protect against vaccine-preventable diseases.[10] Reasons for decreasing confidence varies, but should be addressed on a case-by-case basis.[10] Some people believe vaccines are no longer necessary while others lack trust in the health care system.[10] Some merely have concerns about vaccines and can be positively influenced by education and awareness, while other are adamantly opposed to vaccines altogether.[10] Others will allow vaccinations required for school while refusing others.[10] In 2021, most children received an influenza vaccine in a provider's office, but factors such as language, insurance status, and ability to take time off work reduces the ability from families to go to their primary care provider regularly.[9] Based on experience with influenza immunization challenges, alternative strategies are needed to reach children with COVID-19 vaccine boosters.[9]

All public health professionals and federal, state, and local partners are encouraged to:

- Use a health equity lens when framing information about health disparities.[9]
- Consider key communication principles: use person-first language (e.g., "a person with diabetes" instead of "a diabetic"); avoid unintentional blaming; use preferred terms for select population groups and communities while recognizing that there is not always consistent agreement on these terms.[9]
- Consider how communications, messages, and products are developed and look for ways to improve health equity and inclusivity.[9]
- Increase patient's vaccine confidence by using a motivational interviewing approach.[9]

Conclusions

The COVID-19 pandemic appears to be transitioning from a hyperacute phase to an endemic phase.[1] Recently approved COVID-19 bivalent booster vaccines will provide additional protection against contracting severe viral disease from emerging variants. Addressing barriers to vaccination and increasing vaccine confidence are vital to improving immunization.

Additional Information:

Health Education and Communication Tools

CDC Interim COVID-19 Immunization Schedule

Oregon Health Authority Pharmacy Immunization Protocols

Peer Reviewed by: Liz Breitenstein, PharmD, RPh, Pharmacist Consultant, Oregon Health Authority, COVID-19 Response and Recover Unit (CRRU) and Andrew Gibler, PharmD, RPh Clinical Pharmacy Policy & Programs Manager, Oregon Health Authority, Health Policy & Analytics Division

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Prior Authorization Criteria Update: Myfembree (Relugolix, Estradiol, and Norethindrone) (Gonadotropin-Releasing Hormone Antagonists)

Plain Language Summary:

- Does the new indication for relugolix, estradiol, and norethindrone combination therapy impact current Medicaid policies for medicines used to treat pain associated with endometriosis?
- Endometriosis is a chronic and painful disease that occurs when endometrium (tissue the originates from the lining of the uterus) starts growing outside of the uterus where it does not belong. Estrogen, a female sex hormone, causes this tissue to grow. Later in the menstrual cycle, these patches of endometrial tissue (or lesions) may break down and shed the in the body. This can cause pain throughout the entire month. The most common symptoms of endometriosis include painful periods, pelvic pain between periods, and pain with sexual intercourse. Endometriosis can also cause infertility, or difficulty getting pregnant.
- The most common treatments to relieve pain associated with endometriosis are hormone therapies. Hormone therapies are medicines that decrease the amount of estrogen in the body. Less estrogen will slow the growth of endometrial tissue and stop more lesions from forming outside the uterus. Certain kinds of birth control pills (such as estradiol combined with norethindrone), and medicines called gonadotropin-releasing hormone blockers, stop the production of hormones that tell the ovaries to make estrogen, which decreases the amount of endometrial tissue that grows every month. Many people have lighter and shorter menstrual flows (periods) when they take birth control pills. The gonadotropin-releasing hormone blockers may create an artificial menopause, and monthly periods are prevented.
- Relugolix, estradiol, and norethindrone is a combination gonadotropin-releasing hormone blocker and birth control pill. The side effects of relugolix include symptoms of menopause such as hot flashes, vaginal dryness, and bone loss. Adding the birth control pill may decrease some of these side effects. The risk of bone loss when taking relugolix is very high, which prevents people from taking this medicine longer than 24 months.
- Two 3-month studies showed relugolix combined with estradiol and norethindrone relieved menstrual pain and pelvic pain between periods better than people that did not take any medicine.
- Providers must explain to the Oregon Health Authority (OHA) why a patient needs relugolix, estradiol, norethindrone combination therapy before Medicaid will pay for it. This process is called prior authorization.
- Fee-for-service (FFS) Medicaid pays for birth control pills when prescribed for adolescents and adults and does not require prior authorization.
- The OHA recommends changing the PA policy to include pain associated with endometriosis as a reason to prescribe relugolix, estradiol and norethindrone combination therapy.

Purpose of Update:

- Review evidence for the expanded Food and Drug Administration (FDA)-approved indication for relugolix, estradiol, and norethindrone combination therapy (MYFEMBREE) to manage moderate to severe pain associated with endometriosis.

Recommendation:

- Revise prior authorization (PA) criteria for relugolix, estradiol, and norethindrone combination therapy to include management of moderate to severe pain associated with endometriosis in premenopausal women (**Appendix 1**).

Background:

The gonadotropin-releasing hormone antagonists (GnRH) were last reviewed by the Pharmacy and Therapeutics (P & T) committee in December 2021. At that time, a class update was presented which reviewed comparative evidence for safety and efficacy of oral contraceptives, progestins, GnRH agonists, danazol, and GnRH antagonists for management of moderate to severe pain due to endometriosis. In addition, evidence supporting FDA approval for relugolix, estradiol, and norethindrone combination therapy for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal populations was evaluated. The P & T Committee approved recommendations to maintain relugolix combination therapy as non-preferred on the preferred drug list (PDL) and implement new prior authorization (PA) criteria for GnRH modifiers to evaluate GnRH antagonists, including relugolix, estradiol, and norethindrone combination therapy, separately from GnRH agonists (e.g., leuprolide).

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[1] 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.[1] Medical therapy for endometriosis is based on the observation that ectopic tissue is hormonally responsive.[2] 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.[3] Current first-line therapies to manage pain associated with endometriosis are continuous combined oral contraceptives (COCs) or progestin.[4] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[3,5] Most of the data supporting the use of COCs in managing endometriosis pain is observational.[4]

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).[4] 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.[2] However, continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[3,5] Goserelin, leuprolide, and nafarelin are FDA-approved for six months of continuous use for treatment of pelvic pain caused by endometriosis.[3] 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.[4] The FDA recommends the use of add-back therapy (estrogen, progestin, bisphosphonates) when a GnRH agonist is used for greater than 6 months.[4]

Elagolix and relugolix are GnRH receptor antagonists. Both drugs competitively bind to pituitary GnRH receptors, blocking binding of endogenous GnRH with reversible, dose-dependent suppression of LH and FSH, and ovarian estradiol and progesterone production.[6,7] The oral GnRH antagonist, elagolix, reduces moderate-to-severe endometriosis-associated pain and is FDA-approved as a once-daily low dose or a twice-daily high dose.[6] However, hypoestrogenic-induced declines in bone mineral density mean that elagolix treatment is a maximum duration of 24 months for a low dose (6 months in patients with moderate hepatic impairment) and 6 months for a high-dose regimen.[6] Relugolix combination therapy (40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone) was developed as a once-daily treatment for uterine fibroids, and recently received FDA-approval for management of pain associated with endometriosis.[7] Use of relugolix

combination therapy should be limited to 24 months due to the risk of continued bone loss that may not be reversible.[7] **Table 1** outlines the pharmacotherapies 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[8]

Drug Name (Brand Name)	Formulation	FDA-Approved Endometriosis Dose and Frequency	Safety Precautions (Boxed Warning in Bold)
Anabolic Steroid			
Danazol (DANOCRINE)	Oral Capsule: 50 mg, 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 contraindicate**d -Lipoprotein changes -Androgen effects
Gonadotropin Releasing Hormone Agonists			
Goserelin acetate (ZOLADEX)	Subcutaneous Implant: 3.6 mg	1.6 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-DEPOT)	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 --Use in pregnancy is contraindicated
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 2 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	104 mg SC every 12 to 14 weeks **Duration: Do not use for longer than 2 years (boxed warning)**	**-Loss of BMD** -Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine) -Ectopic pregnancy -Menstrual bleeding irregularities -Use in pregnancy is contraindicated

Norethindrone Acetate (AYGESTIN)	Oral Tablet: 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 (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine) -Worsening depression -Increased risk for thrombosis -Bleeding irregularities -Ectopic pregnancy -Adverse effects on lipid metabolism -Use in pregnancy is contraindicated
Gonadotropin-Releasing Hormone Antagonists			
Elagolix (ORILISSA)	Oral Tablet: 150 mg, 200 mg	Initial: 150 mg PO once daily OR Concomitant dyspareunia: 200 mg PO twice daily Moderate hepatic impairment: 150 mg once daily Duration of therapy: 24 months (150 mg, normal/mild hepatic impairment); 6 months (200 mg, normal/mild hepatic impairment OR 150 mg, moderate hepatic impairment)	-Decreased BMD -Suicidal ideation -Hepatic transaminase elevations -Use in pregnancy is contraindicated
Relugolix, estradiol, and norethindrone (MYFEMBREE)	Oral Tablet: relugolix 40 mg, estradiol 1 mg, & norethindrone 0.5 mg	1 fixed-dose combination tablet PO once daily Duration of therapy: 24 months	-**Thromboembolic disorders and vascular events** -Decreased BMD -Breast cancer or other hormone-sensitive malignancies -Suicidal ideation and mood disorders -Hepatic impairment or transaminase elevations -Gallbladder disease or history of cholestatic jaundice -Hypertension -Menstrual bleeding irregularities -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 endometriosis medical treatment intervention. For pain assessment, an 11-point numeric rating scale (NRS) which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable) has been used.[9] 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.[9] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[10]

The FDA approval for the use of relugolix in management of moderate to severe pain associated with endometriosis was based on two 24-week, phase 3, placebo-controlled, double-blind, randomized controlled trials (RCTs), SPIRIT 1 and 2.[11] The 2 RCTs were conducted in 219 research centers in Africa, Australia, Europe, North America, and South America.[11] Four centers were located in the United States, and 5 centers were based on Poland; all the other countries included only 1 study location.[11] Pre-menopausal women aged 18 to 50 years with moderate to severe pain associated with surgically or directly visualized endometriosis with or without histological confirmation, or histological diagnosis alone within the past 10 years, were eligible for study enrollment.[11] Inclusion criteria included a dysmenorrhea NRS score of 4.0 or higher on 2 or more days and a mean non-menstrual pelvic pain NRS score of 2.5 or higher, or a mean score of 1.25 or higher that included a score of 5.0 or greater on 4 or more days.[11] Patients were excluded from the study if they had a bone mineral density Z-score of less than -2.0 at the lumbar spine, total hip or femoral neck; a history of chronic pelvic pain not caused by endometriosis; or a contradiction to the use of combined hormonal therapy.[11]

Patients were randomized 1:1:1 to receive the relugolix combination product for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks (delayed relugolix combination therapy).[11] The delayed relugolix combination therapy group was included to compare bone mineral density and vasomotor symptoms for relugolix monotherapy with relugolix combination therapy at week 12.[11] SPIRIT 1 enrolled 638 patients to receive relugolix combination therapy (n=212), placebo (n=213), or relugolix delayed combination therapy (n=213).[11] SPIRIT 2 enrolled 623 patients were enrolled to receive relugolix combination therapy (n=208), placebo (n=208), or relugolix delayed combination therapy (n=207).[11] The co-primary endpoints were responder rates at week 24 for dysmenorrhea and non-menstrual pelvic pain, both based on NRS scores and analgesic use.[11] Eligible patients who completed the SPIRIT studies could enroll in a currently ongoing 80-week open-label extension study (SPIRIT EXTENSION) for post-treatment follow-up for safety, specifically for bone mineral density and menses recovery.[11] Twenty-nine percent (n=185) of patients in SPIRIT 1 and 47% (n=288) in SPIRIT 2 were taking opioids (i.e., tramadol 50 mg, codeine 30 mg, or hydrocodone 5 mg; prescribed according respective country's approved product labeling) for pain relief at baseline.[11] Most of the women enrolled in the studies were White (90%), with a mean age of 34 years.[11] Fifteen percent (n=98) of patients terminated study participation early in SPIRIT 1 and 18% (n=118) in SPIRIT 2.[11] Reasons for early termination included adverse events, protocol deviations, loss to follow-up, withdrawal of consent, lack of efficacy, or pregnancy.[11] Withdrawal of consent was the most common reason for study withdrawal.

Responder criteria was defined as achieving a mean reduction in dysmenorrhea NRS score of at least 2.8 points and a mean reduction in nonmenstrual pelvic pain NRS score of at least 2.1 points at week 24 and no increase in use of analgesic medication as recorded in a daily electronic diary.[11] In SPIRIT 1, 74.5% of patients in the relugolix combination therapy group met the dysmenorrhea responder criteria compared with 26.9% patients in the placebo group (treatment difference 47.6%; 95% confidence interval [CI] 39.3 to 56.0; p<0.0001).[11] In SPIRIT 2, 75.1% of patients in the relugolix combination therapy group were dysmenorrhea responders compared with 30.5% of patients in the placebo group (treatment difference 44.6%; 95% CI 35.9 to 53.3; p<0.0001).[11] In SPIRIT 1, 58.5% of patients in the relugolix combination therapy group met the non-menstrual pelvic pain responder criteria versus 39.6% of patients in the placebo group (treatment difference 18.9%; 95% CI 9.5 to 28.2; p<0.0001).[11] In SPIRIT 2, 65.9% of patients were non-menstrual pelvic pain responders in the relugolix combination therapy group compared with 42.5% of patients in the placebo group (treatment difference 23.4%; 95% CI 13.9 to 32.8; p<0.0001).[11] Proportions of responders treated with relugolix combination therapy over 24 weeks compared with placebo-treated responders are summarized in **Table 2**.

Table 2. Proportions of Dysmenorrhea and Non-Menstrual Pelvic Pain Responders at Week 24[7]

	Spirit 1		**Spirit 2**	
	Relugolix 40 mg, estradiol 1 mg, & norethindrone 0. 5mg (n=212)	Placebo (n=212)	Relugolix 40 mg, estradiol 1 mg, & norethindrone 0.5 mg (n=205)	Placebo (n=200)

Dysmenorrhea	74.5% (n=158)	26.9% (n=57)	75.1% (n=154)	30.5% (n=61)
Difference from Placebo 95% Confidence Interval p-value	47.6% 39.3% to 56.0% p<0.0001		44.6% 35.9% to 53.3% p<0.0001	
Non-menstrual pelvic pain	58.5% (n=124)	39.6% (n=84)	65.9% (n=136)	42.5% (n=87)
Difference from placebo 95% Confidence Interval p-value	18.9% 9.5% to 28.2% p<0.0001		23.4% 13.9% to 32.8% p<0.0001	

The most common adverse events reported in the 2 trials were headache, nasopharyngitis, and hot flushes.[11] There were 9 reports of suicidal ideation across both studies (two in the placebo run-in, two in the placebo group, two in the relugolix combination therapy group, and three in the delayed relugolix combination therapy group).[11] No deaths were reported.[11] Least squares mean percentage change in lumbar spine bone mineral density in the relugolix combination therapy versus placebo groups was –0.70% versus 0.21% in SPIRIT 1 and –0.78% versus 0.02% in SPIRIT 2, and in the delayed relugolix combination group was –2.0% in SPIRIT 1 and –1.9% in SPIRIT 2.[11] Decreases in opioid use were seen in cotreated patients compared with placebo.[11]

The SPIRIT studies had limitations. Although the trial population included people with moderate-to-severe endometriosis-associated pain, many screened individuals did not meet the minimum pelvic pain threshold to participate.[11] Most patients enrolled were White, potentially reflecting under-recognition or under-diagnosis of endometriosis, or suboptimal clinical trial engagement among other races and ethnicities.[11] Treatment duration was 6 months, and these studies cannot address efficacy and safety beyond this period.[11] Use of a placebo-controlled study design did not allow for comparison with mainstays of treatment, including hormonal therapies or surgery. However, because the studies were multinational, an active comparator would have to be an approved endometriosis treatment for all countries participating in the study.[11]

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Gonadotropin-Releasing Hormone Antagonists

Goal(s):

- Promote safe use of elagolix and relugolix/estradiol/norethindrone in people with endometriosis-associated pain
- Promote safe use of elagolix/estradiol/norethindrone and relugolix/estradiol/norethindrone for heavy menstrual bleeding associated with uterine fibroids (leiomyoma).
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Initial: Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative lifetime treatment period not to exceed 24 months in patients with normal hepatic function. For patients with moderate hepatic impairment receiving 150 mg once daily, duration of therapy should not exceed 6 months. In patients receiving high dose elagolix therapy (200 mg twice daily), maximum treatment duration is 6 months.
- Elagolix/estradiol/norethindrone renewal: Up to 6 months for elagolix 300 mg dosed twice daily with a total cumulative treatment period not to exceed 24 months
- Relugolix/estradiol/norethindrone renewal: Up to 6 months for relugolix component 40 mg dosed once daily with a total cumulative treatment period not to exceed 24 months

Requires PA:

- Elagolix (ORLISSA)
- Elagolix/estradiol/norethindrone (ORIAHNN)
- Relugolix/estradiol/norethindrone (MYFEMBREE)

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 therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is this request for management of moderate to severe pain associated with endometriosis in a premenopausal patient?	**Yes**: Go to #6	**No:** Go to #12
6. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA- labeled contraindication, or hypersensitivity the first-line therapy options? Note: First-line therapy options such as combined hormonal contraceptives or progestins do not require PA	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine, gemfibrozil, etc.), combined P-glycoprotein inhibitor and moderate CYP3A inhibitor (e.g., erythromycin), combined P-glycoprotein inducer and strong CYP3A inducer (e.g., rifampin)? Note: Elagolix levels are increased when co-administered with OATP1B1 inhibitors. Relugolix levels are increased when co-administered with inhibitors such as erythromycin and decreased when co-administered with inducers such as rifampin. Avoid combinations of these therapies due to drug interactions that can increase the risk of adverse reactions or decrease the efficacy of GnRH antagonists.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients 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 antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
~~8.~~9. 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

Approval Criteria		
~~9.~~10. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #11	**No:** Approve for 6 months ***** FDA approved elagolix dosing for patients with normal liver function or mild liver impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months
~~10.~~11. Is the dose for elagolix 150 mg once daily or relugolix 40 mg /estradiol 1 mg/norethindrone 0.5 mg?	**Yes:** Approve for 6 months (cumulative lifetime treatment) ***** FDA approved elagolix dosing for moderate hepatic impairment: 150 mg once daily for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~12. Is the request for elagolix/estradiol/norethindrone or relugolix/estradiol/norethindrone for management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~12.~~13. Has the patient tried and failed a trial of first line therapy options including at least 1 of the following: a) hormone-releasing IUD OR b) continuous administration of combined hormonal contraceptives OR c) cyclic progestins OR d) tranexamic acid? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the first-line therapy options?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness First-line therapy options such as hormonal contraceptives, progestins, or tranexamic acid do not require PA
~~13.~~14. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients 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 antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months (cumulative, lifetime treatment)

Renewal Criteria		
1. Has the patient been receiving elagolix/estradiol/norethindrone for management of uterine fibroids or relugolix/estradiol/norethindrone for management of uterine fibroids or pain associated with endometriosis?	**Yes:** Go to #4	**No:** Go to #2

Renewal Criteria		
2. Has the patient been receiving therapy with elagolix 150 mg once daily for management of endometriosis?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
3. 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 #4
4. Has the patient's condition* improved as assessed and documented by the prescriber? *For endometriosis: has pain associated with endometriosis improved? For uterine fibroids: has patient experienced at least a 50% reduction in menstrual blood loss from baseline?	**Yes:** Approve for up to 18 months Document physician attestation received. Total cumulative treatment period not to exceed 24 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 2/23; 12/21 (DM), 3/19 (DM),11/18 (DE)
Implementation: TBD; 1/1/22; 5/1/19

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Drug Class Update: Antidepressants

Date of Review: February 2023

Date of Last Review: February 2021
Dates of Literature Search: 01/01/2021 – 12/02/2022

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the use of antidepressants and make recommendations for policy changes if supported by literature identified in this update.

Plain Language Summary:
- The reason we are doing this review is to look at the new evidence on medicines used to treat depression (antidepressants), anxiety, post-traumatic stress disorder (PTSD), and bipolar disorder. The Oregon Health Plan (OHP) fee-for-service (FFS) Medicaid program pays for all antidepressants prescribed by providers.
- Most studies compared antidepressants to the use of a sugar pill called placebo. Studies found the use of antidepressants rarely caused severe adverse events. Mild adverse events, such as dizziness, headaches, and trouble sleeping, often get better after taking them for a period of time.
- Recent new evidence shows antidepressants have benefit compared to placebo for:
  - Improving sadness, interest in activities, and changes in sleep in people with depression
  - Improving sleep and feeling nervous in people with anxiety
  - Improving eating patterns and depression in people with eating disorders
  - Improving pain in people with osteoarthritis
  - Improving depression in people with coronary artery disease (CAD)

Specific types of antidepressant medicines have shown to improve symptoms compared to placebo for these groups:
  - Selective serotonin reuptake inhibitors (SSRIs) for people with PTSD
  - Brexanolone in people who have depression who just had a baby, decreases symptoms of depression more than treatment with placebo. Brexanolone is a type of antidepressant that is only used in persons after having a baby and has to be given by a provider as it is given into the vein.
  - Esketamine for people with moderately severe to severe depression
- Guidelines published updated advice on the best ways to use antidepressants. The following guidelines were updated, and their recommendations support the current FFS policies: National Institute for Health and Care Excellence (NICE), Veterans Administration (VA)/Department of Defense (DOD), American Academy of Neurology (AAN) and Healthcare Improvement Scotland.

- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of antidepressants.

Research Questions:

1. What is the new comparative evidence for efficacy or effectiveness of antidepressants?
2. What is the new comparative evidence for safety or harms of antidepressants?
3. Are there specific subpopulations (e.g., pregnant women, children and adolescents, ethnic groups, or people with certain comorbidities) for which certain antidepressants are better tolerated or more effective than other available antidepressants when used for improvement in symptoms and remission of depression?

Conclusions:

- Evidence for this review comes from nine systematic reviews and meta-analyses, four guidelines, one randomized controlled trial (RCT), two new indications, one new formulation and three safety updates.
- A high quality systematic review and meta-analysis from the Agency for Healthcare, Research and Quality (AHRQ) found antidepressants reduced depressive symptoms more than placebo in adults with depression (standard mean difference [SMD] -0.17 to -0.50 points) (moderate quality evidence).[1] Serious adverse events were rare.
- An AHRQ report in adults found moderate quality evidence that the use of antidepressants is associated with reductions in remission of anxiety symptoms more than placebo (relative risk [RR] 0.83; 95% confidence interval [CI], 0.78 to 0.88).[1]
- There is moderate quality evidence that brexanolone, decreases depressive symptoms, based on the Hamilton Rating Scale for Depression (HAM-D), at day 30, more than placebo in women who are perinatal (least squares mean difference [LSMD] -2.6 points; p=0.02 [CI not reported]), which is lower than what is considered a clinically meaningful difference.[2] Brexanolone may cause excessive sedation and sudden loss of consciousness.
- In children and adolescents, there is low quality evidence that the use of antidepressants for the treatment of anxiety and depression results in reduced symptoms of depression and anxiety compared to placebo.[3] Treatment of anxiety with antidepressants reduced symptom scores, based on the Pediatric Anxiety Rating Scale, by 4 points (95% CI, -5.5 to -2.5 points), which is less than the eight to ten point reduction that is considered clinically me4aningful.[4] Symptom of depression were improved almost 4 points with use of escitalopram and fluoxetine in children and adolescents diagnosed with depression based on the Children's Depression Rating Scale-Revised (CDRS-R).
- A high quality Cochrane systematic review and meta-analysis found low quality evidence that fluoxetine was effective in reducing eating disorder symptom severity and depression symptoms in adolescents and adults.[5] Evidence for use of other antidepressants for eating disorders was limited and of low quality.
- In people with PTSD, treatment with SSRIs were more effective than placebo for elucidating a treatment response, 58% versus 35% (RR 0.66; 95% CI, 0.59 to 0.74) based on moderate strength of evidence.
- A systematic review and meta-analysis on the use of antidepressants for osteoarthritis pain found no clinically significant improvement in pain scores, compared to placebo, but there were more participants who were considered responders (e.g., those with a 50% or greater reduction in 24-hour mean pain) with an absolute improvement of 16% and a number needed to benefit (NNTB) of 6 (high quality evidence for both outcomes).[6]
- In people with CAD and major depressive disorder (MDD), a Cochrane review found moderate strength evidence of improved depression remission rates with antidepressant therapy, as measured by the HAM-D, compared to placebo with an incidence of 496 per 1000 people treated with antidepressants compared to 323 per 1000 people treated with placebo (odds ratio (OR) 2.06; 95% CI, 1.47 to 2.89).[7] Evidence for other outcomes was graded very low to low quality.

- A Cochrane review found esketamine use in people with unipolar MDD to be superior to placebo for remission rates based on the Montgomery-Asberg Depression Rating Scale (MADRS), 17.5% versus 7.2% (OR 2.74; 95% CI, 1.71 to 4.40) (moderate strength evidence).[8]
- A systematic review done by the Drug Effectiveness Review Project (DERP) found low quality evidence demonstrating brexanolone was more effective than placebo in people with postpartum depression (PPD) at increasing remission rates and depression symptoms at 60 hours post infusion.[9]
- Updated treatment guidelines by the NICE, VA/DOD and AAN supports current policy.[10,11,12]
- Guidelines from the Health Improvement Scotland recommend offering short-term antidepressants, in combination with psychological treatments for people with BN (Strong recommendation based on high-quality evidence).[13] Fluoxetine should be considered first-line.
- A fair quality, placebo-controlled randomized controlled trial (RCT) in adults with suicide ideation and MDD found esketamine was superior to placebo for the change in MADRS total score, from baseline to 24 hours post-first dose (least square mean difference [LSMD] -3.9 points; 95% CI, -6.6 to -1.1 points; P=0.006).[14]
- Additional studies on the effectiveness and safety of antidepressants evaluating the Medicaid population are needed.

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

Summary of Prior Reviews and Current Policy:
- Antidepressants are designated preferred or part of the voluntary PDL.
- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics, adverse effects and cost.
- Evidence reviews show esketamine does not decrease the risk of suicide but does slightly improve depressive symptoms in people with treatment-resistant depression (TRD) in adults. (1)
- • Depressive symptoms in adults with major depressive disorder (MDD) with
- acute suicidal ideation or behavior. (1).
- After presentation of the evidence and costs at the February 2021 meeting, the Pharmacy and Therapeutics Committee voted to make duloxetine DR capsules, bupropion HCL XL 24H tablets (Wellbutrin XL & associated generics), and desvenlafaxine succinate ER 24H tablets preferred; and make amoxapine tablets voluntary non-preferred.

Background:
Historically antidepressant medications have been categorized based on mechanism and chemical structure into first-generation (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs, serotonin and norepinephrine reuptake inhibitors [SNRIs], and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, PTSD, bipolar disorder, obsessive compulsive disorder, anxiety disorders and bulimia.[12] Specific antidepressants have Food and Drug Administration (FDA) labeled indications for other conditions including fibromyalgia, diabetic peripheral neuropathy, premenstrual dysphoric disorder, and smoking cessation.[12] All antidepressants have a box warning for suicide risk in young adults and can be associated a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.

Choice in antidepressant is typically dependent on patient preference and adverse effect profile, as current evidence demonstrates little difference in efficacy between agents. Often second-generation antidepressants are recommended as first-line agents due to improved tolerability and decreased risk of adverse events compared to first-generation antidepressants and less risk for overdose. For example in patients with PTSD, first-line recommendations from the VA/DoD for pharmacotherapy include sertraline, paroxetine, fluoxetine, or venlafaxine in patients who are unable to access or choose not to engage in trauma-focused psychotherapy.[13] For the treatment of moderate to severe depression in adults, guidelines from both NICE and the American Psychiatric Association (APA) recommend combination antidepressant and psychotherapy.[14] SSRIs are recommended by NICE as a first-line option, though individual drug choice can vary depending on adverse effects.[14] APA guidelines consider SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options.[14] It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about two-thirds of patients have an inadequate response to initial therapy and about one-third of patients have treatment-resistant depression.[3] There is no consistent definition in the literature for treatment resistant depression, and there is little evidence to guide next steps in therapy after an initial treatment failure.[3] Common treatment options used in clinical practice include trial of a different first-line antidepressant, use of an antidepressant from a different class, and augmentation of current therapy with a second agent.

Goals of treatment for antidepressants typically focus on improvement in symptoms, function, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. There is some evidence that measurement-based care (MBC), via depression rating scales, improves outcomes. However, the recommendation from the VA/DoD for use of these scales was weak due to lack of high quality supporting evidence.[11] Some of the most commonly used rating-scales and thresholds include the MADRS and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[11] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52). [11] Values associated with remission and minimum clinically important differences for each of these scales vary. Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes and typically a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[11] . A 2 point improvement on MADRS may be associated with a clinical improvement and HAM-D scores of 3 to 7 points may be clinically significant.[11]

In Oregon, mental health drug classes, including antidepressants, are carved out of coordinated care organizations and paid for by fee-for-service. Non-preferred products do not automatically require prior authorization, but a few specific agents do have safety criteria including esketamine, brexanolone, and TCAs in children. In the second quarter of 2022, there were over 350,000 claims for an antidepressant medications representing a substantial cost to the OHA.

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.

New Systematic Reviews:

AHRQ – Screening for Depression, Anxiety and Suicide Risk in Adults

A 2022 AHRQ review evaluated screening of primary care patients and treatment of adults with depression, anxiety, or suicide risk.[1] A literature search through September 24, 2021 identified 173 studies for inclusion. Therapies studied were the following: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine, vilazodone, nefazodone, bupropion, mirtazapine, amitriptyline, and trazodone. The findings for the use of antidepressants will be the focus of this class update.

Evidence for the use of pharmacological treatment options in adults came primarily from ten existing systematic reviews, including one high-quality systematic review consisting of 522 studies.[1] All data was from placebo-controlled comparisons. Seven of the included sources were considered good-quality. Additional studies were deemed to be of fair quality. Response to treatment was the primary outcome measured in most of the studies. Symptom severity was measured most commonly by the HAM-D and MADRAS scoring questionnaires with a 50% reduction in symptoms considered as response to treatment. Since there was variability in reporting methods, improvements in symptoms were reported in standardized units for comparison. Clinical significance of symptom changes were deemed to be a small, medium or large effect as determined by Cohen's rule of thumb correlating to sores of 0.20, 0.50, and 0.80, respectively.

All antidepressants studied, in people with depression, resulted in a treatment response, reductions in continuous symptoms and increased remission rates compared to placebo. Symptom severity was reduced from a SMD -0.17 to -0.50, suggesting small improvements in symptoms.[1] Remission rates were increased from 23% to 252% and treatment response ranged from 37% to 213% relative to placebo for all the trials included in the review. Fluoxetine had the most evidence (117 trials) and improved depression symptom severity by SMD -0.23 (95% CI, -0.28 to -0.19). Odds of remission and treatment response was also increased. Combination treatment with medication and psychotherapy decreased depression severity symptoms by a SMD of -0.46 (95% CI, -0.70 to -0.21).[1] A review of SSRIs for depressive symptoms found reductions in severity and remissions compared to placebo. An analysis of 4 trials in older adults demonstrated duloxetine had the most efficacy across all depressive outcomes and fluoxetine had the least improvement. Paroxetine was found to be effective in trials studying people of lower socioeconomic status when compared to placebo. There were few studies evaluating the long-term effects of antidepressant use. One study evaluated paroxetine use at 10 months (6 months on treatment and 4 months off of treatment) demonstrated small reductions in symptom severity (SMD -0.39; 95% CI, -0.74 to -0.04).[1] Duloxetine was also studied for longer than 12 weeks and resulted in improvements in symptom reduction but not remission. Antidepressant therapy was not shown to improve cognitive function or quality of life compared to placebo.

The risk of suicide attempts after the discontinuation of second generation antidepressants was higher with treatment compared to placebo, 0.7% versus 0.3%.[1] A study evaluating the use of duloxetine compared to placebo found that it was associated with a statistically significant greater reduction in suicidality compared to placebo in those ages 25 and older compared to those 18-24 years old.[1] In general, the number of suicide attempts was very small. Fluoxetine and venlafaxine were associated with decreased suicidal thoughts and behaviors in adults and geriatric patients.

The treatment of anxiety with antidepressants was studied in two good quality RCTs. Venlafaxine extended-release improved anxiety symptoms at 24 weeks compared to placebo. In older adults, people taking escitalopram were more likely to demonstrate a treatment response (i.e., clinician rating of improved or very much improved) compared to placebo (OR 1.87; 95% CI, 1.03 to 3.39; p=0.05).[1] The use of SSRIs and TCAs also decreased panic disorder symptoms (e.g., anxiety, panic symptoms, panic attacks, and agoraphobia) more than placebo. Antidepressants were associated with a higher likelihood of remission of anxiety symptoms (RR 0.83; 95% CI, 0.78 to 0.88).[1] For those with social anxiety disorder, use of SSRIs was more likely to result in a treatment response compared to

placebo (RR 1.65; 95% CI, 1.48 to 1.85). In people with GAD and panic disorder, anxiety symptom score improvement ranged from reductions of a SMD of -0.23 for the use of serotonin modulators to a SMD reductions of -1.84 for bupropion.[1]

Evidence on adverse events associated with antidepressant use is mostly based on observational data.[1] Low quality evidence, that was at risk of confounding due to observational data, demonstrated and increase risk of fractures with antidepressants (RR 1.67; 95% CI 1.56 to 1.79; 23 studies). All other risks (e.g., CVD, mortality, dementia, bleeding) lacked enough evidence to form strong conclusions. Serious adverse events were rare. Dropouts related to adverse events were more common in patients taking antidepressants compared to placebo. There is an increased risk of preterm birth with SSRI use in women with depressive symptoms based on observational data (OR 1.6; 95% CI, 1.0 to 2.5).[1]

There was insufficient evidence on long-term treatment with antidepressants and relapse prevention with antidepressant therapy. The most evidence for a sustained response was with combination pharmacotherapy and psychological treatment followed by psychological therapy alone.

AHRQ – Screening for Depression, Anxiety, and Suicide Risk in Children and Adolescents

A 2022 systematic review and meta-analysis evaluated the evidence for screening and treating children and adolescents in the primary care setting with a history of depression, anxiety, and suicide risk.[2] A total of 60 trials were included which evaluated treatment efficacy with behavioral therapy, medications or combination of the two. No studies evaluated the effect of pharmacotherapy on suicide risk. Duloxetine is the only therapy FDA approved for GAD in children and fluoxetine and escitalopram are the only therapies approved for MDD in children 8 and older; however, many medications are used off-label for both conditions.

Six RCTs evaluated pharmacotherapy for anxiety, and one trial evaluated combination therapy with sertraline and cognitive behavioral therapy (CBT).[2] Studies had placebo comparisons, and lasted from 8 to 12 weeks. Therapies included duloxetine, escitalopram, fluoxetine, fluvoxamine and sertraline. Participants had anxiety disorders catorgorized as general anxiety disorder (GAD), social anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder and selective mutism. Pharmacotherapy improved symptom scores based on the Pediatric Anxiety Rating Scale (MD -4 points; 95% CI, -5.5 to -2.5), symptom severity based on the Clinical Global Impressions-Severity (MD -0.84; 95% CI, -1.13 to -0.55), and response rates (RR 2.11; 95% CI, 1.58 to 2.98).[2] Studies evaluating functioning at the end of treatment favored the use of pharmacotherapy.

There were 3 trials that evaluated the use of medications for depression in this population. Studies evaluated escitalopram and fluoxetine and lasted from 8 weeks to 12 months. Pharmacotherapy was shown to improve symptoms based on the CDRS-R. Treatment with antidepressants decreased symptoms by -3.76 points (95% CI, -5.95 to -1.57).[2] Differences in remission rates were not statistically different from placebo when compared to antidepressants. One study evaluating fluoxetine with CBT found higher response rates and higher remission rates compared to placebo. Compared to placebo, symptoms were improved by 8.5 points (95% CI, 13.4 to -3.6) at 6 months, response rates (defined as $\geq$50% reduction in CDRS-R score) were higher at 12 months (OR 3.3 [95% CI, 1.4 to 8.2]), and remission rates (based on Patient Health Questionnaire-9 of less than 5) were improved at 6 months (OR 5.2; 95% CI, 1.6 to 17.3).[2] In subgroup analyses, participants who were treated with antidepressants who were 12 to 17 years of age reported more improvements in functioning and symptom severity compared with those ages 6 to 11 years. There was insufficient evidence on mortality data.

AHRQ – Screening for Eating Disorders in Adolescents and Adults

A 2022 systematic review and meta-analysis evaluated screening tools as well as pharmacotherapies for the treatment of adolescents and adults with eating disorders.[5] Evidence through January 1, 2022 was included. Seventeen trials evaluated therapies to treat eating disorders. Most trials enrolled predominately adult women, mean ages 25 to 44 years.[5]

Five trials evaluated SSRIs in people with binge-eating disorder (BED). Changes in the incidence of BED were of low quality and there was no difference in scores between fluoxetine and placebo (SMD -0.29; 95% CI, -0.83 to 0.24). People with an eating disorder and depression demonstrated improvements in depression scores (SMD -0.6; 95% CI, -0.90 to -0.33).[5] In patients with bulimia nervosa, fluoxetine was found to reduce eating disorder symptom severity and depression symptoms.

Evidence is primarily applicable to adult women and patients with binge-eating disorder or bulimia nervosa. Evidence was limited by the small amount of studies included in the analysis.

AHRQ – Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacological Interventions

A systematic review and meta-analysis done by AHRQ in 2022 evaluated treatments used in people with depression and who are perinatal (pregnant and postpartum).[2] Literature was searched through June 5, 2020, identifying 164 studies. Most of the evidence came from observational studies, inferring a high risk of bias and potential for confounding.

In pregnant and postpartum people with a diagnosis of anxiety, depression, bipolar disorder or schizophrenia, there were 9 RCTs and 10 observational studies evaluating the efficacy of medications in these populations.[2] In people with depression, there was low to moderate quality evidence for the reduction in depression symptoms with antidepressants. Brexanolone at peak doses of 60 to 90 mcg/kg per hour was studied in three trials enrolling women with onset of depressive symptoms in the third trimester, with approximately 30% on concomitant antidepressant therapy. Brexanolone improved depressive symptoms within 60 hours after infusion. At 30 days after treatment based on the HAM-D when compared to placebo (-16.0 versus -14.3 points; LSMD -2.6; p=0.02 [CI not reported]) (moderate strength of evidence), which is not considered clinically significant.[2] There was low quality evidence for the use of sertraline, based on placebo comparisons, in the postpartum period for response (RR 2.24; 95% CI, 0.95 to 5.24; p= 0.01 to 0.05), remission (RR 2.51; 95% CI, 0.94 to 6.70; p=0.01 to 0.05), and improvements in depressive symptoms.[2] Results suggest sertraline may provide benefit but not all findings were significant. Discontinuation of antidepressants during pregnancy in people with bipolar resulted in an increase in depressive symptom recurrence and a shorter time to symptom recurrence (low quality evidence

Harms data for the use of antidepressants in women who are perinatal comes from 5 RCTs and 70 observational trials. Evidence was determined to be low quality.[2] Tricyclic antidepressants and SNRIs were associated with a higher risk of preeclampsia and SNRIs had an increased risk of spontaneous abortion. The use of several antidepressants may be associated with a higher risk of postpartum hemorrhage. Brexanolone was found to increase sedation and somnolence leading to dose interruptions compared to placebo, 5% versus 0%.[2] The use of SSRIs by perinatal (e.g., pregnant or up to 28 days following birth) people may be associated with the following outcomes for their child: an increased risk of respiratory issues, low Apgar scores (determinant of newborn's health), persistent pulmonary hypertension of the newborn, and depression in children.

This review was limited by inclusion of mostly low quality evidence. Due to the observational nature of the data, it is uncertain if harms were due to medications or if they were associated with the mental health diagnosis itself.

There was insufficient evidence for the comparative effectiveness of treatments for anxiety, depression, bipolar disorder or schizophrenia in women during the perinatal period.

Cochrane - Pharmacotherapy for Post-Traumatic Stress Disorder (PTSD)

A Cochrane review published in 2022 evaluated the evidence for the use of pharmacotherapy in people with PTSD.[15] Literature was search until November 2020. The review identified 66 trials, with 54 used in the meta-analysis, that met inclusion criteria. Classes studied were SSRIs, SNRIs, MAOIs, TCAs and noradrengic and specific serotonergic antidepressants (NaSSAs).[15] The majority of studies evaluated paroxetine, fluoxetine and sertraline. The primary outcome was treatment response.

In participants taking SSRIs, there was a higher treatment response compared to placebo (58% vs. 35%; RR 0.66; 95% CI, 0.59 to 0.74) based on moderate quality evidence.[15] Mirtazapine demonstrated a benefit over placebo in one small study (n=26) (RR 0.45; 95% CI, 0.22 to 0.94). Low quality evidence showed a treatment response with amitriptyline compared to placebo (50% vs. 17%; RR 0.60; 95% CI, 0.38 to 0.96).[15] Withdrawal symptoms were more common with SSRIs than placebo (RR 1.41; 95% CI, 1.07 to 1.87) (moderate quality of evidence), which was especially common with paroxetine compared to placebo (RR 1.55; 95% CI 1.05 to 2.29) . Moderate quality of evidence demonstrated the risk of dropouts due to adverse events was higher with amitriptyline compared to placebo (182 per 1000 vs. 167 per 1000; RR 0.92; 95% CI, 0.81 to 1.05).[15]

Cochrane – Antidepressants for Hip and Knee Osteoarthritis

A Cochrane review evaluated efficacy of antidepressants in adults with osteoarthritis. Literature evaluated comparisons between antidepressants and placebo, or other active therapies.[6] Participants were adults with a diagnosis of osteoarthritis and without a mental health diagnosis. Seven trials involving knee osteoarthritis and 2 trials involving knee or hip osteoarthritis lasting 8 to 16 weeks were included. The mean ages of participants included in these trials ranged from 54.5 to 65.9 years and the majority of participants were women.[6] All trials were placebo controlled, and antidepressants could be used with or without non-steroidal anti-inflammatory drugs. The primary outcomes of interest were pain, function, and harms of treatment.

Nine RCTs compared antidepressants to placebo and found a mean difference in pain reduction of -0.59 (95% CI, -0.88 to -0.31) based on a 10-point scale.[6] The absolute difference in pain improvement was 6%, suggesting a small difference which is unlikely to be clinically important (high quality evidence). The number of responders (e.g., those with a 50% or greater reduction in 24-hour mean pain) was higher in those receiving antidepressants with an absolute improvement of 16% and a NNTB of 6 (high quality evidence).[6] There was high quality evidence that physical functioning (0-100 Western Ontario and McMaster Universities Arthritis Index [WOMAC] Total score) was improved with antidepressants, compared to placebo, which was probably clinically significant (mean difference [MD] -5.65; -7.08 to -4.23).[6] There was moderate evidence of no difference in quality of life between antidepressants and placebo. There was a higher chance of withdrawal due to adverse events in participants taking antidepressants compared to placebo with a number needed to harm [NNTH] of 17 (moderate quality of evidence). Serious adverse events were similar between groups, but there was a higher incidence of total adverse events with the use of antidepressants compared to placebo (NNTH 7 based on high quality of evidence).[6]

Cochrane – Psychological and Pharmacological Interventions for Depression in Patients with Coronary Artery Disease

Cochrane performed a systematic review and meta-analysis on the effects of drug therapy and psychological interventions for the treatment of MDD in adults with CAD.[7] The evidence for the use of drug therapy will be presented. There were 21 pharmacotherapy trials that were included in the analysis. Drugs included sertraline, mirtazapine, fluoxetine, escitalopram, paroxetine and nortriptyline. Evidence was searched through August 2020.

There was low quality evidence that the use of antidepressants, compared to placebo, helps to reduce symptoms of depression in the short term (SMD of 0.83 points lower than placebo).[7] Remission rates for depression, as measured by the Hamilton Rating Scale for Depression, were lower with antidepressant therapy with an incidence of 496 per 1000 people treated with antidepressants compared to 323 per 1000 people treated with placebo (OR 2.06; 95% CI, 1.47 to 2.89) (moderate quality evidence).[7] The evidence for mortality outcomes and risk of myocardial infarction (MI) was based on very low quality evidence, and therefore, strong conclusions could not be drawn. There was insufficient evidence for head-to-head comparisons between treatments.

There is a need for additional evidence demonstrating improvement in depressive symptoms in those treated with antidepressants that have CAD and MDD.

Cochrane – Ketamine and other Glutamate Receptor Modulators for Depression in Adults with Unipolar Major Depressive Disorder

A high quality systematic review and meta-analysis evaluated the evidence for the use of ketamine (22 trials), esketamine (8 trials), memantine (2 trials), atomoxetine (1 trial), and riluzole (1 trial) for the treatment of unipolar MDD.[8] Participants in the trials were 18 and older and had a diagnosis of moderate depression (29 trials), severe depression (17), and mild-moderate depression (5). Twenty percent of the included trials enrolled patients with treatment-resistant depression (defined as inadequate response to at least two antidepressants).[8] The primary outcome was the number of participants with response to treatment. The included RCTs were considered to have low risk of bias or unclear risk of bias. The non-randomized trials were deemed to be at high risk of bias.

Ketamine was studied as a single, IV dose in most studies and esketamine was given intranasally twice weekly for four weeks in most studies.[8] Ketamine was shown to possibly increase response and remission of depression symptoms more than placebo or midazolam, but all evidence was considered to be of very low quality. Esketamine was compared to placebo and found to increase remission rates (based on MADRS) at 24 hours (17.5% vs. 7.2%; OR 2.74; 95% CI, 1.71 to 4.40) (moderate strength of evidence).[8] At 24 hours the response rate was also higher in those treated with esketamine compared to placebo, but the evidence was low quality (OR 2.11; 95% CI, 1.20 to 3.68).[8] There was moderate evidence that esketamine improved depression rating scale scores more than placebo based on 4 RCTs (n=824) with a SMD of 0.31 points lower (95% CI, -0.45 to -0.17). Treatment discontinuation was higher with esketamine compared to placebo based on moderate evidence (12.9% versus 4.3%). There was insufficient evidence for the use of memantine, atomoxetine, or riluzole for the use in unipolar MDD.

DERP – Intravenous Brexanolone (Zulresso) and SAGE-217 (Zuranolone) to Treat Postpartum Depression

The evidence for the use of brexanolone and SAGE-217 (not approved in the US) was reviewed by DERP in March of 2021.[9] Brexanolone is indicated for women with PPD and is delivered by the IV route via a 60-hour infusion. Three studies placebo-controlled trials were available for inclusion. Trial duration lasted up to 30 days post-infusion.[9]

Evidence regarding benefit of brexanolone was mixed and dependent on the specific outcome, timepoint, and population. Disease remission was higher with brexanolone compared to placebo at 60 hours based on low quality evidence, but no different at 30-days post infusion.[9] At 60 hours, depression symptoms were improved, based on HAM-D scores (low quality of evidence), but not different when evaluated using the Edinburgh Postnatal Depression Scale (EPDS) based on very low quality of evidence. At 30-days post infusion, there were significant improvements in depression scores based on the HAM-D in women with severe PPD but not in those with moderate PPD, as determined by DERP.[9]

Brexanolone has a Risk Evaluation and Mitigation Strategy program required for use due to the risk of excessive sedation and sudden loss of consciousness. Studies found no significant difference between placebo and brexanolone in treatment-emergent adverse events up to 7 days after therapy initiation.[9]

After review, 280 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[16–26, 17,27–38, 39–46]

New Guidelines:
High Quality Guidelines:

NICE – Depression in Adults: Treatment and Management
In June of 2022 NICE updated their guidance on treating adults with antidepressants.[10] This updates the original guidance from 2009. Pharmacological recommendations will be included, as this is the focus of this updated; however, there are recommendations included in the guidance for the benefits of psychological and psychosocial therapies. Guidelines recommend discussing the choices of therapy, dose and dose adjustments, expected benefits, and potential harms prior to starting therapies. Reviewing expected benefits of treatment, time to effect (approximately 4 weeks), instructions on administration, and withdrawal symptoms should be discussed between patient and provider.[10]

The treatment choice should be guided by the needs and preferences of the individual with depression, taking into account any previous treatments, sedative effects, concomitant illness or medications, and suicide risk.[10] Treatment should be assessed 2 to 4 weeks after starting treatment. SSRIs are recommended as a first-line option for treatment of depression. Other treatment options include SNRIs, TCAs, or combination therapy with CBT.[10] TCAs are dangerous in overdose and should be used with caution in certain populations. If depressive symptoms have a limited response to treatment, the dose can be increased or the treatment can be changed to another medication (in the same class in a different class). Vortioxetine should be reserved for patients that have tried at least 2 previous antidepressants without a desired response due to lack of superiority to other antidepressants and it's high cost.[10] People with ongoing depressive symptoms should be referred to a specialist and may be a candidate for the addition of a second antidepressant from another class or addition of a second-generation antipsychotic.

If treatment is discontinued it should be done after a conversation with the prescriber and the patient should be cautioned on risk of unsteadiness, altered sensation, altered feelings such as irritability, restlessness or agitation, problems sleeping, sweating, abdominal symptoms, and palpitations. All antidepressants can be associated with withdrawal symptoms, especially commonly used treatments such as paroxetine and venlafaxine. Withdrawing therapy may take weeks to months to complete and medications such as paroxetine and venlafaxine are most likely to be associated with withdrawal symptoms.[10] Specific recommendations related to discontinuing fluoxetine include alternate day dosing in those taking fluoxetine 20 mg a day and slow dose tapers every 1-2 weeks for people taking higher doses of 40 to 60 mg daily so effects can be evaluated.[10]

VA – Management of Major Depressive Disorder
The VA published guidance on the treatment of MDD in 2022 with literature searched through January of 2021.[11] The guideline is intended for management of adult patients, 18 and older, with a diagnosis of MDD of any severity. Guideline recommendations range from weak to strong based on evidence. Recommendations related to antidepressant pharmacotherapy will be included.

A collaborative/integrated care model is strongly recommended to treat MDD.[11] The guideline recommends that patients with a history of MDD be evaluated via a quantitative measure for depression severity to guide treatment management. There is a strong recommendation for psychotherapy or pharmacotherapy for treatment of MDD, based on patient preference. Other factors that should be considered are treatment response, severity and chronicity. Certain treatment strategies (e.g., augmentation, combination treatment, switching treatment, and second-line treatments) may be appropriate, depending upon patient

characteristics. Recommendations for initial therapy include bupropion, mirtazapine, SSRIs, trazodone, vilazodone, vortioxetine, or SNRIs (weak recommendation).[11] The following treatments are not recommended as first-line therapies: esketamine, ketamine, MAOIs, nefazodone, and TCAs (weak recommendation). Combination therapy with medication and psychotherapy is weakly recommended for those with severe MDD (PHQ-9 greater than 20 points), persistent major depressive disorder (greater than 2 years), and recurrent depression with more than 2 episodes. There was insufficient evidence for the use of bupropion for augmentation therapy as an add on treatment to an SSRI.[11] A weak recommendation for the use of ketamine or esketamine as augmentation is recommended for people who have MDD and have not responded to several pharmacological therapy trials. The use of antidepressants during pregnancy should be considered and the risks and balances should be weighed in people who responded to therapy prior to pregnancy (strong recommendation). St. John's wort is weakly recommended as monotherapy for pregnant patients with mild MDD who prefer herbal treatments, and are not on therapy that could interact with St. John's wort.[11] There is a strong recommendation that treatment should be continued for 6 months beyond remission to prevent relapse.

American Academy of Neurology - Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary

A 2022 guideline published by the AAN provides recommendations for the treatment of painful diabetic neuropathy (PDN).[12] Literature was searched up until April 2020 and evidence was graded using a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[12] Conflicts of interest were noted for some guideline authors; however, criteria for dealing with conflicts with industry were clearly outlined. Five classes of medications were included in the update: gabapentinoids, SNRIs, TCAs, sodium channel blockers, and SNRI/opioid dual mechanism agents (e.g., tramadol and tapentadol).[12] All pain outcomes were converted to an effect size estimate for efficacy, with a SMD of 0.5 demonstrating a moderate effect. Since the focus of this review is for the use of antidepressants, evidence for their use will be presented.

Evidence for the use of antidepressants for PDN are presented in **Table 2**. Comparisons of therapies found venlafaxine to be similar to carbamazepine for pain intensity (SMD -0.02; 95% CI, -0.32 to 0.35; p>0.05) (moderate quality of evidence).[12] There is moderate evidence that pregabalin is more effective at reducing pain compared to venlafaxine (SMD 0.84; 95% CI, 0.48 to 1.20). Amitriptyline was shown to have similar efficacy to gabapentin for pain intensity (SMD 0.33; 95% CI, -0.32 to 0.98) based on low quality evidence.[12] Combination therapy with duloxetine and pregabalin has similar efficacy to the monotherapy components. A comparison between duloxetine and nortriptyline found duloxetine to be more likely to improve pain (SMD 1.64; 95% CI, 0.63 to 2.65) (low quality of evidence). However, overall TCAs, compared to placebo, demonstrated the largest benefit on pain scores; based on low quality evidence.

The guidelines recommend that all patient with PDN should be given the option of a TCA, SNRIs, gabapentinoids, and/or sodium channel blockers (e.g., anticonvulsants) to help manage pain symptoms (Level B evidence).[12] Evidence for efficacy between the different therapies show similar effects on pain, all with a medium effect size (SMD 0.5). Adverse effect profiles should be considered as well as costs and patient preferences. Due to adverse effects and limited evidence on efficacy in PND, opioids, tramadol and tapentadol should not be used for pain control in PDN (Level C).[12]

Table 2. Recommendations for the Use of Antidepressants for Diabetic Polyneuropathy[12]

Class	Effect size for pain reduction	Grade	Notes
SNRIs (9 studies)	SMD 0.47 (95% CI, 0.34 to 0.60)	Moderate quality of evidence	Most evidence comes from venlafaxine, desvenlafaxine and duloxetine.
TCAs (3 studies)	SMD 0.95 (95% CI, 0.15 to 1.8)	Low quality of evidence	All evidence was for amitriptyline.

SNRI/Opioids (4 studies)	SMD 0.78 (95% CI, 0.54 to 1.03)	Low quality of evidence	Opioids not recommended due to adverse effects.

Abbreviations: CI – confidence interval; SMD – standard mean difference; SNRIs – selective norepinephrine reuptake inhibitors; TCA – tricyclic antidepressants.

Health Improvement Scotland – Eating Disorders

An August 2022 guideline was published to provide evidence for the management of eating disorders.[13] Healthcare Improvement Scotland produces high quality clinical guidelines accredited by NICE. Recommendations are based on the quality of evidence, ranging from 1 to 4. Level 1 evidence is considered high-quality and Level 4 is expert opinion. Eating disorders covered in the guideline are anorexia nervosa (AN), bulimia nervosa (BN) and BED.

Recommendations pertaining to the treatment of eating disorders with antidepressant medications will be presented. Psychological therapies are a cornerstone of treating eating disorders but are out of the scope of this review. Pharmacotherapy with antidepressants is not recommended for treating AN. The guidelines recommend offering antidepressants short-term, in combination with psychological treatments for people with BN (Strong recommendation based on high quality evidence).[13] Fluoxetine is the only FDA treatment approved for the treatment of BN and should be considered first-line (Strong recommendation based on high quality evidence). Other antidepressants can be considered if fluoxetine is not an option.[13] In people with BED, treatment of comorbidities should be treated but evidence does not support the use of medication for BED alone. People with comorbid anxiety and depression should be treated with evidence-based treatment in addition to the eating disorder.

Additional Guidelines for Clinical Context:
No guidelines were excluded due to poor quality.

New Formulations or Indications:

Brexanolone (Zulresso®): A new indication for brexanolone was approved in June of 2022 which expanded use for patients 15 years and older diagnosed with postpartum depression.[47] Brexanolone was previously approved in adults for this indication.

Dextromethorphan and bupropion (Auvelity®): A new dosage formulation, available as a combination product of dextromethorphan and bupropion, was approved in August of 2022.[48] The product is a combination of an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist (dextromethorphan) and sigma-1 receptor agonist and aminoketone and CYP450 2D6 inhibitor (bupropion) indicated for MDD in adults. Approval was based on one placebo-controlled trial and one trial comparing the combination product to bupropion. Both studies were 6 week studies enrolling adult patients. Dextromethorphan/bupropion improved depression symptoms compared to placebo with a decrease in MADRS score of -3.9 points (95% CI, -6.4 to -1.4) more than placebo. The mean baseline MADRS score of participants was 33.4 indicating moderate depression for most patients.[48] Specific results were not available for the second study.

Duloxetine (Drizalma Sprinkle®): In July of 2021, duloxetine received an expanded indication for the use for fibromyalgia in adults with a starting dose of 30 mg a day and a target dose of 60 mg a day.[49] Approval was based on two, double-blind, placebo-controlled RCTs.[49] Treatment with duloxetine 60 mg or 120 mg once daily resulted in improved pain scores as measured by the primary outcome of the proportion of patients with at least a 50% reduction in scores from baseline. The 120 mg dose was not superior to the 60 mg dose and was associated with more adverse reactions.[49] Other formulations of duloxetine are also approved for fibromyalgia.[50]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)[51]	Not Applicable	September 2021	Warnings and Precautions	There is an association between the use of SSRIs and SNRIs and the occurrence of sexual dysfunction that should be included in all labeling.
Vortioxetine tablets[52]	Trintellix®	January 2021	Box Warning	Revised box warning to include increased risk of suicidal thinking and behaviors in pediatric and young adult patients which should be closely monitored. Updated labeling is in response to a pooled analysis which found that treatment in patients 24 years and younger was associated with an increased incidence of suicidal thoughts and behaviors compared to placebo treated patients.
Venlafaxine extended release capsules[53]	Effexor XR®	November 2021	Warnings and Precautions	Post marketing reports suggest an increased risk of serious symptoms upon discontinuation of venlafaxine XR, reported as protracted and severe. Symptoms range from suicide, suicidal thoughts, aggression, violent behavior, visual changes and increased blood pressure after stopping or reducing the dose of venlafaxine XR.

Randomized Controlled Trials:

A total of 312 citations were manually reviewed from the initial literature search. After further review, 311 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 trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Ionescu, et al[14] ASPIRE II	1. Esketamine 84 mg nasal spray twice weekly*	Adults (ages 18 to 64 years) with MDD and active	Change from baseline to 24 hours post-first dose in MADRS total score	1. -15.7 points 2. -12.4 points Esketamine vs. Placebo	Results are most applicable to inpatient treatment of patients with severe disease.

DB, Phase 3, RCT	2. Placebo nasal spray twice weekly* Study duration: 4 weeks	suicidal ideation with intent		LSMD -3.9 (95% CI, -6.6 to -1.1) P=0.006	

Key: * All patients received standard of care (e.g., 5 or more days hospitalization and newly initiated or optimized oral antidepressant[s])
Abbreviations: CI = confidence interval; LSMD = least square mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; RCT = randomized clinical trial.

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51. Viibryd (vilazodone) [prescribing information]. Madison, NJ; Allergan. September 2021.

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53. Effexor XR (venlafaxine extended-release capsules) [prescribing information]. Philadelphia, PA; Pfizer, Inc., November 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION XL	TAB ER 24H	Y
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y

desipramine HCl	NORPRAMIN	TABLET	Y
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	Y
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
duloxetine HCl	CYMBALTA	CAPSULE DR	Y
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
amoxapine	AMOXAPINE	TABLET	V
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V

clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
esketamine HCl	SPRAVATO	SPRAY	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
nefazodone HCl	NEFAZODONE HCL	TABLET	V
paroxetine HCl	PAROXETINE HCL	ORAL SUSP	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
brexanolone	ZULRESSO	VIAL	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II)
Ionescu D, Dong-Jing Fu, Xin Qiu, Rosanne Lane, Pilar Lim, Siegfried Kasper, David Hough, Wayne C Drevets, Husseini Manji, Carla M Canuso
Background: Patients with major depressive disorder (MDD) having active suicidal ideation with intent require immediate treatment.
Methods: This double-blind study (ASPIRE II) randomized adults (aged 18-64 years) with MDD having active suicidal ideation with intent to esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks, given with comprehensive standard of care (hospitalization ≥5 days and newly initiated or optimized oral antidepressant[s]). Change from baseline to 24 hours post-first dose in Montgomery-Asberg Depression Rating Scale total score (primary efficacy endpoint) was analyzed using ANCOVA. Clinical Global Impression-Severity of Suicidality-revised (key secondary endpoint) was analyzed using ANCOVA on ranks of change.
Results: Of 230 patients who were randomized (115 per arm), 227 received study drug and were included in efficacy/safety analyses; 184 (80.0%) completed double-blind treatment. Greater improvement in Montgomery-Asberg Depression Rating Scale total score was observed with esketamine (mean [SD]: -15.7 [11.56]) vs placebo (-12.4 [10.43]), each with standard of care, at 24 hours (least-squares mean difference [SE]: -3.9 [1.39], 95% CI: -6.60, -1.11; 2-sided P = .006). This was also noted at the earlier (4-hour) timepoint (least-squares mean difference -4.2, 95% CI: -6.38, -1.94). Patients in both treatment groups experienced rapid reduction in Clinical Global Impression-Severity of Suicidality-revised score; the between-group difference was not statistically significant. The most common adverse events among esketamine-treated patients were dizziness, dissociation, nausea, dysgeusia, somnolence, headache, and paresthesia.
Conclusion: This study confirmed rapid and robust reduction of depressive symptoms with esketamine nasal spray in severely ill patients with MDD who have active suicidal ideation with intent. Trial Registration: Clinical Trials.gov identifier: NCT03097133.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 18, 2022
Search Strategy:

#	Searches	Results
1	Amitriptyline/ or amitriptyline.mp.	9780
2	bupropion.mp. or Bupropion/	5461
3	citalopram.mp. or Citalopram/	7584
4	desipramine.mp. or Desipramine/	7952
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	517
6	doxepin.mp. or Doxepin/	1512
7	duloxetine.mp. or Duloxetine Hydrochloride/	3140
8	escitalopram.mp. or Escitalopram/	3078
9	fluoxetine.mp. or Fluoxetine/	15314
10	fluvoxamine.mp. or Fluvoxamine/	3225

11	imipramine.mp. or Imipramine/	13487
12	mirtazapine.mp. or Mirtazapine/	2632
13	nortriptyline.mp. or Nortriptyline/	3231
14	paroxetine.mp. or Paroxetine/	6725
15	protriptyline.mp. or Protriptyline/	415
16	sertraline.mp. or Sertraline/	5829
17	trimipramine.mp.	544
18	venlafaxine.mp. or Venlafaxine Hydrochloride/	4861
19	amoxapine.mp. or Amoxapine/	482
20	clomipramine.mp. or Clomipramine/	4096
21	esketamine.mp.	559
22	isocarboxazid.mp. or Isocarboxazid/	415
23	levomilnacipran.mp. or Levomilnacipran/	98
24	nefazodone.mp.	794
25	phenelzine.mp. or Phenelzine/	1677
26	selegiline.mp. or Selegiline/	2982
27	tranylcypromine.mp. or Tranylcypromine/	2300
28	vilazodone.mp. or Vilazodone Hydrochloride/	250
29	vortioxetine.mp. or Vortioxetine/	613
30	brexanolone.mp.	117
31	olanzapine.mp. or Olanzapine/	10259
32	trazodone.mp. or Trazodone/	2279
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	89226
34	limit 33 to (english language and humans and yr="2021 -Current")	2814
35	limit 34 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	312

Appendix 4: Key Inclusion Criteria

Population	Patients with depression, anxiety, or post-traumatic stress disorder
Intervention	Antidepressants listed in **Appendix 1**
Comparator	Antidepressants listed in **Appendix 1** or other active comparator (e.g., psychological therapy)
Outcomes	Function, quality of life, symptoms, morbidity, mortality, significant adverse events
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered 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.

Approval Criteria		
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeuticarget doses)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve requested doses (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 2/23 (KS), 10/21 (SS); 2/21(SS); 7/19 (KS)
Implementation: 1/1/22; 3/1/21; 8/19/19

Brexanolone (Zulresso)

Goal(s):
- To ensure appropriate use of brexanolone in patient with post-partum depression.

Length of Authorization:
- One time use only.

Requires PA:
- Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered 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 this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient an adult with moderate to severe post-partum depression?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with brexanolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple doses of brexanolone have not been studied.	**No:** Go to #5
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 2/23 (KS), 2/21(SS); 7/19 (KS)
Implementation: 8/19/19

Tricyclic Antidepressants

Goal(s):
- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:
- Up to 12 months

Requires PA:

- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

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/

Table 1. FDA-Approved Indications of Tricyclic Antidepressants

Drug	FDA-Approved Indications	Maximum Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg (150 mg for 10-19 years of age)	10~~18~~
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #4
4. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #5
5. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 2/23 (KS), 2/21(SS); 11/19
Implementation: 2/1/2020

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OHSU Drug Effectiveness Review Project Summary Report – FDA-Approved Treatments for Spinal Muscular Atrophy

Date of Review: February 2023 **Date of Last Review:** September 2019

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

Plain Language Summary:

- This document is a summary of research report from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). They studied all the medicines approved in the United States (U.S.) to treat spinal muscular atrophy.
- Spinal muscular atrophy is an inherited condition that destroys motor neurons, which are nerve cells that control muscles involved in speaking, walking, breathing, and swallowing. In spinal muscular atrophy, the muscles weaken over time and waste away. There are 3 types of spinal muscular atrophy: babies with Type 1 usually die before their second birthday. People with Type 2 and Type 3 may live full lives if their symptoms are less severe.
- There are 3 medicines approved in the U.S. to treat SMA: SPINRAZA (nusinersen), ZOLGENSMA (onasemnogene abeparvovec), and EVRYSDI (risdiplam). SPINRAZA is injected into the fluid surrounding the spinal cord every 4 months. ZOLGENSMA is administered only once into the veins. EVRYSDI is a pill that is taken by mouth every day for life.
- The DERP found all 3 medicines improve muscle function and decrease the risk of dying. None of the medicines help the breathing muscles, so some patients may still need a machine called a ventilator to help with breathing. EVRYSDI does not seem to help with a person's quality of life. Quality of life was not studied in people who took SPINRAZA or ZOLGENSMA, so it may be that none of the medicine affect a person's quality of life.
- Most of the side effects with SPINRAZA were because it is injected into the fluid around the spinal cord, which can cause headache, backpain, and nausea. ZOLGENSMA can hurt the liver, so people who receive this medicine must have their liver monitored with regular blood tests.
- Spinal muscular atrophy is a rare disease, so less than 100 people were studied in clinical trials. People in the trials were studied for up to 2 years so it is not clear how well these medicines work beyond 2 years. Currently, there is a longer study with ZOLGENSMA which will see how safe and effective it is after 5 years of receiving the medicine.
- Doctors who prescribe one of these medicines to a person enrolled in the Oregon Health Plan must show that certain criteria have been met to ensure the medicine is used safely and correctly before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of nusinersen (SPINRAZA), onasemnogene abeparvovec (ZOLGENSMA), and risdiplam (EVRYSDI) for treating spinal muscular atrophy (SMA)?
2. What are the harms of nusinersen, onasemongene abeparvovec, and risdiplam for treating SMA?

Author: Deanna Moretz, PharmD, BCPS

3. What are the effectiveness and harms of co-treatment or sequential use of treatments approved by the U.S. Food and Drug Administration to treat SMA?

Conclusions:

- Nusinersen and risdiplam may reduce mortality (low certainty of evidence [CoE]), increase the probability of achieving a motor-milestone response (moderate CoE), and increase motor function (very low CoE) when compared to sham control groups in clinical trials of individuals with SMA.[1] Similar benefits in these outcomes were also observed in non-controlled, single-arm trials of onasemnogene abeparvovec in infants with SMA Type 1 (low CoE).[1]
- There is no evidence to suggest an effect on permanent ventilation (very low CoE) or quality of life (moderate CoE), versus control groups across all 3 treatments.[1]
- Nearly all individuals treated with intrathecal nusinersen experienced post-lumbar puncture AEs such as headache, back pain, and nausea.[1] Onasemnogene abeparvovec may increase the risk of hepatic injury, and treatment requires ongoing liver function monitoring.[1]
- Overall, evidence is limited by a small number of studies with moderate to high risk of bias, and study populations that may not be generalizable to all patients with SMA.[1] No head-to-head studies were identified. Uncertainties about the long-term benefits and harms of SMA treatments remain.[1]
- No clinical evidence is available to support the use of co-treatment or sequential SMA treatment.[1] Such approaches are considered experimental and investigational.[1]
- In May 2022, the FDA revised the risdiplam indication to treatment of SMA in pediatric and adult patients.[2] Dosing recommendations now include guidance for dosing infants less than 2 months of age.[2]

Recommendations:

- Clinical evidence does not support changes to the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Combine prior authorization (PA) criteria for all 3 treatments into one document called “Spinal Muscular Atrophy Drugs” as presented in **Appendix 2** with updates to clarify duration of therapy and FDA-approved age ranges.

Summary of Prior Reviews and Current Policy

- The first medication FDA-approved for all types of SMA in both pediatric and adult populations was intrathecal nusinersen.[3] The Pharmacy and Therapeutics (P & T) Committee approved recommendations to implement clinical PA criteria to ensure appropriate utilization of nusinersen in July 2017. In September 2019, the P & T Committee approved recommendations to implement clinical PA criteria to ensure one-time administration of onasemnogene abeparvovec in appropriate SMA pediatric patients. In addition, clinical PA criteria for nusinersen was revised to include an assessment of onasemnogene abeparvovec administration prior to nusinersen initiation. After evaluating costs in executive session, the Committee recommended creating a class for SMA drugs, and designating onasemnogene abeparvovec as preferred and nusinersen as non-preferred on the PMPDP. In December 2020, risdiplam was reviewed by the P & T Committee and was designated as nonpreferred on the PMPDP with clinical PA criteria to ensure appropriate use.
- The preferred drug list (PDL) status for the SMA drugs is listed in **Appendix 1.** The PA criteria for all 3 SMA treatments is outlined in **Appendix 2.**
- From April 2021 to March 2022, 94 patients on the Oregon Health Plan (OHP) had a SMA-related diagnosis: 22 were in enrolled in the Fee-for-Service (FFS) program and the remaining individuals were enrolled in a coordinated care organization (CCO). During the same time frame, 20 patients in OHP had claims for nusinersen, 5 patients had claims for risdiplam, and one patient received onasemnogene abeparvovec. As of October 2022, 4 of these patients are no longer enrolled in OHP, 11 are enrolled in FFS and 11 are enrolled in CCOs.
- The Health Evidence Review Commission (HERC) has included SMA as a funded condition on lines 71, 292, 345, and 377.[4] In addition, SMA carrier screening for pregnant women is addressed in HERC Guideline Note D17.[4] Genetic screening for SMA (CPT 81239) is funded once in a lifetime.[4]

Methods:
The June 2022 SMA drug class report by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1] The original report is available to P & T Committee members upon request.

The purpose of the DERP reports is to compare the clinical effectiveness and harms of different drugs. DERP reports are not clinical practice guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Background:
Spinal muscular atrophy is an autosomal recessive inherited neuromuscular disorder characterized by degeneration of motor neurons in the spinal cord, which results in progressive weakness, atrophy of skeletal muscles and hypotonia.[5] Disease severity ranges from progressive infantile paralysis and premature death to limited motor neuron loss and normal life expectancy.[6] The incidence of SMA is estimated at 1 in 10,000 live births.[7] SMA is the most common genetic cause of death in infants due to respiratory insufficiency.[8] The phenotype is extremely variable. Patients are classified as SMA type 0 through 4 based on age at onset and motor milestone achievement. SMA Type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.[9] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[5]

SMA Type	SMN2 copy numbers	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1% of cases
1 (severe)	2	0 to 6 months	Unable to sit or roll unassisted	<2 years	3.2 – 7.1 (45% of cases)
2 (intermediate)	2 to 4	7 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
3 (mild)	3 to 4	>18 months	Able to independently stand and walk, which may decline with disease progression	Adulthood	1.5 – 4.6 (30 % of cases)
4 (adult)	4 to 8	10 to 30 years	Ambulatory, may have mild muscle weakness	Adulthood	5% of cases

Spinal muscular atrophy is caused by biallelic deletions or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13 which reduces the overall production of SMN protein.[9] The survival motor neuron protein is essential for motor neuron development and function.[9] The SMN gene region consists of a two almost identical genes: SMN1 and SMN2.[8] The lack of SMN1 in patients with SMA results in a disruption of SMN function which is partially compensated by SMN2 protein synthesis. SMN2 produces transcripts of SMN protein lacking exon 7 which results in an alternatively spliced, truncated, and nonfunctional SMN protein.[8] Due to an incomplete exclusion of exon 7 from SMN2 messenger ribonucleic acid (mRNA), only a small part (10–15%) of the mRNA transcripts contain exon 7, resulting in a small proportion of normal SMN protein (5-10%).[8] The number of copies of SMN2 correlate with the functional status of patients with SMA.[8] Infants with SMN1 biallelic deletions and only two copies of SMN2 have a 97% risk of SMA type 1.[10] The presence of 3 or more copies of SMN2 is

associated with milder SMA symptoms. As the number of SMN2 copies correlates inversely with disease severity, moderate increases in SMN protein levels may have significant beneficial effects.[11]

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. In part because of SMA's rapid progression and the importance of early diagnosis to preserve motor functioning, the disease has been added to newborn screening in the United States.[12] Different methods for a newborn screening have been developed to diagnose SMA from DNA extracted from newborn blood spots, including a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis with the possibility to identify SMN1 and SMN2 deletion as well as to quantify copy numbers of both genes, and a real-time polymerase chain reaction. Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60 in the general population.[13] It is not possible to predict the severity of the SMA phenotype from carrier screening.

Due to the difficulties in quantifying motor abilities in individuals with SMA, several functional motor scales were developed to assess functional status in people with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of children with SMA Type 1.[14] CHOP INTEND was validated in a small population of children (n=27) with SMA aged 3 to 260 months (mean age = 49 months).[15] The Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) was developed by physical therapists to assess individuals with SMA type 2 and 3.[16] The HFMSE motor assessment includes upper and lower limb activities as well as head and trunk control. Inter-rater reliability was tested on 35 children with an inter observer agreement greater than 99%.[16] The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.[17] Sequential use of the HINE allows the identification of early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.[18] The HINE screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.[19] The Motor Function Measure 32 (MFM-32) is an ordinal scale used to assess patients with neuromuscular diseases. It is comprised of 32 items to evaluate physical function. There is no established minimal clinically important difference between point values on the MFM-32. The Revised Upper Limb Module (RULM) was designed to assist in evaluation of young children's ability to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil. It has been validated for use in SMA assessments in a variety of settings. The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) is an assessment tool used to measure major clinical development issues in the early childhood years. Although not specific to SMA, the tool measures 5 standardized developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior. The social-emotional and adaptive behavior portions are completed by parental questionnaire while the other 3 areas are administered with child interaction. This tool has not been validated in SMA patients. **Table 2** provides a summary of each tool, the intended population, and scoring.

Table 2. Motor Function Exams for SMA

Instrument	Domain Evaluated	Intended Population	Number of Items	Grading Scale	Score Range	MCID
6MWT	Aerobic capacity and endurance	Ambulatory patients with SMA	1 item: the distance covered by walking a flat 25-meter course over a 6-minute period	N/A	N/A	50 to 70 meters
BSID-III	Evaluates cognitive, motor, and behavioral development	Infants aged 1 month to 42 months	66 items for motor development	0 = no response 1 = full response	Not scored, testing is to	N/A

					determine ability	
CHOP-INTEND	Motor function	Infants with SMA Type 1	16 items scored 0 to 4	0 = no response 4 = full response	0 to 64	Unknown; clinical trials have used a change of ≥ 4 points
HFSME	Motor function	SMA Types 2 and 3	33 items scored 0 to 2	0 = no response 2 = full response	0 to 66	Change of ≥ 3 points
HINE-2	Motor Milestones	All infants aged 2 months to 24 months	8 milestones with: • 3 items scored 0 to 4 • 4 items scored 0 to 3 • 2 items scores 0 to 2	0 = absence of activity Increasing points correspond to an increased level of milestone achievement	0 to 26	Unknown; however, an increase of ≥ 1 point is unlikely in infants with SMA Type 1
MFM-20	Motor function across 3 domains: standing and transfer (D1), axial and proximal (D2), and distal (D3)	Children under 7 years of age with neuromuscular diseases	20 items scored 0 to 3	0 = no response 3 = full response	0 to 60	MCID has not been established for SMA
MFM-32	Motor function across 3 domains: standing and transfer (D1), axial and proximal (D2), and distal (D3)	Adults and children older than 7 years of age with neuromuscular diseases	32 items scored 0 to 3	0 = no response 3 = full response	0 to 96	MCID has not been established for SMA
RULM	Upper extremity and ADL function	All individuals with SMA; commonly used to assess non-ambulatory individuals	1 unscored entry item; serves as functional class identification. 19 items scored 0 to 2	0 = unable 2 = able, no difficulty	0 to 37	Unknown, can vary: • SMA Type 2: 1.2 to 2.7 points • SMA Type 3: 3 to 6 points • Ambulatory SMA: 0.5 to 1 point • Non-ambulatory SMA: 2 to 4 points
WHO MGRS Milestones	Motor milestones	Children from birth to 5 years of age	6 milestones scored from 1 to 3, or 9 representing an inability to test the milestone	1 = unable 3 = able 9 = unable to test	Not scored, testing is done to determine motor	N/A

					milestone attainment	

Abbreviations: 6MWT: 6-Minute Walk Test; ADL: activities of daily living; BSID-III: Bayley Scales of Infant and Toddler Development; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFSME: Hammersmith Functional Motor Scale Expanded for SMA; HINE-2: Hammersmith Infant Neuromuscular Examination, Section 2; MCID: minimal clinically important difference; MFM-20: Motor Function Measure, 20 items; MFM-32; Motor Function Measure, 32 items; N/A: not applicable; RULM: Revised Upper Limb Module; SMA: spinal muscular atrophy; WHO MGRS: World Health Organization Multicenter Growth Reference Study

Three medications are approved by FDA to treat SMA: nusinersen, onasemnogene abeparvovec, and risdiplam. In 2016, nusinersen was the first treatment approved for pediatric and adult patients with SMA.[3] It is an antisense oligonucleotide (ASO) which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein, which can partially compensate for mutations of the SMN1 gene.[3] Nusinersen must be delivered by repeated intrathecal injections every 4 months after the initial loading dose because ASOs do not efficiently cross the blood-brain barrier.[3] Onasemnogene abeparvovec received FDA approval in 2019.[20] Onasemnogene abeparvovec is an adeno-associated viral serotype 9 (AAV9) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[20] The AAV9 vector is an ideal method of administering gene therapy because it has rapid onset of transgene expression, can cross the blood-brain barrier, is small in size with a simple structure, and has low immunogenicity.[21] Onasemnogene abeparvovec is a one-time intravenous treatment that is designed to deliver a functional SMN1 gene, potentially enabling the production of SMN protein, resulting in the normal development of motor neurons.[20] The safety and effectiveness of repeated administration of onasemnogene abeparvovec have not been evaluated. In addition, its use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been studied.[20] In 2020, risdiplam, an oral solution, received FDA approval to treat SMA.[2] Risdiplam is an SMN2 splicing modifier designed to promote the inclusion of exon 7 to produce full-length SMN2 mRNA, which results in an increased production of functional SMN protein from the SMN2 gene.[2] Risdiplam received FDA approval for the treatment of SMA in patients 2 months of age and older.[2] Dosing is weight-based and must be administered every day for lifetime.[2] The indications approved for all 3 treatments are broader than the populations studied in clinical trials.

DERP Report Summary Findings:

DERP has standardized methods for literature search and assessment, and these can be found detailed in the full report. The literature search for the DERP report was conducted through February 10, 2022.[1] Thirty-one publications met inclusion criteria: 4 randomized controlled trials (RCTs); 8 uncontrolled interventional trials; and 19 cohort studies.[1] All of the cohort studies evaluated nusinersen. **Table 3** summarizes the study details for the RCTs and uncontrolled interventional trials for nusinersen, onasemnogene abeparvovec, and risdiplam. Short-term follow-up, lack of comparator groups, and post-hoc modification of primary endpoints studied increased risk of biases in these studies.[1] All the RCTs were conducted by the drug manufacturers and authors of the RCTs reported conflicts of interest which may also increase risk of biases.[1] Assessment of clinically relevant outcomes (i.e., motor function, respiratory support) were limited to infants under 24 months of age with presymptomatic SMA, SMA Type 1, and SMA Type 2.[1] Risk ratios (RR), 95% confidence intervals (CI), and p-values were calculated by DERP authors using statistical software.

Table 3. Randomized Controlled Trials and Uncontrolled Interventional Studies of FDA-approved Treatments for SMA[1]

Drug (BRAND NAME)	Trial Name	Sample Size	SMA Type	Age	Follow-Up	Risk of Bias
Randomized Controlled Trials						
Nusinersen (SPINRAZA)	ENDEAR	Nusinersen, n=80 Sham control, n=41	Infantile-onset[a]	0 to 7 months	13 months	High
	CHERISH	Nusinersen, n=84 Sham control n=42	Later-onset[b]	2 to 12 years	15 months	Moderate
	EMBRACE	Nusinersen, n=14 Sham control n=7	Infantile-onset[a] or Later-onset[b]	0 to 4 years	14 months	High
Risdiplam (EVRYSDI)	SUNFISH Part 2	Risdiplam, n=120 Placebo, n=60	Type 2 or Non-ambulatory Type 3	2 to 25 years	12 months	Moderate
Uncontrolled Interventional Studies						
Nusinersen (SPINRAZA)	CS1/CS10	n=28	Type 2 or 3	2 to 14 years	14 months	High
	CS2/CS12	n=28	Later-onset[b]	2 to 15 years	36 months	High
	CS3A	n=20	Infantile-onset[a]	3 weeks to 7 months	18 months	High
	NURTURE	n=25	Presymptomatic	< 6 weeks	24 months	High
Onasemnogene abeparvovec (ZOLGENSMA)	STR1VE	n=22	Type 1	< 6 months	18 months	High
	STR1VE-EU	n=126	Type 1	< 6 months	18 months	High
	START	n=15	Type 1	< 6 months	24 months	High
	START LTFU[c]	n=13	Type 1	< 6 months	60 months	High
Risdiplam (EVRYSDI)	FIREFISH Part 1	n=21	Type 1	1 to 7 months	12 months	High

Notes:
a. Infantile-onset defined as symptom onset before 6 months of age
b. Later-onset defined as symptom onset after 6 months of age
c. START LFTU is an ongoing, observational follow-up study to the original START trial with 13 of the 15 original participants for up to 15 years

Abbreviations: FDA: Food and Drug Administration; LTFU: long term follow-up; SMA = spinal muscular atrophy

1. Effectiveness of Nusinersen, Onasemnogene Abeparvovec, and Risdiplam in Treating SMA

Different outcomes including mortality, need for permanent ventilation, quality of life, motor-milestone response, and motor function were used to evaluate medication effectiveness across all the studies.[1]

Mortality

- In 2 RCTs (ENDEAR and EMBRACE; total enrollment=142) some evidence of reduced mortality risk was shown with nusinersen over sham control (low CoE).[1] In the ENDEAR trial, which was conducted in participants with infantile-onset SMA (i.e., SMA Types 1 and 2) the risk of mortality was reduced by 60% with nusinersen compared to control (RR 0.4; 95% CI 0.2 to 0.8; p=0.01; low CoE).[1] In contrast, in the EMBRACE trial which included participants with later-onset SMA (i.e., SMA Types 2 and 3), nusinersen had no effect on mortality compared with sham control (RR 0.2; 95% CI 0.0 to 3.9; p=0.91; low CoE).[2]
- In 3 cohort studies of nusinersen, 3 deaths out of 312 participants (1%) were reported in children with SMA Type 1 after 2 years of treatment (low CoE).[1]

- In 3 uncontrolled trials of onasemnogene abeparvovec (STR1VE, STR1VE-EU, START), 2 deaths out of 70 participants (3%) were reported in infants with SMA Type 1 over 36 months of follow-up (low CoE).[1]
- In 1 uncontrolled trial of risdiplam (FIREFISH Part 1), 3 deaths out of 21 participants (14%) were reported in infants with SMA Type 1 at 12 months (low CoE).[1]

Need for Permanent Ventilation

- In one RCT (ENDEAR, n=122), nusinersen did not reduce the need for permanent ventilation compared to sham control (RR 0.7; 05% CI 0.4 to 1.3; p=0.28; very low CoE).[1]
- In 2 uncontrolled trials with nusinersen (CS3A, NURTURE) a small proportion of participants required permanent ventilation (range 0 to 15%; very low CoE).[1] However, participants in these trials had higher baseline motor scores, and 1 trial was in presymptomatic infants.[1]
- In 3 uncontrolled trials with onasemnogene abeparvovec (STR1VE, STR1VE-EU, START) a small proportion of participants required permanent ventilation (range 8 to 18%; very low CoE).[1]
- In one uncontrolled trial of risdiplam (FIREFISH Part 1) the need for permanent ventilation was observed in 80% of participants (very low CoE).[1]
- In 4 cohort studies of nusinersen no ventilatory support was needed in children with SMA Types 1 to 3 (very low CoE).[1]

Quality of Life

- In one RCT (SUNFISH Part 2, n=180) no evidence of an impact on quality of life was shown with risdiplam compared with placebo (RR 1.2; 95% CI 0.8 to 1.7; p=0.35; moderate CoE).[1]
- No RCTs or uncontrolled trials evaluated the effect of nusinersen or onasemnogene abeparvovec on quality of life.[1]
- In 3 cohort studies of nusinersen, subjective self-reported or caregiver-reported improvements in quality of life were noted in adults with SMA Types 2 to 4 after 14 months; by caregivers of children with SMA Types 1 and 2 after 1 year; and in children and adults with SMA Types 1 to 4 with up to 2 years of follow-up.[1]

Motor-Milestone Response

- In 3 RCTs (ENDEAR, EMBRACE, CHERISH; total enrollment = 268) some evidence of an improvement in motor-milestone response was noted with nusinersen compared with control (very low CoE).[1] Fifteen percent to 79% of infants and children with infantile-onset and later-onset SMA achieved motor-milestone response (very low CoE).[1] However, at baseline, 57% of subjects sat without support in 1 RCT and 100% sat with support and 24% walked without support in another RCT.[1]
    - ENDEAR: RR 38.9; 95% CI 2.4 to 617.7; p<0.01
    - EMBRACE: RR 2.7; 95% CI 0.8 to 9.1; p=0.04
    - CHERISH: RR 3.3; 95% CI 0.8 to 13.7; p=0.08
- In one uncontrolled trial of risdiplam, 67% of infants with SMA Type 1 achieved motor-milestone response (very low CoE) after 12 months of treatment.[1]
- In 2 uncontrolled trials of onasemnogene abeparvovec, 82% to 86% of infants with SMA Type 1 achieved motor-milestone response 18 months post-infusion (very low CoE).[1]

Motor Function

Across studies, various motor scales (**Table 2**) were used to assess change in motor function from pretreatment baseline.[1] The most common scales used were CHOP-INTEND, HFSME, and RULM.[1] Across all 3 treatments increases from CHOP-INTEND baseline score were observed, more frequently in those who began treatment at a younger age.[1] When the HFSME score was used, mixed results were observed.[1] However, younger participants and those less severely affected (i.e., SMA Types 2 and 3) had greater improvements in HFSME scores from baseline.[1] When the RULM score was used, younger children and those less severely affected (i.e., SMA Types 2 and 3) treated with nusinersen demonstrated larger average gains from baseline.[1]

- In 2 RCTs of nusinersen (ENDEAR, CHERISH) and 1 RCT of risdiplam (SUNFISH Part 2) with a total enrollment of 428, some evidence of improved motor function in CHOP-INTEND and HFSME scores was observed with nusinersen and risdiplam compared with control (moderate CoE).[1]
    - Participants with a CHOP-INTEND score 4 points or more increased from baseline at 13 months in ENDEAR: Nusinersen 65% vs. Sham Control 2%; RR, 26.6; 95% CI 3.8 to 185.9; p<0.01.[1]
    - Participants with a HFSME score 3 points or more increased from baseline at 15 months in CHERISH: Nusinersen, 57% vs. Sham Control, 26%; Odds Ratio (OR), 6; 95% CI 2 to 15; p<0.001.[1]
    - HFSME score mean change from baseline (points) in SUNFISH Part 2: Risdiplam, 1.4 vs. Placebo, -0.2; Difference, 0.6; 95% CI -0.5 to 1.7; p=0.39.[1]
- In 1 uncontrolled trial of risdiplam (FIREFISH Part 1) 86% of participants showed a 4 point or greater increase in CHOP-INTEND scores from baseline at 12 months.[1]
- Gains from baseline HFMSE scores were reported in 7 cohort studies of nusinersen in children and adults with SMA Types 2 and 3. However, only 3 of 7 studies reported clinically significant meaningful gains (i.e., increase of 3 points or more).[1]
- No significant change in HFSME score from baseline was reported in 3 cohort studies of nusinersen in adults with SMA Types 2 and 3 and one cohort study of ambulatory children with SMA Types 1 to 3.[1]
- Two cohort studies of nusinersen in adults with SMA Types 2 and 3 who were able to sit at baseline reported meaningful gains in RULM scores.[1]
- No effect on RULM scores were reported in 2 cohort studies of nusinersen versus control of ambulatory adults with SMA Types 2 and 3 and 6 cohort studies of adults with SMA Types 2 to 4.[1]

2. Harms of Nusinersen, Onasemongene Abeparvovec, And Risdiplam

Reporting of harms included AEs, SAEs, and treatment withdrawals due to AEs or SAEs. Across all studies, the most commonly reported AEs regardless of treatment were fever, upper respiratory infections, coughing, and vomiting.[1] Serious adverse events were commonly due to respiratory events regardless of treatment and were more common in younger children and participants with SMA Type 1.[1] An increased risk of treatment-related SAEs due to elevated liver enzymes (i.e., serum aminotransferase) was observed with onasemnogene abeparvovec (low CoE).[1]

Adverse Events

- In 3 RCTs of nusinersen (ENDEAR, EMBRACE, CHERISH) and 1 RCT of risdiplam (SUNFISH Part 2) with a total enrollment of 449, no evidence of an effect on the risk of experiencing one or more AEs was observed with nusinersen or risdiplam over control (moderate CoE).[1]
    - ENDEAR: RR 1.0; 95% CI 0.9 to 1.1; p=0.50
    - EMBRACE: RR 1.2; 95% CI 0.9 to 1.6; p=0.33
    - CHERISH: RR 0.9; 95% CI 0.9 to 1.0; p=0.08
    - SUNFISH Part 2: RR 1.0; 95% CI 0.9 to 1.1; p=0.83
- Across all 3 treatments, at least one AE was experienced by 86% to 100% of participants in 4 RCTs and 89% to 100% of participants in 8 uncontrolled trials.[1]
- In nusinersen studies, AEs relating to lumbar puncture (i.e., nausea) were frequently reported across all ages and SMA subtypes. Post-lumbar puncture headache was reported more frequently by adults in cohort studies (moderate CoE).[1]
- In 3 uncontrolled studies of onasemnogene abeparvovec, 27% to 73% of participants experienced treatment-related AEs due to elevated liver enzymes (i.e., serum aminotransferase) (moderate CoE).[1]

Incidence of Adverse Events Leading to Treatment Discontinuation

- Treatment discontinuation due to AEs was infrequent with nusinersen in 2 RCTs, 3 uncontrolled trials, and 4 cohort studies (moderate CoE).[1]

- Treatment discontinuation due to AEs was not reported for risdiplam or onasemnogene abeparvovec.[1]

Serious Adverse Events

- In 3 RCTs of nusinersen (ENDEAR, EMBRACE, CHERISH) and one RCT of risdiplam (SUNFISH Part 2) (total, n=449), no evidence of an effect on the risk of experiencing one or more SAEs was observed with nusinersen or risdiplam over control (low CoE).[1]
    - ENDEAR: RR, 8; 95% CI 0.7 to 0.9; p=0.01
    - EMBRACE: RR, 1.5; 95% CI 0.6 to 3.8; p=0.40
    - CHERISH: RR, 0.6; 95% CI 0.3 to 1.1; p=0.13
    - SUNFISH Part 2: RR, 1.1; 95% CI 0.6 to 2.1; p=0.80

3.Co-Treatment or Sequential Treatment

One high risk of bias cohort study provided evidence for the effectiveness and harms of co-treatment or sequential treatment in 76 children under 5 years of age who received nusinersen for a mean of 12 months before receiving a single infusion of onasemnogene abeparvovec.[1] Fifty-eight of 76 participants (76%) received pre-treatment with nusinersen.[1] Clinically meaningful gains from baseline CHOP-INTEND scores (i.e., an increase of $\geq$ 4 points) were observed in nusinersen-naïve and nusinersen-treated children 6 months post-infusion.[1] The efficacy and harms of co-treatment or sequential treatment with SMA therapies is unknown and considered to be investigational.[1]

New Indications:

When risdiplam (EVRYSDI) was initially approved in August 2020, the indication was for treatment of SMA in patients 2 months of age and older.[22]
In May 2022, the FDA revised the indication to treatment of SMA in patients less than 2 months of age.[2] Dosing recommendations now include guidance for dosing infants less than 2 months of age.[2]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
Onasemnogene abeparvovec-xioi	ZOLGENSMA	IV	KIT	Y
Nusinersen sodium/PF	SPINRAZA	IT	VIAL	N
Risdiplam	EVRYSDI	PO	SOLN	N

Spinal Muscular Atrophy Drugs~~Nusinersen~~

Goal(s):

- Approve nusinersen (SPINRAZA), onasemnogene abeparvovec (ZOLGENSMA), or risdiplam (EVRYSDI) for funded OHP conditions supported by evidence of benefit (e.g., spinal muscular atrophy).

Length of Authorization:

- Nusinersen: Up to 8 months for initial approval and up to 12 months for renewal.
- Onasemnogene abeparvovec: Once in a lifetime dose.
- Risdiplam: Up to 6 months for initial approval and 12 months for renewal.

Requires PA:

- Nusinersen (billed as a pharmacy or physician administered claim)
- Onasemnogene abeparvovec (billed as a pharmacy or physician administered claim)
- Risdiplam (billed as pharmacy claim)

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/

Table 1. FDA-Approved Dosing For Risdiplam

Age and Body Weight	Recommended Daily Dose of Risdiplam
Less than 2 months of age	0.15 mg/kg
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code. Go to #2	
2. Is this a request for continuation of nusinersen or risdiplam therapy? Note: Onasemnogene abeparvovec is only approved as a single, one-time dose per lifetime	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
~~2.~~3. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~4. Is the requested medication prescribed by a pediatric neurologist or a provider with experience treating SMA?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
~~4.~~5. Is the patient ventilator-dependent (using at least 16 hours per day on at least 21 of the last 30 days)? Note: This assessment does not apply to patients who require ventilator assistance	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Is a baseline motor assessment appropriate for age and/or intended population available such as one of the following assessments? ~~• Is a baseline motor assessment available such as one of the following functional assessment tools:~~ • Hammersmith Infant Neurological Examination, Section 2 (HINE-2) • Hammersmith Functional Motor Scale (HFMSE) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • The Motor Function Measure 32 items (MFM-32) • Upper Limb Module (ULM)	**Yes:** Document date and assessment results Date: _____ Assessment: _____ Results: _____ Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
~~5.~~7. Has the patient had previous administration of onasemnogene abeparvovec (ZOLGENSMA), either in a clinical study or as part of medical care?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
~~6.~~8. Is the request for risdiplam?	**Yes**: Go to #9	**No**: Go to #12
~~7.~~9. Is the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness. Recommended FDA-approved dosage is determined by age and body weight.
~~8.~~10. Is the patient on concomitant therapy with nusinersen?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11

Approval Criteria		
~~9.~~11. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc) or other validated pulmonary function test?	**Yes:** Document baseline results. Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness.
~~10.~~12.Is the request for nusinersen?	**Yes**: Go to #13	**No**: Go to #14
~~11.~~13.Is the patient on concomitant therapy with risdiplam?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Approve for up to 8 months.
~~12.~~14.Is the request for onasemnogene abeparvovec?	Yes: Go to #15	No: Pass to RPh. Deny; medical appropriateness
~~13.~~15.Is the patient on concomitant therapy with risdiplam or nusinersen?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #16
~~14.~~16.Is the patient less than 2 years of age?	**Yes:** Go to # 17	**No:** Pass to RPh. Deny; medical appropriateness
17. Have the following labs been obtained: a) a baseline platelet count AND b) baseline liver function tests (AST, ALT, total bilirubin, and PT) AND c.) baseline troponin-I	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness
~~15.~~18.Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec?	**Yes:** Approve for one time infusion	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?~~Is there evidence of tolerance to therapy through provider assessment?~~	**Yes:** Go to #2	**No:** Pass to RPh; Deny medical appropriateness
2. Has the patient shown a positive treatment response in one of the following areas? • Within one month of renewal request, documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened -OR- • Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease -OR- • Documentation of an improvement or lack of decline in pulmonary function compared to baseline~~Has the patient's motor function improved or stabilized in a meaningful manner from the baseline functional assessment?~~	**Yes:** Approve for 12 months	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: 2/23 (DM); 9/19 (DM); 7/17; 3/17
Implementation: TBD; 11/1/19: 9/1/17; 5/17

Onasemnogene abeparvovec (Zolgensma®) - RETIRE

- **Goal(s):** Approve onasemnogene abeparvovec for funded OHP conditions supported by evidence of benefit (e.g., spinal muscular atrophy).

Length of Authorization:

- Once in a lifetime dose

Requires PA:
Onasemnogene abeparvovec (pharmacy and physician administered 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 medication prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy (SMA) such as pediatric neurologist?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
~~2.~~3. Is the patient less than 2 years of age?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
~~3.~~4. Does the patient have a SMA diagnosis, confirmed by SMN1 gene mutation or deletion… [is missing or not functional by genetic documentation of fewer than 4 copies of SMN2 AND at least one of the following]: • Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); **-OR-** • Compound heterozygous mutation of SMN1 gene (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 (allele 2)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~4.~~5. Does the patient have advanced SMA* (complete paralysis of the limbs, permanent ventilator dependence)? *Note FDA label states efficacy has not been established in these patients	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
~~5.~~6. Has baseline motor ability been documented via: • Hammersmith Infant Neurological Examination, Section 2 (HINE-2) • Hammersmith Functional Motor Scale (HFSME) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • The Motor Function Measure 32 items (MFM-32) • Upper Limb Module (ULM)	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~7. Has the individual been screened for viral infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
~~7.~~8. Is the baseline adeno-associated virus vector (AAV) 9 antibody titer < 1:50? Note: Efficacy has not been established in this population and high anti-AAV9 antibody titers are expected to limit efficacy of therapy.	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~9. Have the following baseline labs been obtained: ~~a)~~c) Platelet count; AND ~~b)~~d) Liver function tests (AST, ALT, total bilirubin, and PT); AND ~~c)~~e) Troponin-I	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~9.~~10. Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
~~10.~~11. Is the patient currently receiving nusinersen?	**Yes:** Go to #12	**No:** Go to #13
~~11.~~12. Are there plans to discontinue nusinersen?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
~~12.~~13. Is there attestation that the patient and provider will comply with case management required by the Oregon Health Authority? Case management includes follow-up assessment to assess treatment success, monitoring, and adverse events.	**Yes:** Approve one time infusion	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 9/19 (DM)
Implementation: TBD; 11/1/19

Risdiplam- RETIRE

Goal(s):
- Approve risdiplam for funded OHP conditions supported by evidence of benefit (e.g., spinal muscular atrophy).

Length of Authorization:
- 6 months

Requires PA:
- Risdiplam

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/

Table 1

Age and Body Weight	Recommended Daily Dosage
Less than 2 months of age	0.15 mg/kg
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy approved by the FFS program?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Recommended FDA-approved dosage is determined by age and body weight.
4. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the patient experiencing symptoms of SMA?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness**.**

Approval Criteria		
Does the patient have advanced SMA disease (ventilator dependence >16 hours/day or tracheostomy)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
6. Has the patient had previous administration of onasemnogene abeparvovec (ZOLGENSMA), either in a clinical study or as part of medical care?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #8
7. Is the patient on concomitant therapy with a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #9
8. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating SMA?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness**.**
9. Is a baseline motor assessment appropriate for age and/or intended population available such as one of the following assessments? • Hammersmith Infant Neurological Examination, Section 2 (HINE-2) • Hammersmith Functional Motor Scale (HFSME) • The Motor Function Measure 32 items (MFM-32) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • Upper Limb Module (ULM) or Revised Upper Limb Module (RULM)	**Yes:** Document baseline results. Go to #11	**No:** Pass to RPh. Deny; medical appropriateness**.**

Approval Criteria		
10. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc) or other validated pulmonary function test?	**Yes:** Document baseline results. Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh; Deny medical appropriateness
2. Has the patient shown a positive treatment response in one of the following areas? • Within one month of renewal request, documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened **-OR-** • Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease **-OR-** •	**Yes:** Approve for additional 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 12/20 (DE)
Implementation: TBD; 1/1/2021

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Drug Class Literature Scan: Substance Use Disorders

Date of Review: February 2023

Date of Last Review: December 2020
Literature Search: 01/01/20 – 11/18/2022

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

Plain Language Summary:

- Is there any new data for medicines that are used to treat substance use disorders that would change how these medicines are covered under the Oregon Health Plan fee-for-service (Open Card) program?
- The Food and Drug Administration (FDA) has approved these medicines to treat substance use disorders:
  - Lofexidine, methadone, buprenorphine, naloxone, and naltrexone to assist with treating opioid use disorder.
  - Naltrexone, acamprosate, and disulfiram to assist with treating alcoholism.
  - Currently, no medicines are approved to assist with treating cocaine or methamphetamine use disorder.
- Studies show that both methadone and buprenorphine help people with opioid use disorder stay in treatment.
  - Methadone may be better than buprenorphine in helping people stay in opioid use disorder treatment, but evidence is mixed. One study found no difference between methadone and buprenorphine in the number of people who stay in treatment.
  - Buprenorphine probably keeps more people in treatment than naltrexone injection or counseling alone.
  - The Veterans Affairs/Department of Defense recommend buprenorphine/naloxone or methadone for opioid use disorder. They suggest naltrexone injection as an alternative medicine if buprenorphine or methadone do not have benefit or are not appropriate for the specific person.
  - In people who are pregnant and dependent on opioids that are not prescribed by a provider, methadone and buprenorphine may have similar benefit. In one study, buprenorphine improved birthweight, longer length of the baby at birth, and decreased risk of the baby being born too early compared with methadone. But there were important flaws in this evidence, so the results should be considered with caution and may not be true for all people. Another study showed methadone and buprenorphine may be similar in effectiveness in reducing adverse outcomes in people who are pregnant and their newborns.
- The Agency of Healthcare Research and Quality found evidence that both methadone and buprenorphine help reduce or stop use of substances in teen-agers and young adults 12 to 25 years of age with substance use disorder. Methadone was more effective for helping young adults to stay in treatment and reduce self-reported substance use.
- Most of the medicines studied in people who had both cocaine and opioid use disorder were ineffective.

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- The Department of Veterans Affairs and Department of Defense recommends oral naltrexone to treat alcohol use disorder. Providers may consider use of acamprosate or disulfiram if naltrexone had no benefit or is not appropriate for the specific person.
- The Oregon Health Plan covers nearly all medicines used to treat substance use disorder. Providers must explain to the Oregon Health Plan if they prescribe lofexidine or more than 24 mg per day of buprenorphine before the Oregon Health Plan will pay for the medicine. This process is called prior authorization. The goal of prior authorization is to make sure these medicines are used in a safe and effective way.

Conclusions:

- Since the last class update, 6 systematic reviews,[1-6] one meta-analysis,[5] and one guideline[7] have been published.
- A 2022 Cochrane Review assessed medication-assisted treatment with buprenorphine or methadone for the treatment of opioid use disorder (OUD) in people dependent on prescription opioids.[1] Methadone and buprenorphine did not differ on some outcomes such as positive urine drug screens at the end of treatment (moderate quality of evidence [QoE]) or the rate of adverse events (low QoE), although result favored methadone for retention and self-reported substance use (low QoE). There was moderate-certainty evidence from 4 studies that showed that buprenorphine monotherapy resulted in higher treatment retention rates over non-opioid treatments (detoxification, extended-release naltrexone injection, or psychological treatment without opioid agonist treatment).[1]
- A 2022 systematic review and meta-analysis evaluated comparative evidence for methadone and buprenorphine to determine the optimal opioid substitution agent to reduce adverse maternal and neonatal outcomes in pregnant individuals using illicit opioids.[2] Data from 16 observational cohort studies and 3 randomized controlled trials (RCTs) showed that buprenorphine was consistently associated with improved birthweight, longer length at birth, and lower risk of prematurity in neonates compared to methadone (low QoE for all outcomes).[2] In 4 RCTs that compared buprenorphine with methadone on improving maternal outcomes, there was a greater risk of maternal adverse effects with methadone and lower treatment retention rates with buprenorphine (low QoE).[2]
- A November 2020 Cochrane Review assessed the effectiveness of medication assisted treatment (MAT) for pregnant patients with OUD.[3] Medication assisted treatments, alone or in combination with a psychosocial intervention, were compared to no intervention, other pharmacological intervention or psychosocial interventions alone.[3] Methadone and buprenorphine may be similar in efficacy and safety for both the patients and their infants (low QoE).[3] There is insufficient evidence to make conclusions for the comparison between methadone and slow-release morphine in this population.[3] More evidence is needed to adequately compare different MAT options for pregnant individuals with MAT.[3]
- A 2020 systematic review by the Agency of Healthcare Research and Quality (AHRQ) reviewed pharmacologic interventions for adolescents and young adults 12 to 25 years of age with substance use disorder (SUD).[4] Evidence was insufficient for most interventions.[4] Most studies enrolled individuals with mixed use of opioids, alcohol, and cannabis.[4] For short-term treatment of OUD in adolescents and young adults, low-quality evidence showed that buprenorphine or buprenorphine-naloxone was more effective in achieving abstinence than clonidine (in one study), was more effective when augmented by memantine (in one study), and was more effective when tapered over longer rather than shorter durations (in 2 studies).[4] There is insufficient evidence of long-term efficacy of pharmacologic or behavioral treatment of OUD in adolescents and young adults.[4] The literature guiding medications for adolescents and young adults with OUD is limited, and more research is needed to evaluate optimal pharmacologic treatment duration and the benefit of adjunctive behavioral interventions.[4]
- A 2021 meta-analysis collated treatment retention rates reported by RCTs and observational studies that compared methadone to buprenorphine or buprenorphine-naloxone for treatment of adults with OUD.[5] The meta-analysis of RCTs and meta-analysis of observational studies both suggest retention rates are similar between methadone and buprenorphine products, based on low-quality evidence.[5]
- A systematic review and meta-analysis of medications for stimulant use disorders (cocaine, methamphetamine) in patients with co-occurring opioid use disorders was published in 2020.[6] Thirty-four trials focused on cocaine use disorder in patients with OUD met inclusion criteria.[6] Twenty-two medications

including anticonvulsants, antidepressants, antipsychotics, methadone, buprenorphine, and psychostimulants were studied.[6] Only 1 medication, a naltrexone implant (not available in the United States [U.S.]) was studied in people with methamphetamine abuse and OUD in Russia.[6] Low-strength evidence from 3 RCTs (n=115) showed that psychostimulants (dexamphetamine or mazindol) may reduce cocaine use, though the difference was not statistically significant (standard mean difference 0.35; 95% Confidence Interval [CI] -0.05 to 0.74).[6] Most of the medications studied for cocaine use compared to placebo were ineffective, although psychostimulants may warrant further study.[6]

- The Department of Veterans Affairs (VA) and Department of Defense (DoD) updated guidance for the management of SUDs in 2021.[7] Naltrexone and topiramate are recommended for alcohol use disorder.[7] Acamprosate and disulfiram are suggested as first-line alternatives and gabapentin is suggested as second-line therapy.[7] For OUD, buprenorphine/naloxone and methadone are recommended, and extended-release naltrexone is suggested as a first-line alternative.[7] There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cannabis use disorder, cocaine use disorder or amphetamine/methamphetamine use disorder.[7]
- In 2022, the Food and Drug Administration (FDA) issued a drug safety communication warning of dental problems associated with buprenorphine products that are dissolved in the mouth (i.e., sublingual, buccal).[8] Reported dental problems include tooth decay, cavities, oral infections, and loss of teeth, which can be serious and have been reported even in patients with no previous history of dental issues.[8]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended.
- Since there has no utilization of lofexidine in the past year, retire prior authorization (PA) criteria for lofexidine. Requests for lofexidine will be addressed through non-preferred PA criteria.
- Review drug costs in the executive session.

Summary of Prior Reviews and Current Policy

- A literature scan of drugs to treat opioid and alcohol use disorders was last presented at the December 2020 P&T Committee meeting. Based on the review of recently published evidence, no changes to the PDL or PA criteria were made by the Committee.
- Currently, buprenorphine sublingual tablets and disulfiram tablets are designated as voluntary non-preferred. Buprenorphine injection (SUBLOCADE), naltrexone formulations, acamprosate, and buprenorphine/naloxone formulations are available as preferred products on the PDL. New products in this class are designated as voluntary non-preferred due to legislation designed to ensure open access to SUD treatments.
- A drug use evaluation (DUE) which assessed utilization of sublingual buprenorphine for off-label prescribing indications after removal of buprenorphine PA criteria for MAT in 2020 was presented to the Pharmacy and Therapeutics (P&T) Committee at the June 2022 meeting.[9] Based on the DUE evidence, no policy changes were implemented. A cohort of fee-for-service (FFS) patients who had paid claims for sublingual buprenorphine from 1/1/19 to 6/30/19 (control group) was compared to a similar group who had paid claims for sublingual buprenorphine from 1/1/20 to 6/30/20 (intervention group).[9] The conclusions from the DUE were as follows:
    - The number of patients prescribed sublingual buprenorphine over the 6-month study period increased by over 20% (from 364 patients to 472 patients after removal of the PA) indicating increased prescribing for sublingual buprenorphine.[9] During this same timeframe the average monthly fee-for-service enrollment increased by about 5% from 2019 to 2020.[9]
    - The proportion of patients prescribed sublingual buprenorphine formulations with a diagnosis of OUD was similar before and after the PA removal (89% vs. 87%, respectively).[9]
        - Similar rates were observed for the subgroup of patients prescribed combination buprenorphine/naloxone.[9]

- In a subgroup of patients with paid claims for sublingual buprenorphine monotherapy, the proportion of patients without a diagnosis of OUD increased after removal of the PA from 6.5% to 20.6%. However, this group still represents a small proportion of the overall population with claims for sublingual buprenorphine (4.4%).[9]

- In the third quarter of 2022 (July through September 2022), most of the Oregon Health Plan (OHP) FFS pharmacy claims for SUD medications were for oral buprenorphine/naloxone (63%), followed by sublingual buprenorphine (21%), and oral naltrexone (13%). In the second quarter of 2022 (April through June 2022) most of the physician administered SUD claims were for oral buprenorphine/naloxone (65%) and oral buprenorphine (33%). Physician administered claims include physician offices and MAT clinics.
- **Appendix 1** lists the current PDL status for drugs used in treat SUD. Doses of buprenorphine and buprenorphine/naloxone that exceed 24 mg per day, in addition to lofexidine, are subject to the clinical PA criteria outlined in **Appendix 5**.

Methods:
A Medline literature search for new systematic reviews and 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:
<u>Opioid Agonist Treatment for People Dependent on Prescription Opioids</u>
A 2022 Cochrane Review assessed opioid agonist treatment with buprenorphine or methadone for the treatment of opioid use disorder (OUD) in people dependent on prescription opioids.[1] Literature was searched through January 2022 for RCTs of adults and adolescents with OUD that compared: 1) full opioid agonist (methadone, morphine, oxycodone, or codeine) versus a different full opioid agonist or partial opioid agonist (buprenorphine) for maintenance treatment; and 2) full or partial opioid agonist versus non-opioid agonist treatments (detoxification, extended-release naltrexone injection, or psychological treatment without opioid agonist treatment).[1]

Eight RCTs met inclusion criteria (n=709).[1] Four studies compared methadone and buprenorphine in people with dependence on prescription opioids. Four studies compared buprenorphine to either a buprenorphine taper (in addition to psychological treatment; 3 studies) or extended-release naltrexone injection (1 study).[1] Seven studies were conducted in an outpatient setting.[1] One study recruited participants who were admitted to hospital, with one group randomized to initiate buprenorphine as an inpatient while the other 2 groups offered a brief intervention and treatment referral information.[1] People with chronic non-cancer pain and OUD were recruited for the studies, and one study specifically recruited participants who misused buprenorphine by injecting it.[1] Seventy percent of the people in the studies were male. The average age was 32 years.[1] The average duration of the 4 studies that compared methadone and buprenorphine was 21 weeks; and the average duration of the 4 studies that compared buprenorphine to detoxification, extended-release naltrexone injection, or psychological treatment was 14 weeks.[1] Seven of the 8 studies were conducted in the U.S.; one study was conducted in Iran.[1] The primary outcomes were continued opioid

use, treatment retention, and adverse effects.[1] Overall, the evidence was of low quality.[1] All studies were randomized and open-label, which posed risk for performance and detection bias.[1] There was also meaningful amounts of missing data that posed high risk of attrition bias because patient attrition rates were high and varied between groups.

Low-certainty evidence from 3 studies showed a difference that favored methadone versus buprenorphine for the outcome of overall self-reported opioid use at end of treatment (risk ratio (RR) 0.49, 95% CI 0.28 to 0.86; n=165). Moderate-certainty evidence from one study did not find a difference in days of self-reported opioid use between methadone and buprenorphine (mean difference (MD) 1.41 days, 95% CI 3.37 lower to 0.55 days higher; n=129).[1] Low-certainty evidence from 4 studies also showed a difference in favor of methadone versus buprenorphine for retention in treatment (RR 1.21, 95% CI 1.02 to 1.43; n=379).[1] Low-certainty evidence from 3 studies showed no difference between methadone and buprenorphine with substance use as measured with urine drug screens at end of treatment (RR 0.81, 95% CI 0.57 to 1.17; n=206). There was low-certainty evidence from 3 studies that did not find a difference in adverse events between methadone and buprenorphine (RR 1.13, 95% CI 0.66 to 1.93; n=206).[1]

When buprenorphine monotherapy was compared to non-opioid treatment, low-certainty evidence from 4 studies showed that buprenorphine resulted in fewer opioid positive urine drug tests at end of treatment (RR 0.66, 95% CI 0.52 to 0.84; n=270). However, 4 studies did not find a difference in self-reported opioid use in the 30 days prior to the end of treatment period between buprenorphine and non-opioid treatment (RR 0.63, 95% CI 0.39 to 1.01; n=276).[1] There was low-certainty evidence from 3 studies that did not find a difference in the number of days of unsanctioned opioid use between buprenorphine and non-opioid treatment (MD −0.19, 95% CI −0.47 to 0.09; n=205).[1] There was moderate-certainty evidence from 4 studies that showed that buprenorphine resulted in higher treatment retention rates over non-opioid treatment (RR 3.02, 95% CI 1.73 to 5.27; n=333).[1] There was moderate-certainty evidence from 3 studies that buprenorphine and non-opioid treatments may not differ in adverse events (RR 0.50, 95% CI 0.07 to 3.48; n=252).[1]

In summary, methadone or buprenorphine did not differ on some outcomes such as positive urine drug screens at the end of treatment (moderate QoE) or the rate of adverse events (low QoE), although on the outcomes of retention and self-reported substance use some results favored methadone (low QoE).[1] However, treatment with buprenorphine appears more effective treatment retention rates then non-opioid treatments like detoxification, extended-release naltrexone injection, or psychological treatment (moderate QoE).[1] Patient preference, availability of treatment clinics, and the clinical assessment of the provider will help determine which MAT will result in higher odds of patient success.

<u>Buprenorphine versus Methadone in Pregnancy</u>

A 2022 systematic review and meta-analysis evaluated comparative evidence for methadone and buprenorphine to determine the optimal opioid substitution agent to reduce adverse maternal and neonatal outcomes in pregnant individuals using illicit opioids.[2] Few RCTs studied this population, so observational cohort studies were included.[2] Case-reports, case-series, and case-control studies were excluded.[2] Twenty studies (4 RCTs and 16 cohort studies) met inclusion criteria and included 7251 patients (methadone; n=4146, buprenorphine; n=3105).[2] Study locations included Europe (8), North America (10) and Oceania (2).[2] Maternal outcomes of interest included adverse associated with treatment, retention in treatment, illicit drug use, death, and mode of delivery (vaginal or cesarean section).[2] Neonatal outcomes were stillbirth, birthweight, growth (total body length at birth and small for gestational age), premature birth, opioid withdrawal treatment, and congenital anomalies.[2] All the studies were at high risk of bias.[2]

Data from 16 cohort studies and 3 RCTs showed that compared to methadone, buprenorphine was associated with greater newborn birth weight (weighted mean difference [WMD] 343 grams; 95% CI 40 to 645 in RCTs and WMD and 184 grams; 95% CI 121 to 247 in cohort studies); longer body length at birth (WMD 2.28 cm; 95% CI 1.06 to 3.49 in RCTs and WMD, 0.65 cm; 95% CI 0.31 to 0.98 in cohort studies); and reduced risk of prematurity (RR 0.41; 95% CI 0.18 to 0.93 in

RCTs and RR 0.63; 95% CI 0.53 to 0.75 in cohort studies; low QoE for all outcomes).[2] Neonatal abstinence syndrome, congenital anomalies, and stillbirths were similar between methadone and buprenorphine (low QoE).[2]

One RCT (n=175) documented maternal adverse effects associated with treatment.[2] There were 14 (16%) serious adverse effects and 83 (93%) adverse effects in the methadone arm, and 8 (9%) serious adverse effects, and 66 (77%) adverse effects in the buprenorphine arm (low QoE).[2] Three RCTs reported treatment retention.[2] The risk of early withdraw from treatment was higher with buprenorphine (32%) compared with methadone (32% vs. 20%; RR 1.60; 95% CI 1.00 to 2.55; low QoE).[2] Two cohort studies reported measures of additional opioid use throughout pregnancy.[2] One study reported 15/90 (17%) of patients used heroin in the buprenorphine group versus 20/45 (44%) in the methadone group.[2] In the other cohort study, 14/16 (88%) patients used additional opioids in the buprenorphine group, and 128/136 patients (94%) of patients in the methadone group.[2] When the results of these two studies were pooled, there was no difference between groups (RR 0.61; 95% CI 0.25 to 1.49; low QoE).[2] The rate of cesarean section was measured in 11 studies (8 cohort studies and 3 RCTs).[2] Buprenorphine was associated with lower cesarean sections versus methadone in cohort studies (RR 0.90; 95% CI 0.84 to 0.98; low QoE).[2] However, no differences in cesarean sections were observed in the RCTs (RR 0.84; 95% CI 0.52 to 1.36; low QoE).[2] No maternal deaths were reported in any studies.[2]

In summary, this systematic review concluded that compared to methadone, buprenorphine was consistently associated with improved birthweight, longer length at birth, and lower risk of prematurity in neonatal offspring based on data from 15 low-quality observational cohort studies and 3 RCTs with a high risk of bias.[2] In the 4 RCTs with high risk of bias, there was a greater risk of maternal adverse effects with methadone and lower treatment retention rates with buprenorphine.[2] However, given high risk of biases in these studies, the results should be interpreted with caution.

Maintenance Agonist Treatments for Opiate-Dependent Pregnant Women

A 2020 Cochrane Review assessed the effectiveness of MAT for pregnant individuals with OUD.[3] Medication-assisted treatment, alone or in combination with a psychosocial intervention, was compared to no intervention, other pharmacological intervention or psychosocial interventions alone.[3] The prevalence of opioid use among pregnant individuals can range from 1% to 2%, to as high as 21%.[3] Neonatal complications of opioid use include opioid withdrawal, postnatal growth deficiency, microcephaly, neuro-behavioral problems, increased neonatal mortality, and a 74-fold increase in sudden infant death syndrome.[3] Pregnancy is recognized as an opportunity to change lifestyle behaviors, and while abstinence from opioids during pregnancy is ideal, withdrawal from opioids during pregnancy is not recommended.[10]

Literature was searched through February 2020 for RCTs which evaluated the efficacy of MAT pregnant individuals with OUD.[3] Studies starting after delivery were excluded.[3] Four RCTs including 271 pregnant patients met inclusion critieria.[3] Three trials compared methadone with buprenorphine (n=223) and one trial compared methadone with oral slow-release morphine (n=43).[3] Two RCTs were from Austria (outpatients), one from the US (inpatients) and a fourth multicenter, international study was conducted in Austria, Canada and the US.[3] The trials continued for 15 to 18 weeks.[3] Three studies had adequate allocation concealment and were double-blind.[3] A major flaw of the studies was attrition bias: 3 out of 4 had a high dropout rate (30% to 40%), which was unbalanced between groups.[3] In the studies that compared methadone with buprenorphine, the quality of the evidence ranged from very low to moderate because of inconsistency in some outcomes between studies, high attrition, and small sample sizes.[3] The quality of the evidence was low in the single trial that compared methadone with slow-release morphine because of the small sample size studied.[3]

Outcomes of interest included child health status, neonatal mortality, treatment retention, and substance use.[3] There was no evidence of a difference in the dropout rate from treatment between methadone and buprenorphine (RR 0.66, 95% CI 0.37 to 1.20, 3 studies; n=223; moderate QoE).[3] No difference in the use of primary substances between methadone and buprenorphine was found (RR 1.81, 95% CI 0.70 to 4.68; 2 studies; n=151; low QoE).[3] Birth weight was higher

with buprenorphine versus methadone in the 2 trials that reported data (MD -530 g, 95% CI -662.78 to -397.22; n=19 and MD -215 g, 95% CI -238.93 to -191.07; n=131) although the results could not be pooled due to very high heterogeneity (very low QoE).[3] The number of newborns treated for neonatal abstinence syndrome did not differ between groups (RR 1.19, 95% CI 0.87 to 1.63; 3 studies; n=166; low QoE).[3] Only one study that compared methadone with buprenorphine reported adverse events.[3] In mothers, there were 14/89 (16%) serious adverse events in the methadone group and 8/86 (9%) in the buprenorphine group, with no difference in the number of mothers with serious adverse events (RR 1.69; 95% CI 0.75 to 3.83; n=175; low QoE). In newborns, there were more serious adverse events (6/73; 8%) in the methadone group than in the buprenorphine group (1/58; 2%), with no difference in the number of newborns with serious adverse effects (RR 1.22; 95% CI 1.07 to 1.39; n=131; low QoE).[3]

In the methadone versus slow-release morphine RCT there were no dropouts in either treatment group.[3] Slow-release morphine was superior to methadone for abstinence from heroin use during pregnancy (RR 2.40, 95% CI 1.00 to 5.77; n=48 participants; low QoE).[3] No adverse effects were reported for the pregnant patients. One child in the methadone group had central apnea and one child in the morphine group had obstructive apnea.[3]

In summary, methadone and buprenorphine may be similar in efficacy and safety for the treatment of OUD in pregnant patients and their neonates.[3] There is insufficient evidence to adequately compare methadone and slow-release morphine.[3] There is a need for more RCTs of adequate sample size that compare MAT in pregnant individuals with OUD.[3]

Agency Of Healthcare Research and Quality: Interventions for Substance Use Disorders in Adolescents and Young Adults

An AHRQ systematic review of interventions for adolescents and young adults aged 12 to 25 years with substance use disorder (SUD) was published in 2020.[4] Both behavioral and pharmacological interventions used for adolescents or young adults with SUD, excluding tobacco, were evaluated.[4] In studies that assessed relapse or reduction in substance use, RCTs with a minimum of 10 patients per arm, and nonrandomized comparative studies or single group studies enrolling at least 100 patients per arm were included.[4] Pharmacologic interventions were divided into those used primarily for SUD or primarily to manage psychiatric comorbidities.[4] One hundred eighteen studies met inclusion criteria.[4] The most commonly reported outcomes included frequency of substance use and abstinence.[4] Evidence was described for 3 major categories of interventions: 1) brief behavioral interventions (consisting of 1 or 2 encounters), typically targeted at adolescents with problematic use; 2) intensive (i.e., 3 or more encounters) behavioral interventions; and 3) pharmacological treatments used to treat OUD.[4] For the purposes of this literature scan, the evidence for medications used to treat OUD will be highlighted.

Most studies enrolled some combination of individuals with mixed use of alcohol, cannabis, opioids, and occasionally other drugs.[4] Two studies evaluated users of methamphetamine, cocaine or ecstasy.[4] However these 2 studies only evaluated behavioral interventions and had methodological concerns including incomplete blinding, incomplete outcome data and poor compliance with interventions.[4] Studies often combined different types of interventions, making comparisons of specific interventions difficult.[4] The available studies did not consistently report a common set of outcomes, which limited the ability to combine information from potentially relevant studies.[4] For most outcomes, individual studies were deemed to have a high risk of bias due to incomplete outcome data, poor compliance, and lack of blinding.[4]

Four comparative studies assessed pharmacologic or combination pharmacologic and behavioral interventions to reduce opioid use in a total of 330 individuals with OUD.[4] Risk of bias was high for all studies.[4] The most significant areas of potential bias across the 4 trials included incompleteness of outcome data reporting and low compliance with the interventions.[4] Participants in the studies were on average 17 to 23 years of age (range across studies 14 to 25 years).[4] In the studies, 59% of participants were male (range across studies 39–66%) and 80% were White (range 70–97%).[4] In addition, 52% reported heroin as the primary substance of use (range from 21 to 91%) and 44% reported injection or intravenous opioid use (range from 24 to 70%).[4] All studies reported on co-use of at least

one other substance: including alcohol, cannabis, cocaine, and amphetamines.[4] All 4 studies assessed sublingual buprenorphine-naloxone or buprenorphine monotherapy combined with behavioral interventions for short-term opioid detoxification.[4] One study compared buprenorphine with clonidine and another study augmented buprenorphine-naloxone treatment with 15 or 30 mg of memantine.[4] No studies of methadone or naltrexone were identified.[4] A meta-analysis was not feasible due to the small number of participants and study heterogeneity.[4] Primary outcomes were reduction of opioid use and maintenance of abstinence. Treatment retention was a secondary outcome in 1 study.[4]

An extended course (12 weeks) of buprenorphine led to a more than greater likelihood of opioid abstinence at 3 months (measured as percent of patients with negative urine screens) compared to a short course (2 weeks) of buprenorphine (1 RCT; n=154; odds ratio [OR] 2.4; 95% CI 1.0 to 5.9; low QoE).[4] Another study (n=53) showed a slow buprenorphine taper over 56 days was more effective than a rapid buprenorphine taper over 28 days in maintaining abstinence at 2 months (OR 2.59; 95% CI 0.73 to 9.18; low QoE).[4] A third study found that buprenorphine performed better for abstinence at 1 month compared to clonidine, although the confidence interval was very wide (OR 4.00, 95% CI 1.00 to 16.0; 1 study; n=36; low QoE).[4] This study reported treatment retention as a secondary outcome.[4] The study retained 72% of participants in the buprenorphine group compared with 39% in the clonidine group (p=0.04).[4] A fourth study compared buprenorphine-naloxone plus memantine 15 mg, buprenorphine-naloxone plus memantine 30 mg, and buprenorphine-naloxone plus placebo in 80 individuals with OUD.[4] Participants in the buprenorphine-naloxone-memantine 30 mg group had improved abstinence at 3 months compared with participants who received buprenorphine-naloxone-memantine 15 mg (OR 9.20, 95% CI 2.62 to 32.28) or placebo (OR 9.20, 95% CI 2.69 to 31.46; moderate QoE for both outcomes).[4]

In summary, for short-term treatment of OUD in adolescents and young adults, low-quality evidence showed that buprenorphine or buprenorphine-naloxone was more effective in achieving abstinence than clonidine (in one study), was more effective when augmented by memantine (in one study), and was more effective when tapered over longer rather than shorter durations (in 2 studies).[4] There is insufficient evidence of long-term efficacy of pharmacologic or behavioral treatment of OUD in adolescents and young adults.[4] The literature guiding medications for adolescents and young adults with OUD is limited, and more research is needed to evaluate optimal pharmacologic treatment duration and the benefit of adjunctive behavioral interventions.[4]

Treatment Retention of Adults with Opiate Use Disorder Who Received Medication Assisted Treatment

A 2021 meta-analysis summarized treatment retention rates reported by RCTs and observational studies which compared oral methadone to buprenorphine or buprenorphine-naloxone for treatment of adults with OUD.[5] Studies with a behavioral focus or placebo comparisons were excluded.[5] Data were extracted separately for two different definitions of treatment retention: length of time retained in the study and presence on the final day of a study.[5] Separate random effects meta-analyses were performed for RCTs and controlled observational studies.[5] Among 7603 studies reviewed, 10 RCTs and 3 observational studies met inclusion criteria (n=5065).[5] All RCTs were found to have low or unclear risk of bias due to incomplete outcome data.[5] There was an unclear or high risk of bias relating to blinding of outcome assessments, allocation concealment, and random sequence generation.[5] For observational studies, 2 studies were had moderate risk of bias and one study had low risk of bias based on the 8-item tool derived from the Joanna Briggs Institute (JBI) Cohort Study Critical Appraisal Instrument for observational studies.[11] The JBI tool considered studies on the following criteria: selection of the study groups, comparability of the groups, addressing bias and confounding factors, and ascertainment of the outcome of interest.[5]

Across studies, the average treatment retention rate was highly variable (RCTs: buprenorphine 20.0 to 82.5% and methadone 30.7 to 83.8%; and observational studies: buprenorphine 20.2 to 78.3% and methadone 48.3 to 74.8%; low QoE).[5] No difference in treatment retention was observed between buprenorphine and methadone in RCTs based on the time period retained in the study (standardized mean difference [SMD] -0.07; 95% CI -0.35 to 0.21; p=0.63; 4 RCTs; n=334; I^2= 37%; low QoE).[5] A meta-analysis was not feasible for observational studies where treatment retention was measured as the length of time retained in the

study.[5] No difference between buprenorphine and methadone was observed where treatment retention was defined as presence on the final study day in RCTs (RR 0.89; 95% CI 0.73 to 1.08; p=0.24; 8 RCTs; n=718; I^2= 56%; low QoE) or in observational studies (RR = 0.75; 95% CI 0.36 to 1.58; 3 studies; n=3498; I^2= 98%; p=0.45; low QoE).[5] In summary, studies suggest treatment retention may be similar for methadone and buprenorphine (or buprenorphine-naloxone), with wide variation across studies.[5]

Stimulant Use Disorders in Patients with Co-Occurring Opioid Use Disorders

A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders was published in 2020.[6] The 2020 systematic review is part of a larger 2018 report commissioned by the U.S. Veterans Health Administration (VHA) that examined the benefits and harms of medications for cocaine and methamphetamine use disorders.[12] Among treatment-seeking people with OUD, reports of past-month methamphetamine use nearly doubled from 18.8% to 34.2% between 2011 and 2017.[13] Similarly, amongst people with prescription OUD in 2015, 31.5% reported cocaine use disorders in the prior year.[14]

The literature search for randomized controlled trials in multiple databases was conducted through April 2019.[6] Thirty-four trials that focused on cocaine use disorder in patients with OUD met inclusion criteria.[6] Twenty-two medications including anticonvulsants, antidepressants, antipsychotics, methadone, buprenorphine, and psychostimulants were studied.[6] Only 1 medication, a naltrexone implant (not available in the U.S.) was studied in people with methamphetamine abuse and OUD in Russia.[6] Most studies enrolled participants stabilized on opioid maintenance therapy, generally methadone.[6] Primary outcomes were abstinence defined as stimulant-negative urine screens for 3 or more consecutive weeks; overall use defined as the proportion of stimulant-negative urine specimens; and retention defined as the proportion of participants who completed treatment.[6]

None of the 6 studies that assessed abstinence found significant differences between groups.[6] Moderate-strength evidence from 10 RCTs (n=1006) showed that antidepressants (desipramine, bupropion, and fluoxetine) worsened retention compared to placebo (RR of drop out, 1.22; 95% CI 1.05 to 1.41).[6] Combined retention data from 3 RCTs (n=292) show moderate-strength evidence of worse retention with anticonvulsants compared with placebo (RR 0.86, 95% CI 0.76 to 0.97), and low-strength evidence for no effect on cocaine use or abstinence in cocaine users with comorbid OUD.[6] Two RCTs provide insufficient-strength evidence for treating cocaine use disorder with antipsychotics (risperidone or aripiprazole) in people with comorbid OUD.[6] There was moderate-strength evidence that disulfiram worsened treatment retention (6 RCTs, n=605, RR 0.86, 95 % CI 0.77 to 0.95).[6] Low-strength evidence from 3 RCTs showed that psychostimulants (dexamphetamine or mazindol) may reduce cocaine use, though the difference was not statistically significant (n=115; standard MD 0.35; 95 % CI -0.05 to 0.74).[6] Three trials compared buprenorphine directly with methadone in people with cocaine use disorder, and moderate strength of evidence showed no significant difference in treatment retention when all three studies were pooled (N = 309, RR 1.17, 95 % CI 0.91 to 1.51).[6] There was only 1 trial for methamphetamine use disorder, which showed insufficient-strength evidence for a naltrexone implant in treating methamphetamine use disorder.[6] Most of the medications studied for cocaine use were ineffective, although psychostimulants warrant further study.[6]

After review, 18 systematic reviews were excluded due to poor quality,[15-18] wrong study design of included trials (e.g., observational only),[19-21] comparator (e.g., no control or placebo-controlled),[22,23] or outcome studied (e.g., non-clinical).[24-33]

New Guidelines:

Veterans Affairs/Department of Defense: Management of Substance Use Disorders

The VA/DoD Evidence-Based Practice Work Group published updated guidance for the management of substance use disorders in August 2021.[7] This guideline is designed to assist providers in screening, assessing, and treating patients with SUD.[7] For amphetamine, cocaine or methamphetamine use disorder, cognitive

behavioral therapy combined with contingency management has proven to be most effective.[7] Contingency management refers to treatment approaches that provide incentives (such as desirable times with monetary value) for achieving specific treatment goals.[7] For the purposes of this literature scan, key pharmacologic recommendations for OUD and alcohol use disorder (AUD) will be summarized.

Opioid Use Disorder

Patients who are provided medically supervised withdrawal, particularly those who do not receive formal, structured non-pharmacotherapy treatment, have high risk of relapse with resultant morbidity and mortality.[7] Furthermore, evidence suggests opioid agonist treatment (OAT) is more effective than other pharmacotherapies over time and improves safety.[7] Long-term methadone treatment has decades of demonstrated effectiveness.[7] Studies have also shown buprenorphine to be used successfully in office-based settings over increasingly longer periods.[7] Additionally, patients utilizing buprenorphine to assist with opioid discontinuation demonstrate positive patient outcomes when used for longer-term treatment versus a quick taper.[7]

There are situations where medically supervised withdrawal from opioids may be preferred over long-term OAT.[7] Examples include a taper of opioids using methadone, buprenorphine, or other symptom-treatment medications if patients: 1) are entering an environment that requires abstinence from any opioids (e.g., prison, court-ordered abstinence-based treatment programs), 2) wish to receive non-opioid treatment (e.g., treatment with injectable naltrexone), and 3) are in a profession that prohibits opioids (e.g., military, healthcare provider, air traffic controller).[7] Buprenorphine can provide relatively short, safe, medically supervised withdrawal treatment.[7] There is no consensus on the treatment duration for short-term medically supervised withdrawal from opioids.[7] Opioid withdrawal management is only indicated under certain circumstances (e.g., for patients with OUD who will be treated with extended-release naltrexone or because a patient chooses not to be treated with OAT).[7] If medically supervised opioid withdrawal is indicated, the preferred approach is initial stabilization with methadone or buprenorphine followed by a short or extended taper.[7]

Treatment retention is a metric of success utilized by some studies.[7] One study concluded that there are no statistically significant differences in treatment retention between methadone and buprenorphine; one study found methadone was superior to placebo; and three RCTs concluded buprenorphine may be more effective than methadone.[7] Buprenorphine and methadone have both been found to be more effective than clonidine.[7] No evidence was identified to support the addition of clonidine to a regimen of buprenorphine or methadone.[7] The quality of the evidence was low due to small sample sizes, high attrition rates, and imprecision.[7]

Recommendations to Manage Opioid Use Disorder:

- Recommend *against* withdrawal management without MAT due to high risk of relapse and overdose (strong recommendation; low QoE).[7]
- For patients with OUD for whom opioid withdrawal management is indicated:
    - Buprenorphine/naloxone in any setting; or
    - Methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program (weak recommendation; low QoE).[7]
    - If methadone and buprenorphine is contraindicated or unavailable, clonidine or lofexidine are reasonable second-line agents (weak recommendation; low QoE).[7]
- For patients with OUD for whom MAT is recommended:
    - Buprenorphine/naloxone in any setting or methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program (strong recommendation; high QoE); or
    - Extended-release intramuscular naltrexone (weak recommendation; low QoE).[7]
- There is insufficient evidence to recommend any specific FDA-approved formulation or routes of delivery of buprenorphine (without naloxone).[7]
- There is insufficient evidence to recommend for or against oral naltrexone.[7]

Pregnant Individuals with Opioid Use Disorder

In 2012, the incidence of maternal opioid use at delivery had increased more than 4-fold in the previous 10 years.[7] Similarly, the incidence of neonatal abstinence syndrome identified at delivery increased almost 3-fold during the same time period.[7] Methadone is the most common medication to treat pregnant women with OUD and has been associated with positive maternal and neonatal outcomes.[7] Since the advent of buprenorphine to treat OUD, there has been increased interest in using it to treat OUD in pregnancy.[7] Buprenorphine has been found to improve maternal and infant outcomes among pregnant patients with OUD, particularly with incidence and severity of neonatal abstinence syndrome and opioid-use related outcomes.[7] One RCT showed that treatment with buprenorphine was associated with similar maternal and infant outcomes compared with methadone.[7] There is currently no evidence to suggest that buprenorphine/naloxone carries additional risk compared to buprenorphine alone in pregnancy.[7]

The workgroup did not issue specific recommendations for managing pregnant individuals with OUD. However the guidance states that patient choice is an important factor in deciding between methadone and buprenorphine in pregnancy.[7] Providers should consider the availability of medication, as buprenorphine is more widely available in some settings than methadone.[7]

Alcohol Use Disorder

Three drugs are FDA-approved for the treatment of AUD: naltrexone, acamprosate, and disulfiram. Topiramate and gabapentin have been studied in AUD treatment, but are not FDA-approved for this indication. Moderate-quality evidence showed that naltrexone improved alcohol consumption outcomes (e.g., percent heavy drinking days, number of drinks per day, return to heavy drinking, and percent drinking days) in people with moderate to severe AUD.[7] A 2010 Cochrane meta-analysis of 50 RCTs (n=7793) showed naltrexone reduced the risk of heavy drinking by 83% compared to placebo (RR 0.83; 95% CI 0.76 to 0.90) and decreased drinking days by almost 4% compared to placebo (MD-3.89; 95% CI -5.75 to -2.04).[34] Although the efficacy of naltrexone is modest in preventing heavy drinking, it has poor efficacy in maintaining abstinence when compared to placebo. Side effects associated with naltrexone, including initial transient nausea, tend to be minimal, and there are options for or once-daily dosing or monthly injection to improve adherence.[7] A 2014 meta-analysis found topiramate improved combined abstinence and heavy drinking outcomes and may decrease alcohol reinforcement and the propensity to drink by reducing craving for alcohol through antagonism of glutamate receptors and inhibition of dopamine release.[35] While topiramate is not approved for AUD by the FDA, there is moderate-quality evidence that the drug significantly reduces heavy drinking and improves abstinence.[7] Topiramate may cause dizziness, negative cognitive effects, or weight loss. In the absence of contraindications, there is insufficient evidence to recommend one of these medications over the other and treatment should be individualized.[7]

Acamprosate and disulfiram may reduce alcohol consumption when used for the treatment of AUD, based on low-quality evidence.[7] Acamprosate may act by normalizing central glutamatergic dysregulation in AUD, thereby relieving symptoms of prolonged alcohol withdrawal.[7] Numerous European trials found acamprosate effective in improving consumption outcomes; however, some US trials have failed to show such benefits.[7] Two meta-analyses found acamprosate improved alcohol consumption outcomes relative to placebo, most notably return to drinking after abstinence.[7] Moderate-quality evidence of significantly elevated rates of certain adverse events (e.g., anxiety, diarrhea, and vomiting) suggests there is some level of harm associated with acamprosate.[7] The frequent daily dose administration required and large tablet size presents a challenge to many patients and can negatively affect treatment adherence.[7] Acamprosate may be considered for patients with AUD who are also taking prescribed opioids or who have significant hepatic damage/impairment since it is not subject to hepatic clearance.[7] Patients who are highly motivated, abstinent before initiation, and not discouraged by the burden of three-times daily dosing are well suited for acamprosate.[7]

A meta-analysis of 22 RCTs showed statistically significant efficacy of disulfiram for AUD compared to a variety of control conditions.[7] Because the action of disulfiram depends on the expectation of adverse effects, it should not be given to patients who are unable to consider the consequences of alcohol consumption while taking disulfiram.[7] Low-quality evidence suggests there are potential harms associated with disulfiram, including increased risk of adverse events.[7] Disulfiram should only be used when abstinence is the goal, established with patient concurrence, and when initiated with addiction-focused counseling.[7] There was low-quality evidence for all reported disulfiram outcomes as a result of very serious limitations for overall abstinence outcomes and serious limitations for other consumption outcomes (i.e., return to drinking, percent drinking days).[7]

The effects of gabapentin likely occur through modulation of gamma-aminobutyric acid (GABA) activity in the amygdala associated with AUD.[7] The need for frequent daily dosing may make adherence difficult for some patients. There are increased concerns regarding the misuse potential of gabapentin. [7] Low-quality evidence from one RCT showed that gabapentin in combination with counseling significantly improved rates of abstinence and heavy drinking in individuals with alcohol dependence; however, the single-site setting and high dropout rate raised concerns regarding its potential for bias and limited generalizability.[7] Another RCT demonstrated the addition of gabapentin to oral naltrexone improved drinking outcomes relative to naltrexone alone in the first 6 weeks after drinking cessation.[7] Gabapentin may be an option for patients with AUD and co-occurring neuropathic pain, or for some with sleep disorders.[7] Also, since gabapentin is eliminated renally, it may be an option for patients with clinically significant hepatic disease.[7] More research is needed on the safety and effectiveness of gabapentin for AUD.[7]

Recommendations to Manage Alcohol Use Disorder:

- For patients with moderate or severe AUD:
    - Naltrexone (oral or extended-release) or topiramate (strong recommendation; moderate QoE).[7]
    - Acamprosate or disulfiram (weak recommendation; low QoE).[7]
- For patients with moderate or severe AUD for whom naltrexone, topiramate, acamprosate or disulfiram is contraindicated or ineffective:
    - Gabapentin (weak recommendation; low QoE).[7]

After review, one guideline was excluded due to poor quality.[36]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[37]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Buprenorphine	BUPRENEX	06/17/2022	Warnings	Buprenorphine may prolong the QT interval by 15 msec or more. This QTc prolongation effect does not appear to be mediated by hERG channels and is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT-prolonging agents is not known. Consider these observations in clinical decisions when prescribing buprenorphine to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart

				failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia.
Methadone	DOLOPHINE METHADOSE	06/02/2021	Use in Specific Populations: Pregnancy	Most available data on methadone use in pregnancy do not indicate an increased risk of major malformations. Pregnant individuals in a methadone treatment program have improved prenatal care leading to reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to pregnant individuals who use illicit drugs.

Buprenorphine Sublingual and Buccal Administration: FDA Drug Safety Communication

The FDA issued a drug safety communication in January 2022 regarding transmucosal administration of buprenorphine.[8] Dental problems have been reported with buprenorphine products dissolved in the mouth.[8] The dental problems include tooth decay, cavities, oral infections, and loss of teeth.[8] They can be serious and have been reported even in patients with no history of dental issues.[8] Three hundred five cases of dental problems have been identified (131 cases classified as serious) with buprenorphine products dissolved in the mouth.[8] These only include cases reported to FDA or published in the medical literature, so there may be additional cases. The average age of the patients was 42 years, but those as young as 18 years were also affected.[8] Most cases were in patients using the medicines for OUD; however, 28 cases of dental problems occurred in patients using it to treat pain.[8] In 26 cases, patients had no prior history of dental problems.[8] Some cases reported dental problems occurring as soon as 2 weeks after treatment began, with the median time to diagnosis being approximately 2 years after starting treatment.[8] Many cases were reported by health care professionals and provided documentation of extensive dental adverse events. Of the 305 cases, 113 mentioned two or more teeth were affected.[8] The most common treatment for these dental problems was tooth extraction/removal, which was reported in 71 cases.[8]

The FDA advises practitioners to refer their patients to a dentist as soon as possible after starting transmucosal buprenorphine.[8] Counsel patients about the potential for dental problems and the importance of taking extra steps after the medicine has completely dissolved, including to gently rinse their teeth and gums with water and then swallow.[8] Patients should be advised to wait at least 1 hour before brushing their teeth. Dentists treating someone taking a transmucosal buprenorphine product should perform a baseline dental evaluation and caries risk assessment, establish a dental caries preventive plan, and encourage regular dental checkups.[8]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
naltrexone microspheres	VIVITROL	INTRAMUSC	SUS ER REC	Y
acamprosate calcium	ACAMPROSATE CALCIUM	ORAL	TABLET DR	Y
buprenorphine	SUBLOCADE	SUBCUT	SOLER SYR	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	SUBLINGUAL	FILM	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	SUBLINGUAL	FILM	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	SUBLINGUAL	TAB SUBL	Y
buprenorphine HCl/naloxone HCl	ZUBSOLV	SUBLINGUAL	TAB SUBL	Y
naltrexone HCl	DEPADE	ORAL	TABLET	Y
naltrexone HCl	NALTREXONE HCL	ORAL	TABLET	Y
naltrexone HCl	REVIA	ORAL	TABLET	Y
disulfiram	DISULFIRAM	ORAL	TABLET	V
buprenorphine HCl	BUPRENORPHINE HCL	SUBLINGUAL	TAB SUBL	V
lofexidine HCl	LUCEMYRA	ORAL	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 181 citations were manually reviewed from the initial literature search. After further review, 180 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 trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Trivedi MH, et al[38] DB, MC, PC, RCT	1. Naltrexone ER 380 mg IM every 3 weeks and Bupropion ER 450 mg po once daily Vs. 2. Placebo IM and PO once daily 2 stages lasting 6 weeks each	Adults aged 18 to 65 yo with moderate or severe methamphetamine use disorder Stage 1: n=403 Stage 2: n=225 (Sequential parallel comparison study design: Participants who did not respond to placebo in Stage 1 were re-	Response: defined as at least 3 methamphetamine-negative urine samples out of 4 samples obtained at 6 and 12 weeks	Percent of Responders in Stage 1 1. 18/109 (16.5%) 2. 10/294 (3.4%) Percent of Responders in Stage 2 1. 13/114 (11.4%) 2. 2/111 (1.8%) Weighted treatment effect (both stages combined) 1. 13.6% 2. 2.5% Difference: 11.1 ± 2.5% 95% CI: not calculated	Low attrition and high adherence to trial regimen may limit generalizability to general population 69% of participants were men, which limits applicability to women 71% of participants were White Sequential parallel study design may be difficult to replicate

	Total duration: 12 weeks	randomized 1:1 to treatment or placebo in Stage 2)		Wald z-test statistic: 4.53; P<0.001	Use of weighted combination for response analysis enhanced he likelihood of detecting treatment efficacy
Abbreviations: DB = double-blind; ER = extended release; IM = intramuscular; MC = multi-center; PC = placebo-controlled; PO = oral; RCT = randomized clinical trial; SL = sublingual; YO = years old					

Appendix 3: Abstracts of Comparative Clinical Trials

Bupropion and Naltrexone in Methamphetamine Use Disorder[38]

BACKGROUND: The use of naltrexone plus bupropion to treat methamphetamine use disorder has not been well studied.

METHODS: We conducted this multisite, double-blind, two-stage, placebo-controlled trial with the use of a sequential parallel comparison design to evaluate the efficacy and safety of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day) in adults with moderate or severe methamphetamine use disorder. In the first stage of the trial, participants were randomly assigned in a 0.26:0.74 ratio to receive naltrexone–bupropion or matching injectable and oral placebo for 6 weeks. Those in the placebo group who did not have a response in stage 1 underwent rerandomization in stage 2 and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for an additional 6 weeks. Urine samples were obtained from participants twice weekly. The primary outcome was a response, defined as at least three methamphetamine-negative urine samples out of four samples obtained at the end of stage 1 or stage 2, and the weighted average of the responses in the two stages is reported. The treatment effect was defined as the between-group difference in the overall weighted responses.

RESULTS: A total of 403 participants were enrolled in stage 1, and 225 in stage 2. In the first stage, 18 of 109 participants (16.5%) in the naltrexone–bupropion group and 10 of 294 (3.4%) in the placebo group had a response. In the second stage, 13 of 114 (11.4%) in the naltrexone–bupropion group and 2 of 111 (1.8%) in the placebo group had a response. The weighted average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1 percentage points (Wald z-test statistic, 4.53; P<0.001). Adverse events with naltrexone–bupropion included gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia. Serious adverse events occurred in 8 of 223 participants (3.6%) who received naltrexone–bupropion during the trial.

CONCLUSIONS: Among adults with methamphetamine use disorder, the response over a period of 12 weeks among participants who received extended-release injectable naltrexone plus oral extended-release bupropion was low but was higher than that among participants who received placebo. (Funded by the National Institute on Drug Abuse and others)

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to November Week 2 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to November 18, 2022

1. acamprosate.mp.	844
2. exp DISULFIRAM/	1191
3. exp NALTREXONE/	5931
4. BUPRENORPHINE/	5779
5. BUPRENORPHINE, NALOXONE DRUG COMBINATION/	492
6. lofexidine.mp.	125
7. Methadone/	8047
8. Alcoholism/	37128
9. Substance-Related Disorders/	66270
10. Methamphetamine/	8265
11. Cocaine/	15321
12. Analgesics, Opioid/	54199
13. Cannabis/	8248
14. 1 or 2 or 3 or 4 or 5 or 6 or 7	19436
15. 8 or 9 or 10 or 11 or 12 or 13	177014
16. 14 and 15	8352
17.limit 16 to (english language and humans and yr="2020 -Current" and (clinical trial, phase iii or meta-analysis or practice guideline or randomized controlled trial or "systematic review"))	181

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose transmucosal buprenorphine products for off-label indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Transmucosal buprenorphine products that exceed an average daily dose of 24 mg per day

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. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #3
3. Is the requested medication a preferred agent?	**Yes:** Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #4

Approval Criteria		
4. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *12/22 (DM); 12/20 (DM); 11/19; 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *TBD; 1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*

Lofexidine - RETIRE

Goals:
- Encourage use of substance use disorder medications on the Preferred Drug List.
- Restrict use of lofexidine to medically appropriate use based on FDA-approved indications.

Length of Authorization:
- Up to 14 days

Requires PA:
- Lofexidine

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.

Approval Criteria		
2. Is this an FDA approved indication? (mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults)	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 14 days of total therapy. Note: FDA approved indication is for up to 14 days of therapy AND Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: 12/22 (DM); 12/20 (DM); 11/19; 1/19
Implementation: TBD; 3/1/19

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Drug Evaluation: Buprenorphine for Pain

Date of Review: February 2023
End Date of Literature Search: 11/11/2022
Generic Name: Buprenorphine, buprenorphine/naloxone
Brand Name: multiple
PDL Classes: Opioid & Alcohol Substance Use Disorders; Long-acting Opioids

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

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

Plain Language Summary: Is buprenorphine better at treating non-cancer pain or safer than other opioids?

- Opioids are a medicine used to treat severe pain. Opioids are not better at improving pain or function compared to other types of non-opioid pain medicines but they do have greater risk of overdose, death, and addiction. Opioid medicine is only recommended when other pain medicines have been tried and do not control pain well enough.
- Long-acting opioid medicines are designed to release medicine in the body over an extended period of time, but they have a higher risk of overdose and death compared to short-acting opioid medicines. The U.S. Food and Drug Administration has approved long-acting opioid medicines only when short-acting opioid medicines have been tried and do not control pain well enough. Several national guidelines also recommend short-acting opioids over long-acting opioids for most people.
- Buprenorphine is an opioid that works differently than other opioid medicines. Most buprenorphine is prescribed for opioid use disorder, but some long-acting buprenorphine is designed to help manage chronic pain. Very little is known about whether buprenorphine controls pain better or is safer than other opioid medicines. A few very short studies (with durations of less than 6 months) do not show that buprenorphine is better at treating pain or safer than other opioids for pain treatment. The U.S. Food and Drug Administration has the same safety cautions and warnings for buprenorphine as other opioids.
- People who already take an opioid medicine may have serious withdrawal symptoms if they abruptly stop taking the medicine (symptoms may be anxiety, pain, sleep problems, upset stomach, and craving opioids). Prescribers and their patients should work together to find a therapy that will decrease risks of opioid therapy and treat the patient's pain. Switching from other opioids to buprenorphine may be one option for patients and providers to consider, but we do not yet know if buprenorphine decreases risk of overdose or addiction when it is used to manage chronic pain.

Author: Sarah Servid, PharmD

- The Oregon Health Plan covers buprenorphine for opioid use disorder. Providers must explain to the Oregon Health Plan why therapy is needed if they prescribe a long-acting buprenorphine medicine for pain or if they prescribe more than 24 mg per day of buprenorphine for opioid use disorder. This process is called prior authorization. The goal of prior authorization is to make sure these medicines are used safely.
- We recommend that the Oregon Health Plan cover long-acting opioid medicines only when other pain medicines including short-acting opioids do not control pain well enough.

Research Questions:

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

Conclusions:

- General recommendations for opioid therapy
    - Guidelines from the Department of Defense and Department of Veterans Affairs (VA/DOD) and National Institute for Health and Care Excellence (NICE) continue to recommend against initiation of opioids (including buprenorphine) for chronic pain.[1-3] In patients with chronic pain, opioids are associated with a small improvement in pain and function compared to placebo. Current evidence does not demonstrate any clinical benefit in efficacy of opioids (as a class of medications) compared to alternative non-opioid analgesics for treatment of chronic pain.[4] Long-term opioid therapy has been associated with serious risks including increased risk of overdose and development of substance use disorder. [4] Recent guidelines typically recommend initiation of opioids only when:[1,5,6]
        - alternative therapies have been maximized,
        - potential benefits outweigh risks,
        - clinician and patient have discussed realistic benefits and risks of treatment and established goals of therapy, and
        - there is an established plan to reassess therapy and discontinue treatment if benefit is not established.
    - For acute pain, non-opioid therapy (including nonpharmacological treatment) should be maximized before starting an opioid.[6]
    - In patients with chronic pain already established on opioid therapy, current guidelines all recommend careful reassessment of risks and benefits including shared decision making for discontinuation of opioids or risk mitigation for continued therapy.[1,3,5,6] Withdrawal symptoms have been documented with abrupt discontinuation of opioids (including buprenorphine) during post-marketing studies.
    - Long-acting, scheduled opioids generally result in exposure to a higher daily dose compared to short-acting, as-needed opioids and are associated with increased risk of overdose and death (low quality evidence).[4,6] The Department of Defense and Department of Veterans Affairs (VA/DOD) and Centers for Disease Control (CDC) guidelines recommend against use of long-acting opioid formulations for acute pain, as an as-needed medication, or when initiating opioid therapy for chronic pain.[1,6]

- Buprenorphine efficacy
    - There is moderate quality from direct and indirect evidence that buprenorphine provides similar reduction in pain intensity with short-term use (less than 6 months) compared to other opioids for patients with chronic pain. There is insufficient evidence to compare buprenorphine to other opioids for acute pain or for chronic pain beyond 6 months.[4] Data is significantly limited by lack of long-term studies, and there is low quality evidence that efficacy of opioids, in general, may attenuate with long-term use (over 3 to 6 months).[6]
- Buprenorphine safety
    - There is low quality evidence that buprenorphine is not safer than other opioids for treatment of chronic pain.[1,6] Literature referencing improved safety of buprenorphine primarily references assumed benefits based on the mechanism of action. However, data from well-controlled, comparative trials are lacking, and indirect comparisons from short-term trials show similar rates of common adverse events, serious adverse events, and withdrawals due to adverse events compared to other opioids. Regulatory agencies (including the U.S. Food and Drug Administration [FDA]) recommend similar precautions for buprenorphine as other opioids. All formulations have warnings for risks for abuse, misuse, addiction, respiratory depression, overdose, neonatal opioid withdrawal syndrome, withdrawal symptoms, adrenal insufficiency, and hepatic adverse events.
    - Most guidelines do not recommend buprenorphine over other opioids. However, the Department of Veterans Affairs and Department of Defense (VA/DOD) 2022 guideline for the treatment of chronic pain includes a suggestion for use of buprenorphine instead of full agonist opioids for patients prescribed daily opioids for chronic pain (weak recommendation for therapy).[1] The systematic literature review supporting this recommendation found low quality evidence that buprenorphine was equally effective at controlling pain compared to other opioids and insufficient evidence evaluating safety of buprenorphine compared to other opioids. In the absence of any evidence, guideline authors note that the theoretical safety profile of buprenorphine based on the mechanism of action as a partial agonist and status as a schedule III substance may decrease long-term risks compared to full opioid agonists (which are classified as schedule II substances and have known overdose risks).[1] However, benefits of buprenorphine should be weighed against the lack of evidence for improved safety compared to other opioids. Buprenorphine should be used with caution, especially in patients who are opioid-naïve, patients who are opioid-experienced with low or intermittent dosing, and patients that have concomitant use of other central nervous system depressants.[1] Most studies have not evaluated buprenorphine in these populations, and labeling for buprenorphine includes precautions for overdose in all of these groups.[1]
- Subgroups
    - Very little evidence compares buprenorphine to other opioids in specific groups of people. Studies that evaluate specific groups of patients who may be at increased risk of harms from opioids are based on opioids as a drug class and do not compare individual opioids. There are no validated tools which can accurately identify patients who may be at risk for opioid overdose, addiction, abuse, or misuse.[4,6]
    - There is low quality evidence that use of opioids in combination with benzodiazepines and gabapentinoids increases risk of overdose.[4,6] There is insufficient evidence that buprenorphine differs from other opioids when combined with other sedating agents.
    - Higher doses of opioids are associated with increased risk of overdose, mortality, abuse, dependence, addiction, falls and major trauma, injury from traffic accidents, and endocrine-related adverse events compared to lower doses (low quality evidence).[4,6] However, there is no minimum dose threshold for which there is no overdose risk.[6]
    - There is insufficient evidence that long-acting buprenorphine is associated with less risk for overdose compared to other long-acting opioids. Adverse events were similar when buprenorphine was compared to other long-acting opioids based on low quality evidence from short-term studies (follow-up of 6 months or less).[4,6]
    - There is insufficient evidence to compare buprenorphine to other opioids for pain in treatment-naïve patients. Labeling for buprenorphine includes a warning for risk of overdose in this population, and long-acting formulations are only recommended if immediate-release opioids are inadequate.[7-10] Trials evaluating buprenorphine for pain have primarily enrolled patients with a prior history of opioid use.

- There is insufficient evidence to know whether buprenorphine is safer or more effective than other opioids when used for pain in specific patient demographics or in patients with specific comorbidities.[4] Opioid overdose may be more frequent in younger people and in patients with comorbid opioid use disorder (OUD).[1] In patients with comorbid OUD, current guidelines recommend patients be treated with appropriate medication assisted treatment (MAT) (irrespective of presence or absence of pain).[1,6] Recommended first-line treatments for MAT include buprenorphine or methadone. There is low quality evidence that both buprenorphine and methadone provide similar improvements in pain intensity, physical functioning, and adverse events in patients with OUD.[11] Most trials evaluating efficacy and safety of buprenorphine for pain excluded patients with behavioral health issues including substance use disorders.

Recommendations:

- No PDL changes are recommended for buprenorphine based on the clinical evidence.
- Because long-acting opioid formulations are associated with increased risk of overdose and death compared to short-acting opioids, update PA criteria to limit use of all long-acting opioids to patients who have inadequate pain relief with short-acting opioids (see **Appendix 5**).

Summary of Current Policy:

- In Oregon fee-for-service (FFS) Medicaid, various buprenorphine formulations are categorized by their FDA-approved indication.
- Opioid products that are indicated for OUD are available without prior authorization. These include sublingual buprenorphine formulations, provider administered oral methadone, and subcutaneous buprenorphine injections.
- Prior authorization is required for all long-acting opioid formulations including transdermal buprenorphine patches and buccal films.
- Acute use of short-acting opioids (up to 7 days) does not require prior authorization. Providers can prescribe up to 2 prescriptions of short-acting opioids every 90 days without PA, and can request longer-term opioid therapy through the prior authorization process.
- Long-term opioid treatment for both short-acting or long-acting formulations can be approved when benefits outweigh potential risks and with appropriate ongoing monitoring.

Background:

Pain management is an important aspect for a variety of acute and chronic conditions. Both non-pharmacologic treatments (such as rehabilitative therapy, chiropractic or osteopathic manipulation, and acupuncture) and pharmaceutical analgesics play an important role in management of pain. Prescription analgesics commonly prescribed for pain management include non-steroidal anti-inflammatory agents (NSAIDs), acetaminophen, topical analgesics, muscle relaxants, and opioids. Evidence supporting specific interventions varies depending on the condition, but current guidelines routinely recommend non-opioid pharmaceuticals and non-pharmacologic treatments for the initial treatment of acute or chronic pain. Most guidelines, medical societies, and public health agencies have recently recommended against routinely prescribing opioids due to increasing evidence of harms reported in observational and epidemiologic studies. These harms include increased mortality, development of opioid use disorder, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[1] Opioids have also been implicated in impaired cognitive function and development of new onset depression.[1] These factors have resulted in a decreased dispensing rate of prescription opioids from practitioners over time. However, harms have also been documented with rapid discontinuation or tapering of prescription opioids, including risk of suicidal ideation, suicide, and overdose following opioid discontinuation.[1] And, despite a decrease in prescription opioid use, death due to drug overdoses have continued to increase in recent years.[1] In 2019, over 70% of the 71,000 deaths the United States due to drug overdose involved an opioid.[1] The number of people who die from an accidental opioid overdose has also surpassed deaths from motor vehicle accidents.[1] The COVID-19 pandemic has only exacerbated this trend, with preliminary CDC data showing an increase of nearly 30% in drug

overdoses from 2019 to 2020.[1,12] Similar trends have been observed in Oregon. Provisional data indicate that overdose deaths of all types has increased by more than 76% from 2011 to 2021, with overdose deaths specifically related to fentanyl and other synthetic opioids increasing by 83% from 2020 to 2021.[13] Fentanyl or fentanyl analogues, including illicitly manufactured derivatives, were the most common type of opioid identified (present in approximately 48% of all overdose deaths in 2021).[13]

The opioid epidemic started in predominantly white communities; but in recent years, literature has documented varying impacts across ethnic groups. For example, recent epidemiologic trends demonstrate that overdose deaths increased disproportionally among non-Hispanic Black individuals compared to other racial and ethnic groups from 2018 to 2019. Historically, patients from racial and ethnic groups that have experienced historical and current discrimination are also less likely to receive adequate care for pain.[1] Black patients were also less likely to be referred to a pain specialist, less likely to receive prescription opioids, and more likely to be discontinued from opioids in the presence of positive test for illicit opioid use compared to white patients.[1] These racial disparities highlight important differences in care that may impact access to services and outcomes with treatment.

While illicit opioids (such as heroin and non-prescription fentanyl) have been implicated in increased death rates over time, the American Medical Association has reported that nearly half of all heroin users started with an addiction to a prescribed opioid medication before switching to heroin due to ease of access.[1] Thus, there is a need for prescribers to carefully consider risks and benefits before initiating opioid therapy, engage patients in shared decisions regarding continuation of opioids, and to address management of pain and risk mitigation based on individual patient circumstances.

Improvement in pain severity or intensity is one of the most commonly reported efficacy outcomes for pain studies. However, outcomes evaluating the impact of treatment on disability, function, and quality of life are equally important. Pain intensity measurements used in clinical trials include the visual analog scale (VAS; scale, 0-100 or 0-10) and numerical rating scale (NRS; scale, 0-10).[14] The NRS and VAS are highly correlated and can be interpreted equally. For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[15] Similar MCID values have been shown with 100-point scales.[16] The proposed MCID thresholds for chronic pain and low back pain are about 2 points on the 0 to 10-point scale or 20 points on the 0 to 100-point scale.[14] The impact of opioids on disability is also frequently studied in clinical trials of low back pain. Measurements commonly used include the Oswestry Disability Index scores (range, 0-100) and the Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[14] The Oswestry Disability Index and RMDQ tools are also highly correlated and share similar properties.[14] Similarly, a 10-point difference in 0-100 scales for chronic disability is considered a “minimal” difference and 20-point differences are considered to be “clinically important”.[14] The Brief Pain Inventory (BPI) is widely used in pain specialty and research settings, but is impractical for clinicians caring for patients in the office due to instrument length and scoring complexity.[17] An ultra-brief pain measure derived from the BPI was developed and validated in patients with chronic pain in 2009.[17] This 3-item scale assesses pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) using a VAS ranging from 0 (no pain/no interference) to 10 (pain as bad as you imagine/complete interference).[17] The PEG scale proved to be a reliable and valid measure of pain among primary care patients with chronic musculoskeletal pain and diverse Veterans Affairs (VA) ambulatory patients.[17] The PEG was also comparable to the BPI in terms of responsiveness to between patients with and without pain improvement at 6 months.[17] For these reasons, the PEG scale was added to the OHP clinical PA criteria for opioids in 2016. Important safety outcomes include common adverse events, adverse events resulting in discontinuation of treatment, development of opioid use disorder, addiction, misuse or abuse, overdose, and death.

The available literature directly evaluating comparative data for opioids is small, particularly in the setting of chronic pain. Most randomized controlled trials (RCTs) evaluating opioid therapy use a placebo comparator, and studies evaluating efficacy and safety of opioids rarely exceed 6 months.[4] Opioids can be divided into several categories based on their mechanism of action and include full mu opioid agonists (e.g., morphine, hydrocodone, hydromorphone, oxycodone,

fentanyl, and methadone), partial mu opioid agonists (e.g., buprenorphine), and opioid agonists which target additional receptors (e.g., tramadol, tapentadol). Short-term use of opioids consistently results in greater analgesia than with few serious adverse events.[4,6,18] However, long-term observational studies of opioid therapy have documented risks for increased mortality, development of opioid use disorder, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[1,4,6] Therefore, there is need to identify safer options for the treatment of chronic pain. The OHP Pharmacy and Therapeutics (P&T) Committee previously evaluated the efficacy and safety of tramadol compared to other opioids, and there is current interest in whether buprenorphine differs from other opioids.

Buprenorphine is a schedule III-controlled substance and is available in a variety of formulations. Formulations of buprenorphine which are FDA-approved for treatment of OUD include subcutaneous injections (SUBLOCADE) and sublingual films or tablets with or without naloxone (SUBOXONE, ZUBSOLV, SUBUTEX). Buprenorphine formulations which are indicated for treatment of severe pain include buccal films (BELBUCA), transdermal patches (BUTRANS), and intramuscular or intravenous injections (BUPRENEX). In Oregon fee-for-service (FFS) Medicaid, various buprenorphine formulations are categorized by their FDA-approved indication. Therefore, transdermal patches and buccal films are categorized as long-acting opioids and subject to clinical prior authorization (PA) criteria for opioids. Subcutaneous injections and sublingual formulations are categorized as MAT for OUD and are available without PA. The preferred drug list (PDL) and clinical PA criteria do not apply to intramuscular and intravenous injections as these are expected to be administered by healthcare providers to manage acute pain. Warnings and precautions included in the FDA labeling for long-acting buprenorphine formulations are consistent with other opioids.[9,10] Boxed warnings include risk of addiction, abuse, misuse, overdose, respiratory depression, risks with concomitant sedatives, accidental exposure, and neonatal abstinence syndrome.[9,10] Other precautions include risk for severe hypotension, withdrawal symptoms, and respiratory depression in patients with pulmonary disease, cachexia, elderly, increased intracranial pressure, or brain injury.[9,10] Use should be avoided in patients with gastrointestinal obstruction or adrenal insufficiency and use should be reserved for when alternatives (including IR opioids) are inadequate or contraindicated.[9,10] Labeling for buprenorphine formulations indicated for OUD have similar precautions for adverse events including addiction, abuse, misuse, respiratory depression, withdrawal, and neonatal abstinence syndrome.[7,8,19]

Switching between opioid products typically requires careful monitoring for withdrawal symptoms, breakthrough pain, respiratory depression, and overdose. Many protocols describing transition from other opioids to buprenorphine require patients to exhibit mild withdrawal symptoms before initiation of buprenorphine therapy in order to avoid risk of overdose based on inter-patient variability in opioid potency.[9,20] FDA labeling for buccal buprenorphine recommends providers taper a patient's current opioid to less than 30 MME before initiating treatment.[9] Labeling for transdermal buprenorphine recommends other scheduled opioids be discontinued at the time of the first transdermal dose.[10] A few recent protocols have described a strategy of administering very low doses of sublingual buprenorphine (i.e., microdosing) before discontinuation of current opioid therapy in order to avoid withdrawal symptoms when transitioning from other opioids to buprenorphine.[21-24] However, much of the evidence is for this method is based on case reports and case series involving fewer than 10 patients.[21-24]

Because buprenorphine is a partial mu opioid agonist, it may have potential advantages compared to full opioid agonists. Pharmacokinetic properties of buprenorphine are listed in **Table 1**. Potential advantages of buprenorphine cited in the literature have included ceiling effect for respiratory depression, improved safety in elderly and renal disease due to favorable metabolic processes, increased efficacy for neuropathic pain, less development of tolerance, lack of hyperanalgesic effect, and antidepressant effects.[25] Potential disadvantages of buprenorphine include high affinity for the opioid receptor, which may limit the utility of naloxone rescue for reversal of an overdose.[9,10] However, these claims are generally based on assumptions about mechanism and pharmacology, and not well designed prospective studies. Additionally, several publications which cite advantages of buprenorphine also note manufacturer funding.[25] This review will evaluate available literature examining efficacy and safety of buprenorphine compared to other opioids.

Table 1. Buprenorphine Pharmacology and Pharmacokinetic Properties.[26,27]

Parameter	Sublingual tablet/film	Transdermal patch	Buccal tablet	SC Injection
Absorption	Variable between patients but variability within each individual patient is low. Ingestion of liquids decreases systemic exposure by 23%-59% (dependent on pH of the liquid).	Application of a heating pad onto the transdermal system may increase blood concentrations of buprenorphine by 26-55%.	Variable between patients but variability within each individual patient is low. Ingestion of liquids decreases systemic exposure by 23%-37% (dependent on pH of the liquid)	Precipitation following injection results in a solid depot which will gradually release buprenorphine via diffusion and biodegradation of the depot.
Bioavailability (relative to IV)	Variable for different products. There is a relative increase in exposure with film compared to tablets. Buprenorphine concentration for ZUBSOLV® 5.7 mg is roughly equivalent to SUBOXONE® 8 mg Buprenorphine: ~29%	15%	46-65%	Not reported
Half-Life (adults)	Buprenorphine: ~37 hours SUBOXONE®: 24-42 hours BUNAVAIL®: 16.4-27.5 hours	~26 hours	27.6 ± 11.2 hours	43 to 60 days
Mechanism of Action	high-affinity binding to mu opioid receptors in the CNS which results in analgesic effects; displays partial mu agonist effects and weak kappa antagonist activity			
Distribution and Protein Binding	CSF concentrations are ~15-20% of plasma concentrations; Vd: 430 liters Protein binding: ~96% primarily to alpha- and beta globulin			
Metabolism	Primarily hepatic via N-dealkylation by CYP3A4 to norbuprenorphine, an active metabolite. Inhibitor of CYP2D6 and CYP3A4.			
Elimination	~70% via feces (33% as unchanged drug; 21% as norbuprenorphine) 27-30% via urine (9.4% as conjugated drug; 11% as conjugated norbuprenorphine)			

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; IV = intravenous; mg = milligram; Vd = volume of distribution

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 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:

Multiple high quality systematic reviews have been published in recent years which evaluate evidence of opioids for acute and chronic pain. For many of these reviews, evidence for opioids is presented as a class of drugs compared to placebo and the efficacy and safety of individual agents is not evaluated. The evidence presented in this review will focus primarily on evidence that evaluates comparative data of buprenorphine to other opioids for the management of acute and chronic non-cancer pain. Evidence that evaluates efficacy and safety opioids as a class of medications will not be discussed in detail. Both buprenorphine and methadone are recommended as first-line treatment options for MAT in patients with OUD. Evidence supporting management of buprenorphine for OUD will not be included in this review.

A systematic review from AHRQ published in 2020 and updated in March 2022 evaluated evidence of opioids for chronic pain.[4] The review specifically evaluated evidence regarding effectiveness based on type of opioid (pure agonist, partial agonist, or opioids with a mixed mechanism). For pain relief, there was moderate quality evidence of no difference in efficacy outcomes between buprenorphine and pure opioid agonists. Direct comparative evidence was limited to 3 RCTs, and subgroup analyses from placebo-controlled data were used to supplement conclusions. Two RCTs (n=415) directly compared transdermal buprenorphine to tramadol with no difference in pain intensity, sleep, discontinuation due to adverse events, or specific adverse events. One small RCT (n=46) compared buprenorphine to transdermal fentanyl and found no difference in pain intensity, function, mood or adverse events.[4] Placebo-controlled data were available from 38 trials of pure opioid agonists and 8 trials of buprenorphine (5 evaluated transdermal patch and 2 evaluated buccal formulation) and 16 trials evaluated mixed opioids (tramadol or tapentadol).[4] Subgroup analyses of the placebo-controlled data showed no interactions between type of opioid (full, partial, or mixed) and effects on pain, function, pain response, SF-36 health status, sleep or depression. Similarly, no difference in short-term harms based on the mechanism of action was found.[4] Compared to placebo, opioids of all types were associated with increased rates of study participant discontinuation due to adverse events (number needed to harm [NNH] of 10; moderate quality evidence) and common adverse events, but were not associated with serious adverse events in short-term RCTs.[4] Adverse events more common than placebo included somnolence (NNH 11), nausea (NNH 7), vomiting (NNH 14), constipation (NNH 7), dizziness (NNH 12) and pruritus (NNH 14). Pruritus was only adverse event which demonstrated a statistical difference based on type of opioid with higher risk associated with pure agonists and mixed mechanism opioids compared to buprenorphine.[4] However, the analysis was limited to 3 trials of buprenorphine. Pooled analyses for each type of opioid are presented in **Table 2** for each outcome.

Table 2. Subgroup analysis for efficacy outcomes compared to placebo based on opioid type[4]

Outcome	Overall	Pure agonists	Partial agonists	Mixed mechanism	p-value for interaction
Pain response*; RR (95% CI)	1.35 (1.24 to 1.48)	1.39 (1.24 to 1.60)	1.45 (1.20 to 1.76)	1.27 (1.10 to 1.51)	0.47
Pain; MD (95% CI)	-0.79 (-0.93 to -0.67)	-0.82 (-1.04 to -0.63)	-0.71 (-0.90 to -0.49)	-0.81 (-1.04 to -0.60)	0.85
Function; SMD (95% CI)	-0.22 (-0.28 to -0.16)	-0.20 (-0.30 to -0.10)	-0.25 (-0.46 to -0.03)	-0.22 (-0.30 to -0.15)	0.72
SF-36 physical function; MD (95% CI)	1.64 (1.10, 2.17)	1.82 (0.48 to 2.96)	2.20 (-0.82 to 5.13)	1.54 (0.82 to 2.15)	0.80
Sleep; SMD (95% CI)	-0.25 (-0.32 to -0.19)	-0.26 (-0.40 to -0.17)	-0.28 (-0.45 to -0.13)	-0.23 (-0.36 to -0.15)	0.92
Depression; SMD (95% CI)	0.00 (-0.22 to 0.18)	-0.01 (-0.19 to 0.20)	0.31 (0.02 to 0.60)	-0.35 (-1.03 to 0.13)	0.14
Discontinuation due to AEs; RR (95% CI)	2.25 (1.86 to 2.73)	2.06 (1.57 to 2.75)	2.28 (1.08 to 5.01)	2.55 (1.93 to 3.36)	0.64
Serious Adverse Events; RR (95% CI)	1.23 (0.88 to 1.74)	1.42 (1.01 to 2.01)	1.27 (0.68 to 2.38)	0.95 (0.39 to 2.34)	0.48
Somnolence; RR (95% CI)	2.97 (2.44 to 3.66)	2.72 (2.01 to 3.78)	2.80 (1.47 to 4.95)	3.40 (2.60 to 4.69)	0.43
Nausea; RR (95% CI)	2.46 (2.17 to 2.80)	2.29 (1.90 to 2.74)	1.99 (1.29 to 3.19)	2.97 (2.50 to 3.54)	0.06

Vomiting; RR (95% CI)	3.57 (2.98 to 4.34)	3.17 (2.36 to 4.31)	3.65 (2.34 to 5.86)	4.19 (3.22 to 5.68)	0.32
Constipation; RR (95% CI)	3.38 (2.96 to 3.92)	3.21 (2.74 to 3.87)	2.53 (1.56 to 4.55)	3.82 (3.20 to 4.89)	0.10
Dizziness; RR (95% CI)	2.66 (2.37 to 2.99)	2.43 (1.92 to 3.08)	2.85 (1.99 to 4.30)	2.80 (2.39 to 3.28)	0.48
Headache; RR (95% CI)	1.06 (0.95 to 1.17)	0.96 (0.79 to 1.14)	1.23 (0.87 to 1.67)	1.09 (0.94 to 1.29)	0.31
Pruritus; RR (95% CI)	3.51 (2.47 to 5.16)	4.02 (2.44 to 6.48)	1.18 (0.80 to 1.91)	4.77 (3.01 to 7.95)	0.02[+]

Abbreviations: AE = adverse events; CI = confidence interval; MD = mean difference; RR = relative risk; SF-36 = short-form 36; SMD = standard mean difference.
*Commonly defined as >30% improvement from baseline; [+]statistically significant difference between groups

Because data from RCTs were not powered or designed to evaluate long-term harms (e.g., opioid use disorder, dependence, overdose), evidence on serious long-term adverse events was derived primarily from observational studies.[4] Several large observational studies provided low quality evidence that opioids are generally associated with increased risk for abuse, dependence, addiction, overdose, mortality, myocardial infarction, fracture, falls, and endocrine dysfunction (erectile dysfunction, female reproductive dysfunction, androgen deficiency).[4] Based on observational studies, opioids were also generally associated with increased risk of overdose in combination with a benzodiazepine (especially with short-term use) or gabapentinoids (particularly at higher gabapentinoid doses) based on low quality evidence.[4] Higher doses of opioid were also generally associated with increased risk of cardiovascular events, road trauma events (when limited to drivers), endocrine dysfunction, mortality, overdose, abuse, dependence or addiction compared to lower doses (based on low quality evidence).[4] In some studies, risk for falls and fractures was highest at the start of therapy and decreased with longer-term use.[4]

Evidence related to the type of opioid and risk for OUD, overdose, fracture, falls or cardiovascular events was very limited.[4] Only one study reported data on buprenorphine compared to other opioids. An observational study of 9,500 patients identified an increased risk of hip fracture for patients prescribed opioids (age adjusted incidence 3.47 vs. 1.94 per 100 person-years, hazard ratio [HR] 1.96, 95% CI, 1.27 to 3.02).[4] Risk was not statistically significant for patients prescribed codeine or dihydrocodeine (HR 1.70, 95% CI, 0.89 to 3.26) but was statistically significant for patients prescribed buprenorphine (HR 1.98, 95% CI, 1.33 to 2.95) and other full opioid agonists (HR 2.72, 95% CI, 1.25 to 5.93) compared to no opioid use.[4] Several studies also evaluated risk of short-acting opioids compared to long-acting opioids. In a single small study, transdermal buprenorphine 20 mcg/hr was associated with increased rate of discontinuation due to adverse events compared to short-acting oxycodone 40 mg/day (13% vs. 7%, relative risk [RR] 1.82, 95% CI, 1.02 to 3.26), but specific adverse events were similar between groups and data were limited by the enriched study design.[4] A large cohort study (n=840,606) found that long-acting opioids were associated with increased risk of overdose compared to short-acting opioids (HR 2.33, 95% CI, 1.26 to 4.32). Risk was highest with initiation (HR 5.2, 95% CI, 1.89 to 14.72 at ≤14 days) and decreased with longer duration of exposure (HR 1.50, 95% CI, 0.68 to 3.33 at >60 days).[4] However, opioids evaluated in this study did not include long- or short-acting buprenorphine formulations. A subsequent case control study (n=2,311 cases) was identified in the 2022 update with similar results, but the types of opioids included in the study (i.e., partial vs. full agonists) were not reported.[4,28] Short-term studies of long-acting opioids did not indicate differences in effectiveness or harms with buprenorphine compared to other opioids.[4] Three trials compared transdermal buprenorphine to another long-acting opioid (sustained release tramadol or transdermal fentanyl) with no differences in efficacy (pain, sleep, function, mood) or safety (discontinuation due to adverse events, specific adverse events).[4] No studies were identified which evaluated efficacy and safety of opioid rotation compared to maintenance of current opioid therapy. In patients with pain and comorbid OUD, there was no difference between methadone and buprenorphine/naloxone for outcomes of study retention, pain, function, positive urine drug screen, or illicit drug use (low quality evidence from 2 RCTs).[4]

A 2017 systematic review from CADTH evaluated the evidence for efficacy and safety of buprenorphine for treatment of chronic non-cancer pain.[29] Literature was evaluated from 2011 through 2016. Nine RCTs and 4 systematic reviews (including 18 publications) were included in the evidence review. All the direct comparative evidence evaluated transdermal buprenorphine. Two of the RCTs evaluated buccal buprenorphine. Most evidence was compared to placebo. Active

comparators included tramadol (n=2 studies), morphine (n=1 study), transdermal fentanyl (n=2 studies), codeine (n=1 study), and oxycodone (n=1 study).[29] Most of the identified RCTs had significant risk of bias which limit interpretation of the findings. Seven of the RCTs had high attrition (>30%) or differential drop-out rates between groups.[29] All RCTs except two were manufacturer-funded, and the 2 RCTs without manufacturer funding were open-label studies that were poorly reported and designed.[29] The 4 systematic reviews performed quality assessment of the included trials but it was unclear how they accounted for quality in their conclusions. One network meta-analysis did not provide enough information about their methods to assess the appropriateness of their data analysis. Overall, authors found evidence that buprenorphine resulted in modest pain improvement compared to placebo but no evidence that buprenorphine differed from other opioids.[29] Compared to placebo, the overall benefit of buprenorphine was small and magnitude of benefit failed to achieve clinically meaningful improvements referenced in the literature for several studies.[29] The most common adverse events associated with buprenorphine use were nausea, constipation, vomiting, dizziness, headache, somnolence and application site reactions. There was insufficient evidence to suggest that buprenorphine is associated with fewer harms than other opioids.[29]

A 2014 Cochrane systematic review evaluated opioids for pain associated with osteoarthritis of the hip or knee.[30] The review primarily evaluated oral or transdermal opioids compared to placebo, but results were also stratified based on type of opioid. Twenty-two RCTs were included in the review, and 4 RCTs were identified which evaluated transdermal buprenorphine compared to placebo.[30] Median treatment duration was 4 weeks (range 3 days to 6 months), and median daily dose was 59 daily morphine milligram equivalents (MME; range 13 to 160 MME).[30] Results were generally limited by unclear trial methodology, inadequate reporting of results, small magnitude of benefit, and evidence of publication bias. Opioids were generally associated with a small improvement in pain (standardized mean difference [SMD] -0.31; 95% CI -0.46 to -0.16) and function (SMD -0.26; 95% CI -0.35 to -0.17) compared to placebo.[30] These differences would correspond to an absolute difference of 0.7 cm on a 0 to 10 visual analogue pain scale and a difference of 0.6 points on a standardized Western Ontario and McMaster Universities Arthritis Index (WOMAC) disability scale ranging from 0-10.[30] Results for the buprenorphine subgroup were similar for these outcomes (pain SMD -0.19, 95% CI -0.3 to -0.09 and function SMD -0.23, 95% CI -0.40 to -0.05).[30] Pain improvement was largest in short-term studies and decreased with more than 4 weeks of treatment.[30] Adverse events were more common with opioid treatment than placebo (RR 1.49, 95% CI 1.35 to 1.63 and NNH 14, 95% CI 11 to 19) with no evidence that adverse events differed based on type of opioid.[30] Discontinuations due to adverse events were also more common with opioid treatment (RR 3.76, 95% CI 2.93 to 4.82; NNH 21, 95% CI 15 to 30) and results for the buprenorphine subgroup were similar (RR 3.10, 95% CI 1.38 to 6.94).[30] Most identified trials were industry funded. Overall, authors concluded that opioids provide small benefits for relief of pain and improved function although the magnitude of benefit was of questionable clinical significance. Serious risks associated with long-term use (including discontinuations due to adverse events, addiction, and opioid dependence) likely outweigh any small, long-term benefit.[30]

A Cochrane review published in 2022 evaluated efficacy and safety of opioid agonist treatment in people dependent on pharmaceutical opioids.[11] The review included trials that assessed at least 30 days of maintenance treatment for OUD. Studies with a mixed population of patients who used pharmaceutical opioids or heroin had to have at least 80% of patients with dependence on pharmaceutical opioids.[11] Outcomes of interest for this review included comparisons of partial and full opioid agonists for adverse events, pain, function, and quality of life. Four trials were included which compared methadone to buprenorphine in adults and adolescents with OUD related to pharmaceutical opioids.[11] The mean duration of treatment was 17.4 weeks, and trials primarily included male patients (70%) with a mean age of 32 years.[11] All 4 trials were open-labeled and had unclear allocation concealment. Two of the trials had unclear randomization methods and 3 studies had high or unclear risk for attrition bias. One trial which compared methadone and buprenorphine had high risk of reporting bias and included data on only one outcome (retention in treatment).[11] There was no difference between methadone and buprenorphine for the outcomes of adverse events (RR 1.13; 95% CI 0.66 to 1.93; n=206; low quality evidence).[11] There was also no difference in pain intensity (SMD -0.12, 95% CI -0.73 to 0.50; 3 studies; n=163), physical functioning reported using the 36-item short form (SF-36) scale (MD 1.28; 95% CI -3.83 to 6.39; 1 study; n=127), and none of the studies reported overall quality of life.[11]

An AHRQ systematic review, initially published in 2020 with literature searches updated in 2022, evaluated the efficacy and safety of pharmacologic (opioid and non-opioid) and non-pharmacologic treatments for acute pain.[18] The review did not find any evidence comparing buprenorphine to other opioids for acute back pain, neck pain, peripheral neuropathic pain, post-operative pain, dental pain, or sickle cell crisis.[18] One trial (n=89) compared sublingual buprenorphine 0.4 mg to intravenous morphine 5 mg in patients with an extremity fracture. Mean difference in pain intensity was not different at one hour post-treatment (the average improvement was 2.2 points on 0-10 NRS for both groups).[18] No other efficacy or safety outcomes were reported. A small, fair quality trial (n=26) compared intramuscular buprenorphine 0.3 mg to intramuscular meperidine 100 mg in patients with kidney stone pain. Pain intensity at 12 hours was improved more with buprenorphine compared to meperidine (4.2 vs. 1.2; MD 3.0; 95% CI 2.8 to 3.2) and was associated with less use of rescue medication (92% vs. 46%; RR 2.00, 95% CI 1.09 to 3.67).[18] There was no difference in reported adverse events including nausea and vomiting.[18]

A 2021 systematic review evaluated feasibility, efficacy, and safety of transition to buprenorphine in patients prescribed long-term opioids for chronic pain.[20] Authors used high quality methods to conduct the review including duplicate study identification, data extraction, and quality assessment. Outcomes were prespecified and the quality of evidence was considered in conclusions. However, most studies identified for the review had high risk of bias, lacked a comparison group, and had significant heterogeneity.[20] The review identified 22 studies published through November 2022 including 5 RCTs, 7 case-control or cohort studies, and 10 uncontrolled pre-post studies.[20] Primary outcomes of interest included precipitated opioid withdrawal, pain intensity, pain interference with daily activities, adverse events, and healthcare utilization. Diagnoses of patients included chronic musculoskeletal pain, neuropathic pain, fibromyalgia, and chronic cancer pain. Reasons for transitioning to buprenorphine ranged from escalating opioid doses, aberrant opioid use, adverse effects with current therapy, inadequate analgesia, and drug combinations that increase risk for overdose (e.g., high doses or combination sedative use).[20] In 13 of 22 studies, patients had concomitant OUD, and 4 studies explicitly excluded patients with OUD.[20] Often problematic behavior, aberrant opioid use, or opioid dependence was observed, even in studies that excluded patients with OUD. Previous opioid use also differed among participants with average daily doses of 60-500 MME in the studies. The range of included daily doses was 10 MME to 3,200 MME.[20] The method used to transition to buprenorphine and the buprenorphine dosing regimen also differed between studies. Nine studies required participants to exhibit mild withdrawal symptoms before starting buprenorphine, 8 studies required participants to wait 8-24 hours before initiating buprenorphine, and 3 studies required participants to wait overnight.[20] One study evaluated microdosing of buprenorphine to mitigate withdrawal symptoms and 10 studies allowed use of a variety of other medications to mitigate symptoms.[20] Some studies included a taper for buprenorphine and others established patients on stable doses of buprenorphine maintenance therapy. Sublingual or buccal buprenorphine was used in 13 studies, 2 studies used transdermal buprenorphine, and 2 studies used multiple formulations.[20] Ten studies were conducted in the outpatient or clinic setting and 7 studies were solely in the inpatient setting or started the transition during an inpatient stay before continuing with outpatient treatment.[20] Results were described narratively, and all outcomes were graded as very low quality, indicating a high degree of uncertainty that the study results represent the true treatment effect. Precipitated opioid withdrawal was evaluated in 7 studies and occurred in 3-6% of patients.[20] In most studies, symptoms were mild, but severe withdrawal was observed in some participants (especially those on high opioid doses). Pain intensity was described in 17 studies and was improved in 12 of these studies after transitioning to buprenorphine.[20] Effect size was smaller in studies with control groups and in patients with doses of opioids exceeding 200 MME prior to switching.[20] There was also variability observed based on the study population, the tool used to evaluate pain intensity, and the rationale for switching to buprenorphine.[20] In one study, higher doses of buprenorphine (16 mg daily) were associated with improved pain compared to lower doses (2 mg daily; OR 0.42; 95% CI 0.20-0.90).[20] Only 4 studies evaluated impact of pain on daily functioning after switching with improvement in some individuals but with significant heterogeneity based on population and the tool used to evaluate function. Retention rates (described in 14 studies) ranged from 33 to 93%.[20] Adverse effects (described in 10 studies) were common and similar to other opioids.[20] Severe adverse effects or discontinuation due to adverse effects were less common but long-term follow up was often not systematically evaluated after switching to buprenorphine. No studies evaluated healthcare utilization. The authors concluded that buprenorphine was likely non-inferior to other opioids for pain control based on very low quality evidence.[20] Careful transition to buprenorphine is possible with minimal adverse effects, but the optimal protocol to switch patients to buprenorphine is not known.[20] Only 10 studies reported

following participants for at least 6 months and follow-up periods were not consistent in the observational studies.[20] The significant heterogeneity and small number of patients studied limits the ability to identify important long-term outcomes such as overdose, mortality, and development of opioid use disorder.

A 2017 Cochrane review evaluated adverse events associated with medium and long-term use for chronic non-cancer pain.[31] The review included 61 studies (n=18,679 patients).[31] Trials were included if they evaluated opioid use of 2 weeks or more, and most studies evaluated opioids over 6 to 16 weeks. Outcomes evaluated included any adverse event, serious adverse events and withdrawals due to adverse events. Differences between opioids was not evaluated. However, compared to placebo, opioid therapy was associated with an increased risk of any adverse event (78% vs. 54%; RR 1.42, 95% CI 1.22 to 1.66), withdrawals due to adverse events (25.1% vs. 7.1%; RR 3.40, 95% CI 3.02 to 3.82), and serious adverse events (7.5% vs. 4.0%; RR 2.75, 95% CI 2.06 to 3.67) based on moderate quality evidence.[31] Several other specific adverse events were also more common with opioid treatment than placebo including constipation, dizziness, drowsiness or somnolence, nausea, sweating based on moderate quality evidence.[31] There was very low quality evidence that pruritus, vomiting, hot flushes, and fatigue were more common with opioid treatment compared to placebo.[31]

Systematic reviews have evaluated opioids for acute pancreatitis pain (2013),[32] chronic non-cancer pain in children and adolescents (2017),[33] chronic neuropathic pain (2015),[34] acute pain in the pre-hospital setting,[35] and high-dose opioids (>200 daily MME) in chronic non-cancer pain.[36] Overall, these reviews did not identify trials that evaluated sublingual, buccal or transdermal buprenorphine for treatment of pain. Other systematic reviews did not identify any direct comparative data for buprenorphine in chronic low back pain (2013).[37]

After review, 30 systematic reviews were excluded due to poor quality (e.g., network meta-analyses, inadequate reporting of methods), comparator (e.g., non-opioid or placebo-controlled), wrong population (e.g., cancer pain, substance use disorder), or outcome studied (e.g., non-clinical).

Guidelines:
CDC guidelines were updated in 2022 and addressed the use of opioids for treatment of acute pain (less than 1 month), subacute pain (1 to 3 months), and chronic pain (more than 3 months) pain.[6] The guideline excluded cancer-related pain, pain related to sickle cell disease or palliative care. Recommendations were based primarily on 5 systematic reviews from AHRQ on treatments for opioids, non-opioids, and nonpharmacologic treatments for chronic pain, treatment for episodic migraine, and treatment for acute non-migraine pain.[6] Evidence from these reviews was supplemented by a contextual evidence review of resource allocation and patient and provider values and preferences. Recommendations were graded according to evidence type (**Table 3**) and grouped into category A or B recommendations. Most recommendations were made based on type 4 (low quality) evidence.[6] Recommendation categories were determined based primarily on 4 factors: the quality of the evidence, balance between desirable and undesirable outcomes, values and preferences, and resource allocation (e.g., costs to patients or health systems).[6] Category A recommendations are more likely to apply to all people in the group and category B recommendations indicate that the recommendation might not apply to all people and clinicians should employ shared decision-making to find the most appropriate decision for the specific clinical situation. The guideline was intended to serve as a clinical tool to improve patient-centered decisions related to pain management and was not intended to serve as inflexible standards of care.[6]

Table 3. CDC Categorization for Evidence Types and Recommendations

Evidence Type	Description	Approximate AHRQ strength of evidence equivalent
Type 1	randomized clinical trials or overwhelming evidence from observational studies	High
Type 2	randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies	Moderate

Type 3	observational studies, or randomized clinical trials with notable limitations	Low
Type 4	clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations	Low with serious limitations

Opioids generally provided a small improvement in pain and function compared to placebo, but were also associated with short-term harms with evidence of pain attenuation with longer-term use between 3-6 months.[6] Twelve recommendations highlighted in **Table 4** were included to guide the use of opioids.[6] Specific recommendations for initiation and choice in therapy are outlined below, and additional recommendations for monitoring are included in **Table 4**.

- Clinicians should maximize the use of non-opioid therapies (including any non-pharmacological therapies appropriate for the condition) before prescribing opioids for acute, subacute, and chronic pain. No difference in pain or function was found between opioids and NSAIDs for multiple chronic conditions.[6]
- Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks.
- Clinicians should use caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants. Concomitant use has been associated with increased risk of overdose and death in observational studies.
- When starting opioid therapy, prescribe short-acting opioid formulations instead of long-acting opioid formulations. Evidence demonstrates treatment response of pain and function is generally consistent across duration of action of the opioid product (short or long-acting) and opioid type (full agonists, partial agonists, or mixed mechanisms) for chronic pain.[6] Time-scheduled use of extended-release opioids was not more effective or safe than intermittent use of short-acting opioids and has been associated with greater total average daily doses than short-acting formulations.[6] With regard to harms, a fair quality observational study found a higher risk of overdose with long-acting opioids versus immediate-release opioids.[6] No distinction was made between extended-release buprenorphine and other extended-release opioid formulations. Risk was highest with initial treatment and decreased with longer exposure.[6] The FDA recommends long-acting opioid formulations for pain severe enough to require daily, around-the-clock treatment, and when other treatment options, including non-opioids and short-acting opioids, are ineffective, intolerable, or provide inadequate pain relief.[6] Long-acting opioids should not be used on an as-needed basis.
- Prescribe the lowest dose and shortest duration indicated based on patient specific risk factors. Data from observational studies show short-term opioid use is associated with progression to long-term opioid use and long-term opioid use is associated with increased risk for serious harms (including opioid use disorder and overdose).[6] Harms related to opioid use increases with higher opioid doses, without a minimum dose below which there is no risk.
- For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. In patients established on long-term opioid therapy, tapering or discontinuing opioids can be difficult and be associated with significant harms. A collaborative, patient-centered approach to opioid tapering is recommended. If patients remain on opioid treatment, incorporation of risk mitigation strategies should be considered.
- No specific recommendations were made for buprenorphine, though guideline authors note that it may have utility for patients on high-dose opioids when risks outweigh benefits but who are unable to taper and who do not meet criteria for opioid use disorder.[6] Based on limited, emerging evidence, transitioning to buprenorphine may be one strategy to assist patients with decreasing total opioid dose. However, caution is advised when transitioning between full opioid agonists and buprenorphine. The current standard method to transition to buprenorphine from a full agonist is to wait until the patient exhibits mild to moderate withdrawal symptoms before starting buprenorphine, then to titrate buprenorphine under supervision every 2 hours

to control withdrawal symptoms.[6] Protocols to transition patients vary significantly, but have been described in both the inpatient and outpatient settings.[6] Several case series have also described a low-dose initiation approach (i.e., microdosing) of buprenorphine to avoid and mitigate withdrawal symptoms during transition, but evidence for this new approach is limited.[6] Guideline authors note that the comparative efficacy and harms of buprenorphine compared to full opioid agonists is an important area for future research.[6]

Table 4. CDC Recommendations for Prescribing Opioids for Pain[6]

	Recommendation	Evidence Type	Category
Determining Whether or Not to Initiate Opioids for Pain			
1	Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy.	3	B
2	Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks.	2	A
Selecting Opioids and Determining Opioid Dosages			
3	When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids.	4	A
4	When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients.	3	A
5	For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue such as warning signs of impending overdose (e.g., confusion, sedation, or slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages.	4	B
Deciding Duration of Initial Opioid Prescription and Conducting Follow-up			
6	When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.	4	A

7	Clinicians should evaluate benefits and risks with patients within 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients.	4	A
Assessing Risks and Addressing Potential Harms of Opioids			
8	Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone.	4	A
9	When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.	4	B
10	When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.	4	B
11	Clinicians should use caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants.	3	B
12	Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death.	1	A

Chronic Pain

Guidelines from the U.S. Department of Defense and Veterans Affairs were updated in May 2022 for the management of opioids in patients with chronic pain.[1] Management of acute pain was not addressed in this guideline. General recommendations for use and monitoring of opioids for chronic pain were consistent with the CDC guideline recommendations outlined above. Careful evaluation of risks and benefits of long-term opioid therapy is particularly recommended in younger patients or patients with co-occurring substance use disorders as these populations may have increased risk of adverse events.[1]

The guideline evaluated evidence for, and use of, specific types of opioids in several circumstances.

- Prescription of long-acting opioids was *strongly recommended against* for acute pain, on an as-needed basis, or when planned long-term opioid therapy is initiated.[1] Authors did not differentiate between long-acting buprenorphine buccal or transdermal formulations and other long-acting opioid formulations. This recommendation was based on moderate quality evidence from a large retrospective cohort study which found an increased risk of treatment for OUD when patients were prescribed long-acting opioids compared to short-acting opioids.[1] A second study identified that patients prescribed long-acting opioids and schedule II opioids had a 4.7-times increased risk to die from an overdose than patients prescribed non-schedule II opioids based on low quality evidence.[1]
- For patients on daily, moderate to high dose, long-term opioids for chronic pain, use of buprenorphine is *weakly recommended* instead of full agonist opioids.[1] Overall, there was insufficient evidence that compared buprenorphine to other opioids.[1] The authors felt, however, that the theoretical safety profile of buprenorphine based on the mechanism of action as a partial agonist and status as a schedule III substance may potentially decrease long-term risks compared to full opioid agonists which are classified as schedule II substances and have well known overdose risks.[1]
    - Evidence for this recommendation included three systematic reviews in patients with chronic pain, neuopathic pain, and low back pain evaluated opioids compared to placebo or non-opioid analgesics. There were no direct comparative data evaluating buccal and transdermal buprenorphine versus other opioids, and outcomes were generally not reported for specific opioids. Indirect comparative data from 2 network

meta-analyses evaluated opioids for chronic pain and chronic low back pain. In patients with chronic low back pain, buprenorphine did not differ from hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and tapentadol for most efficacy outcomes.[1] There was low quality evidence that buprenorphine may achieve 30% pain reduction more than tramadol, but several study biases like lack of reporting on duration of chronic pain and prior treatments of opioids limit this evidence.[1] Because of the narrow inclusion criteria for trials in this analysis, applicability to other populations and other chronic pain conditions is also unclear. The second network meta-analyses evaluated safety of tapentadol to other opioids. Serious adverse events and discontinuation due to adverse events did not differ between tapentadol and buprenorphine.[1] Compared to tapentadol, buprenorphine may be associated with a lower rate of any adverse event based on low quality evidence.[1] This difference in any adverse event was primarily driven by differences in constipation with tapentadol compared to buprenorphine.[1]

  - The authors noted that this recommendation for buprenorphine should be weighed against the paucity of evidence, especially in patients who are opioid-naïve, patients who are opioid-experienced with low or intermittent dosing, and patients who concomitantly use other central nervous system depressants.[1] Most studies reported a maximum follow-up of 1 to 6 months, trials commonly lacked adequate description of methods to control for bias, and most studies were funded by industry.[1] RCTs also often excluded patients at highest risk for poor outcomes. For example, patients with behavioral health comorbidities, including substance use disorders, were excluded. Long-term observational trials have also shown a higher opioid dose and longer duration of prescribed opioids leads to increased risk of treatment for OUD and fatal overdoses.[1] The authors concluded that any potential benefit of short-term opioid therapy is likely outweighed by these serious adverse events, even in carefully selected patients.[1]

- For management of chronic pain in the setting of co-occurring OUD, there was insufficient evidence to compare methadone, buprenorphine, or extended-release naltrexone injection and make a recommendation for one drug therapy over another.[1] The authors recommend OUD be treated in accordance with current guidelines.
  - A systematic literature search identified a single RCT (n=159) that compared extended-release naltrexone and buprenorphine/naloxone for treatment of chronic pain in the setting of OUD over 12 weeks. Pain intensity did not significantly worsen in either treatment group over 12 weeks, but evidence was limited by low study retention, imprecision, risk of bias, and applicability issues as patients with severe chronic pain were not encouraged to participate.[1]
  - Supporting evidence also included a systematic review (14 studies, n=3128) which evaluated the impact chronic pain had on outcomes in patients with OUD. Evidence was limited by inconsistency across outcome definitions and risk of bias. Chronic pain was associated with comorbid psychiatric conditions (OR 2.18; 95% CI 1.6 to 2.9), but did not impact any outcomes for patients on buprenorphine or buprenorphine/naloxone.[1]
  - Based on this evidence, it was concluded that the presence of chronic pain is not a reason to withhold MAT in patients with comorbid OUD.[1]

Guidelines updated in May 2021 from the Department of Defense/Veterans Administration for the management of patients with chronic multisystem illness (CMI) also included recommendation for opioids for treatment of chronic pain.[38] CMI was defined as presence of multiple symptoms (e.g., fatigue, headache, myalgias, arthralgias, concentration problems, gastrointestinal disorders) associated with more than one body system which persist for more than 6 months and interfere with daily functioning. CMI is typically considered when other health conditions have been ruled out. The presence of other conditions like fibromyalgia, irritable bowel syndrome, or chronic fatigue, however, does not preclude diagnosis of CMI. Patients with CMI often have multiple comorbidities. These guidelines *strongly recommend against* the long-term use of opioids for the management of chronic pain in patients with CMI.[38] A systematic review did not identify any studies which evaluated the short- or long-term efficacy of opioids in patients with CMI. Harms and burden of long-term opioid therapy, including risk of overdose and development of OUD, have been associated with opioid prescribing. There is also a lack of high quality evidence which shows that

long-term opioid therapy improves pain, function, or quality of life. Given the lack of evidence, recommendations were made to avoid initiation of opioids for chronic pain in patients with CMI and to prescribe naloxone to mitigate risk in patients who are already established on chronic opioid therapy.[38]

NICE guidelines for the management of chronic pain in adults over 16 years of age were updated in 2021.[3] Recommendations were applicable to chronic primary and secondary pain. Chronic primary pain was defined as pain that persists or recurs for more than 3 months in the absence of a clear underlying condition or cause such as fibromyalgia. Chronic secondary pain pertains to pain related to or caused by an underlying condition. NICE recommendations were based on an evidence review which evaluated treatments for chronic pain and included recommendations for both non-pharmacological and pharmacological treatments. No evidence was identified which evaluated efficacy of the following interventions for chronic pain (defined as >3 months): opioids, acetaminophen, steroids, anesthetics/steroid combination, ketamine and anti-psychotics. One common reason studies of opioids were excluded from the review was because they studied pain caused by other conditions like cancer, neuropathic pain, and musculoskeletal disease, instead of chronic primary pain.[3] No studies identified evaluated the safety of opioids versus placebo, no treatment, or usual care for longer than 6 months. Three observational studies with high risk of bias were included to assess harms of chronic opioid use. Two of the studied assessed opioid use in Medicaid populations and one assessed opioid use in U.S. veterans. Risk of opioid abuse or misuse in these 3 studies ranged from 1.3% to 5.9%.[3] All-cause mortality with opioid use greater than 180 days was 1.1%.[3] No evidence was identified for cognitive impairment, fractures and falls, sexual dysfunction, endocrine impairment, immune dysfunction, sleep apnea, cardiovascular events, self-harm, suicide, or depressive symptoms or mood disturbances in relation to opioids.[3]

Recommendations for pharmacological management included the following:[3]

- Consider an antidepressant like amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine or sertraline in adults with chronic primary pain after discussion of risks and benefits. A consultation with a specialist is recommended for use of antidepressants to manage chronic pain in adolescents less than 18 years of age.
- Do not initiate any of the following medications for chronic primary pain: opioids, acetaminophen, NSAIDs, antiepileptic drugs including gabapentinoids, antipsychotics, benzodiazepines, corticosteroid or local anesthetic/corticosteroid trigger point injections, ketamine, or local anesthetics (topical or intravenous).
- For patients already prescribed non-recommended therapy for chronic pain, recommendations were consistent with CDC and Veterans Administration guidelines for chronic pain including re-evaluation of therapy and shared decision-making to reduce, discontinue, or safely continue the medication.

Guidelines from the Scottish Intercollegiate Guidelines Network for treatment of chronic pain were updated in 2019.[5] No recommendations were made for one opioid over another. Instead, opioid therapy is recommended only for short- to medium-term duration in carefully selected patients with chronic non-malignant pain if other therapies have been insufficient and benefits outweigh risks of serious harms such as addiction, overdose and death.[5] At initiation of therapy, expected outcomes should be established; if not attained, it is recommended that the provider and patient a planned agreement in advance to reduce and stop opioids. Assessment of effectiveness and harms, including signs of abuse and addiction, should occur early after initiation and be reassessed annually, or more frequently if needed.[5] Screening tools to evaluate patients at risk for OUD may be useful as part of a more comprehensive reassessment, but should not be the only tool used. Patients on greater than 50 MME daily should be reviewed more frequently to detect emerging harms. Patients prescribed more than 90 MME should be referred to a pain specialist.[5]

Osteoarthritis

Guidelines from the Department of Defense and Veterans Affairs for the management of osteoarthritis were updated in 2020.[39] Therapies with strong recommendations included use of topical NSAIDs for pain associated with osteoarthritis of the knee.[39] There was insufficient evidence for topical NSAIDs or capsaicin in treatment of osteoarthritis of the hip.[39] There were weak recommendations for topical capsaicin for osteoarthritis of the knee and weak recommendations for acetaminophen or oral NSAIDs for osteoarthritis of the hip and knee. Adjunctive duloxetine also had weak recommendations for osteoarthritis of the knee if there is an inadequate response or contraindications to acetaminophen or NSAIDs.[39] The following recommendations were made for use of opioids:

- The guideline recommend against initiating opioids, including tramadol, for pain associated with osteoarthritis of the hip and knee (weak recommendation against treatment; very low quality of evidence).[39] Other recommendations were consistent the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Non-pharmacological treatment is recommended for pain associated with osteoarthritis; when pharmacological treatment is deemed necessary, non-opioids are recommended over opioids.[39] In patients with persistent pain despite alternative non-opioid or non-pharmacologic treatments, patients should be carefully evaluated to determine if potential benefits of opioid therapy outweigh risks. If opioid therapy is needed, the shortest duration and the lowest effective dose should be used with routine monitoring.[39]
- Opioid recommendations were made based on systematic reviews and RCTs which compared opioids to placebo or active control.[39] No studies were identified in the systematic review that included buprenorphine. Overall, opioids consistently reduced pain intensity more than placebo for hip and knee osteoarthritis, but effect sizes were small and did not often achieve clinically significant differences.[39] Physical functioning was also improved with opioids, but effect was small.[39] Opioids had a higher risk of harms than placebo, including withdrawal due to adverse events, withdrawal symptoms from opioids, and serious adverse events.[39] Trials that compared opioids to non-opioid analgesics like NSAIDs and acetaminophen showed similar, or improved efficacy, with the non-opioid analgesic for function and pain reduction.[39] The trials had short durations of 1-17 weeks.[39]

Guidelines from NICE for management of osteoarthritis were updated in 2022.[40] Recommendations for pharmacologic treatment were consistent with 2020 guidelines from the Department of Defense and Veterans Affairs. Pharmacologic therapies are recommended only in conjunction with non-pharmacologic therapies and to support therapeutic exercise.

- Topical NSAIDs are recommended for osteoarthritis of the knee and may be considered for osteoarthritris associated with other joints.[40] If topical NSAIDs are ineffective, an oral NSAID can be considered based on individual risks for gastrointestinal, renal, liver, cardiovascular, and pregnancy-related adverse events.[40]
- Codeine and acetaminophen are recommended only for infrequent, short-term pain relief, and only when other pharmacological treatments are contraindicated, intolerable, or ineffective.[40]
- Opioids, excluding codeine, are not recommended because risks outweigh benefits for patients with osteoarthritis.[40]

Evidence for these recommendations included only a few studies that evaluated buprenorphine for osteoarthritis. One trial compared transdermal buprenorphine to oral tramadol and 2 studies that compared transdermal buprenorphine to placebo.[40] No difference in pain was found between buprenorphine and tramadol based on low quality evidence (NRS 0-10 scale: MD 0.18 lower; 95% CI 0.9 lower to 0.54 higher); in addition, no difference in serious cardiovascular events was found at 12 weeks based on very low quality evidence (60 more per 1,000; 95% CI 0 fewer to 120 more).[40] There was insufficient evidence for all other efficacy and safety outcomes. The guideline noted that trials of transdermal opioids have generally failed to include patients over 75 years of age, and there are little data to guide choice of therapy with regard to route of administration for this patient population.[40]

Low Back Pain

Guidelines were updated in February 2022 from the Department of Defense and Veterans Affairs for the management of patients with low back pain.[41] There were no non-pharmacologic or pharmacologic treatments which had a strong recommendation for treatment. Pharmacotherapy recommended for management of low back pain included duloxetine and NSAIDs (weak recommendation for treatment).[41] There was insufficient evidence to recommend gabapentin, pregabalin, tricyclic antidepressants, topical analgesics, or short-term use of muscle relaxants for low back pain.[41] Recommendations were made against the use of opioids, acetaminophen, investigational monoclonal antibodies, systemic corticosteroids, and chronic use of muscle relaxants (weak recommendation against treatment).[41] There was a strong recommendation against the use of benzodiazepines for low back pain.[41] Recommendations against use of opioids were primarily made based on the following evidence:

- A systemic review and meta-analysis of 21 RCTs in patients with chronic low back pain.[42] Trials were included if they were at least 4 weeks duration. Four of the trials evaluated transdermal or buccal buprenorphine against placebo. No head-to-head comparative evidence between opioids were identified except one study that compared tapentadol with oxycodone.[42] Subgroup analyses did not include buprenorphine compared to other opioids. Compared to placebo, opioids had a greater reduction in disability based on moderate quality evidence and improved pain severity based on moderate to low quality evidence for various pain measures at 4 to 15 weeks.[42] No differences in serious adverse events or mortality with short-term use were found based on low quality evidence. Subgroup analyses indicate that discontinuation of opioids was more common with longer-term studies greater than 12 weeks' duration. There was insufficient evidence to evaluate efficacy and safety of long-term opioid therapy greater than 6 months.[42] Study limitations included lack of assessment of abuse and addiction. Most studies excluded patients who may be at higher risk for overdose or dependence. Patients with comorbid somatic or psychiatric diseases and current or previous substance use were excluded.[42] Applicability to Medicaid populations was further limited as none of the studies were conducted in the primary care setting. Trials also lacked patient diversity as most enrolled participants were middle-aged White women.[42] It is unclear how inclusion of a broader population of patients, particularly patients with comorbidities, or different healthcare settings like primary care, into clinical trials could impact existing evidence.
- Two systematic reviews that evaluated the efficacy and safety of opioids in chronic and acute low back pain.[14,43] These reviews were also included in the 2017 VA/DOD guideline for chronic pain. The reviews showed modest improvement with opioids compared to placebo for pain intensity in patients with acute or chronic low back pain (MD of -8.1 on a 0-100 visual analogue scale and MD -0.43 on a 0-10 numeric rating scale). The proportion of patients who achieved a clinically important improvement in pain intensity of 30% or greater was not reported. In a meta-analysis of 3 RCTs, function was not clinically improved over 30-91 days with opioid therapy compared to placebo, but results were limited by wide confidence intervals.[14] The other meta-analysis demonstrated a small, clinically unimportant difference in function compared to placebo (SMD of -0.26, or about 1 point on a 24 point Roland-Morris Disability Questionnaire).[43] There was insufficient direct comparative evidence from both of these systematic review to evaluate different opioids for outcomes of pain or function. Two trials compared transdermal buprenorphine to placebo and provide low quality evidence for a small improvement in pain (<1 point on a 10-point scale) which is like other opioids. There is insufficient evidence with transdermal buprenorphine to determine differences in function compared to placebo in patients with chronic low pain.[43] Adverse events were more common with opioids than placebo (68.9% vs. 49.1%, respectively). In 4 trials, more than 50% of patients discontinued opioid treatment due to adverse events or lack of efficacy.[14,41]

Overall, guideline authors concluded that the small potential benefit with short-term opioid use over 4-15 weeks may be substantially outweighed by the potential serious harms of opioids including potentially fatal respiratory depression, overdose, misuse, abuse, addiction, and diversion.[41]

Guidelines from NICE for the management of low back pain and sciatica were published in 2016 and last updated in 2020.[44] Recommendations were made against use for opioids, gabapentinoids, other antiepileptics, oral corticosteroids, and benzodiazepines due to lack of evidence for benefit and evidence of harm associated with these treatments.[44] A systematic review of treatments for sciatica and low back pain failed to identify evidence for use of opioids compared to

placebo, usual care, or other treatments.[44] Studies of patients with mixed chronic pain were excluded. In the absence of specific evidence, the following recommendations for opioids were made based on clinical experience of the guideline committee:[44]

- Do not offer opioids for management of *chronic* sciatica or *chronic* low back pain because risks of long-term use likely outweigh benefits.
- Do not routinely offer opioids for managing *acute* low back pain.
- Codeine with or without acetaminophen may be considered for acute low back pain if an NSAID is contraindicated, intolerable or ineffective.
- For patients already established on opioid therapy, a discussion of risks, including risk of withdrawal, are recommended. A plan with shared decision making on whether to discontinue these agents should be formulated.

Other guidelines which briefly mention the use of opioids include:

- NICE guidelines updated in 2018 for the management of acute pyelonephritis.[45] Low doses of codeine can be considered for acute pain management in patients over 12 years of age if pain is not controlled with acetaminophen alone. No recommendations were made for other opioids or for long-term use of opioids.[45]
- NICE guidelines for the treatment of neuropathic pain were published in 2013 and last updated in 2020.[2] Recommendations for initial choice of treatment include amitriptyline, duloxetine, gabapentin, or pregabalin.[2] If initial treatment is ineffective or not tolerated, switching therapy to another one of these agents is recommended.[2] Tramadol is only recommended if acute rescue therapy is needed.[2] There are recommendations against long-term use of tramadol for neuropathic pain. NICE recommends against use of other opioids unless recommended by a specialist.[2] Referral to a specialist is recommended upon initial assessment if patients have severe pain, if pain significantly impacts quality of life or function, or if their underlying health condition has deteriorated.[2]

<u>Additional Guidelines for Clinical Context:</u>

In response to increasing post-marketing reports of harms associated with abrupt discontinuation or rapid dose reduction with opioids, the US department of Health and Human Services (HHS) published guidance in October 2019 for clinicians on appropriate dose reduction and discontinuation of long-term opioids.[46] Methods used to develop this guideline were not reported, though at least some recommendations were adapted from the Oregon Pain Guidance Workgroups.[46] Recommendations in this guideline were not graded, and the quality of the recommendations could not be assessed.[46] These guidelines emphasize the importance of care coordination and individualized patient care during initiation of an opioid taper plan in order to avoid risks associated with rapid discontinuation. Risks of abrupt or rapid tapers can include withdrawal symptoms, worsening pain, psychological stress, suicidality, seeking opioids from high-risk sources, and loss of patient trust.[46] Required tapering should be avoided, particularly when benefits of opioid therapy continue to outweigh risks. Instead, the decision to taper opioids should be based on a shared decision between the patient and provider.[46] Use of shared decision making when developing tapers helps to establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations.[46] The HHS guidelines recommend tapering to a reduced dose or discontinuation of opioid therapy be considered in the following circumstances:[46]

- When pain improves
- When pain and function are not meaningfully improved
- Upon receipt of higher doses without documented benefit from higher dose
- When there is evidence of opioid misuse
- With significant adverse effects which affect quality of life or function
- When the patient experiences an overdose or with warning signs for overdose of confusion, sedation or slurred speech

- With co-prescribing of sedating medications or comorbid conditions that increase risk for adverse events
- With long-term prescribing and current risk-benefit assessment is unclear

Various tools and methods recommended to support dosage reduction include individualized dose reductions based on patient history and goals and supportive therapy using a multidisciplinary treatment approach to improve outcomes.[46] Guidelines emphasize flexible taper plans, integration of non-pharmacologic and non-opioid pharmacologic treatments into the treatment plan, use of behavioral health supports, and addition of appropriate symptomatic treatment as needed.[46] They also suggest transitioning to buprenorphine for patients who are unsuccessful with slow tapers when risks of opioid therapy outweigh benefits.[46]

After review, one guideline was excluded due to poor quality.[47]

Dependence and Abuse Potential:
Buprenorphine is currently categorized as a schedule III substance by the Drug Enforcement Agency (DEA), whereas many other long-acting opioids are categorized as schedule II substances. Data on abuse potential of buprenorphine was primarily derived from short-term studies with few participants in controlled clinical settings.[48-53] There are few small pharmacokinetic studies conducted in controlled clinical settings which evaluate risk of overdose and respiratory depression with buprenorphine compared to other opioids,[54,55] but it is unknown if these results could be generalized to the real world. Large observational cohort studies have documented increased risk of death and overdose with long-acting opioid formulations. This risk is thought to be due to increased opioid exposure associated with scheduled, around-the-clock, long-acting formulations versus short-acting opioids, which may be used more frequently on an as-needed basis.[28,56,57] Long-acting formulations of buprenorphine were not included in these studies.

The utility of naloxone for reversal of respiratory depression caused by buprenorphine has also been evaluated in controlled clinical settings with healthy participants, but the applicability of these results to a larger population in the outpatient setting is unclear.[54] FDA labeling for transdermal and buccal buprenorphine notes that rescue doses of naloxone may not be effective for reversal of respiratory depression associated with buprenorphine, and higher doses of naloxone may not provide higher odds of reverasal.[9,10] The effects of naloxone may be delayed by 30 minutes or more.[9,10]

In a 2020 report from the National Poison Data System, buprenorphine was identified in a total of 4,958 exposure cases, of which 2,948 cases were single exposures involving only buprenorphine.[58] Thirty-eight percent of single exposures (n=1,143) were in children less than or equal to 5 years of age and almost 50% (n=1,450) were in adults at least 20 years of age.[58] The exposure was classified as unintentional in 56% of cases (n=1,667) and intentional in 30% of exposures (n=883).[58] Over 70% of cases (n=2,107) received treatment in a healthcare facility. The proportion of patients who received naloxone after exposure was not reported. Medical outcomes for these exposures were classified according to symptom severity. Forty percent of cases (n=1,172) were classified as having no symptoms or only mild symptoms, defined as typically not needing an intervention. Moderate or major outcomes occurred in 623 (21%) and 125 (4%) cases, respectively.[58] Moderate outcomes were classified as symptoms severe enough to warrant treatment and major outcomes are typically classified as life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).[58] Two fatalities were identified from single exposure to buprenorphine.[58] Cases involving a single substance generally reflect most exposures, identified at 87.7% from these data, but are responsible for only 44.7% of fatalities.[58]

Randomized Controlled Trials:

A total of 328 citations were manually reviewed from the initial literature search. After further review, all studies except 4 RCTs were excluded because of wrong study design (e.g., observational), comparator (e.g., no control, non-opioid control, or placebo-controlled), outcome studied (e.g., non-clinical), or inclusion in the systematic reviews described above. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Londhe, et al. 2020.[59] Single site, RCT N=200	1. Transdermal buprenorphine 5 mcg/h applied after surgery for 15 days 2. IV APAP 1 gm and tramadol 50 mg every 8 h for 2 days before switching to oral treatment Duration: 7 days	Patients with total knee arthroplasty India	Pain intensity assessed using 0-100 visual analogue scale for up to 7 days post-surgery	Day 1 post-surgery 1. 30 2. 40 Day 7 post-surgery 1. 10 2. 30 P=0.0083 over 7 days	High risk for selection bias: Method to allocate patients to groups was even/odd allocation which is not random. High risk for performance and detection bias: Blinding of patients, providers, and outcome assessors was not reported. Attrition was not documented.
Lee, et al. 2017.[60] OL, MC, NI, RCT N=136	1. Transdermal buprenorphine 5-20 mcg/h weekly 2. Tramadol/APAP 37.5/325mg tablets given twice daily (titrated up to 4 tablets twice daily as needed) Dose was titrated based on pain intensity Duration: 6 weeks	Adults with persistent postoperative pain (NRS ≥4) at 14-90 days after lumbar fusion surgery South Korea	Improvement in pain intensity at 6 weeks on the NRS scale (non-inferiority margin of 1.5)	Pain improvement from baseline to 6 weeks 1. 2.02 ± 2.14 2. 2.76 ± 1.45 MD 0.74; lower 97% CI was -1.45 indicating buprenorphine was not non-inferior to tramadol/APAP	High risk for performance and detection bias due to open label design. High risk for attrition bias (36% did not complete the study).
Kim, et al. 2017.[61] Single-center, OL, NI, RCT N=71	1. Transdermal buprenorphine 5 mcg/h patch 2. Oral tramadol 150-300 mg daily Patients were randomized at 36 h post-surgery and patient-controlled analgesia was discontinued at 72 h post-surgery Duration: 4 weeks	Adults with single level posterior lumbar interbody fusion surgery South Korea	Pain intensity for lower back pain at 7 days post surgery (measured by 1-10 visual analogue scale; non-inferiority margin of 1.5)	Pain intensity at 7 days 1. 3.59 ± 1.62 2. 3.50 ± 1.61 MD 0.09 (95% CI -0.75 to 0.94) Pain severity with buprenorphine was non-inferior to tramadol at 7 days	Unclear risk of selection bias as randomization method was not specified. High risk for performance and detection bias due to open label design. High risk for attrition bias (11 and 18% of patients had missing outcome data at 7 days in tramadol and buprenorphine groups, respectively).

Desai, et al. 2017.[62] Single-center, OL, RCT N=50	1. Transdermal buprenorphine 10 mcg/h patch applied the day before surgery 2. Tramadol 50 mg pre-operatively and three times daily post-operatively Duration: 7 days	Adults undergoing surgery for proximal femur fractures India	Pain intensity at up to 7 days post-surgery (0-100 visual analogue scale)	Results presented graphically. Pain scores were improved with buprenorphine compared to tramadol starting 24 hours post-surgery.	High risk of selection bias. Random number table used for randomization, but allocation concealment was not reported. Baseline pain scores at rest appeared to differ between groups. High risk of performance bias due to open-label design though outcome assessors were unaware of treatment groups. High risk of reporting bias as statistical analyses and differences between groups were not reported.

Abbreviations: APAP = acetaminophen; CI = confidence interval; DB = double blind; h = hour; IV = intravenous; MC = multicenter; MD = mean difference; NI = non-inferiority; NRS = numeric rating scale; OL = open label; RCT = randomized controlled trial

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Appendix 1: Current Preferred Drug List

Substance Use Disorder, Opioid and Alcohol

Generic	Brand	Form	Route	PDL
buprenorphine	SUBLOCADE	SOLER SYR	subcutaneous	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	FILM	sublingual	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	FILM	sublingual	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	TAB SUBL	sublingual	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	TAB SUBL	sublingual	Y
buprenorphine HCl/naloxone HCl	ZUBSOLV	TAB SUBL	sublingual	Y
buprenorphine HCl	BUPRENORPHINE HCL	TAB SUBL	sublingual	V

Opioids, Long-acting

Generic	Brand	Form	PDL
fentanyl	FENTANYL	PATCH TD72	Y
morphine sulfate	MORPHINE SULFATE CR	TABLET ER	Y
morphine sulfate	MORPHINE SULFATE ER	TABLET ER	Y
morphine sulfate	MS CONTIN	TABLET ER	Y
buprenorphine	BUPRENORPHINE	PATCH TDWK	N
buprenorphine	BUTRANS	PATCH TDWK	N
buprenorphine HCl	BELBUCA	FILM	N
buprenorphine HCl	BUPRENORPHINE HCL	FILM	N
fentanyl	FENTANYL	PATCH TD72	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	CAP ER 12H	N
hydrocodone bitartrate	ZOHYDRO ER	CAP ER 12H	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	TAB ER 24H	N
hydrocodone bitartrate	HYSINGLA ER	TAB ER 24H	N
hydromorphone HCl	EXALGO	TAB ER 24H	N
hydromorphone HCl	HYDROMORPHONE ER	TAB ER 24H	N
levorphanol tartrate	LEVORPHANOL TARTRATE	TABLET	N
methadone HCl	METHADONE HCL	ORAL CONC	N
methadone HCl	METHADONE INTENSOL	ORAL CONC	N
methadone HCl	METHADOSE	ORAL CONC	N
methadone HCl	METHADONE HCL	SOLUTION	N
methadone HCl	METHADONE HCL	SYRINGE	N
methadone HCl	METHADONE HCL	TABLET	N
methadone HCl	METHADOSE	TABLET	N
methadone HCl	DISKETS	TABLET SOL	N
methadone HCl	METHADONE HCL	TABLET SOL	N
methadone HCl	METHADOSE	TABLET SOL	N

morphine sulfate	KADIAN	CAP ER PEL	N
morphine sulfate	MORPHINE SULFATE ER	CAP ER PEL	N
morphine sulfate	MORPHINE SULFATE ER	CPMP 24HR	N
oxycodone HCl	OXYCODONE HCL ER	TAB ER 12H	N
oxycodone HCl	OXYCONTIN	TAB ER 12H	N
oxycodone myristate	XTAMPZA ER	CAP SPR 12	N
oxymorphone HCl	OXYMORPHONE HCL ER	TAB ER 12H	N
tapentadol HCl	NUCYNTA ER	TAB ER 12H	N
tramadol HCl	CONZIP	CPBP 17-83	N
tramadol HCl	TRAMADOL HCL ER	CPBP 17-83	N
tramadol HCl	CONZIP	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	TAB ER 24H	N
tramadol HCl	ULTRAM ER	TAB ER 24H	N
tramadol HCl	TRAMADOL HCL ER	TBMP 24HR	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 11, 2022

1	exp buprenorphine/ or exp buprenorphine, naloxone drug combination/	6994
2	exp Pain/	445711
3	exp Chronic Pain/	20923
4	noncancer pain.mp.	1117
5	2 or 3 or 4	445935
6	1 and 5	1234
7	limit 6 to (english language and humans)	771
8	limit 7 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	328

Appendix 3. Abstracts of Randomized Comparative Trials

Londhe S, Patwardhan M, Shah R, Oak M. Efficacy and Safety of Buprenorphine Transdermal Patch for Immediate Postoperative Analgesia After Total Knee Arthroplasty Surgery. *The Journal of arthroplasty.* 2020;35(6S):S178-S181.

BACKGROUND: Total knee arthroplasty (TKA) is associated with moderate-to-severe postoperative pain. Satisfactory perioperative analgesia is essential for a good and predictable surgical outcome. Effective postoperative pain control is a major challenge to the treating surgeon and his team. Old age and multiple comorbidities restrict the choice of analgesics one can offer. Transdermal buprenorphine (TDB), widely used in chronic pain management, has been rarely studied in acute postoperative setting. The purpose of this study was to compare the safety and efficacy of a TDB patch to conventional analgesics after knee arthroplasty surgery., METHODS: A prospective randomized study was conducted with 200 patients aged 60-75 years undergoing TKA surgery under neuraxial anesthesia. All patients received periarticular local anesthetic infiltration and epidural/femoral nerve block infusion for 72 hours postoperatively. Group A received the TDB patch 5 mcg applied at the end of surgery. Group B received a combination of paracetamol and tramadol. All patients received intravenous diclofenac as rescue analgesia. Pain scores at rest, on movement, and side effects, if any, were compared over 7 days using the numerical rating scale score., RESULTS: Pain scores at rest and on movement were significantly lower in group A (P values .008 and .01). Rescue analgesia requirement was also significantly less in this group. Only one patient had clinically significant respiratory depression, and 3 patients had local erythema., CONCLUSION: Our data shows that the TDB patch is more efficacious in reducing postoperative pain after TKA surgery and can be safely used with fewer systemic side effects when compared to conventional analgesics.

Lee JH, Kim J-H, Kim J-H, et al. Efficacy and Safety of Transdermal Buprenorphine versus Oral Tramadol/Acetaminophen in Patients with Persistent Postoperative Pain after Spinal Surgery. *Pain research & management.* 2017;2017:2071494.

PURPOSE: Control of persistent pain following spinal surgery is an unmet clinical need. This study compared the efficacy and safety of buprenorphine transdermal system (BTDS) to oral tramadol/acetaminophen (TA) in Korean patients with persistent, moderate pain following spinal surgery., METHODS: Open-label, interventional, randomized multicenter study. Adults with persistent postoperative pain (Numeric Rating Scale [NRS] >= 4 at 14-90 days postsurgery) were enrolled. Patients received once-weekly BTDS (n = 47; 5 mug/h titrated to 20 mug/h) or twice-daily TA (n = 40; tramadol 37.5 mg/acetaminophen 325 mg, one tablet titrated to 4 tablets) for 6 weeks. The study compared pain reduction with BTDS versus TA at week 6. Quality of life (QoL), treatment satisfaction, medication compliance, and adverse events (AEs) were assessed., FINDINGS: At week 6, both groups reported significant pain reduction (mean NRS change: BTDS -2.02; TA -2.76, both $P < 0.0001$) and improved QoL (mean EQ-5D index change: BTDS 0.10; TA 0.19, both $P < 0.05$). The BTDS group achieved better medication compliance (97.8% versus 91.0%). Incidence of AEs (26.1% versus 20.0%) and adverse drug reactions (20.3% versus 16.9%) were comparable between groups., IMPLICATIONS: For patients with persistent pain following spinal surgery, BTDS is an alternative to TA for reducing pain and supports medication compliance. This trial is registered with Clinicaltrials.gov: NCT01983111.

Kim H-J, Ahn HS, Nam Y, Chang B-S, Lee C-K, Yeom JS. Comparative study of the efficacy of transdermal buprenorphine patches and prolonged-release tramadol tablets for postoperative pain control after spinal fusion surgery: a prospective, randomized controlled non-inferiority trial. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2017;26(11):2961-2968.

PURPOSE: To compare the efficacy of a transdermal buprenorphine patch (5, 10, 15, and 20 mug/h) with that of oral tramadol (150, 200, 250, and 300 mg) for postoperative pain control after single level spinal fusion surgery., METHODS: The present study (ClinicalTrials.gov, number NCT02416804) was a prospective, randomized controlled non-inferiority trial designed to determine the efficacy of buprenorphine TDS for alleviating postoperative pain following patient controlled analgesia (PCA) in persons underwent a single level posterior lumbar interbody fusion surgery through 1:1 allocation. The primary outcome was the Visual Analog Pain Scale (VAS) score for postoperative back pain at 7 days after surgery. The non-inferior margin of the VAS

was set at delta = 1.5 points., RESULTS: The VAS score (primary outcome) for postoperative back pain at 7 days after surgery in the Buprenorphine group was not inferior compared to the Tramadol group. The overall changes in VAS scores for postoperative pain during follow-up assessments over a 2-week period did not differ between both groups. However, the VAS scores for postoperative pain significantly improved with time after surgery in both groups. The patterns of changes in the VAS scores for postoperative pain during the follow-up period were not significantly different between the both groups., CONCLUSIONS: The efficacy of buprenorphine TDS was not inferior to that of oral tramadol medication for alleviating postoperative pain in the subacute period from 72 h after surgery, following PCA administration. In addition, adverse events were similar between both groups.

Desai SN, Badiger SV, Tokur SB, Naik PA. Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study. *Indian journal of anaesthesia.* 2017;61(3):225-229.

BACKGROUND: Transdermal buprenorphine, which is used in chronic pain management, has rarely been studied for use in acute pain management. The aim of this study was to compare the safety and efficacy of transdermal buprenorphine patch to oral tramadol for post-operative analgesia, following proximal femur surgeries., METHODOLOGY: Fifty adult patients undergoing surgery for hip fracture under spinal anaesthesia were included in this study. One group (Group TDB) received transdermal buprenorphine 10 mcg/h patch applied a day before the surgery and other group received oral tramadol 50 mg three times a day for analgesia (Group OT). They were allowed to take diclofenac and paracetamol tablets for rescue analgesia. Pain scores at rest, on movement, rescue analgesic requirement and side effects were compared between the groups over 7 days. Chi-square and independent sample t-test were used for categorical and continuous variables, respectively., RESULTS: Resting pain scores and pain on movement were significantly lower in TDB Group on all 7 days starting from 24 h post-operatively. Rescue analgesic requirement was significantly lower in TDB Group compared to OT Group. All the patients needed rescue analgesic in OT Group whereas 68% of the patients needed the same in TDB Group. Incidence of vomiting was less and satisfaction scores were much higher in TDB Group as compared to OT Group (79% vs. 66%, P < 0.001)., CONCLUSION: Transdermal buprenorphine can be safely used for post-operative analgesia and is more efficacious in reducing post-operative pain after 24 hours, with fewer side effects when compared to oral tramadol.

Appendix 4: Key Inclusion Criteria

Population	Patients with acute or chronic non-cancer pain
Intervention	Buprenorphine (sublingual, buccal, subcutaneous, transdermal formulations)
Comparator	Other opioids (including different buprenorphine formulations)
Outcomes	Pain, quality of life, function, discontinuation due to adverse events, serious adverse events including death, overdose, respiratory depression, abuse/misuse, or development of substance use disorder
Setting	Outpatient setting

Appendix 5: Proposed Prior Authorization Criteria

Long-acting Opioid Analgesics

Goals:

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

Length of Authorization:

- ~~Initial:~~ 90 days (except 12 months for end-of-life, sickle-cell disease, severe burn, or cancer-related pain)

~~Renewal: Up to 6 months~~

Covered Alternatives:

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

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain, or pain associated with sickle cell disease or severe burn injury are exempt from this PA.

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

Opioid	90 MME/day	Notes
Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	

Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

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

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

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
MS CONTIN	3 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day

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

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the patient being treated for pain associated with sickle cell disease, severe burn injury, cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes**: Approve for 12 months	**No**: Go to #3

3. Is the patient concurrently on other short- or long-acting opioids? Note: patients may receive a maximum of one opioid product regardless of formulation. There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness	**No**: Go to #4
4. Is the request for a patient already established on any opioid treatment for >6 weeks (long-term, chronic treatment)? Note: long-acting opioids are not recommended for initial treatment due to increased risk of death, overdose, and abuse. If trial of an opioid is necessary, short-acting opioids are recommended for initial treatment.	**Yes**: Go to #5 ~~**Renewal Criteria**~~	**No**: Pass to RPh. Deny; medical appropriateness.~~Go to #3~~
~~2. Is the diagnosis funded by the OHP?~~ ~~Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.~~	~~**Yes:** Go to #4~~	~~**No:** Pass to RPh. Deny; not funded by the OHP.~~ ~~Note: Management of opioid dependence is funded by the OHP.~~
~~3.~~5. ~~Is the requested medication a preferred agent?~~	~~**Yes:** Go to #6~~	~~**No:** Go to #5~~

4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
5.6. Is the patient being treated for pain associated with sickle cell disease, severe burn injury, cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #7
6. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
7. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
8. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past month that opioid prescribing is appropriate?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness

9. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #11
10. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
11.9. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
12. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #14 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

13.10. ~~Has the patient had a urinary drug screen (UDS) within the past 3 months to verify absence of illicit drugs and non-prescribed opioids?~~	~~**Yes:** Approve for up to 90 days.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Note: Management of opioid dependence is funded by the OHP.~~

Renewal Criteria		
~~What is the patient's diagnosis?~~	~~Record ICD10 code~~	
~~Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?~~	~~**Yes**: Go to #3~~	~~**No**: Go to **Approval Criteria**~~
5. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #~~4~~6
6. Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #~~5~~7 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #~~6~~8	**No:** Pass to RPh. Deny. Medical appropriateness
8. Has the patient had a urinary drug screen (UDS) in the past 1 year and verified absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #9~~7~~	**No:** Pass to RPh. Deny. Medical appropriateness

9. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline (e.g., prior to opioid use)? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #11~~9~~ Document tool used and score vs. baseline: _____	**No:** Go to #10~~8~~
10. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #11~~9~~	**No:** Pass to RPh. Deny. Medical appropriateness
11. Is the request for an increased cumulative dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #12~~0~~	**No:** Go to #15~~3~~
12. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13~~1~~
13. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14~~2~~
14. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #15~~3~~	**No:** Pass to RPh; deny; medical appropriateness

15. Is there recent reassessment (within the past 3 months) assessing risks and benefits of treatment, with documentation to support ongoing therapy? ~~Does the patient have any of the following risk factors for overdose?~~ ~~a. Concomitant CNS depressants (i.e., benzodiazepines, muscle relaxants, sedating antipsychotics, etc.)~~ ~~b. Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2~~ ~~c. Recent urine drug screen indicating illicit or non-prescribed opioids~~ ~~d. Concurrent short- and long-acting opioid use~~ ~~Diagnosis of oOpioid use disorder~~ ~~History of opioid overdose~~ ~~e.~~a. ~~Household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose~~	**Yes:** Go to #16 ~~Document number of risk factors~~	**No:** Pass to RPh. Deny; medical appropriateness
16. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #17~~5~~	**No:** Pass to RPh. Deny; medical appropriateness.

17. Does the patient have a pain contract on file with the prescriber?	**Yes:** Approve for 3 months~~d duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less):~~ ~~Risk factors:~~ ~~>=3: 2 month~~ ~~1-2: 4 months~~ ~~0: 6 months~~	**No:** Pass to RPh. Deny; medical appropriateness

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Prioritized-List.aspx
**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the following guidelines on opioid prescribing:

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

Selecting the optimal timing and approach to tapering depends on multiple factors. The decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations, allowing for pauses during the taper, and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:

a. Assess for substance use disorder and transition to appropriate medication assisted treatment if there is diversion or non-medical use,
b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
c. Slow taper for patients with no acute safety concerns. May consider starting with a taper of ≤10% of the original dose per month and assess the patient's functional and pain status at each visit.

4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
   a. Assess the patient behaviors that may be suggestive of a substance use disorder
   b. Address increased pain with use of non-opioid pharmacological and non-pharmacological options.
   c. Evaluate patient for mental health disorders.
   d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

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

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

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Drug Class Update: Select Biologics for Rare Conditions

Date of Review: February 2023

Date of Last Review: December 2021
Dates of Literature Search: 01/01/2021 – 10/21/2022

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

Plain Language Summary:

- This review looks at new evidence for specialized medicines (eculizumab, inebilizumab, satralizumab, ravulizumab, efgartigimod alfa and pegcetacoplan) used to treat 4 rare diseases. These medicines work in different ways to block triggers that cause the immune system to attack itself.
- The Food and Drug Administration has approved these medicines to treat specific conditions:
    - Eculizumab to treat myasthenia gravis, parxoysmal nocturnal hemoglobinura, atypical hemolytic uremic syndrome, and neuromyelitis optica spectrum disorder.
    - Inebilzuamb and satralizumab to treat neuromyelitis optica spectrum disorder.
    - Ravlizumab to treat adults and children with atypical hemolytic uremic syndrome, parxoysmal nocturnal hemoglboinura and myasthenia gravis.
    - Efgartigimod alfa to treat myasthenia gravis.
    - Pegcetacoplan to treat adults with paroxysmal nocturnal hemoglobinura.
- Myasthenia gravis is a long-term condition which causes certain eye, arm, leg, and lung muscles to become weak and tired. This affects people's vision and their ability to talk, swallow, breathe, and walk.
- Ravulizumab recently received approval to treat myasthenia gravis. The study lasted 26 weeks and 175 adults with myasthenia gravis were included in this study. At 26 weeks, patients treated with ravulizumab had more improvement in the ability to conduct "activities of daily living" (i.e., talk, chew, brush teeth, get up from a chair) than those who received no medicine.
- Paroxysmal nocturnal hemoglobinuria is a rare condition in which red blood cells are attacked by the body's immune system and fall apart. Red blood cells carry oxygen to tissues inside the body. When the red blood cells fall apart, the hemoglobin inside the cells is released. When there are not enough red blood cells, also known as anemia, people can feel tired, out of breath, and tend to bruise or bleed easily. People with this condition need to get frequent blood transfusions to relieve pain, fatigue, and shortness of breath.
- Atypical hemolytic uremic syndrome occurs when red blood cells break apart and blood clots form in the small blood vessels, which can lead to kidney damage, high blood pressure, and anemia. Children and adults are both affected by this condition.
- Neuromyelitis optica spectrum disorder occurs when the immune system attacks the nerves in the eyes and central nervous system. This can lead to the nerves of the eyes or the spinal cord becoming inflamed. Inflammation of the nerves of the eyes causes pain when moving the eyes and loss of vision. Spinal

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cord inflammation can happen to different parts of the spinal cord and may cause muscle spasms and weakness leading to back pain, leg pain and bladder or bowel dysfunction. These symptoms are most severe during an attack or relapse of neuromyelitis optica spectrum disorder.

- Providers must explain to the Oregon Health Authority why someone needs eculizumab, inebilizumab, satralizumab, ravulizumab, efgartigimod alfa or pegcetacoplan before Medicaid will pay for it. This process is called prior authorization.

Purpose for Class Update:

Review evidence for the complement inhibitor, ravulizumab, which was recently Food and Drug Administration (FDA) approved for treatment of generalized myasthenia gravis (gMG), and assess new evidence for other biologic immunosuppressive agents used to treat rare conditions including gMG, paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic-uremic syndrome (aHUS), and neuromyelitis optica spectrum disorder (NMOSD).

Research Questions:

- What is the comparative efficacy or effectiveness of biologic immunosuppressants indicated for treating gMG, PNH, aHUS, and NMOSD?
- What are the comparative harms of biologic immunosuppressants in patients with gMG, PNH, aHUS, and NMOSD?
- Are there certain sub-populations (based on age, gender, race, ethnicity, comorbidities, disease duration or severity) in which eculizumab, ravulizumab inebilizumab, pegcetacoplan, efgartigimod alfa, or satralizumab may be more effective or cause more harm?

Conclusions:

- Since the last review of this class, one Cochrane review evaluated the safety and efficacy of eculizumab and ravulizumab in people with aHUS.[1] Four new guidelines were also recently published, with recommendations for treatment of NMOSD with satralizamb,[2] use of ravulizumab for treatment of aHUS,[3] and use of ravulizumab or pegcetacoplan for management of people with PNH.[4,5]
- A March 2021 Cochrane systematic review evaluated the benefits and harms of 2 treatments for aHUS.[1] After 26 weeks of eculizumab therapy, a 70% reduction in the number of patients requiring dialysis and complete thrombotic macroangiopathic response was observed in 60% of treated patients (4 studies; n=100 adults and children).[1] After 26 weeks of ravulizumab therapy, complete thrombotic macroangiopathic response was observed in 54% of patients and a 59% reduction in the number of patients requiring dialysis (1 study; n=58 adults).[1] All studies had a high risk of bias. Serious adverse events (SAEs) occurred in 37% of patients who received eculizumab, and meningococcal infection occurred in 2 patients. Serious adverse events occurred in 52% of patients treated with ravulizumab and no meningococcal infections were reported in this study.[1] When compared with historical data, treatment with eculizumab or ravulizumab appears to offer favorable outcomes in patients with aHUS, based upon very low-quality evidence.[1] Longer term follow-up data are needed to better understand treatment duration, adverse outcomes and risk of disease recurrence associated with these 2 therapies.[1]
- There is insufficient evidence to base conclusions on the comparative safety and efficacy of biologic agents approved to treat NMOSD, gMG, aHUS and PNH specific to demographic characteristics, socioeconomic status, concomitant medications, severity of disease, or co-morbidities, for individuals with these rare conditions.
- In April 2021, the Canadian Agency for Drugs and Technologies in Health (CADTH) issued recommendations for the use of satralizumab in people with NMOSD who are anti-aquaporin-4 (AQP4) positive.[2] Patients must have had at least 1 relapse of NMOSD in the 12 months before initiation despite an adequate trial of other accessible preventive treatments for NMOSD, or the patient cannot tolerate other preventive treatments for NMOSD (i.e., azathioprine, mycophenolate, rituximab).[2]
- In June 2021, the National Institute for Health and Care Excellence (NICE) published guidance for the use of ravulizumab as an option for treating aHUS in people weighing 10 kg or more or more who have not received a complement inhibitor before or who have responded to 3 months of eculizumab.[3]

- In March 2022, CADTH published recommendations for the use of ravulizumab in patients with PNH.[4] Only patients with adequate treatment response to eculizumab are eligible to switch directly to ravulizumab.[4]
- In March 2022, NICE issued guidance for the use of pegcetacoplan as an option for treating PNH. Adults who continue to have anemia after at least 3 months of treatment with a C5 inhibitor (i.e, eculizumab, ravulizumab) are eligible to switch to pegcetacoplan.[5]
- In April 2022, ravulizumab (ULTOMIRIS) received expanded FDA-approval for treatment of adult patients with anti-acetylcholine receptor (AChR) antibody positive gMG.[6]
- A new subcutaneous (SC) formulation of ravulizumab was approved in July 2022 for use in adults with PNH and aHUS after efficacy was demonstrated in adults weighing more than 40 kg with PNH.[6]

Recommendations:
- Recently published clinical evidence does not support any changes to the Preferred Drug List (PDL).
- Revise clinical prior authorization (PA) criteria for ravulizumab to include use in adults with generalized MG who are anti-AChR antibody positive and update dosing guidance for use in MG. Add SC dosing recommendations for adults with PNH and aHUS to ravulizumab PA criteria.
- Evaluate costs in the executive session.

Summary of Prior Reviews and Current Policy:
- In April 2021, the Pharmacy and Therapeutics (P&T) Committee reviewed evidence for eculizumab, inebilizumab, and satralizumab, which had received FDA approval for the treatment adults with NMOSD. The committee approved recommendations to: 1) create a new class of drugs on the PDL entitled "Biologics for Rare Diseases" and include eculizumab, inebilizumab, satralizumab in this new class; 2) implement clinical PA criteria for each monoclonal antibody to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (OHP); and 3) make eculizumab non-preferred and to add satralizumab and inebilizumab to the PDL.
- At the same April meeting, the evidence for the use eculizumab of in treating PNH, aHUS and gMG was reviewed and ravulizumab for PNH and aHUS in adults was reviewed. The P&T Committee approved to add ravulizumab to the "Biologics for Rare Diseases" drug class as a non-preferred agent with clinical PA criteria to ensure safe and appropriate use.
- In December 2021, the P&T Committee reviewed pegcetacoplan for treatment of adults with PNH. The Committee approved to add pegcetacoplan to the "Biologics for Rare Diseases" drug class with clinical PA criteria to ensure appropriate use and maintain pegcetacoplan as non-preferred. In addition, clinical PA criteria for ravulizumab were revised to reflect the expanded indication for use in pediatric patients aged 1 month and older with PNH or aHUS.
- In April 2022, the P&T Committee reviewed efgartigimod for treatment of gMG. The Committee approved to maintain efgartigimod as non-preferred in the "Biologics for Rare Diseases" drug class with clinical PA criteria to ensure safe and appropriate use.
- For the class of "Biologics for Rare Diseases" ravulizumab, inebilizumab, and satralizumab are preferred on the PDL (**Appendix 1)**, and all the other agents are non-preferred. All medications in this class require PA (**Appendix 3**).

Background:
Eculizumab is FDA-approved for 4 indications including: 1) reducing hemolysis in patients with PNH; 2) inhibiting complement-mediated thrombotic microangiopathy in patients with aHUS; 3) treatment of adults with anti-AChR antibody positive gMG; and 4) treatment of adults with anti-AQP4 antibody positive NMOSD.[7] Inebilizumab and satralizumab are FDA-approved for the treatment of adults with anti-AQP4 antibody positive NMOSD.[8,9] Pegcetacoplan is FDA-approved for treatment of adults with PNH.[10] Ravulizumab, a C5 complement inhibitor engineered from eculizumab, is FDA-approved for treatment of PNH

and aHUS, and was recently approved for treatment of gMG.[6] Efgartigimod is approved for treatment of adults with anti-AChR antibody positive gMG.[11] A summary of these medications, their mechanism of action, and their FDA-approved indications is presented in **Table 1**.

Table 1. FDA Indications of Biologics for Rare Diseases in Adults (Unless Otherwise Noted)[12]

Medication	Mechanism of Action	aHUS	gMG (ANTI-AChR antibody positive)	PNH	NMOSD (anti-AQP4 antibody positive)
Eculizumab (SOLIRIS)	C5 complement inhibitor	X	X	X	X
Efgartigimod alfa (VYVGART)	Neonatal Fc receptor blocker		X		
Inebilizumab (UPLINZA)	CD19 inhibitor (B-cell surface antigen)				X
Pegcetacoplan (EMPAVELI)	C3 complement inhibitor			X	
Ravulizumab (ULTOMIRIS)	C5 complement inhibitor	X (Patients 1 month of age and older)	X	X (Patients 1 month of age and older)	
Satralizumab (ENSPRYNG)	IL-6 inhibitor				X

Abbreviations: aHUS=atypical hemolytic uremic syndrome; AChR=acetylcholine receptor; AQP4=aquaporin-4; Fc=crystallizable fragment; FDA=Food and Drug Administration; gMG=generalized myasthenia gravis; IL=interleukin; NMOSD=neuromyelitis optica spectrum disorder; PNH=paroxysmal nocturnal hemoglobinuria

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder in which antibodies to acetylcholine receptors bind at the post-synaptic neuromuscular junction of skeletal muscles.[13] The thymus gland is thought to produce the anti-AChR antibodies which disrupt neuromuscular transmission.[13] The estimated prevalence of MG is 14 to 20 cases per 100,000 people, or approximately 36,000 to 60,000 cases in the United States.[13,14] Myasthenia gravis occurs at any age, but there tends to be a bimodal distribution to the age of onset, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance).[13] Myasthenia gravis presentation can be broadly classified as ocular or generalized MG. It characteristically presents with muscle weakness that worsens with repeated use (fatigable weakness), often initially involving the ocular muscles and manifesting as intermittent ptosis and diplopia.[15] Ultimately, the disease generalizes throughout the body in two-thirds of patients, leading to weakness of bulbar, neck, limb, and respiratory muscles.[15] In the most common type of MG, autoantibodies are produced that target the AChR, reducing the number of functional AChRs, and causing morphological damage to the endplate membrane, resulting in the clinical phenotype of fatigable muscle weakness.[16] Approximately 85% of people with MG test positive for AChR antibodies.[17] In AChR antibody-positive MG, the production of autoantibodies by pathogenic B cells is T cell-dependent.[16]

The Myasthenia Gravis Activities of Daily Living (MG-ADL) is a patient-reported, physician administered scoring tool.[18] Eight domains (talking, chewing, swallowing, breathing, ability to brush teeth, ability to arise from chair, vision and eyelid droop) are scored on a scale of 0 (normal) to 3 (severe).[18] A total score of 24 is possible; higher scores indicate more disability.[19] A 2-point reduction in the MG-ADL score is considered meaningful clinical improvement.[18] The Quantitative Myasthenia Gravis (QMG) score is a validated 13-item disease-severity physician-reported assessment tool.[20] This tool evaluates muscle strength based on quantitative testing of sentinel muscle groups: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item).[20] The scores are not weighted, but each item is graded on a scale of 0 (no weakness) to 3 (severe weakness).[20] Total scores range from 0 to 39, higher scores represent greater disease burden.[20] A 3-point reduction in QMG total score considered clinically meaningful improvement.[21]

Novel biological agents offer selective, target-specific immunotherapy for MG refractory to initial therapy with anticholinesterase inhibitors (i.e., pyridostigmine) or systemic corticosteroids.[14] Complement inhibitors, anti-interleukin antibodies, and B-cell inhibitors are some of the immunomodulators currently being evaluated in clinical trials for MG treatment.[14] Neonatal Fc receptor inhibitors prevent immunoglobulin recycling and cause rapid reduction in pathogenic antibody levels.[22] In October 2019, the Myasthenia Gravis Foundation of America (MGFA) appointed a task force to update treatment guidance for MG.[23] The MGFA guidance recommends eculizumab be considered in the treatment of severe, refractory, anti-AchR antibody-positive gMG.[23] Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies (i.e., ravlizumab, efgartigimod) have been unsuccessful in meeting treatment goals.[23] The 3 FDA-approved biologic treatments for adults with gMG who are anti-AChR antibody-positive are presented in **Table 2**.

Table 2. FDA-Approved Biologic Treatments for Adults with Generalized Myasthenia Gravis[6,7,11]

	Eculizumab (SOLIRIS)	**Ravulizumab (ULTOMIRIS)**	**Efgartigimod Alfa (VYVGART)**
Administration Route	Intravenous Infusion	Intravenous Infusion	Intravenous Infusion
Recommended Dose	-Loading Dose: 900 mg at weeks 0, 1, 2, 3 and 1200 mg at week 4 -Maintenance Dose: 1,200 mg every 2 weeks	-Loading Dose: 2,400 mg to 3,000 mg per weight-based recommendations as a single dose -Maintenance Dose: 3,000 mg to 3,600 mg per weight-based recommendations every 8 weeks 2 weeks after the loading dose.	10 mg/kg (maximum dose 1.2 g) once weekly for 4 weeks. Subsequent treatment cycles may be administered based on clinical evaluation and no sooner than 50 days from the start of the previous treatment cycle.
Primary Binding Target	Complement Protein C5		Neonatal Fc Receptor
Contraindications	-Unresolved *Neisseria meningitides* infection -Not vaccinated against *Neisseria meningitides*		-Immunization with live vaccines during treatment
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections		None
Abbreviations: Fc = crystallizable fragment; g = grams; kg = kilograms; mg = milligrams; REMS = Risk Evaluation and Mitigation Strategies			

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare, complement-mediated hemolytic anemia, with occurrence estimated as high as 15.9 individuals per million worldwide.[24] This condition presents with a variety of symptoms, the most prevalent of which are aplastic anemia, hemoglobinuria, fatigue and shortness of breath.[25] Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, bone marrow failure.[25] The rarity of the disease and nonspecific symptoms can result in significant delays in diagnosis.[25] The condition is genetic, with the mutations occurring on the X-linked gene.[25] This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA) produces a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes.[25] A chronic state of hemolysis ensues and can be exacerbated if the

complement system is activated by stress due to surgery, trauma, or other triggers for inflammation.[25] Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in LDH levels are common in classic PNH.[26] Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classic PNH and are a direct consequence of intravascular hemolysis and the release of free hemoglobin.[26]

Complement inhibitor treatment can relieve PNH-associated symptoms, eliminate transfusion dependence, prevent thrombosis, and relieve pain, but it does not mitigate aplastic anemia. Allogeneic hematopoietic stem cell transplantation is the only curative treatment for PNH.[27] Pegcetacoplan can inhibit both intravascular and extravascular hemolysis; by contrast, ravulizumab and eculizumab target C5, which affects only intravascular hemolysis. National Institute for Health and Care Excellence guidance from 2021 recommends ravulizumab as an option for treating PNH in adults when hemolysis and clinical symptoms suggest high disease activity or disease is clinically stable after eculizumab treatment for at least 6 months.[28] A comparison of the 3 FDA-approved biologic agents to treat PNH is presented in **Table 3**.

Table 3. FDA-Approved Biologic Treatments for Paroxysmal Nocturnal Hemoglobinuria[6,7,10]

	Eculizumab (SOLIRIS)	**Ravulizumab (ULTOMIRIS)**	**Pegcetacoplan (EMPAVELI)**
Administration Route	Intravenous	Intravenous or Subcutaneous	Subcutaneous
Approved Age Range	Adults	Adults and pediatric patients 1 month of age and older	Adults
Recommended Dose	-Loading Dose: 600 mg at weeks 0, 1, 2, 3 and 900 mg at week 4 -Maintenance Dose: 900 mg every 2 weeks	<u>Adult</u> -Loading Dose: • 2,400 mg to 3,000 mg IV single dose per weight-based recommendations -Maintenance Dose: • 3,000 mg to 3,600 mg IV every 8 weeks per weight-based recommendations OR • 490 mg SC once a week starting 2 weeks after IV loading dose. Must weigh ≥ 40 kg <u>Pediatric</u> -Loading Dose: • 600 mg to 1,200 mg IV single dose per weight-based recommendations -Maintenance Dose: • 300 mg to 2,700 mg IV every 4 to 8 weeks per weight-based recommendations	1,080 mg SC twice weekly
Primary Binding Target	Complement Protein C5		Complement Protein C3
Contraindications	-Unresolved *Neisseria meningitides* infection -Not vaccinated against *Neisseria meningitides*		-Unresolved serious infection caused by encapsulated bacteria -Not vaccinated against encapsulated bacteria

Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections	Mandatory REMS program due risk of life-threatening and fatal meningococcal infections and infections caused by encapsulated bacteria (i.e., *S. pneumoniae and H. influenzae*)
Abbreviations: IV = intravenous; REMS = Risk Evaluation and Mitigation Strategies; SC = subcutaneous		

Atypical Hemolytic-Uremic Syndrome

Atypical HUS can present at any age and is of acute onset in 20% of cases.[29] Approximately 35% to 42% of cases occur in children under the age of 18 years.[30] The clinical presentation depends upon the extent of microvascular injury and thrombosis, as well as ischemic injury to various organ systems.[29] Patients with aHUS present with hemolytic anemia, thrombocytopenia and impaired renal function. Renal impairment is frequent; the most common manifestations are proteinuria, hematuria, hypertension, and azotemia.[29] A majority of patients require chronic renal replacement therapy.[29] Hypertension is often moderate to severe, due to vascular disease and volume expansion.[29] Atypical HUS presents as a systemic disease, and extra-renal features are seen in 20% and a catastrophic presentation with multi-organ involvement in 5% of patients.[29]

This uncommon disorder is caused by a genetic abnormality in the complement alternative pathway resulting in over-activation of the complement system and formation of microvascular thrombi.[29] Abnormalities of the complement pathway may be in the form of mutations in key complement genes or autoantibodies against specific complement factors. By preventing membrane attack complex formation, eculizumab and ravulizumab inhibit the mechanism by which aHUS causes pathology, making these drugs effective treatments for people with aHUS.[29] Eculizumab is approved for treatment of aHUS in pediatric and adult patients.[7] Eculizumab dosing for aHUS in adults begins with a 900 mg loading dose every week for 4 weeks, followed by 1,200 mg for the fifth dose, and then 1,200 mg every 2 weeks thereafter.[7] Dosing for children weighing more than 5 kg is weight-based for induction and maintenance dosing.[7] Ravulizumab is approved for treatment of aHUS in adults and pediatric patients 1 month of age and older. Intravenous dosing of ravulizumab in patients with aHUS is the same as the recommended PNH dosing (**Table 3**). Subcutaneous dosing of ravulizumab is not approved for use in pediatric patients.[6]

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder is a rare, autoimmune, severe demyelinating disease of the CNS that predominantly involves inflammation of the optic nerve and spinal cord.[31] The pathogenesis is unknown, but it appears to be related to B-cell autoimmunity directed against aquaporin-4, the dominant water channel in the central nervous system.[31] Features of NMOSD include acute attacks of rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course.[31] Neuromyelitis optica had long been considered a subtype of multiple sclerosis (MS) due to the similarities between the clinical presentations of MS and NMOSD.[32] However, recent evidence indicates NMOSD is usually associated with a specific biomarker, AQP4-immunoglobulin-G (IgG) antibody, which differentiates NMOSD from MS.[33] The prevalence of NMOSD is estimated at around 0.1 to 10 persons per 100,000 individuals, affecting approximately 15,000 individuals in the United States.[33] A 2019 to 2020 review of medical claims in the Oregon Medicaid population shows approximately 0.4 persons per 100,000 individuals have a diagnosis of NMOSD. The reported incidence of NMOSD in women is up to 10 times higher than in men.[34] It is difficult to determine exact prevalence rates as many NMOSD cases are never diagnosed and many others are misdiagnosed as MS.[32]

The EDSS score is a quantitative measure of disability based on a standard neurological examination.[2] Validity of this tool has been established in patients with MS, but not NMOSD.[2] The EDSS is an ordinal scale that ranges from 0 points (normal exam) to 10 points (death) that increases in half-points increments once an

EDSS of 1.0 has been reached.[2] An EDSS score of 1.0 to 4.5 refers to people who are fully ambulatory, with scores of 5.0 to 9.5 defined as impaired ambulation.[2] No minimal clinically important difference (MCID) has been defined for patients for NMOSD. In patients with MS with a baseline EDSS score of 1 to 5.5, the MICID is an increase of 1.0 points. When the baseline EDSS score is 6 or greater, a 0.5 increase in EDSS score is considered clinically important.[2] The 3 FDA-approved biologics for adults with NMOSD who are anti-AQP4 antibody positive are presented in **Table 4**.

Table 4. FDA-Approved Treatments for Adults with Neuromyelitis Optica Spectrum Disorder[7-9]

	Eculizumab (SOLIRIS)	**Inebilizumab-cdon (UPLIZNA)**	**Satralizumab-mwge (ENSPRYNG)**
Administration Route	Intravenous	Intravenous	Subcutaneous
Recommended Dose	-Loading Dose: 900 mg at weeks 0, 1, 2, 3 and 1200 mg at week 4 -Maintenance Dose: 1200 mg every 2 weeks	-Loading Dose: 300 mg at weeks 0, 2 -Maintenance Dose: 300 mg every 6 months	-Loading Dose: 120 mg at weeks 0, 2, 4 -Maintenance Dose: 120 mg every 4 weeks
Primary Binding Target	Complement Protein C5	CD19 on B cells	IL-6 Receptor
Contraindications	-Unresolved *Neisseria meningitides* infection -Not vaccinated against *Neisseria meningitides*	-Active Hepatitis B infection -Active or Untreated Tuberculosis	
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections	None	
Abbreviations: IL=interleukin; mg=milligram; REMS = Risk Evaluation and Mitigation Strategies			

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 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.

New Systematic Reviews:

Cochrane: Interventions for Atypical Hemolytic Uremic Syndrome

A March 2021 Cochrane systematic review evaluated the benefits and harms of 2 biologic treatments for aHUS.[1] Literature was searched through September 2020 for all RCTs and non-randomized clinical trials.[1] Given the rare incidence of aHUS, prospective single-arm studies were also included in the review.[1] Five single-arm studies which evaluated terminal complement inhibition for the treatment of aHUS met inclusion critieria.[1] All patients had evidence of renal impairment, thrombocytopenia and hemolysis (LDH above the upper limit of normal).[1] Four studies evaluated eculizumab in children and adults (n=100) and one study evaluated ravulizumab in adults (n=58).[1] All included studies were of non-randomized, single-arm design with a high risk of bias.[1]

In the eculizuamb studies, 37/100 patients were undergoing dialysis at the initiation of eculizuamab therapy.[1] Of these patients, 26 discontinued regular dialysis after 26 weeks of eculizumab treatment which represents a 70% reduction in the number of patients requiring dialysis.[1] In the ravulizuamb study, dialysis was discontinued in 17/29 (59%) of patients who required dialysis at baseline.[1] Complete thrombotic macroangiopathic response was achieved in 60% of patients at 26 weeks and 65% of patients at two years after treatment with eculizumab.[1] After 26 weeks of ravulizumab therapy, complete thrombotic macroangiopathic response was achieved in 54% of patients and a 59% reduction in the number of patients requiring dialysis was observed.[1] Substantial improvements were seen in estimated glomerular filtration rate and health-related quality of life in both eculizumab and ravulizumab studies.[1] However, it is challenging to draw firm conclusions from this low-quality evidence.[1]

Serious adverse events occurred in 37% of patients treated with eculizumab. The types of SAEs were not[35] reported. The most commonly reported adverse events (AEs) included diarrhea (23%), fever (21%), headache (19%), upper respiratory tract infection (19%), cough (17%) and urinary tract infection (10%).[1] Meningococcal infection occurred in 2 patients (2%) treated with eculizumab.[1] Both patients had received meningococcal vaccination against serogroups A, C, W, and Y but had not been prescribed long-term antibiotics.[1] Serious adverse events occurred in 52% of patients treated with ravlizumab.[1] The most commonly reported SAEs with ravulizumab included malignant hypertension (3%) and infections including pneumonia (5%), and septic shock (3%).[1] The most commonly reported AEs included headache (36%), diarrhea (31%), vomiting (26), hypertension (22%), nausea (22%) and urinary tract infection (17%).[1] No patients treated with ravulizumab developed meningococcal infection.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria),[35] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[36-38]

New Guidelines:

Canadian Agency for Drugs and Technologies in Health: Satralizumab for Treating Neuromyelitis Optica Spectrum Disorder

In April 2021, CADTH issued recommendations for the use of satralizumab in NMOSD.[2] Evidence from 2 RCTs demonstrated that satralizumab, alone or in combination with immunosuppressants (i.e., corticosteroids, azathioprine, or mycophenolate), reduced the frequency of NMOSD relapses compared with placebo.[2] Only two-thirds of patients enrolled in these RCTs were AQP4 antibody-positive.[2] The trials did not report health-related quality of life or disability outcomes for the AQP4 antibody–positive subgroup.[2] Direct comparative efficacy and harms data for satralizumab versus immunosuppressants, eculizumab, or rituximab are presently unavailable.[2]

- CADTH Recommendation: Satralizumab should only be covered to treat patients who have NMOSD that is AQP4 positive.[2] Patients must have had at least 1 relapse of NMOSD in the 12 months before initiation despite an adequate trial of other accessible preventive treatments for NMOSD, or the patient cannot tolerate other preventive treatments for NMOSD (i.e., azathioprine, mycophenolate, rituximab). Patients must have an EDSS score of 6.5 points or less to begin treatment, as this was required in the 2 RCTs that showed improvement in reducing NMOSD replapses with satralizumab.[2]

National Institute for Health and Care Excellence: Ravulizumab for Treating Atypical Hemolytic Uremic Syndrome

In June 2021, NICE published guidance for the use of ravulizumab in treating aHUS in people weighing 10 kg or more.[3] Clinical trial evidence suggests that ravulizumab is effective for treating aHUS, but ravulizumab has not been compared directly with eculizumab.[3] The results of indirect comparisons are uncertain, but it is likely that ravulizumab and eculizumab are equally effective because they both inhibit complement C5.[3] Because ravulizumab is administered less frequently than eculizumab (every 8 weeks versus every 2 weeks) it may improve quality of life and access to care.[3] Ravulizumab costs less than eculizumab and the cost-effectiveness estimates are within what NICE normally considers an acceptable use of National Health Service (NHS) resources.[3]

- NICE Recommendation: Ravulizumab is an option for treating aHUS in people weighing 10 kg or more who have not a complement inhibitor before or whose disease has responded to 3 months of eculizumab treatment.[3]

Canadian Agency for Drugs and Technologies in Health: Ravulizumab for Treating Paroxysmal Nocturnal Hemoglobinuria

In March 2022, CADTH published recommendations for the use of ravulizumab for PNH treatment.[4] Evidence from 2 open-label, active-controlled, noninferiority RCTs in adults with PNH showed that ravulizumab had a similar benefit as eculizumab in controlling hemolysis within blood vessels and removing the need for blood transfusions.[4] Although IV infusions of ravulizumab are less frequent than for eculizumab, there was not enough evidence to show that health-related quality of life is better with ravulizumab than with eculizumab due to the lack statistical testing for health-related quality of quality of life outcomes and the open-level study design of both studies.[4] There is no evidence to suggest ravulizumab is more effective than eculizumab in treating PNH.[4] There is insufficient evidence to demonstrate that patients who do not respond or lose response to treatment with eculizumab will benefit from ravulizumab treatment.[4]

- CADTH Recommendation: Only patients already receiving eculizumab treatment with adequate treatment response should be eligible to directly switch to ravulizumab treatment.[4]

National Institute for Health and Care Excellence: Pegcetacoplan for Treating Paroxysmal Nocturnal Hemoglobinuria

In March 2022, NICE issued guidance for the use of pegcetacoplan in treating adults with PNH.[5] Current treatments for PNH include C5 inhibitors such as eculizumab and ravulizumab. Some people still experience anemia and symptoms of PNH while receiving these treatments.[5] Clinical trial evidence suggests that pegcetacoplan improves hemoglobin levels and hematological symptoms of PNH for people who have anemia while taking eculizumab.[5] Pegcetacoplan is likely to have the same clinical benefits for people who have anemia while taking ravulizumab, because ravulizumab is very similar to eculizumab.[5]

- NICE Recommendation: Adults who continue to have anemia after at least 3 months of treatment with a C5 inhibitor (i.e, eculizumab, ravulizumab) are eligible to switch to pegcetacoplan.[5]

New Formulations and Indications:

In April 2022, ravulizumab (ULTOMIRIS) received expanded FDA approval for treatment of adult patients with generalized MG who are AchR antibody-positive.[6] In a double-blind, placebo-controlled, phase 3 RCT (CHAMPION-MG) of 175 adults with AChR antibody-positive MG, participants received ravulizumab infusions per protocol every 8 weeks after initial loading doses or placebo for 26 weeks.[39] Ravulizumab loading doses (2400, 2700, or 3000 mg) and maintenance doses (3000, 3300, or 3600 mg) were weight-based.[39] At baseline, patients had mild to moderate symptoms (median MG-ADL score 9) and most were taking glucocorticoids or other immunosuppressants.[39] The primary endpoint was change from baseline in MG-ADL total score, a patient-reported scale that assesses the ability to perform daily activities.[39] At 26 weeks, patients treated with ravulizumab had greater improvements in the MG-ADL score than those assigned to placebo (least squares mean reduction -3.1 versus -1.4, respectively; treatment difference, -1.6; $p < 0.001$).[39] Five-point improvement in the Quantitative Myasthenia Gravis score at 26 weeks (a secondary endpoint) was also greater in ravulizumab-treated adults compared with placebo (30.0% vs. 11.3%; $p=0.005$).[39] In additional secondary endpoints, improvements in quality of life and extent of fatigue, no differences between ravulizumab and placebo were observed.[39] The rate of AEs was similar between groups and the most frequently reported AEs were headache, diarrhea, and nausea.[39] On the basis of these results, ravulizumab was approved by the FDA for use in AChR antibody-positive patients with generalized MG.[6]

A new subcutaneous (SC) formulation of ravulizumab was approved in July 2022 for adults with PNH and aHUS.[6] The SC route of ravulizumab administration was studied in adults weighing more than 40 kg with PNH.[40] Subcutaneous ravulizumab was assessed in a multi-center, randomized, open-label, Phase 3 study (ALXN1210-PNH-303) conducted in 136 adult patients with PNH who were clinically stable after having been treated with eculizumab for at least 3 months prior to study entry.[40] Patients were randomized 2:1 to receive SC dosing for the entire study period (3 years) or initiation with IV ravulizumab for 10 weeks followed

by SC dosing for the rest of the study.[40] The primary endpoint was serum ravulizumab trough concentration at day 71.[40] Noninferiority was determined between IV and SC dosing regimens of ravulizumab. The FDA-approved SC dosing regimen of ravulizumab is 490 mg once a week administered via an on-body delivery system over 20 minutes.[6] The complete dose requires 2 pre-filled cartridges of 245 mg each.[6] The prescribing information provides instructions for switching from SC to IV administration of ravulizumab (or vice versa) or initiating ravulizumab after being treated with eculizumab.[6] The most frequently reported AEs in the adults with PNH who received SC ravulizumab included local injection site reactions (27%) diarrhea (13%) and headache (13%).[6]

New FDA Safety Alerts:

Table 4. 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)
Ravulizumab	ULTOMIRIS	4/2022	Warnings and Precautions	Infusion-Related Reactions[6] In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures. Adverse Reactions[6] The safety of ULTOMIRIS has been evaluated in 175 adult patients with generalized MG, including 169 patients who received at least one dose of ULTOMIRIS, 142 patients who were exposed for at least 6 months, and 95 who were exposed for at least 12 months. In a randomized, double-blind, placebo-controlled trial (ALXN1210-MG-306), the most frequent AEs (≥10%) with ULTOMIRIS were diarrhea and upper respiratory tract infection. Serious adverse reactions were reported in 20 (23%) patients with generalized MG receiving ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent SAEs were infections reported in at least 8 (9%) patients treated with ULTOMIRIS and in 4 (4%) patients treated with placebo. Of these infections, one fatal case of COVID-19 pneumonia was identified in a patient treated with ULTOMIRIS and one case of infection led to discontinuation of ULTOMIRIS.

Randomized Controlled Trials:

A total of 87 citations were manually reviewed from the initial literature search. After further review, 867 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).

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8. UPLINZA (inebilizumab-cdon) Intravenous Injection Prescribing Information. Gaithersburg, MD; Viela Bio, Inc. June 2020.
9. ENSPRYNG (satralizumab) Subcutaneous Injection Prescribing Information. South San Francisco, CA; Genentech USA, Inc. August 2020.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
inebilizumab-cdon	UPLIZNA	VIAL	Y
ravulizumab-cwvz	ULTOMIRIS	VIAL	Y
satralizumab-mwge	ENSPRYNG	SYRINGE	Y
eculizumab	SOLIRIS	VIAL	N
efgartigimod alfa-fcab	VYVGART	VIAL	N
pegcetacoplan	EMPAVELI	VIAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to October Week 4 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 26, 2022

1	exp Hemoglobinuria, Paroxysmal/	1995
2	exp Atypical Hemolytic Uremic Syndrome/	958
3	exp Myasthenia Gravis/	8139
4	eculizumab.mp.	1913
5	ravulizumab.mp.	77
6	Complement C3/ or pegcetacoplan.mp.	5113
7	efgartigimod.mp.	35
8	1 or 2 or 3	11049
9	4 or 5 or 6 or 7	6930
10	8 and 9	1081
11	limit 10 to (english language and humans and yr="2021 -Current")	190
12	limit 11 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	32

Ovid MEDLINE(R) 1996 to October Week 3 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 26, 2022

1	exp Neuromyelitis Optica/	3873
2	inebilizumab.mp.	61
3	eculizumab.mp.	1915
4	satralizumab.mp.	52
5	2 or 3 or 4	1966
6	1 and 5	103
7	limit 6 to (english language and humans and yr="2021 -Current")	55

Inebilizumab-cdon (UPLIZNA)

Goal(s):
- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:
Up to 12 months

Requires PA:
- Inebilizumab-cdon (UPLIZNA) pharmacy and physician administered 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 this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
~~2.~~3. Is the diagnosis funded by OHP?	**Yes:** Go to #~~5~~6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4~~Pass to RPh. Deny; not funded by the OHP.~~

Approval Criteria		
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
~~3.~~5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 6~~4~~
~~4.~~6. Is the request for Neuromyelitis Optica Spectrum Disorder in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	**Yes:** Go to #7~~5~~	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~7. Has the patient been screened for Hepatitis B and tuberculosis infection before starting treatment?	**Yes:** Go to #8~~6~~	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~8. Does the patient have active Hepatitis B or untreated latent tuberculosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 4/21
Implementation: 5/1/21

Ravulizumab (ULTOMIRIS)

Goal(s):
- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:
- Up to 12 months

Requires PA:
- Ravulizumab (ULTOMIRIS) pharmacy and physician administered 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 this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
~~2.~~3. Is the diagnosis funded by OHP?	**Yes:** Go to #5~~3~~	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4~~Pass to RPh. Deny; medical appropriateness~~
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
~~3.~~5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 6~~4~~
~~4.~~6. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2-week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #7~~5~~	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis for a patient with one of the following indications: • at least 1 month of age or older and weighs at least 5 kg with atypical Hemolytic Uremic Syndrome (aHUS) or Paroxysmal Nocturnal Hemoglobinuria (PNH) or • an adult with generalized myasthenia gravis (gMG) who is anti-acetylcholine receptor (AchR) antibody positive? Note: Ravulizumab is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).	**Yes:** Go to #8~~6~~	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~8. Is the request for intravenous dosing?	**Yes:** Go to # 9~~7~~	**No:** Go to # 10~~8~~
9. ~~7.~~ Does the requested intravenous dosing align with the FDA- approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~7.~~10. Is the request for subcutaneous (SC) administration of ravlizumab 490 mg SC once a week in an adult weighing 40 kg or greater with PNH or aHUS? Note: Subcutaneous administration of ravulizumab is not approved for use in pediatric patients.	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness ~~Note: Subcutaneous administration of ravulizumab is not approved for use in pediatric patients.~~

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Intravenous Weight-based Infusion Dosing for Ravulizumab in Adults and Pediatric Patients aged 1 month and older with PNH, aHUS, or gMG[1]

Body Weight	Indications	Loading Dose	Maintenance Dose (begins 2 weeks after loading dose)
5 to 9 kg	aHUS and PNH	600 mg	300 mg every 4 weeks
10 to 19 kg	aHUS and PNH	600 mg	600 mg every 4 weeks
20 to 29 kg	aHUS and PNH	900 mg	2,100 mg every 8 weeks
30 to 39 kg	aHUS and PNH	1,200 mg	2,700 mg every 8 weeks
40 to 59 kg	aHUS, gMG, and PNH	2,400 mg	3,000 mg every 8 weeks
60 to 99 kg	aHUS, gMG, and PNH	2,700 mg	3,300 mg every 8 weeks
100 kg or greater	aHUS, gMG, and PNH	3,000 mg	3,600 mg every 8 weeks
Abbreviations: aHUS = atypical hemolytic uremic syndrome; gMG = generalized myasthenia gravis; PNH = paroxysmal nocturnal hemoglobinuria			

1. ULTOMIRIS (Ravulizumab-cwvz) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals Inc. 7/2022.

Eculizumab (SOLIRIS)

Goal(s):
- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:
- Up to 12 months

Requires PA:
- Eculizumab (SOLIRIS) pharmacy and physician administered 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 this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~2.~~3. Is the diagnosis funded by OHP?	**Yes:** Go to #~~5~~3	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4~~Pass to RPh. Deny; not funded by the OHP.~~
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
~~3.~~5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #64
~~4.~~6. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2-week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #7~~5~~	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~5.~~7. Is the diagnosis one of the following: • Neuromyelitis Optica Spectrum Disorder in an adult who is anti-aquaporin-4 (AQP4) antibody positive, • Paroxysmal Nocturnal Hemoglobinuria (PNH), • atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	**Yes:** Go to #~~86~~	**No:** Go to #~~97~~
~~6.~~8. Does the requested dosing align with FDA-approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
~~7.~~9. Is the request for a diagnosis of myasthenia gravis in an adult patient who is Acytelcholine Receptor (AChR) antibody-positive?	**Yes:** Go to # ~~108~~	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~10. Has the patient tried: • at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR • at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?	**Yes:** Go to #~~119~~	**No:** Pass to RPh. Deny; medical appropriateness
~~9.~~11. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Eculizumab[1]

	Eculizumab		
FDA-approved Indications	• Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody • Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) • Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) • Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody positive		
Recommended NMOSD dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended PNH dose in patients 18 yo and older	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter		
Recommended aHUS dose in patients less than 18 yo	**Body Weight** 5 kg to 9 kg 10 kg to 19 kg 20 kg to 29 kg 30 kg to 39 kg ≥ 40 kg	**Induction Dose** 300 mg weekly x 1 dose 600 mg weekly x 1 dose 600 mg weekly x 2 doses 600 mg weekly x 2 doses 900 mg weekly x 4 doses	**Maintenance Dose** 300 mg at week 2; then 300mg every 3 weeks 300 mg at week 2; then 300mg every 2 weeks 600 mg at week 3; then 600mg every 2 weeks 900 mg at week 3; then 900 mg every 2 weeks 1200 mg at week 5; then 1200 mg every 2 weeks
Recommended aHUS dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended ~~generalized~~ gMG dose	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)		

1. SOLIRIS (eculizumab) Solution for Injection Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 2/23 (DM); 12/21; 4/21
Implementation: 5/1/21

Satralizumab-mwge (ENSPRYNG)

Goal(s):
- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:
- Up to 12 months

Requires PA:
- Satralizumab-mwge (ENSPRYNG) pharmacy and physician administered 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 #~~43~~	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3~~Pass to RPh. Deny; not funded by the OHP.~~

Approval Criteria		
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is this an FDA approved indication?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
~~3.~~5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 64
~~4.~~6. Is the request for Neuromyelitis Optica Spectrum Disorder in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	**Yes:** Go to #7~~5~~	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~7. Has the patient been screened for Hepatitis B and tuberculosis infection prior to initiating treatment?	**Yes:** Go to #8~~6~~	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~8. Does the patient have active Hepatitis B or untreated latent tuberculosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 4/21
Implementation: 5/1/21

Pegcetacoplan (EMPAVELI)

Goal(s):
- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:
- Up to 12 months

Requires PA:
- EMPAVELI (pegcetacoplan) pharmacy and physician administered 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.

Approval Criteria		
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
~~2.~~3. Is the diagnosis funded by OHP?	**Yes:** Go to #~~43~~	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4 ~~Pass to RPh. Deny; medical appropriateness~~
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
~~3.~~5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 64
~~4.~~6. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2-week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #~~75~~	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~5.~~7. Is the diagnosis for an adult (age 18 years or older) with Paroxysmal Nocturnal Hemoglobinuria?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 12/21
Implementation: 1/1/22

Efgartigimod (VYVGART)

Goal(s):
- Restrict use to OHP-funded conditions.
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- VYVGART (efgartigimod) pharmacy and physician administered 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 #~~4~~5	**No:** **No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3.~~Pass to RPh. Deny; not funded by the OHP.~~
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
~~3.~~4. Is this an FDA approved indication?	**Yes**: Go to #~~5~~3	**No:** Pass to RPh. Deny; medical appropriateness
~~Is the request for efgartigimod made by, or in consultation with, a neurologist or rheumatologist~~	~~**Yes:** Go to #5~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~4.~~5. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6~~4~~
~~5.~~6. Does the patient have an active infection?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7

Approval Criteria		
~~6.~~7. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically included hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella. Immunization with live vaccines is not recommended during efgartigimod treatment.	**Yes:** Go to #8~~7~~. Document physician attestation of immunization history	**No:** Pass to RPh. Deny; medical appropriateness. Administer vaccines before initiation of a new treatment cycle of efgartigimod
~~7.~~8. Does the patient have a positive serological test for anti-acetylcholine receptor (AchR) antibodies?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~9. Does the patient have a Myasthenia Gravis Foundation of America Clinical Classification of class II, III or IV?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
~~9.~~10. Does the patient have a myasthenia gravis-specific activities of daily living scale (MG-ADL) total score of 5 points or more?	**Yes:** Go to #11 Record baseline MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness
~~10.~~11. Has the patient received or is currently receiving two immunosuppressant therapies (as monotherapy or in combination) for at least one year without adequate symptom control or do they have contraindications to these therapies? Example immunosuppressant therapies: - Azathioprine - Cyclosporine - Mycophenolate mofetil - Tacrolimus - Methotrexate - Cyclophosphamide	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of immunosuppressant therapy

Approval Criteria		
~~11.~~12. Is the request for efgartigimod dosing that corresponds to FDA labeling? • 10 mg/kg once weekly for 4 weeks • For patients weighing 120 kg or more, the recommended dose is 1200 mg per infusion	**Yes:** Approve for up to two cycles. Each cycle is 1 dose/week for 4 weeks. The second cycle should not be administered sooner than 50 days from start of previous cycle.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has it been 50 days or more from the start of the previous efgartigimod treatment cycle?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is this request for the first renewal of efgartigimod?	**Yes**: Go to #3	**No:** Go to #4
3. Has the patient experienced a reduction in symptoms of at least 2 points from MG-ADL total baseline score?	**Yes**: Approve for up to 5 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient maintained a stable MG-ADL score over the last 12 months of efgartigimod therapy?	**Yes**: Approve for up to 7 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness

Implementation: TBD; 5/1/22