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, August 4th, 2022 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. Approval of Agenda	R. Citron (OSU)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Approval of Minutes	R. Citron (OSU)
	E. Department Update	A. Gibler (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. CMS Annual Report	
	B. Review Standards and Methods for Evidence Assessment	
	C. Pharmacy and Therapeutics Operating Procedures	
	D. Quarterly Utilization Reports	
	1. Public Comment	
1:25 PM	III. DUR ACTIVITIES	
	A. ProDUR Report	L. Starkweather (Gainwell)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)
	1. Second-Generation Antipsychotic Use in Children and Adolescents	
	2. Updated 2021 Treatment Guidelines for Sexually Transmitted Infections	
	IV. PREFERRED DRUG LIST NEW BUSINESS	
1:40 PM	A. Estrogens Class Update	K. Sentena (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

2:00 PM	B. PCSK9 Modulators Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Leqvio® (inclisiran) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	M. Herink (OSU)
2:20 PM	C. Oral Thyroid Hormones 1. Class Review 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:40 PM	D. Oral Beta Blocker Class Update 1. Class Update 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:10 PM	BREAK	
3:20 PM	E. Nasal Allergy Inhaler Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:40 PM	F. Sedative Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Quviviq™ (daridorexant) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
4:00 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Patrick DeMartino, MD	Physician	Pediatrician	Portland	December 2022
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022
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
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Vacant	Physician			December 2024

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 2nd, 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; Caryn Mickelson, PharmD; Robin Moody, MPH; Russ Huffman, PMHNP; Mark Helm, MD; Cat Livingston, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Lan Starkweather, PharmD; Megan Herink, PharmD; Gary Karagodsky, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH

Audience: Amy Breen, Teva; Amy Burns, AllCare CCO; **Heidi Behm, OHA Public Health TB Program**; Brandie Feger, Advanced Health; **Charlie Lovan, AbbVie**; Chris Tanaka, ViiV HealthCare; Danielle Addis, AGIOS; Gloria Zepeda, P4 Pharmacy Student; Jason Kniffin; John Stancil, Artia Solutions; Jonathan Frochtzwajg, CAP; Josh Whittington, BMS; Kaitlyn Molina, Samaritan Health Plan; Kevin Hinthorne, LEO Pharma; Kristen Tjaden; Liz Breitenstein, OHA; Lori Howarth, Bayer; Mark Germann, LEO Pharma; Mark Kantor, AllCare Health; Matt Worthy, OHSU; Melissa Snider, Gilead Sciences; Michael Foster, BMS; Mike Donabedian, Sarepta Therapeutics; Olaf Reinwald, Global Blood Therapeutics; **Patrick Harvey, MSL Supernus Pharmaceuticals**; Rick Frees, Vertex; **Rochelle Yang, Teva**; Saghi Maleki, Takeda Pharmaceuticals; Tiffany Jones, PacificSource; Tiina Andrews, Umpqua Health Alliance; Trish Olson, SK Life Science; Uche Mordi, BMS; **Valerie Ng, LEO Pharma; Victoria Romo-LeTourneau, Pfizer**; YJ Shukla, EOCCO/Moda Health; **Thu-Mai Duong, Sanofi**

(*) Provided verbal testimony
Written testimony: Posted to OSU Website

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I. CALL TO ORDER

A. Roll Call & Introductions
- Called to order at approx. 1:32 p.m., introductions by Committee and staff

B. Conflict of Interest Declaration – no new conflicts of interest were declared

C. Approval of Agenda and April 2022 Minutes presented by Roger Citron
ACTION: Motion to approve, 2nd, Dr. Helm abstained and everyone else in favor

D. Department Update provided by Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

A. **Tetracycline Quantity Limit**
Recommendation:
- Incorporate the proposed quantity limits in the Tetracycline prior authorization criteria

B. **Oncology Prior Authorization (PA) Updates**
Recommendations:
- Add: Carvykti™ (ciltacabtagene autoleucel); Pluvicto™ (lutetium Lu 177 vipivotide tetraxetan); Opdualag™ (nivolumab; relatlimab-rmbw); and Vonjo™ (pacritinib) to Table 1 in the Oncology Agents PA criteria

C. **Orphan Drug Policy Updates**
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Vijoice® (alpelisib) and Pyrukynd® (mitapivat) 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
- **Pre- and Post-Exposure Prophylaxis of HIV**
- **Anti-SARS-CoV-2 Therapeutics can Effectively Treat, Prevent COVID-19 Infection**

IV. DUR NEW BUSINESS

A. **Sublingual Buprenorphine Policy Evaluation:** Sarah Servid, PharmD
Recommendation: No policy changes recommended
ACTION: Motion to approve, 2nd, all in favor

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B. **ADHD Drug Utilization Evaluation and DERP Summary:**
Dave Engen, PharmD; Gary Karagodsky, PharmD; Megan Herink, PharmD
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Continue to monitor for the use of combination therapies and evaluate for any changes in trends over time
- Consider education about the need for appropriate treatment of mental health disorders in those with ADHD
- Evaluate costs in executive session
Public Comment: Patrick Harvey, Supernus Pharmaceuticals
ACTION: The Committee recommended adding Qelbree adult max dose to the tale and to look at max doses for ER versions in the table and bring back to the October meeting
Motion to approve, 2nd, five in favor and one opposed

V. PREFERRED DRUG LIST NEW BUSINESS

A. **Diuretic Literature Scan with New Drug Evaluation (NDE)**: Megan Herink, PharmD
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Maintain finerenone as non-preferred on the PDL
- Implement PA to limit use to patients with CKD and T2DM on background therapy with an ACE-I or ARB
- Evaluate costs in executive session
Public Comment: Patrick Harvey, Supernus Pharmaceuticals
ACTION: The Committee recommended adding Qelbree adult max dose to the tale and to look at max doses for ER versions in the table and bring back to the October meeting
Motion to approve, 2nd, five in favor and one opposed

B. **Targeted Immune Modulators for Asthma and Drugs for Inflammatory Skin Conditions**
Deanna Moretz, PharmD
Recommendations:
- Update PA criteria for drugs used to manage Atopic Dermatitis (AD) to reflect update to Guideline Note 21 to include facial involvement in the severity assessment of inflammatory skin conditions and add severe vitiligo as a funded condition
- Rename AD and psoriasis PA criteria to “Topical Agents for Inflammatory Skin Conditions”
- Add topical ruxolitinib and maintain as non-preferred

- Rename "Monoclonal Antibodies for Severe Asthma" PA criteria "TIMs for Severe Asthma and Atopic Dermatitis"
- Add oral abrocitnib, injectable tralokinumab and tezepelumab injection and maintain as non-preferred
- Include severe AD as an FDA-approved diagnosis for upadacitinib in the "TIMs for Autoimmune Conditions" PA
- Revise PA criteria to reduce the threshold for blood eosinophils to 150 cells/µL for monoclonal antibodies prescribed for eosinophilic asthma, update definition of severe asthma exacerbation, and include use of OCS in asthma exacerbation criteria
- Evaluate costs in executive session

Public Comment: Valeri Ng, LEO Pharma; Charles Lovan, AbbVie; Victoria Romo-LeTourneau, Pfizer; Rochelle Yang, Teva Pharmaceuticals; Thu-Mai Duong, Sanofi
ACTION: Motion to approve, 2nd, all in favor

C. **Mycobacterium Agents Class Review:** Sara Fletcher, PharmD
Recommendations:
- Add the Mycobacterium Agents class to the PDL
- Make bedaquiline preferred given strong recommendations for use in drug-resistant TB
- Make rifampin and isoniazid preferred first-line treatment regimens for both drug-susceptible TB and latent TB
- Make pyrazinamide and ethambutol preferred components of first-line treatment regimens for drug-susceptible TB
- Make rifapentine preferred as a component of a first-line treatment regimen for latent TB and an alternative regimen for drug susceptible pulmonary TB
- Evaluate costs in executive session

Public Comment: Heidi Behm, OHA Public Health TB Program
ACTION: The Committee instead recommended removing the PA requirement and PDL status for bedaquiline and keep all agents open access
Motion to approve, 2nd, all in favor

E. **Estrogen Class Update**: Deferred

VI. EXECUTIVE SESSION

Members Present:; Stacy Ramirez, PharmD; Caryn Mickelson, PharmD; Robin Moody, MPH; Russ Huffman, PMHNP; Mark Helm, MD; Cat Livingston, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Lan

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Starkweather, PharmD; Megan Herink, PharmD; Gary Karagodsky, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **ADHD Drug Utilization Evaluation and DERP Summary**
Recommendation: Make methylphenidate tab ER 24 (Concerta and its generic) preferred
ACTION: Motion to approve, 2nd, all in favor

B. **Diuretic Literature Scan with NDE:**
Recommendation: No changes to the PDL were recommended
ACTION: Motion to approve, 2nd, all in favor

C. **Targeted Immune Modulators for Asthma and Drugs for Inflammatory Skin Conditions**
Recommendation: Make topical steroid products betamethasone-propylene glycol cream, clobetasol propionate solution, desoximetasone cream, and hydrocortisone cream products that have utilization preferred changes
ACTION: Motion to approve, 2nd, all in favor

D. **Mycobacterium Agents Class Review**
Recommendation: Remove PDL coding for bedaquiline and keep all agents open access
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Review Standards and Methods for Quality Assessment of Evidence
Updated: August 2022

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.

~~5.~~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.

~~6.~~7. The following are preferred sources that provide high quality evidence at this time:

    a. Drug Effectiveness Review Project~~Pacific Northwest Evidence-based Practice Center~~ 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)
    f. BMJ Clinical Evidence

~~7.~~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
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

~~8.~~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: August 2022

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 ~~will~~ are also ~~be required~~ 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 ~~must~~ 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 ~~for evaluation by staff~~ 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.
    ~~f.~~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. ~~Written public comments submitted during the draft comment period prior to posting of final documents are only considered by staff. Written public comment submitted based on final documents will be submitted to the P&T Committee for consideration.~~ 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.

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Pharmacy Utilization Summary Report: January 2021 - December 2021

Eligibility	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Total Members (FFS & Encounter)	1,155,608	1,165,327	1,176,534	1,186,439	1,195,359	1,203,243	1,212,729	1,222,901	1,230,474	1,238,036	1,249,056	1,258,864	1,207,881
FFS Members	110,971	104,212	106,887	108,646	109,364	105,833	109,457	112,375	108,825	111,347	109,132	112,664	109,143
OHP Basic with Medicare	7,781	7,599	7,743	7,998	8,048	7,967	8,110	8,273	8,141	8,429	8,051	8,195	8,028
OHP Basic without Medicare	11,524	11,224	11,074	11,063	11,039	10,911	10,947	11,003	10,811	10,888	10,718	10,697	10,992
ACA	91,666	85,389	88,070	89,585	90,277	86,955	90,400	93,099	89,873	92,030	90,363	93,772	90,123
Encounter Members	1,044,637	1,061,115	1,069,647	1,077,793	1,085,995	1,097,410	1,103,272	1,110,526	1,121,649	1,126,689	1,139,924	1,146,200	1,098,738
OHP Basic with Medicare	76,328	77,441	78,598	79,521	80,356	81,391	82,240	83,030	83,993	84,715	86,139	86,570	81,694
OHP Basic without Medicare	67,172	67,155	66,975	67,232	67,380	67,600	67,639	67,674	68,041	67,983	68,260	68,173	67,607
ACA	901,137	916,519	924,074	931,040	938,259	948,419	953,393	959,822	969,615	973,991	985,525	991,457	949,438

Gross Cost Figures for Drugs	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	YTD Sum
Total Amount Paid (FFS & Encounter)	$93,408,427	$89,817,431	$105,358,858	$100,561,627	$97,856,356	$104,503,435	$100,587,172	$103,731,489	$105,333,949	$97,263,770	$100,367,881	$102,693,046	$1,201,483,442
Mental Health Carve-Out Drugs	$10,188,372	$10,196,300	$12,110,755	$11,746,987	$11,387,525	$12,046,328	$11,632,196	$11,834,531	$11,282,498	$10,845,336	$11,006,710	$11,202,381	$135,479,919
OHP Basic with Medicare	$26,605	$27,401	$8,529	$7,638	$5,904	$5,729	$2,855	$5,699	$4,725	$8,509	$5,705	$2,848	$112,148
OHP Basic without Medicare	$4,007,981	$4,074,811	$4,679,151	$4,597,425	$4,351,340	$4,647,641	$4,468,898	$4,505,698	$4,324,796	$4,007,238	$4,054,139	$4,178,622	$51,897,740
ACA	$6,100,012	$6,035,622	$7,354,332	$7,061,461	$6,950,335	$7,307,323	$7,072,067	$7,234,583	$6,875,517	$6,747,918	$6,864,095	$6,933,331	$82,536,595
FFS Physical Health Drugs	$4,476,647	$4,155,163	$5,053,223	$4,754,690	$4,392,860	$4,835,236	$4,616,174	$4,679,939	$4,545,344	$4,525,345	$4,487,694	$4,566,391	$55,088,708
OHP Basic with Medicare	$160,402	$142,248	$158,512	$162,078	$168,217	$178,775	$167,423	$169,604	$164,977	$165,943	$171,172	$158,416	$1,967,766
OHP Basic without Medicare	$1,356,464	$1,131,622	$1,270,918	$1,225,033	$1,016,511	$1,183,292	$1,156,192	$1,203,299	$1,138,769	$1,201,471	$1,027,593	$1,116,563	$14,027,728
ACA	$2,840,636	$2,764,862	$3,504,330	$3,214,016	$3,090,980	$3,333,421	$3,159,514	$3,144,382	$3,049,729	$3,001,802	$3,124,984	$3,191,642	$37,420,297
FFS Physician Administered Drugs	$1,492,046	$1,877,260	$1,559,400	$1,354,911	$1,174,909	$1,707,623	$1,383,158	$1,271,310	$1,113,019	$1,445,910	$1,205,841	$1,092,361	$16,677,747
OHP Basic with Medicare	$163,515	$227,493	$107,630	$103,825	$159,776	$118,782	$114,522	$129,793	$112,192	$82,754	$180,038	$189,391	$1,689,711
OHP Basic without Medicare	$333,840	$781,586	$455,386	$289,205	$266,609	$740,489	$357,635	$202,704	$220,737	$580,726	$347,753	$234,558	$4,811,228
ACA	$515,181	$485,240	$476,858	$520,258	$372,077	$406,899	$531,515	$478,068	$448,198	$424,094	$348,825	$419,343	$5,426,557
Encounter Physical Health Drugs	$60,784,684	$58,134,612	$68,340,804	$64,932,824	$63,403,477	$66,964,653	$64,703,503	$65,517,282	$64,357,734	$63,589,252	$66,092,572	$68,066,151	$774,887,549
OHP Basic with Medicare	$622,754	$587,809	$380,824	$411,499	$391,922	$456,688	$424,688	$398,680	$415,765	$399,374	$446,876	$473,345	$5,410,223
OHP Basic without Medicare	$14,931,579	$14,192,814	$16,782,340	$15,982,190	$15,499,834	$16,277,245	$15,562,420	$16,283,841	$15,446,501	$15,477,082	$16,311,073	$16,377,587	$189,124,509
ACA	$44,568,110	$42,665,205	$50,312,904	$47,693,452	$46,707,970	$49,192,629	$47,562,620	$47,804,245	$47,637,585	$46,957,582	$48,575,541	$50,322,527	$570,000,371
Encounter Physician Administered Drugs	$16,466,678	$15,454,096	$18,294,675	$17,772,215	$17,497,586	$18,949,595	$18,252,142	$20,428,428	$24,035,354	$16,857,927	$17,575,063	$17,765,761	$219,349,519
OHP Basic with Medicare	$800,010	$677,832	$1,005,360	$916,396	$906,871	$948,524	$804,892	$886,966	$861,029	$961,998	$873,500	$820,633	$10,464,009
OHP Basic without Medicare	$3,721,275	$3,151,350	$3,878,852	$3,762,664	$4,137,220	$4,071,553	$4,009,789	$3,946,786	$10,669,655	$3,782,248	$4,185,155	$4,257,182	$53,573,729
ACA	$11,505,555	$11,168,750	$13,061,226	$12,760,352	$12,161,845	$13,733,699	$12,858,243	$15,230,484	$12,172,590	$11,943,074	$12,243,784	$12,483,984	$151,323,585

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: July 21, 2022

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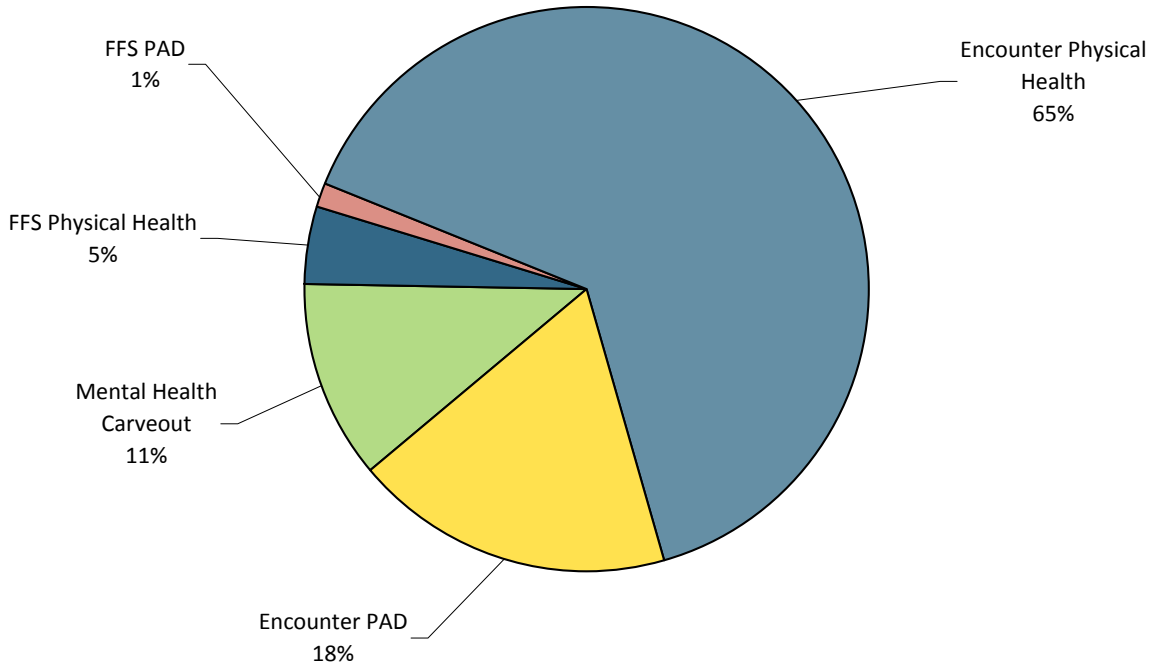
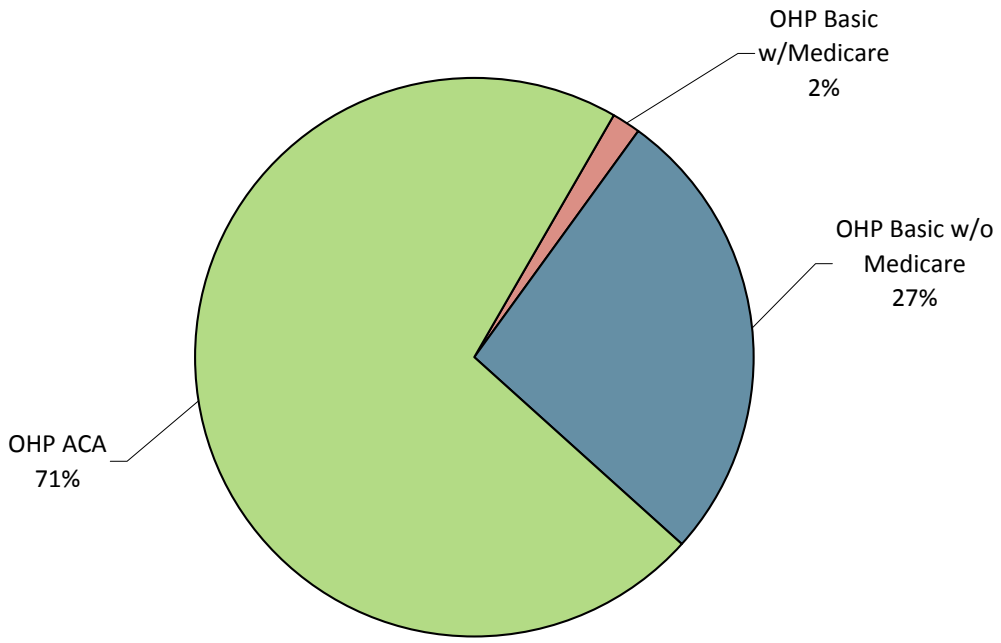
Pharmacy Utilization Summary Report: January 2021 - December 2021

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

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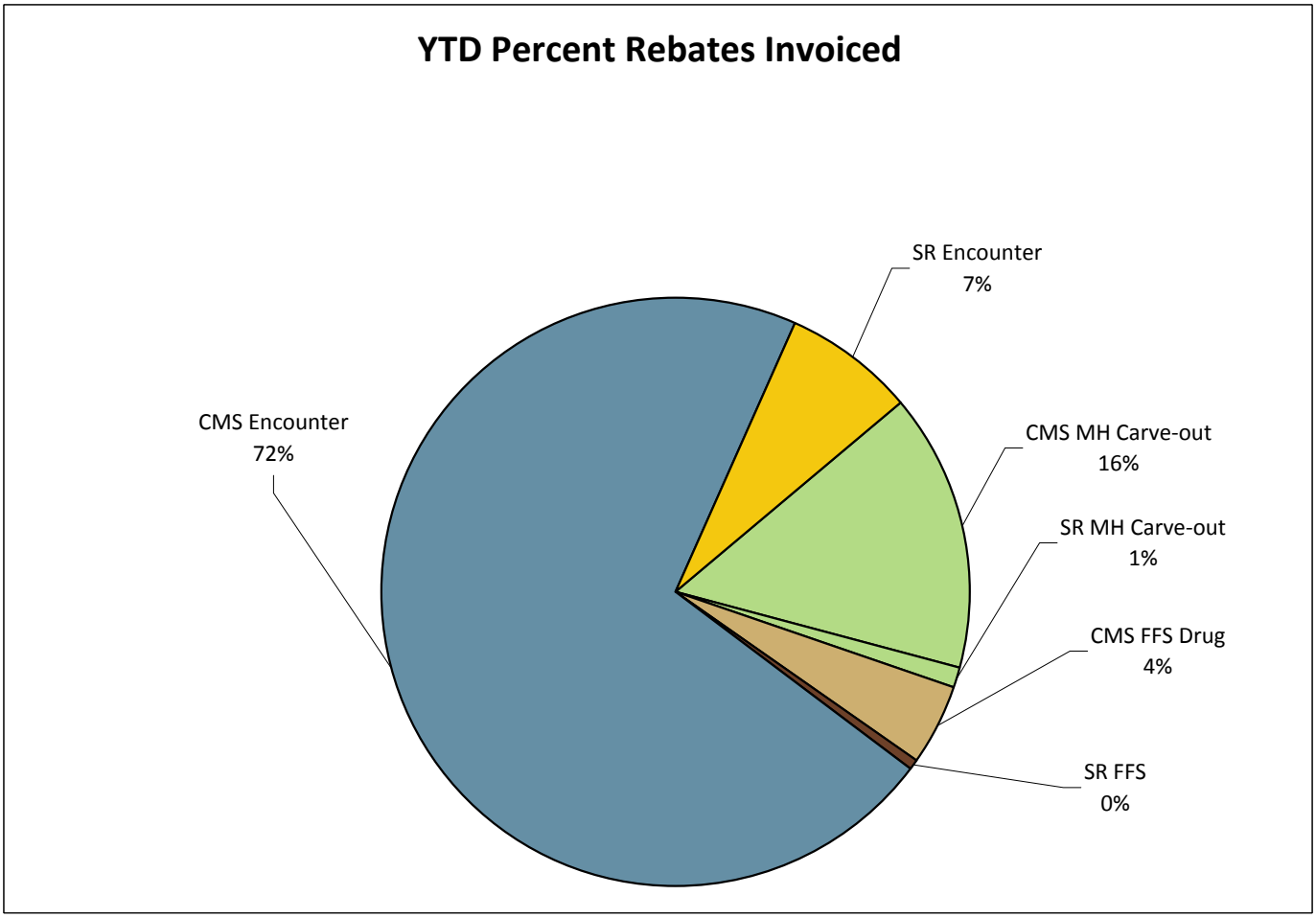
Pharmacy Utilization Summary Report: January 2021 - December 2021

Quarterly Rebates Invoiced	2021-Q1	2021-Q2	2021-Q3	2021-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$117,168,246	$122,058,290	$117,739,012	$118,539,959	$475,505,506
CMS MH Carve-out	$16,651,938	$19,349,824	$18,561,201	$17,631,029	$72,193,993
SR MH Carve-out	$1,484,299	$1,416,550	$1,618,690	$1,795,371	$6,314,910
CMS FFS Drug	$6,041,617	$5,354,878	$4,654,601	$4,782,744	$20,833,841
SR FFS	$540,442	$512,938	$452,218	$547,805	$2,053,403
CMS Encounter	$84,175,733	$86,733,485	$83,485,861	$85,093,809	$339,488,889
SR Encounter	$8,274,216	$8,690,615	$8,966,441	$8,689,200	$34,620,471

Quaterly Net Drug Costs	2021-Q1	2021-Q2	2021-Q3	2021-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$171,416,470	$180,863,129	$191,913,599	$181,784,738	$725,977,936
Mental Health Carve-Out Drugs	$14,359,189	$14,414,466	$14,569,333	$13,628,028	$56,971,017
FFS Phys Health + PAD	$12,031,681	$12,352,413	$12,502,124	$11,992,994	$48,879,212
Encounter Phys Health + PAD	$145,025,600	$154,096,250	$164,842,142	$156,163,716	$620,127,708



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

Last Updated: July 21, 2022

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Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$80.83	$77.07	$89.55	$84.76	$81.86	$86.85	$82.94	$84.82	$85.60	$78.56	$80.35	$81.58	$82.90
Mental Health Carve-Out Drugs	$8.82	$8.75	$10.29	$9.90	$9.53	$10.01	$9.59	$9.68	$9.17	$8.76	$8.81	$8.90	$9.35
FFS Physical Health Drugs	$40.34	$39.87	$47.28	$43.76	$40.17	$45.69	$42.17	$41.65	$41.77	$40.64	$41.12	$40.53	$42.08
FFS Physician Administered Drugs	$13.45	$18.01	$14.59	$12.47	$10.74	$16.14	$12.64	$11.31	$10.23	$12.99	$11.05	$9.70	$12.78
Encounter Physical Health Drugs	$58.19	$54.79	$63.89	$60.25	$58.38	$61.02	$58.65	$59.00	$57.38	$56.44	$57.98	$59.38	$58.78
Encounter Physician Administered Drugs	$15.76	$14.56	$17.10	$16.49	$16.11	$17.27	$16.54	$18.40	$21.43	$14.96	$15.42	$15.50	$16.63

Claim Counts	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Total Claim Count (FFS & Encounter)	1,071,755	1,010,919	1,163,436	1,134,120	1,123,717	1,161,495	1,128,678	1,126,500	1,093,349	1,094,019	1,094,960	1,107,868	1,109,235
Mental Health Carve-Out Drugs	182,949	172,693	197,108	186,937	183,883	191,470	188,061	190,974	185,252	183,260	185,522	188,508	186,385
FFS Physical Health Drugs	37,988	35,897	42,162	41,551	41,038	41,608	38,334	38,665	36,767	35,427	35,152	35,844	38,369
FFS Physician Administered Drugs	11,236	10,115	11,204	10,488	10,034	9,935	9,981	9,314	9,055	9,362	8,749	8,994	9,872
Encounter Physical Health Drugs	722,961	682,042	787,699	773,273	768,065	796,207	770,666	772,631	754,521	751,361	751,064	765,342	757,986
Encounter Physician Administered Drugs	116,621	110,172	125,263	121,871	120,697	122,275	121,636	114,916	107,754	114,609	114,473	109,180	116,622

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$87.15	$88.85	$90.56	$88.67	$87.08	$89.97	$89.12	$92.08	$96.34	$88.91	$91.66	$92.69	$90.26
Mental Health Carve-Out Drugs	$55.69	$59.04	$61.44	$62.84	$61.93	$62.91	$61.85	$61.97	$60.90	$59.18	$59.33	$59.43	$60.54
FFS Physical Health Drugs	$117.84	$115.75	$119.85	$114.43	$107.04	$116.21	$120.42	$121.04	$123.63	$127.74	$127.67	$127.40	$119.92
FFS Physician Administered Drugs	$132.79	$185.59	$139.18	$129.19	$117.09	$171.88	$138.58	$136.49	$122.92	$154.44	$137.83	$121.45	$140.62
Encounter Physical Health Drugs	$84.08	$85.24	$86.76	$83.97	$82.55	$84.10	$83.96	$84.80	$85.30	$84.63	$88.00	$88.94	$85.19
Encounter Physician Administered Drugs	$141.20	$140.27	$146.05	$145.83	$144.97	$154.98	$150.06	$177.77	$223.06	$147.09	$153.53	$162.72	$157.29

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$23.42	$23.47	$23.02	$22.30	$21.87	$22.92	$22.24	$22.44	$21.87	$22.05	$22.64	$22.90	$22.60
Mental Health Carve-Out Drugs	$17.97	$17.97	$17.58	$17.26	$17.01	$17.05	$17.01	$16.68	$16.14	$16.23	$16.45	$16.36	$16.97
FFS Physical Health Drugs	$70.09	$70.63	$74.19	$73.46	$72.99	$78.72	$78.38	$78.55	$77.98	$78.27	$81.74	$81.49	$76.37
Encounter Physical Health Drugs	$22.65	$22.72	$22.04	$21.28	$20.88	$21.96	$21.16	$21.54	$21.01	$21.20	$21.86	$22.28	$21.71

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$551.96	$556.48	$549.82	$472.95	$426.96	$463.31	$519.15	$504.70	$497.99	$510.13	$537.35	$526.19	$509.75
Mental Health Carve-Out Drugs	$1,124.67	$1,108.91	$1,052.61	$1,030.81	$1,018.33	$1,013.57	$1,012.88	$1,019.09	$1,005.20	$964.75	$932.31	$950.98	$1,019.51
FFS Physical Health Drugs	$332.60	$304.14	$289.49	$232.96	$191.83	$226.23	$264.98	$257.43	$268.77	$312.48	$283.57	$268.25	$269.39
Encounter Physical Health Drugs	$528.54	$534.38	$531.13	$453.96	$409.63	$443.37	$499.52	$484.19	$476.96	$487.68	$523.22	$512.57	$490.43

Generic Drug Use Percentage	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Generic Drug Use Percentage	89.3%	89.1%	88.6%	86.9%	85.7%	86.7%	88.1%	87.7%	87.3%	87.8%	88.1%	87.7%	87.8%
Mental Health Carve-Out Drugs	96.6%	96.2%	95.8%	95.5%	95.5%	95.4%	95.5%	95.5%	95.5%	95.5%	95.3%	95.4%	95.6%
FFS Physical Health Drugs	81.8%	80.7%	78.8%	74.3%	71.3%	74.6%	77.5%	76.2%	76.1%	78.9%	77.2%	75.4%	76.9%
Encounter Physical Health Drugs	87.9%	87.8%	87.3%	85.5%	84.1%	85.3%	86.9%	86.3%	85.9%	86.4%	86.8%	86.4%	86.4%

Preferred Drug Use Percentage	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Avg Monthly
Preferred Drug Use Percentage	86.70%	86.60%	86.56%	89.71%	89.80%	89.70%	89.98%	89.92%	89.83%	89.81%	89.76%	89.69%	89.0%
Mental Health Carve-Out Drugs	77.24%	76.90%	76.91%	93.02%	93.05%	93.04%	93.11%	93.08%	93.01%	93.12%	92.99%	93.01%	89.0%
FFS Physical Health Drugs	94.41%	94.16%	94.20%	94.35%	94.38%	94.36%	94.68%	94.90%	94.70%	94.80%	94.96%	94.97%	94.6%
Encounter Physical Health Drugs	88.69%	88.66%	88.59%	88.68%	88.79%	88.67%	89.00%	88.91%	88.82%	88.78%	88.73%	88.65%	88.7%

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: July 21, 2022

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

Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,984,242	15.8%	5,574	$1,253	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,562,589	8.1%	1,595	$2,234	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$3,181,746	7.2%	2,709	$1,175	Y
4	STRATTERA*	ADHD Drugs	$2,748,630	6.2%	6,035	$455	Y
5	REXULTI	Antipsychotics, 2nd Gen	$2,033,478	4.6%	1,692	$1,202	V
6	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,923,412	4.4%	885	$2,173	Y
7	INVEGA TRINZA	Antipsychotics, Parenteral	$1,017,892	2.3%	145	$7,020	Y
8	ARISTADA	Antipsychotics, Parenteral	$823,807	1.9%	354	$2,327	Y
9	TRINTELLIX	Antidepressants	$809,398	1.8%	1,882	$430	V
10	INVEGA	Antipsychotics, 2nd Gen	$732,784	1.7%	1,823	$402	V
11	SERTRALINE HCL	Antidepressants	$583,681	1.3%	59,662	$10	Y
12	BUPROPION XL	Antidepressants	$547,636	1.2%	41,258	$13	Y
13	DULOXETINE HCL	Antidepressants	$515,032	1.2%	36,964	$14	Y
14	FLUOXETINE HCL	Antidepressants	$481,637	1.1%	44,037	$11	Y
15	TRAZODONE HCL	Antidepressants	$473,868	1.1%	46,682	$10	
16	VIIBRYD	Antidepressants	$470,136	1.1%	1,521	$309	V
17	ESCITALOPRAM OXALATE	Antidepressants	$404,520	0.9%	41,166	$10	Y
18	CAPLYTA	Antipsychotics, 2nd Gen	$335,832	0.8%	242	$1,388	V
19	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$313,410	0.7%	26,014	$12	
20	LAMOTRIGINE	Antiepileptics (non-injectable)	$310,634	0.7%	28,904	$11	Y
21	CHOLBAM*	Bile Therapy	$298,829	0.7%	3	$99,610	N
22	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$261,039	0.6%	262	$996	Y
23	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$245,173	0.6%	19,511	$13	Y
24	VENLAFAXINE HCL ER	Antidepressants	$239,853	0.5%	19,000	$13	Y
25	SABRIL	Antiepileptics (non-injectable)	$234,798	0.5%	10	$23,480	N
26	BIKTARVY	HIV	$234,474	0.5%	98	$2,393	Y
27	TRIKAFTA*	Cystic Fibrosis	$224,997	0.5%	26	$8,654	N
28	LYBALVI	Antipsychotics, 2nd Gen	$222,416	0.5%	177	$1,257	V
29	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$221,332	0.5%	19,834	$11	Y
30	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$214,153	0.5%	3,036	$71	V
31	BUPROPION XL	Antidepressants	$211,484	0.5%	1,140	$186	V
32	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$208,210	0.5%	1	$208,210	
33	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$204,467	0.5%	7	$29,210	
34	Elosulfase Alfa, Injection	Physican Administered Drug	$195,241	0.4%	13	$15,019	
35	VENLAFAXINE HCL ER	Antidepressants	$182,440	0.4%	2,170	$84	V
36	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$181,574	0.4%	19	$9,557	Y
37	CITALOPRAM HBR	Antidepressants	$179,711	0.4%	20,747	$9	Y
38	Inj Pembrolizumab	Physican Administered Drug	$178,148	0.4%	42	$4,242	
39	AMITRIPTYLINE HCL*	Antidepressants	$176,536	0.4%	14,125	$12	Y
40	MIRTAZAPINE	Antidepressants	$163,055	0.4%	11,531	$14	Y
		Top 40 Aggregate:	**$32,532,293**		**460,896**	**$10,587**	
		All FFS Drugs Totals:	**$44,176,467**		**709,400**	**$607**	

*** 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

Last updated: July 21, 2022

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	CHOLBAM*	Bile Therapy	$298,829	3.1%	3	$99,610	N
2	SABRIL	Antiepileptics (non-injectable)	$234,798	2.4%	10	$23,480	N
3	BIKTARVY	HIV	$234,474	2.4%	98	$2,393	Y
4	TRIKAFTA*	Cystic Fibrosis	$224,997	2.3%	26	$8,654	N
5	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$208,210	2.2%	1	$208,210	
6	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$204,467	2.1%	7	$29,210	
7	Elosulfase Alfa, Injection	Physican Administered Drug	$195,241	2.0%	13	$15,019	
8	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$181,574	1.9%	19	$9,557	Y
9	Inj Pembrolizumab	Physican Administered Drug	$178,148	1.8%	42	$4,242	
10	IBRANCE*	Antineoplastics, Newer	$153,838	1.6%	11	$13,985	
11	CONCERTA*	ADHD Drugs	$152,793	1.6%	409	$374	N
12	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$152,781	1.6%	523	$292	
13	LANTUS SOLOSTAR*	Diabetes, Insulins	$143,229	1.5%	422	$339	Y
14	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$139,987	1.4%	235	$596	Y
15	HUMIRA(CF) PEN*	Targeted Immune Modulators	$134,955	1.4%	49	$2,754	Y
16	STELARA*	Targeted Immune Modulators	$131,220	1.4%	19	$6,906	N
17	Etonogestrel Implant System	Physican Administered Drug	$119,248	1.2%	158	$755	
18	Epoetin Beta Esrd Use	Physican Administered Drug	$111,822	1.2%	17	$6,578	
19	VYVANSE*	ADHD Drugs	$110,625	1.1%	675	$164	Y
20	EPIDIOLEX*	Antiepileptics (non-injectable)	$98,314	1.0%	101	$973	N
21	ELIQUIS	Anticoagulants, Oral and SQ	$96,280	1.0%	287	$335	Y
22	Aflibercept Injection	Physican Administered Drug	$92,360	1.0%	199	$464	
23	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$86,194	0.9%	2,683	$32	Y
24	COSENTYX PEN (2 PENS)*	Targeted Immune Modulators	$82,306	0.9%	28	$2,940	Y
25	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$75,964	0.8%	1,316	$58	Y
26	Mirena, 52 Mg	Physican Administered Drug	$74,540	0.8%	101	$738	
27	VIMPAT	Antiepileptics (non-injectable)	$71,288	0.7%	78	$914	Y
28	ENBREL SURECLICK*	Targeted Immune Modulators	$70,109	0.7%	15	$4,674	Y
29	AFINITOR DISPERZ*	Antineoplastics, Newer	$68,547	0.7%	6	$11,425	
30	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$65,931	0.7%	7	$9,419	
31	FLOVENT HFA	Corticosteroids, Inhaled	$63,427	0.7%	458	$138	Y
32	ADVATE	Antihemophilia Factors	$60,497	0.6%	4	$15,124	
33	PROMACTA	Thrombocytopenia Drugs	$57,033	0.6%	10	$5,703	Y
34	Gammagard Liquid Injection	Physican Administered Drug	$56,936	0.6%	33	$1,725	
35	Mifepristone, Oral, 200 Mg	Physican Administered Drug	$56,148	0.6%	665	$84	
36	SKYRIZI PEN*	Targeted Immune Modulators	$54,848	0.6%	3	$18,283	N
37	REVLIMID	STC 30 - Antineoplastic	$52,523	0.5%	5	$10,505	
38	XYWAV	STC 47 - Sedative Non-barbiturate	$49,889	0.5%	3	$16,630	N
39	Injection, Vedolizumab	Physican Administered Drug	$49,393	0.5%	18	$2,744	
40	BUDESONIDE-FORMOTEROL FUMAR	Corticosteroids/LABA Combination, Inhaled	$48,474	0.5%	221	$219	Y
		Top 40 Aggregate:	**$4,742,238**		**8,978**	**$13,406**	
		All FFS Drugs Totals:	**$9,679,413**		**116,898**	**$618**	

*** 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

Last updated: July 21, 2022

ProDUR Report for April through June 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	3	0	5	0.0%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	1,822	415	0	1,407	1.2%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	7,399	1,839	5	5,554	5.2%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	122,549	16,563	60	75,921	65.3%	**13.5%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	28,761	7,233	3	21,508	20.2%	**N/A**
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	751	153	0	598	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	3	3	0	0	0.0%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	810	216	0	594	0.5%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	433	123	0	310	0.2%	**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	6	3	0	3	0.0%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	34	31	0	3	0.0%	**91.2%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	9,122	2,395	0	6,720	6.4%	**N/A**
		Totals	**171,698**					**0.0%**

ProDUR Report for April through June 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)	7,717	1,316	6,401	78,810	9.8%	8.1%
ER	Prozac (Fluoxetine)	5,608	913	4,695	57,029	9.8%	8.2%
ER	Lexapro (Escitalopram)	5,298	791	4,507	53,452	9.9%	8.4%
ER	Celexa (Citalopram)	2,253	364	1,889	25,838	8.7%	7.3%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	7,170	1,190	5,980	74,025	9.6%	8.0%
ER	Trazodone	6,436	1,061	5,375	59,720	10.7%	8.9%
ER	Cymbalta (Duloxetine)	4,853	759	4,094	47,857	10.1%	8.5%
ER	Remeron (Mirtazapine)	1,884	304	1,580	15,170	12.4%	10.3%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	4,581	973	3,607	31,707	14.4%	11.3%
ER	Abilify (Aripiprazole)	3,649	538	3,111	28,196	13.0%	11.0%
ER	Zyprexa (Olanzapine)	2,633	539	2,094	19,578	13.4%	10.7%
ER	Risperdal (Risperidone)	1,956	373	1,583	13,426	14.6%	11.8%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	3,443	509	2,934	34,497	9.9%	8.5%
ER	Lorazepam	315	95	220	12,117	2.6%	1.8%
ER	Alprazolam	163	32	131	7,377	2.2%	1.7%
ER	Diazepam	98	24	74	4,211	2.3%	1.7%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,037	1,105	4,932	45,116	13.3%	10.9%
ER	Intuniv (Guanfacine)	1,691	220	1,471	12,571	13.4%	11.7%
ER	Suboxone (Buprenorphine/Naloxone)	115	39	76	1,971	5.7%	3.8%

ProDUR Report for April through June 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	April	3,623	149	211	658	4	2,399	68	0	134
ER	May	4,016	170	246	749	3	2,560	112	0	176
ER	June	3,848	199	241	659	6	2,503	87	0	153
	Total =	**11,487**	**518**	**698**	**2,066**	**13**	**7,462**	**267**	**0**	**463**
	Percentage of Total Overrides =		**4.5%**	**6.1%**	**18.0%**	**0.1%**	**65.0%**	**2.3%**	**0.0%**	**4.0%**

ProDUR Report for April through June 2022			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
Apr-22	DC	6	$394.86
Apr-22	DD	30	$7,457.73
Apr-22	ER	245	$56,073.38
Apr-22	HD	2	$36.17
Apr-22	ID	34	$5,044.29
Apr-22	LR	6	$268.56
Apr-22	MX	2	$46.98
Apr-22	TD	20	$4,275.85
		April Savings =	**$73,597.82**
May-22	DD	17	$2,144.70
May-22	ER	44	$13,024.50
May-22	ID	16	$2,375.01
May-22	LR	1	$142.60
May-22	TD	1	$275.55
		May Savings =	**$17,962.36**
Jun-22	DD	6	$130.02
Jun-22	ER	52	$13,574.18
Jun-22	ID	14	$1,953.66
Jun-22	TD	3	$1,873.39
		June Savings =	**$17,531.25**
		Total 2Q2022 Savings =	**$109,091.43**

Drug Use Research & Management Program
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Retro-DUR Intervention History by Quarter FFY 2021 - 2022

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		13	6	
		Unique Patients Identified		13	6	
		Total Faxes Successfully Sent		8	4	
		Prescriptions Changed to Recommended Within 6 Months of Intervention		6	1	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$24,273	$3,006	
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	61	103	74	
		Unique Patients Identified	62	105	75	
		Total Faxes Successfully Sent	45	73	41	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	36	58	27	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$41,973	$42,482	$9,296	
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	191	262	131	
		Unique Patients Identified	193	271	131	
		Total Faxes Successfully Sent	133	186	77	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	100	115	38	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$40,995	$32,279	$3,114	

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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	30	33	13	1
		Total Faxes Successfully Sent	9	17	7	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	4	5	1	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	3		
		Prescriptions Unchanged after 3 Months of Fax Sent	19	14		
		Safety Monitoring Profiles Identified	1	2		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$2,883	$4,357	$358	

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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	801	796	783	
		High risk patients identified	9	4	7	
		Prescribers successfully notified	9	4	4	
		Patients with change in antipsychotic drug in following 90 days	1			
		Patients with continued antipsychotic therapy in the following 90 days	7	3	4	
		Patients with discontinuation of antipsychotic therapy in the following 90 days	1			

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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	81	45	55	
		Total prescribers identified	80	45	54	
		Prescribers successfully notified	80	44	50	
		Patients with claims for the same antipsychotic within the next 90 days	35	27	18	
		Patients with claims for a different antipsychotic within the next 90 days	5	1	3	

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Retro-DUR Intervention History by Quarter FFY 2021 - 2022

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	5	213	80	
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	2	55	23	
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	19	604	172	
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed		109	26	
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	13	18	14	
		Letters Sent To Providers	9	9	10	
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	50	40	1	
		Letters Sent To Providers	64	45		
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	16	13	15	
		Letters Sent To Providers	11	11	8	
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed			18	
		Letters Sent To Providers			5	
	Lock-In	RetroDUR Profiles Reviewed	20	4	11	1
		Letters Sent To Providers	4		2	
		Locked In	3	0	2	0
	Polypharmacy	RetroDUR Profiles Reviewed	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: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	90	85	102	16
		Total prescribers identified	90	85	102	16
		Prescribers successfully notified	90	85	102	8
		Patients with discontinuation of therapy within next 90 days	25	19	38	16
		Patients with new prescription for naloxone within next 90 days	3	7	4	
		Average number of sedative drugs dispensed within next 90 days	22	27	19	0
		Average number of sedative prescribers writing prescriptions in next 90 days	22	27	19	0
	Denied Claims due to Antipsychotic Dose Consolidation	Total patients identified	79	56	75	
		Patients with a paid claim for the drug (based on HSN) within 14 days	53	30	29	
		Patients without a paid claim within 14 days	26	26	27	
	ICS/LABA	ICS/LABA Denials	15	20	23	3
		Disqualified	4	6	7	
		Faxes Sent	1	1	2	
		Fax Sent - SABA		1		
		No Subsequent Pulmonary Claims	1		2	
	Oncology Denials	Total patients identified	1	2	1	
		Total prescribers identified	1	2	1	
		Prescribers successfully notified	1	2	1	
		Patients with claims for the same drug within the next 90 days	1	1		
		Patients with claims for any oncology agent within the next 90 days	1	2		

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	TCAs in Children	TCA Denials in Children	27	29	57	2
		Total patients identified	6	13	22	
		Total prescribers identified	6	13	22	
		Prescribers successfully notified	3	11	13	
		Patients with claims for a TCA within the next 90 days		2	2	
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days	2		1	

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Second-Generation Antipsychotic Use in Children and Adolescents

Sarah Servid, Pharm.D., Oregon State University Drug Use Research and Management Group

In children and adolescents, second-generation antipsychotics have been studied for a variety of conditions including autism, schizophrenia/first-episode psychosis, and bipolar I disorder. Drugs with Food and Drug Administration (FDA) approval in children or adolescents are listed in **Table 1**. However, antipsychotics are often prescribed off-label for other conditions or age groups despite the lack of evidence and potential safety concerns. The goal of this newsletter is to review the evidence for antipsychotic use in children, describe appropriate place in therapy and guideline monitoring recommendations, and provide resources for alternative first-line therapies in young children.

Table 1. Current FDA approved indications and ages of second-generation antipsychotics in children and adolescents

Drug	Schizophrenia	Bipolar I disorder	Irritability associated with Autism	Tourette's Disorder
aripiprazole[1]	≥13 yrs	≥10 yrs	≥6 yrs	≥6 yrs
asenapine[2]		≥10 yrs		
lurasidone[3]	≥13 yrs	≥10 yrs		
olanzapine[4]	≥13 yrs	≥13 yrs		
paliperidone[5]	≥12 yrs			
quetiapine[6]	≥13 yrs	≥10 yrs		
risperidone[7]	≥13 yrs	≥10 yrs	≥5 yrs	

Efficacy of Antipsychotics

A recent systematic review from the Drug Effectiveness Review Project (DERP) evaluated effectiveness and harms of antipsychotic use in children and adolescents up to 17 years of age.[8] The review identified randomized controlled trials (RCTs) in the following 4 different conditions: schizophrenia, bipolar disorder, autusm spectrum disorders, and disruptive behavior/ impulse control/conduct disorders (e.g. oppositional defiant disorder).[8] The primary outcome for most studies was symptom improvement (based on a variety of rating scales; **Table 2**). Very few of these scales have well defined or commonly accepted minimum clinically important differences. For all conditions, there was a lack of data for outcomes such as progression through school, reduction in hospitalizations, efficacy for acute symptoms, or improved engagement in social settings.

Schizophrenia and First Episode Psychosis

The DERP review identified 8 placebo-controlled RCTs and 8 head-to-head studies evaluating antipsychotics in patients with schizophrenia or first episode psychosis.[8] Average age at study enrollment was 15 years and trials ranged from 6 to 52 weeks. Most studies required participants to have moderate to severe symptoms at baseline (Positive and Negative Symptom Scale [PANSS] score ≥20 and Clinical Global Impressions-Improvement [CGI-I] ≥3).[8] In general, antipsychotics demonstrated symptom improvement compared to placebo, but most studies directly comparing drug treatment demonstrated no difference between drug therapies.[8] Quality of evidence ranged from very low to moderate depending on the specific comparison. Data was limited by small sample sizes, high attrition rates, and in most cases, only one study was available to support each comparison.[8]

Table 2. Common assessment scales for symptom severity[8]

Scale	Description
Aberrant Behavior Checklist-Irritability subscale (ABC-I)	15 items each rated on a 0 to 3 Likert scale (range 0-45)*
Clinical Global Impressions-Improvement (CGI-I)	7-point Likert scale (range of very much improved to very much worse)
Children's Depression Rating Scale (CDRS)	17 items assessing depressive symptoms (range 17-113)*
Nisonger Child Behavior Rating Form (NCBRF) - conduct problems subscale	16 items rated on a 0-3 Likert scale (range 0-48)*
Positive and Negative Symptom Scale (PANSS)	30 items (total range 30-210; usual range 60-150)*
Young Mania Rating Scale (YMRS)	11 items assessing mania over the prior 48 hours (range of 0-60)*

* higher scores indicate more severe disease

Bipolar Disorder

In patients with bipolar disorder, 9 RCTs evaluated efficacy of antipsychotics in children compared to placebo.[8] Only 2 drugs (aripiprazole and quetiapine) were supported by more than a single RCT, and outcomes were graded as very low to low quality evidence due to short treatment periods, a high placebo response, high attrition, and small sample sizes.[8] Only one small head-to-head RCT of risperidone versus quetiapine was identified (n=22). Average age at study enrollment was 13-14 years, and study duration ranged from 3 to 72 weeks.[8] Most studies required participants to have moderate to severe symptoms at baseline (Young Mania Rating Scale [YMRS] total score ≥20 and CGI-I ≥4). Use of olanzapine, risperidone and aripiprazole resulted in a mean improvement in mania symptoms of 6 to 9 points on the YMRS compared to placebo.[8] The most commonly cited minimum clinically important difference for the YMRS is a change of 6 points.[9] There was no change in YMRS with quetiapine vs. placebo (one RCT; n=316).[8] In general, assessments of depressive symptoms based on the revised Children's Depression Rating Scale (CDRS-R) did not show consistent improvement compared to placebo for quetiapine, asenapine, or aripiprazole.[8] CDRS-R was improved in one

RCT of lurasidone versus placebo (mean difference of 5.7 points), but differences were small and results of this study may have been influenced by high placebo response rates.[8]

Autism Spectrum Disorder

Aripiprazole and risperidone are the primary medications studied in autism. The DERP report identified 14 RCTs evaluating these 2 products, including 2 head-to-head studies.[8] Ten of these studies evaluated outcomes at 8 weeks, and the longest study duration was 6 months.[8] Most studies were in children 8 to 11 years of age and 2 studies evaluated therapy in patients as young as 4 or 5 years of age.[8] Commonly studied outcomes included irritability symptoms and global clinical improvement. Most patients were required to have moderate to severe agitation at baseline (Aberrant Behavior Checklist-Irritability subscale [ABC-I] scores of at least 18). Compared to placebo, symptoms of irritability improved with risperidone (change in ABC-I of -12.1 to -14.9 vs. -3.6 to -6.5 with placebo; 3 RCTs, N=331) and aripiprazole (ABC-I change of -11.4 to -14.4 vs. -5 to -8.4 with placebo; 4 RCTs, N=493).[8] A minimum clinically important difference in ABC-I has not been established. CGI-I scores showed similar trends with significant symptom improvement with risperidone or aripiprazole compared to placebo. Two RCTs directly compared effects of aripiprazole and risperidone with no difference in ABC-I or CGI-I scores between groups (N=120).[8] Only one other antipsychotic, lurasidone, has been studied for symptoms of irritability and demonstrated no improvement in ABC-I, mixed results with CGI-I, and no dose response compared to placebo (1 RCT, N=150, moderate quality evidence).[8]

Disruptive Behavior, Impulse Control or Conduct Disorder

Eight RCTs evaluating quetiapine or risperidone vs. placebo in patients with disruptive behavior or conduct disorders were included in the DERP report. Trial durations ranged from 2 to 52 weeks.[8] All trials had moderate to high risk of bias with small sample sizes and high attrition rates. Most evidence evaluated risperidone compared to placebo (4 RCTs; n=640); evidence supporting other drugs was limited.[8] Patients had a mean NCBRF-conduct problems score of 32 to 34 at baseline indicating severe symptoms.[8] Use of risperidone improved symptom severity on the NCBRF scale by an average of 15-16 points compared to 6-7 points in patients randomized to placebo.[8] In an open-label extention trial, symptom improvement was maintained over 48 weeks.[8] There is no well established minimum clinially important difference for the NCBRF conduct problems subscale.

Safety of Antipsychotics

Adverse events frequently associated with antipsychotics include metabolic effects (e.g., weight gain and diabetes), extrapyramidal symptoms (e.g., akathisia, dyskinesia and dystonia), cardiovascular effects (e.g., prolonged QT interval), and hormonal effects (e.g., increased prolactin levels).[8] A summary of the relative frequency of these adverse events by drug in the general population is available from the Mental Health Clinical Advisory Group. Current evidence in children and adolescents supports these general trends,[8] though incidence may differ between adult and pediatric patients. For example, metabolic adverse events may be more frequent in children compared to adults.[10] However, because RCTs are often of short duration, many of the long-term effects of antipsychotic use in children and adolescents remain unknown, and the specific frequency and severity of adverse effects for pediatric patients is difficult to determine.

In the majority of clinical trials, use of antipsychotics was associated with increased changes in weight compared to placebo.[8] However, many studies did not evaluate statistical differences between groups. In children with autism, studies with longer duration were associated with increased weight gain, though the exact amount of weight gain which can be correlated with antipsychotic use is difficult to poinpoint in a young, growing population.[8] In patients with schizophrenia or bipolar disorder, olanzapine was associated with more weight gain compared to other antipsychotics.[8] Risperidone was consistently associated with elevated prolactin levels for all conditions.[8] Elevated prolactin levels were also reported with paliperidone in patients with schizophrenia.[8] In contrast, aripiprazole was associated with lower prolactin levels.[8] For patients with schizophrenia, risperidone was also associated with higher rates of extrapyramidal symptoms compared to other drugs.[8] Use of aripiprazole, risperidone, asenapine, and lurasidone were all associated with akathisia.[8]

Because of these adverse effects, guidelines recommend frequent evaluation and discontinuation if therapy has not demonstrated clinically meaningful improvements in symptoms. Recommended monitoring before treatment includes weight, height, waist and hip measurements, pulse and blood pressure, blood glucose, hemoglobin A1c (A1C), lipid, and prolactin levels, assessment of any movement disorders, nutritional status, diet and level of physical activity.[11,12] During initial treatment, follow-up should occur within the first 3 to 4 weeks. Identifying treatment goals, anticipated duration of treatment and pre-specified plans for stopping therapy prior to treatment initiation can assist when evaluating benefits and risks of therapy. Once therapy is stable, reassessment for adverse events should occur at every 4 to 6 months.[12,13] If adverse events occur, management strategies may include switching to a different antipsychotic or addition of adjunctive behavioral or medication therapy to target the adverse effect (e.g., addition of metformin for metabolic effects).[10,14] However, to date, there is limited evidence to support any single approach.

Guideline recommendations

Recommendations from the National Institute for Health and Care Excellence (NICE) for use of antipsychotics in children are described in **Table 3**. First-line therapy for many psychiatric conditions in children focuses on non-pharmacological treatment. Antipsychotic use in children or adolescents is typically only recommended in conjunction with a child/adolescent psychiatrist. Specifically, consultation with a specialist is recommended upon initiation of an antipsychotic for psychosis or schizophrenia, autism, conduct disorder or oppositional defiant disorder and for any patient with bipolar disorder younger than 14 years of age.[11-13,15] In all cases, frequent reassessment is required to evaluate efficacy and monitor for adverse effects.

Table 3. NICE guidance for appropriate antipsychotic use

Condition	Appropriate Use In Patients Under 19 Years of Age
Psychosis or schizophrenia[12]	➢ Only recommended if there are sufficient symptoms to definitively diagnose psychosis or schizophrenia ➢ Use is recommended in conjunction with psychological interventions such as CBT. CBT is most effective when combined with medication.
Bipolar Disorder[15]	➢ May be considered to treat mania, hypomania, or moderate to severe depressive symptoms. ➢ Routine use for >12 weeks is not recommended.
Autism[13]	➢ Routine use is not recommended. ➢ Recommended only with severe behavior non-responsive to psychosocial therapy. ➢ Treatment discontinuation is recommended within 6 weeks if efficacy is not established.
Conduct Disorder or Oppositional Defiant Disorder[11]	➢ Routine use is not recommended. ➢ Risperidone may be considered for short-term management of severely aggressive behavior. ➢ Treatment discontinuation is recommended within 6 weeks if efficacy is not established.
ADHD, PTSD, Anxiety, Mood[16] or Sleep Disorders	➢ Use of antipsychotics is not typically recommended ➢ For psychotic, recurrent depression or depression unresponsive to treatment, augmentation of an antidepressant with an antipsychotic may be considered in combination with intensive psychological therapy

Abbreviations: ADHD = attention deficit-hyperactivity disorder; CBT = cognitive behavioral therapy; PTSD = post-traumatic stress disorder

In patients with schizophrenia, guideline recommendations focus on early and regular monitoring for both treatment benefit and adverse events (see above for monitoring parameters and frequency). Specific recommendations on use of antipsychotics in children with autism and conduct disorders focus on frequent evaluation of therapy to establish benefit and assess adverse events.[13] Before prescribing antipsychotics, providers should identify the target behavior that's challenging, decide on an appropriate measure to monitor effectiveness, review effectiveness and adverse effects after 3-4 weeks, and stop treatment if there is no indication of clinically important response at 6 weeks.[13] Measures to evaluate effectiveness should include both frequency and severity of the targeted behavior and one measure to evaluate global impact. Guidelines recommend starting with a low dose and using the minimum effective dose needed for benefit. Similarly, when transferring care into the primary care setting, the specialist should communicate the monitoring plan, selection of target behaviors, potential for minimally effective dosing, planned duration of treatment and plans for stopping treatment.[13]

Oregon Medicaid Policy

In 2021, the Oregon Pharmacy and Therapeutics Committee recommended implementation of safety edits in young children (≤ 5 years of age) on Medicaid with antipsychotic use. While use of antipsychotics in this population has steadily decreased over time, there is still a small proportion of children on Medicaid less than 6 years of age prescribed antipsychotics (66 patients in 2020 and 55 patients in 2021). This safety edit is intended to ensure appropriate antipsychotic use and monitoring for this population.

Alternative non-pharmacological therapies are available for common disorders in children such as autism or challenging behavior. The Oregon Health Authority (OHA) covers a wide range of non-pharmacological applied behavioral analysis-based interventions including parent training, early intensive behavioral intervention, play/interaction based interventions, and joint attention interventions. Alternative first-line options for treatment of irritability or challenging behavior associated with autism include psychosocial interventions targeted to anticipate and prevent behavior that challenges and develop a care plan with the patient and caregivers which includes steps to address triggers that may provoke challenging behavior.[13] For example, care plans may include addressing and treating coexisting physical, mental health and behavioral conditions, providing support for family and caregivers, and/or making adjustments to increase structure and minimize unpredictability within the environment.[13] Additional resources available to providers in Oregon are available below.

Resources

- Safety edit for Medicaid patients ≤ 5 years of age
- Oregon Psychiatric Access Line: free, same-day (Monday through Friday) psychiatric phone consultation service for primary care providers in Oregon. Provides Care guides.
- Provider resources for alternative first-line therapies in early childhood including parent-child interaction therapy
- OHA Resources for Applied Behavior Analysis
- Programs with local supports for patients including the Early Assessment and Support Alliance for youth with psychosis

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Updated 2021 Treatment Guidelines for Sexually Transmitted Infections

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Introduction

Sexually transmitted infections (STIs) can lead to long-term health consequences such as infertility, facilitate human immunodeficiency virus (HIV) transmission, and contribute to infant morbidity and mortality.[1] In 2019, more than 2.5 million cases of chlamydia, gonorrhea, and syphilis were reported in the United States (U.S.).[2] This was an all-time high of reported STIs for the sixth consecutive year.[2] From 2014 to 2018, reported cases of primary and secondary syphilis, congenital syphilis, gonorrhea, and chlamydia rose by 71%, 185%, 63%, and 19%, respectively.[3] Additionally, human papillomavirus (HPV), the most common STI, accounts for 14 million new infections each year.[3] Data from 2019 demonstrate that STI rates were higher in youth aged 15-24 compared to other age groups and in racial and ethnic groups who have been most impacted by historic and contemporary injustices or health inequities compared to patients identifying as white.[2]

In response to bacterial resistance trends, the Centers for Disease Control and Prevention (CDC) treatment guidelines for STIs were updated in 2021.[1] In addition, a National Strategic Plan was developed to provide guidance in STI prevention, care, and treatment for all people while living free from stigma and discrimination.[3] This newsletter will summarize pertinent changes to recent CDC guidance for clinical prevention of STIs and treatment regimens for chlamydia, gonorrhea and syphilis. A previous Oregon State newsletter discussed the role of pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) in prevention of HIV transmission.[4]

Clinical Prevention

Primary prevention of STIs includes assessment of behavioral risk and biologic risk (i.e., testing for risk markers for STIs and HIV acquisition or transmission).[1] Pre-exposure vaccination is one of the most effective methods for preventing transmission of HPV, hepatitis A virus, and hepatitis B virus, all of which can be sexually transmitted.[1] HPV vaccination is recommended routinely for males and females 11 or 12 years of age and can be administered beginning at 9 years of age.[5] HPV vaccination is recommended through 26 years of age for those not previously vaccinated.[5] In addition, hepatitis A and B vaccines are recommended for men who have sex with men, persons who inject drugs, persons with chronic liver disease, and persons with HIV or hepatitis C infections who have not had hepatitis A or hepatitis B infections.[6] Hepatitis A vaccine is also recommended for persons who are homeless.[7]

Recommendations For Treatment Of Chlamydia Trachomatis

Chlamydial infection is the most frequently reported bacterial infectious disease in the U.S., and prevalence is highest among people less than 25 years of age.[1] Treatment of *C. trachomatis* prevents adverse reproductive health complications, continued sexual transmission, and vertical transmission to neonates during birth.[1] Additionally, treatment of sex partners can prevent reinfection and infection of other partners. Recommended antibiotics for treatment of chlamydia are outlined below. In patients who are pregnant, clinical experience and published studies indicate that azithromycin is safe to use and is the recommended regimen for pregnant patients.[8-10] Doxycycline is contraindicated during the second and third trimesters of pregnancy because of risk for tooth discoloration.[11] Human data indicate that levofloxacin presents a low risk to the fetus during pregnancy but has potential for toxicity during breastfeeding, while data from animal studies suggest concerns regarding cartilage damage to neonates.[11]

Recommended CDC Antibiotic Regimen for Chlamydial Infection for Adolescent and Adults:
Doxycycline 100 mg orally 2 times per day for 7 days
Alternative Regimens:
Azithromycin 1 gram orally in a single dose
OR
Levofloxacin 500 mg orally once daily for 7 days

Recommendations For Treatment Of Neisseria Gonorrhoeae

In the U.S., an estimated 1,568,000 new *N.gonorrhoeae* infections occur each year, and gonorrhea is the second most commonly reported bacterial communicable disease.[1] Urethral infections caused by *N. gonorrhoeae* can produce symptoms among men that cause them to seek curative treatment soon enough to prevent sequelae, but often not soon enough to prevent transmission to others.[1] Among women, gonococcal infections are commonly asymptomatic or might not produce recognizable symptoms until complications (e.g., pelvic inflammatory disease [PID]) have occurred.[1] PID can result in tubal scarring that can lead to infertility or ectopic pregnancy.[1]

Gonorrhea treatment is complicated by increasing antimicrobial resistance.[12] Emergence of fluoroquinolone-resistant *N. gonorrhoeae* in 2007 in the U.S. prompted CDC to cease recommending fluoroquinolones for gonorrhea treatment, leaving cephalosporins as the main class of antimicrobials available for gonorrhea treatment in the U.S.[12] A key change from prior guidance is that dual therapy with ceftriaxone and azithromycin is no longer recommended as of 2020.

Recommended CDC Antibiotic Regimen for Uncomplicated Gonococcal Infection of the Cervix, Urethra or Rectum:
Ceftriaxone 500 mg IM in a single dose for persons weighing < 150 kg. Persons weighing ≥ 150 kg should receive **Ceftriaxone** 1 gram IM for a single dose.

Alternative Regimens:
Gentamicin 240 mg IM in a single dose **PLUS Azithromycin** 2 gram orally in a single dose ***OR***
Cefixime 800 mg orally in a single dose

Expedited Partner Therapy

Expedited partner therapy (EPT) is a harm-reduction strategy and the clinical practice of treating the sex partners of persons with diagnosed chlamydia or gonorrhea, who are unable or unlikely to seek timely treatment, by providing medications or prescriptions to the patient as allowable by law.[1] Patients then provide partners with these therapies without the health care provider having examined the partner. Medical providers should routinely offer EPT to patients with chlamydia when the provider cannot ensure that all of a patient's sex partners from the previous 60 days will seek timely treatment.[1] If the patient has not had sex during the 60 days before diagnosis, providers should offer EPT for the patient's most recent sex partner.[1] In Oregon, the prescriber would follow OAR 855-041-4005 and write multiple prescriptions: one Rx for the patient and one Rx for each unnamed partner(s) writing "EPT Partner" on each Rx. The partner would fill their own Rx, or the patient would have to have their partner's pharmacy coverage information to fill it for them.

Because EPT must be an oral regimen and current gonorrhea treatment involves a single intramuscular (IM) injection of ceftriaxone 500 mg, EPT for gonorrhea should be offered to partners unlikely to access timely evaluation after linkage is explored.[1] The partner may be treated with a single 800 mg dose of oral cefixime, if a chlamydia infection in the patient has been excluded.[12] If a chlamydia test result has not been documented, the partner may be treated with a single dose of oral cefixime 800 mg plus oral doxycycline 100 mg 2 times per day for 7 days.[12]

Syphilis Testing and Treatment Among Pregnant Women

During 2012–2019, congenital syphilis rates in the U.S. increased from 8.4 to 48.5 cases per 100,000 births, a 477.4% increase.[2] Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care, methamphetamine or heroin use, incarceration of the woman or her partner, and unstable housing or homelessness.[1] In the U.S., all pregnant women should be screened for syphilis at the first prenatal visit, even if they have been tested previously.[13] Testing in the third trimester and at delivery can help prevent congenital syphilis cases.[14] Pregnant women should be retested for syphilis at 28 weeks' gestation and at delivery if the mother lives in a community with high syphilis rates or is at risk for syphilis acquisition during pregnancy (e.g., having a substance use disorder, having an STI during pregnancy, having multiple sex partners, having a new sex partner, or having a sex partner with an STI).[1] Additionally, any woman who has a fetal death after 20 weeks' gestation should be tested for syphilis.[1]

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy and for treating patients in all stages of syphiilis.[1] Selection of the appropriate penicillin preparation is important because the bacteria that causes syphilis, *Treponema pallidum*, can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by certain forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for syphilis treatment.[1] Reports have indicated that practitioners have inadvertently prescribed combination long- and short-acting benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) recommended in the U.S. for treating primary, secondary, and latent syphilis.[1] A single dose of benzathine penicillin 2.4 million units IM is recommended for adults with primary and secondary syphilis.[1] Certain evidence indicates that additional therapy is beneficial for pregnant women to prevent congenital syphilis.[15] For pregnant women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose.[15] Pregnant women with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin G.[1] Additional guidance for management of adults with latent, tertiary, or neurosyphilis, as well as syphilis in infants, children, and pregnancy can be accessed at the CDC website: https://www.cdc.gov/mmwr/volumes/70/rr/rr7004a1.htm.

Recommended CDC Antibiotic Regimen for Adults with Primary and Secondary Syphilis:
Benzathine Penicillin 2.4 million units IM as a single dose

Conclusion

Less than 20 years ago, gonorrhea rates in the U.S. were at historic lows, syphilis was close to elimination, and advances in chlamydia diagnostics made it easier to detect infections.[2] That progress has been lost, due in part to challenges to the U.S. public health system.[2] Organizations across the nation are partnering to prevent STIs by leveraging innovative approaches such as telehealth/telemedicine, developing partnerships with pharmacies and retail health clinics, and establishing STI express clinics to meet patients where they are with the testing and prevention services they urgently need.[2] As part of the clinical encounter, health care providers should routinely obtain sexual histories from their patients and address risk reduction and treatment regimens as recommended in the CDC guidance[1] and STI National Strategic Plan.[3]

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Drug Class Update: Estrogens

Date of Review: August 2022

Date of Last Review: January 2017
Dates of Literature Search: 09/01/2016 - 04/04/2022

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

Plain Language Summary:

- This review looks at whether new evidence should change the current policy for estrogens.
- Estrogens are taken by mouth, applied to the skin or inserted within the vagina.
- Estrogens and progestins are medicines used to treat hot flashes and other issues in people who are going through menopause. Providers also prescribe estrogens to people to prevent broken bones associated with bone disease and for some types of cancers.
- Use of estrogens increases risk of breast cancer, stroke, blood clots, gallbladder disease and urinary leakage. Estrogen applied to the skin have a lower risk of breast cancer than estrogens taken by mouth, but there is still an increased risk compared to taking no estrogen. People that have a uterus often take estrogen with a progestin to reduce the risk of endometrial cancer.
- Estrogens have both benefits and risks when used to prevent diabetes, colorectal cancers and heart disease. The United States Preventative Services Task Force (USPSTF) does not recommend estrogens for prevention of these conditions.
- Two new medicines are approved to treat menopause symptoms called Bijuva and Imvexxy. No studies show that they improve menopause symptoms compared to other estrogens.
- Fee-for-service (FFS) Medicaid pays for estrogen medicines. Certain estrogen medicines require the provider to explain why the specific estrogen in needed before paying for it. This is called a prior authorization.
- The Drug Use Research Management program does not recommend any changes to the estrogen policy.

Purpose for Class Update:
A comprehensive literature search and evaluation on the comparative efficacy and safety of estrogen preparations was performed based on evidence published since the last update in 2017.

Research Questions:

1. Is there new comparative evidence on the effectiveness of estrogen therapies, used as monotherapy or in combination with progestins, for the treatment of menopausal symptoms or prevention of osteoporosis?
2. Is there new comparative evidence on the harms of estrogen products?
3. Are there subpopulations of women in which certain estrogen products have demonstrated superior efficacy or increased risk of harms?

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Conclusions:

- There were two systematic reviews, two guidelines, two safety warnings and two safety alerts identified since the last review in January of 2017.
- There is moderate quality evidence from a Cochrane review evaluating long-term hormone therapy (HT) (at least 1 year) for perimenopausal and menopausal women that HT reduces in the risk of fracture.[1] There is moderate quality evidence that combination HT increases the risk of stroke, venous thromboembolism (VTE) and gallbladder disease.[1]
- Hormone therapy for the primary prevention of chronic conditions in postmenopausal women was the focus of a 2017 Agency for Healthcare Research and Quality (AHRQ) review.[2] There is moderate to high quality evidence demonstrating the risk of diabetes and fractures is reduced with the use of estrogen alone. Combination estrogen and progestin therapy was found to decrease the risk of colorectal cancers, diabetes and fractures based on moderate to high quality of evidence. Increased risk of harms associated with estrogen use and combination HT included: gallbladder disease, breast cancer, stroke, VTE and urinary incontinence.[2]
- Guideline updates from National Institute for Health and Care Excellence (NICE) and the European Alliance of Associations for Rheumatology (EULAR) support the current policy on estrogens.[3,4]
- Two new formulations of estradiol were approved since the last review. Estradiol/progesterone 1 mg/100 mg combination product (Bijuva) capsules were approved for the use of moderate to severe vasomotor symptoms based on one placebo-controlled trial.[5] Estradiol vaginal inserts (Imvexxy) 4 mcg and 10 mcg were approved for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.[6]
- There was insufficient evidence on subgroup populations, such as differences in ethnicities and race, time since onset of menopausal symptoms and women with an intact uterus.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on evaluation of the clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- No changes were made to the estrogen derivatives PDL as a result of the update in 2017.
- Current policy consists of a prior authorization (PA) criteria requiring an Oregon Health Plan (OHP) approved diagnosis.

Background:

Estrogens are part of hormone replacement therapy used for reducing menopausal symptoms.[1] Estrogen is often used in combination with progestin products. The FDA approved uses for HT are for the treatment of menopausal symptoms and prevention of osteoporosis.[2] Estrogen is also used off-label for gender dysphoria disorder and palliative care in metastatic breast and prostate cancer.[7]

Menopause causes decreased estrogen levels with corresponding cessation of menstrual cycle, vasomotor symptoms, musculoskeletal, urogenital and psychological symptoms.[3] Symptoms can be associated with decreased quality of life affecting families and work environments. Menopause alone has been identified as a risk factor for cardiovascular disease (CVD).[2] Approximately 60% to 80% of women experience menopausal symptoms, 20% of them are considered severe symptoms. Prevalence varies between different ethnic groups and cultures, with a higher incidence in Black and Hispanic women.[8]

Treatment recommendations for menopausal symptoms include the use of lubricants and gels as well as lifestyle modifications (e.g., weight loss, smoking cessation). Estrogen products are considered the most effective treatment for vasomotor symptoms and should be considered in women who need additional treatment for menopausal symptoms who do not have contraindications. In women with an intact uterus, estrogen is given in combination with progestins to avoid hyperplasia or carcinoma.[8] A reduction in 50% or more in the frequency and severity of vasomotor symptoms is considered a clinically meaningful effect.[8] Estrogen is available as the following dosage formulations: oral, vaginal, intranasal, transdermal or subcutaneous implant. Estrogen derivatives include estradiol, estradiol valerate synthetic conjugated estrogens, ethinyl estradiol, or conjugated equine estrogen (**Appendix 1**).

Evidence for the long-term benefits and risks of HT has been mixed. Findings from the Women's Health Initiative (WHI) found HT prevented fractures and colon cancer, but noted an increased risk of cardiovascular (CV) events and breast cancer.[9] Mixed evidence has also suggested the use of HT in older women for prevention of CV disease, osteoporosis and cognitive decline. Observational studies of HT have demonstrated a reduced risk of coronary heart disease (CHD); however, findings from randomized controlled trials (RCTs) failed to demonstrate CHD benefits.[2] The United States Preventative Services Task Force (USPSTF) recommends against the use of HT for the primary prevention of chronic conditions.[10]

Oregon Health Plan (OHP) fee-for-service (FFS) population 125 women received oral estrogen products (99% preferred formulations), 35 patients received topical estrogen products (100% preferred formulations) and 22 patients received transdermal estrogen products (49% preferred formulations) based on claims from the first quarter of 2022. The overall cost for the class does not represent a substantial monetary burden to OHP.

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.

New Systematic Reviews:

Hormone Replacement Therapy

Cochrane – Long-term Hormone Replacement Therapy for Perimenopausal and Postmenopausal Women
A 2017 review evaluated the literature to determine the effects of long-term HT, at least 1 year's timeframe, on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women.[1] The use of HT (e.g., estrogens with or without progestins) were included in the systematic review. Routes of administration included oral, transdermal, subcutaneous, or intranasal. Most studies used moderate doses of estrogen (e.g., conjugated equine estrogens [CEE] 0.625 mg daily, estradiol 1 mg, transdermal estradiol 0.05 mg twice weekly). The dose of progesterone used in continuous combination estrogen and progesterone regimens were the following; medroxyprogesterone acetate (MPA) 2.5 mg daily, MPA 10 mg daily and 1 mg norethindrone daily. Twenty-two studies were included (n=43,637) involving predominately healthy postmenopausal women of whom most were 60 years and

older (range of 26 to 91 years).[1] Only 30% of women were 50-59 years, which is the age of women who most often seek the use of estrogen for the management of vasomotor symptoms.[1] Most of the evidence was found to be at low risk of bias.

The use of combined continuous HT, moderate dose estrogen and medroxyprogesterone, was associated with moderate quality of evidence for all of the outcomes studied. Findings are presented in **Table 1**.[1] There were more coronary events, stroke, VTE, breast cancer, gallbladder disease and death from lung cancer with the use of HT compared to placebo. There was a reduction in the risk of clinical fractures with HT versus placebo. The use of estrogen only HT are also presented in **Table 1**. Moderate strength of evidence found an increased the risk of stroke, VTE with follow-up of 1-2 years and gallbladder disease with estrogen compared to placebo.[1] The risk of breast cancer and clinical fractures was reduced with the use of HT compared to placebo. There was no effect on the risk of coronary disease with the use of estrogen only HT.

Table 1. Hormone Therapy in Postmenopausal Women[1]

Outcome	Follow-up	Results	Quality of Evidence
Combined Continuous Hormone Therapy Compared to Placebo			
Coronary events (MI or cardiac death)	Mean/median 1 year	RR 1.89 (95% CI, 1.15 to 3.10)	Moderate
Stroke	Mean 3 years	RR 1.46 (95% CI, 1.02 to 2.09)	Moderate
Venous thromboembolism (DVT or PE)	Mean/median 1 year	RR 4.28 (95% CI, 2.49 to 7.34)	Moderate
Breast cancer	Median 5.6 years	RR 1.27 (95% CI, 1.03 to 1.56)	Moderate
Death from lung cancer	Median 8 years	RR 1.74 (95% CI, 1.18 to 2.55)	Moderate
Gallbladder disease	Mean 5.6 years	RR 1.64 (95% CI, 1.30 to 2.06)	Moderate
All clinical fractures	Mean 5.6 years	RR 0.78 (95% CI, 0.71 to 0.86)	Moderate
Estrogen Only Hormone Therapy compared to Placebo			
Coronary events (MI or cardiac death)	Mean 7.1 years	RR 0.94 (95% CI, 0.78 to 1.13)	Moderate
Stroke	Mean 7.1 years	RR 1.33 (95% CI, 1.06 to 1.67)	Moderate
Venous thromboembolism (DVT or PE)	1-2 years	RR 2.22 (95% CI, 1.12 to 4.39)	Moderate
Venous thromboembolism (DVT or PE)	Mean 7.1 years	RR 1.32 (95% CI, 1.00 to 1.74)	Moderate
Breast cancer	Mean 7.1 years	RR 0.79 (95% CI, 0.61 to 1.01)	Moderate
Gallbladder disease	Mean 7.1 years	RR 1.78 (95% CI, 1.42 to 2.24)	Moderate
All clinical fractures	Mean 7.1 years	RR 0.73 (95% CI, 0.65 to 0.80)	Moderate

Abbreviations: CI – confidence interval; DVT – deep vein thrombosis; MI – myocardial infarction; PE – pulmonary embolism; RR – relative risk.

There is good evidence for the use of HT for relief of menopausal symptoms associated with menopause. Evidence suggests additional benefit for prevention of postmenopausal osteoporosis but is reserved for patients who are unable to take non-estrogen options. Estrogens should not be used for primary or secondary prevention CV disease. Estrogens should be avoided in women who are at high risk of CV disease, thromboembolic disease or certain cancers (e.g., breast, uterine).[1]

AHRQ – Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women

The AHRQ did a systematic review and meta-analysis for the U.S. Preventive Services Task Force in 2017. The objective was to evaluate the benefits and risks of HT for primary prevention of chronic conditions in postmenopausal women.[2] Evidence was searched through August of 2016 and ongoing surveillance of the literature occurred through August 2017. Most studies included healthy women who were perimenopausal or postmenopausal with one year or more of HT. Seventeen fair-quality trials were identified and met eligibility criteria for inclusion into the review.[2] The WHI was the largest contributor to the data. Analyses were divided into those women who used estrogen alone and those who took combination therapy with estrogen and progestin therapy.

There are benefits and risks identified with both estrogen alone and combination estrogen plus progestin therapy (**Tables 2 and 3**).[2] There was no increased risk or benefit of all-cause mortality in women who took estrogen alone or estrogen plus progestin based on moderate to high quality of evidence.

Table 2. Risks and Benefits of Estrogen Monotherapy compared to Placebo[2]

Outcome	Population	Cases/Quality of Evidence
Benefits of Therapy		
Diabetes (new diagnosis requiring medication)	Per 10,0000 women over 6.8 to 7.2 years	137 fewer cases/moderate
Fractures	Per 10,000 women over 6.8 to 7.2 years	382 fewer cases/high
Risks of Therapy		
Gallbladder disease*	Per 10,000 women 5.4 to 7.1 years	213 more cases/moderate
Stroke	Per 10,000 women 5.4 to 7.1 years	79 more cases/moderate
Venous thromboembolism	Per 10,000 women 5.4 to 7.1 years	78 more cases/moderate
Urinary incontinence†	Per 10,000 women during a 1 year follow-up	1,261 more cases/moderate
Key: * Gallbladder disease was defined as cholecystitis and cholelithiasis); † Urinary incontinence was defined as stress, urge and overall		

Table 3. Risks and Benefits of Estrogen Plus Progestin Therapy compared to Placebo[2]

Outcome	Population	Cases/Quality of Evidence
Benefits of Therapy		
Colorectal cancer	Per 10,0000 women over 5.0 to 5.6 years	33 fewer cases/moderate
Diabetes (new diagnosis requiring medication)	Per 10,000 women over 5.0 to 5.6 years	77 fewer cases/moderate
Fractures	Per 10,000 women over 5.0 to 5.6 years	222 fewer cases/high
Risks of Therapy		
Invasive breast cancer	Per 10,000 women 4.0 to 5.6 years	52 more cases/high
Probable dementia	Per 10,000 women 4.0 to 5.6 years	88 more cases/moderate
Gallbladder disease	Per 10,000 women 4.0 to 5.6 years	116 more cases/moderate
Stroke	Per 10,000 women 4.0 to 5.6 years	53 more cases/high
Venous thromboembolism	Per 10,000 women 4.0 to 5.6 years	120 more cases/moderate
Urinary incontinence†	Per 10,000 women follow-up of 1 year	876 more cases/moderate
Key: * Gallbladder disease was defined as cholecystitis and cholelithiasis); † Urinary incontinence was defined as stress, urge and overall		

Limitations to the evidence were lack of comparisons between the different types, doses and delivery routes of HT. Subgroup analyses and trials were not powered to detect differences in preventative outcomes. There was insufficient data on the use of HT in women who were younger and nonwhite ethnicity.

After review, 16 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).[11–26]

New Guidelines:
High Quality Guidelines:

NICE – Menopause: Diagnosis and Management
The National Institute for Health and Care Excellence originally published guidance for the management of menopause in 2015 and has since provided updates in 2019 and 2021.[3] All recommendations include routine assessment of symptoms to tailor therapy to current needs of women experiencing menopause. Treatment recommendations for management of menopausal symptoms are outlined in **Table 4**.[3] Vasomotor symptoms should not be treated with SSRIs, SNRIs, or clonidine as first-line treatment. Isoflavones or black cohosh may relieve vasomotor symptoms; however, preparation may vary, drug interactions have been reported, multiple preparations are available and safety is unknown.

Vaginal estrogens relieved symptoms of urogenital atrophy without the safety risks associated with systemic estrogen products. Oral HT increases the risk of VTE and can present early in treatment and increases with age.[3] The risk of VTE is not significantly increased with the use of transdermal products. After discontinuation of HT the increased risk of VTE is eliminated. Women who are at increased risk of VTE or who have a body mass index greater than 30 kg/m^2 should consider transdermal HT instead of oral therapy.[3] Additional risks with HT include an increased incidence of stroke; however, the evidence is low to very low quality. There was no additional CV risk noted with HT use in women under the age of 60 years and there was no increased risk of CV mortality. Low quality evidence found no increased risk of diabetes with the use of HT. The use of HT had no benefit or risk of developing or preventing dementia based on very low to moderate quality of evidence.[3] There is low to moderate quality of evidence that HT reduces the risk of fragility fracture, even upon HT discontinuation.

Additional safety updates on the increased risk of breast cancer with HT was added to the guidance.[27] The increased risk is with all HT preparations except for vaginal estrogens. The increased risk persists for more than 10 years after the HT is discontinued. The shortest duration and lowest dose of HT should be utilized.

Table 4. NICE Recommendations for Management of Menopausal Symptoms[3]

Symptom	Recommendation	Quality of Evidence
Vasomotor Symptoms	• Offer HT after discussing the short-term (up to 5 years) and longer-term benefits and risks • Options include: - Estrogen and progestin to women with a uterus - Estrogen alone to women without a uterus	• Very low to moderate quality • Limited data beyond 1 year
Urogenital Atrophy	• Vaginal estrogens should be offered (even if taking systemic HT) and continue treatment as long as needed to relieve symptoms • Vagina estrogens should be offered to women in whom HT is contraindicated	• Very low to moderate quality

Psychological Symptoms	• Recommended HT for women with low mood due to menopause • There is no clear evidence for the use of SSRIs or SNRIs to ease low mood in women with menopausal symptoms who have not been diagnosed with depression	• Very low quality of evidence
Altered Sexual Function	• Consider testosterone supplementation for menopausal women with low sexual desire if HT is not effective	• Very low quality of evidence
Abbreviations: HT – hormone therapy; SNRIs- serotonin norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors		

<u>EULAR – Recommendations for Women's Health and the Management of Family Planning, Assisted Reproduction, Pregnancy and Menopause in Patients with Systemic Lupus Erythematosus and/or Antiphospholipid Syndrome</u>

A 2017 guideline completed by EULAR updated the recommendations for the use of HT in women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS).[4] Guideline methodology was well described and authors reported no conflicts of interest. The evidence was graded from level 1 to 3, with level 1 evidence being the highest level, consisting of RCTs or meta-analyses, level 2 is sufficient evidence with questionable confidence in the evidence and level 3 being the lowest level of evidence. Grading of the recommendations ranged from A to D. Grade A is based on high level of evidence, Grade B recommendations are based on level 1 evidence with concerns of validity, Grade C is based on level 1 or 2 evidence and Grade D is based on expert opinion.[4] The focus of this review will be on the recommendations for the use of estrogens in women with SLE and/or APS. Other therapies will be discussed according to their corresponding class update. The use of estrogen products, as part of HT, can be used for women with severe vasomotor menopausal symptoms that have SLE which is stable/inactive based on negative antiphospholipid antibodies (aPL).[4] There is no evidence of severe exacerbations of SLE with the use of HT in RCTs lasting up to 24 months. In women with APS, the benefits of the use of HT should be weighed against the risk of thrombotic and CV risks. Evidence is limited on the optimal duration of HT; however, it is recommended that the shortest duration possible be used.

Additional Guidelines for Clinical Context:

<u>Endocrine Society – Pharmacological Management of Osteoporosis in Postmenopausal Women</u>

The recommendations for the use of HT were included in the guidelines for the management of osteoporosis in postmenopausal women issued by the Endocrine Society.[28] Recommendations were based off a systematic review and meta-analysis; however, specifics of the search were not included. The evidence was graded from very low quality to high quality. The strength of recommendations were designated as "recommended" and "we suggest" based on the evidence. Fifty percent of authors had conflicts of interest and funding was provided by the Endocrine Society, which partners with industry. Recommendations will be included for clinical context but not used for policy decisions.

The use of estrogen only HT is recommended for postmenopausal women with hysterectomy who are at high risk of fracture to prevent all types of fractures with the following patient characteristics; under 60 years of age or < 10 years past menopause; at low risk of deep vein thrombosis, those who are not candidates for the use of bisphosphonates or denosumab, bothersome vasomotor symptoms, climacteric symptoms, without contraindications, no history of stroke or myocardial infarction, without breast cancer, and willing to take HT.[28] This is a suggested recommendation supported by moderate quality of evidence.

After review, 5 guidelines were excluded due to poor quality or insufficient evidence.[29–33]

New Formulations or Indications:

Estradiol and progesterone capsules (Bijuva): In 2018 a new drug approval was granted for the estradiol/progesterone 1 mg/100 mg combination product indicated for women with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.[5] Combination estradiol/progesterone was shown to reduce moderate to severe vasomotor symptoms, frequency and severity, more than placebo in one 12-week, randomized, single-arm study (n=726). At 12 weeks reduction in mean weekly frequency of symptoms were reported as clinically meaningful with a difference from placebo in the estradiol/progesterone arm of -16.58; p<0.001.[5] The severity of weekly moderate to severe vasomotor symptoms was reduced with estradiol/progesterone by -0.57 (p<0.001) compared to placebo at week 12. Four cases of breast cancer were diagnosed over the year-long safety study, 2 in patients treated with estradiol/progesterone 0.5 mg/100 mg and 2 in the estradiol/progesterone 1 mg/100 mg and none in the placebo group. As with other estrogen products there is a black box warning for the risk of increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[5] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

Estradiol vaginal inserts (Imvexxy): Estradiol vaginal inserts 4 mcg and 10 mcg were approved in 2018 for the treatment of moderate to severe dyspareunia, symptom of vulvar and vaginal atrophy, due to menopause.[6] Evidence for approval was from one 12-week, double-blind, placebo-controlled, study of 574 women who were postmenopausal. For moderate to severe symptoms of dyspareunia associated with postmenopausal vulvar and vaginal atrophy at 12 weeks compared to baseline were associated with reductions; estradiol 4 mcg, estradiol 12 mcg and placebo, -1.52 (p = 0.0149 compared to placebo), -1.69 (p<0.0001 compared to placebo) and -1.28, respectively.[6] As with other estrogen products there is a black box warning for the risk of increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[6] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

New FDA Safety Alerts:

Table 5. 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)
Estradiol Topical[34]	Divigel Vivelle-DOT	December 2019 October 2021	Boxed Warning	The boxed warning was updated to document that the risk of increased adverse CV events and dementia seen with higher CE doses with lower have not been fully studied and these risks can't be excluded with lower CE doses. The risk of CV events, dementia and breast cancer with combination therapy (e.g., low CE with MPA), have also not been studied and therefore, an increased risk cannot be excluded. The risks and benefits should be discussed with the patient.
Estradiol Topical[34]	Climara Alora Estraderm Minivelle Elestrin Estrogel Divigel Menostar	November 2017	Warnings and Precautions	There is evidence for an increased risk of ovarian cancer with the use of HT. The exact duration of HT use associated with an increased risk of ovarian cancer is not known.

Abbreviations: CE – conjugated estrogens; CV – cardiovascular; COC - combination oral contraceptives; HT – hormone therapy; MPA – medroxyprogesterone acetate.

Randomized Controlled Trials:

No new RCTS were identified. A total of 1,168 citations were manually reviewed from the literature search. Only trials reporting new comparative evidence were considered for inclusion. After manual review RCTs were excluded due to wrong study design, comparator, outcome studied, or lack of reported comparative outcome data.

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Appendix 1: Current Preferred Drug List

Estrogens, Oral

Generic	Brand	Form	PDL
estradiol	ESTRACE	TABLET	Y
estradiol	ESTRADIOL	TABLET	Y
estrogens,conj.,synthetic A	CENESTIN	TABLET	Y
estropipate	ESTROPIPATE	TABLET	Y
estropipate	OGEN	TABLET	Y
drospirenone/estradiol	ANGELIQ	TABLET	N
estradiol/norethindrone acet	ACTIVELLA	TABLET	N
estradiol/norethindrone acet	AMABELZ	TABLET	N
estradiol/norethindrone acet	ESTRADIOL-NORETHINDRNE ACETAT	TABLET	N
estradiol/norethindrone acet	LOPREEZA	TABLET	N
estradiol/norethindrone acet	MIMVEY	TABLET	N
estradiol/norgestimate	PREFEST	TABLET	N
estradiol/progesterone	BIJUVA	CAPSULE	N
estrogen,con/m-progest acet	PREMPHASE	TABLET	N
estrogen,con/m-progest acet	PREMPRO	TABLET	N
estrogen,ester/me-testosterone	ESTRATEST	TABLET	N
estrogen,ester/me-testosterone	ESTRATEST H.S.	TABLET	N
estrogen,ester/me-testosterone	ESTROGEN-METHYLTESTOSTERONE	TABLET	N
estrogen,ester/me-testosterone	SYNTEST D.S.	TABLET	N
estrogens, conjugated	PREMARIN	TABLET	N
estrogens,conj/bazedoxifene	DUAVEE	TABLET	N
estrogens,esterified	ESTRATAB	TABLET	N
estrogens,esterified	MENEST	TABLET	N
norethindrone ac-eth estradiol	FEMHRT	TABLET	N
norethindrone ac-eth estradiol	FYAVOLV	TABLET	N
norethindrone ac-eth estradiol	JINTELI	TABLET	N
norethindrone ac-eth estradiol	NORETHINDRON-ETHINYL ESTRADIOL	TABLET	N

Estrogens, Topical

Generic	Brand	Form	PDL
estradiol	ALORA	PATCH TDSW	Y
estradiol	DOTTI	PATCH TDSW	Y
estradiol	ESTRADERM	PATCH TDSW	Y
estradiol	ESTRADIOL (TWICE WEEKLY)	PATCH TDSW	Y
estradiol	LYLLANA	PATCH TDSW	Y
estradiol	MINIVELLE	PATCH TDSW	Y
estradiol	VIVELLE-DOT	PATCH TDSW	Y

estradiol	CLIMARA	PATCH TDWK	Y
estradiol	ESTRADIOL (ONCE WEEKLY)	PATCH TDWK	Y
estradiol	ELESTRIN	GEL MD PMP	N
estradiol	ESTROGEL	GEL MD PMP	N
estradiol	DIVIGEL	GEL PACKET	N
estradiol	MENOSTAR	PATCH TDWK	N
estradiol	EVAMIST	SPRAY	N
estradiol/levonorgestrel	CLIMARA PRO	PATCH TDWK	N
estradiol/norethindrone acet	COMBIPATCH	PATCH TDSW	N

Estrogens, Vaginal

Generic	Brand	Form	PDL
estradiol	ESTRADIOL	TABLET	Y
estradiol	VAGIFEM	TABLET	Y
estradiol	YUVAFEM	TABLET	Y
estrogens, conjugated	PREMARIN	CREAM/APPL	Y
estradiol	ESTRACE	CREAM/APPL	N
estradiol	ESTRADIOL	CREAM/APPL	N
estradiol	ESTRING	VAG RING	N
estradiol acetate	FEMRING	VAG RING	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 04, 2022
Search Strategy:

#	Searches	Results
1	vasomotor system.mp. or Vasomotor System/	9471
2	Osteoporosis, Postmenopausal/	13826
3	hypoestrogenism.mp.	496
4	vagina atrophy.mp.	3
5	vulva atrophy.mp.	0
6	estrogen replacement therapy.mp. or Estrogen Replacement Therapy/	16825
7	estrogen.mp. or Estrogens/	186764
8	estradiol.mp. or Estradiol/	128143
9	estropipate.mp.	61
10	ethinyl estradiol.mp. or Ethinyl Estradiol/	10611
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	278558
12	limit 11 to (english language and humans and yr="2016 -Current")	26502
13	limit 12 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	1168

Appendix 3: Key Inclusion Criteria

Population	Women with menopausal symptoms, individuals with hypoestrogenism or osteoporosis
Intervention	Estrogen derivatives (monotherapy and with progestins)
Comparator	Placebo or other active treatments for menopausal symptoms, hypoestrogenism, or postmenopausal osteoporosis prevention
Outcomes	Improvement in the frequency or severity of menopausal symptoms, estrogen levels or decreased fracture rates
Timing	Onset of mild to moderate menopausal symptoms or relevant diagnosis
Setting	Outpatient

Estrogen Derivatives

Goal(s):

- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred estrogen derivatives
- All estrogen derivatives for patients <18 years of age

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 estrogen requested for a patient ≥18 years old?	**Yes:** Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • ~~Preferred products do not require a co-pay.~~ Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Have **all** of the following criteria been met? • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met. See: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-127.docx	**Yes:** Approve for up to 6 months	**No**: Pass to RPh. Deny; medical appropriateness
6. Is the medication requested for hypogonadism?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny; not funded by the OHP

P&T / DUR Review: *6/22 (KS), 1/17 (SS); 11/15 (KS)*
Implementation: *4/1/17; 1/1/16*

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Drug Class Update with New Drug Evaluation: PCSK9 Modulators Focused Update

Date of Review: August 2022

Date of Last Review: August 2021
Dates of Literature Search: 08/31/2021 – 05/31/2022
Brand Name (Manufacturer): LEQVIO (Novartis)
Dossier Received: yes

Generic Name: Inclisiran

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

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of proprotein convertase subtilisin kexin type 9 (PCSK9) modulators for the prevention of cardiovascular (CV) mortality and CV events in patients with established atherosclerotic cardiovascular disease (ASCVD) and patients with high CV risk.
- Analyze the data supporting the efficacy and safety of inclisiran and determine its appropriate place in therapy.

Research Questions:

1. Is there any new comparative evidence for PCSK9 modulators in reducing CV outcomes in patients treated for the primary or secondary prevention of CV disease?
2. Is there new comparative evidence for the safety of PCSK9 modulators in patients being treated for the primary or secondary prevention of CV disease?
3. What are the comparative benefits and harms of inclisiran in patients with familial hypercholesterolemia, ASCVD or at high CV risk CV patients who cannot achieve adequate low-density lipoprotein cholesterol (LDL-C) reduction with their current lipid-lowering regimen?
4. Are there specific subpopulations for which inclisiran is better tolerated or more effective than other available dyslipidemia drugs when used for CV risk reduction?

Conclusions:

- There is high quality evidence that inclisiran significantly reduces LDL-C from baseline compared to placebo with a high magnitude of benefit in patients with ASCVD and heterozygous familial hypercholesterolemia (HeFH) with an LDL-C reduction ranging from -48% to -52% and low-quality evidence of a reduction in patients with an ASCVD risk equivalent.[1,2] However, there is no data evaluating inclisiran on clinical outcomes, including CV events, CV mortality and all-cause mortality.
- Consistent LDL-reductions were seen across subgroups defined by baseline demographic characteristics and disease comorbidities. However, there is limited data in non-white populations and insufficient evidence evaluating subgroups comparable to Medicaid recipients.
- There is no new high quality comparative evidence evaluating other PCSK9 modulators, including evolocumab or alirocumab.

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Recommendations:

- No PDL changes recommended. Evaluate comparative costs in executive session.
- Due to its unknown benefit on CV outcomes, maintain inclisiran as non-preferred on the PDL and modify prior authorization (PA) criteria for the PCSK9 modulators to limit inclisiran to its FDA indication and to those who have tried agents with evidence of CV risk reduction.

Summary of Prior Reviews and Current Policy

- There is high quality evidence that alirocumab and evolocumab decrease the risk of cardiovascular disease (CVD) and myocardial infarction (MI) compared to placebo in patients with CVD or at high CV risk with a modest absolute risk difference of 1-2%.[3] There is high quality evidence that alirocumab also decreases all-cause mortality compared to placebo (absolute risk difference of 1%). There is low quality evidence of no consistent benefit on CV outcomes or all-cause mortality with either alirocumab or evolocumab compared to ezetimibe and statins.
- There remains insufficient evidence evaluating alirocumab or evolocumab in lower CV risk patients, and long-term efficacy and safety beyond 3 years is lacking.
- There is high quality evidence that alirocumab significantly reduces LDL-C compared to placebo in adults with homozygous familial hypercholesterolemia (HoFH) on background statin therapy with a percent change reduction from baseline at week 12 of -26.9% versus 8.6%. There is insufficient evidence that alirocumab reduces risk of CVD or mortality in patients with HoFH. [4]
- Evolocumab and alirocumab currently require prior authorization for approval to limit use to patients with CVD or familial hypercholesterolemia at high risk for CV events who require additional LDL-C lowering despite use of other lipid-lowering agents, including statins.

Background:

The association between hypercholesteremia, and particularly elevated low-density lipoprotein cholesterol (LDL-C), and cardiovascular disease (CVD) is well established. In addition to optimizing a healthy lifestyle, prevention of ASCVD events involves optimization of treatments that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until more recently, only statins had strong and consistent evidence demonstrating ASCVD risk reduction. Therefore, statin therapy remains the cornerstone of treatment for both primary and secondary prevention of ASCVD. However, combination or non-statin therapy to reduce ASCVD risk beyond statin use may be necessary for high-risk populations.

The utilization and place in therapy of non-statin therapy has significantly evolved over the past few decades from being routine add-on therapy targeting specific LDL-C goals to having no clear indication based on a lack of data showing an improvement on CV outcomes. The recent publication of the 2018 American College of Cardiology/American Heart Association guidelines for the treatment of blood cholesterol once again re-define the role of non-statin therapy.[5] A consistent approach is to reserve non-statin add-on therapy to high-risk populations on maximally tolerated statin therapy who may require additional LDL-C lowering and to use agents which have demonstrated an improvement in CV outcomes. The updated guidelines consider an LDL-C threshold of 70 mg/dl reasonable to add a non-statin agent in those with clinical ASCVD. [5]

Currently, only ezetimibe, icosapent ethyl and the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have shown a modest benefit on clinical outcomes of interest when added to statin therapy (**Tables 1 and 2**). Ezetimibe, an inhibitor of intestinal cholesterol absorption, is indicated as an adjunct to reduce elevated cholesterol and LDL-C.[6] It is generally well tolerated and can lower LDL-C by up to 25% when added to statin therapy. The IMPROVE-IT trial provides modest evidence for use of ezetimibe in combination with a statin for secondary prevention of CV events.[7] In patients with recent acute coronary

syndrome (ACS), ezetimibe produced an incremental reduction in the primary composite endpoint, and specifically reduced nonfatal ischemic stroke, but did not reduce all-cause mortality or CV mortality.

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[8,9] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C with reductions of up to 60% when combined with statin therapy. Both agents are approved as an adjunct with other lipid-lowering therapies (statins, ezetimibe) for primary hyperlipidemia (heterozygous familial hypercholesterolemia) and in patients with clinical ASCVD who require additional lowering of LDL-C. Additionally, they are both FDA approved for the risk reduction of MI, stroke, and coronary revascularization in adults with established CVD based on clinical outcome data from the FOURIER and ODYSSEY OUTCOMES trial **(Tables 1 and 2).**[8,10 11]

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins[7,10-12]

	FOURIER	ODYSSEY	IMPROVE-IT	REDUCE-IT
Non-Statin Study Drug	Evolocumab	Alirocumab	Ezetimibe	Icosapent ethyl 2 gm BID
Patient Population	MI, CVA or PAD	4-52 weeks post-ACS	ACS (prior 10 days)	CVD or DM and ≥ risk factor with TG ≥ 150 mg/dl
Median LDL-C	92 mg/dl	92 mg/dl	95 mg/dl	75 mg/dl (median TG 216 mg/dl)
% on High Intensity Statin	69%	89%	6%	30%
% on Ezetimibe	5%	3%	100%	6.5%
Study Duration	26 months	34 months	6 years	5 years

Abbreviations: ACS: acute coronary syndrome: BID: twice daily; CVA: cerebrovascular accident; CVD: cardiovascular disease; DM: diabetes mellitus; LDL-C: low density lipoprotein cholesterol MI: myocardial infarction; PAD: peripheral artery disease; TG: triglyceride

Table 2: Summary of Results from Cardiovascular Outcome Trials[7,10-12]

Outcome	Evolocumab ARR/NNT	Alirocumab ARR/NNT	Ezetimibe ARR/NNT	Icosapent ARR/NNT
CV Composite Outcome	1.5% / 67	1.6% / 63	2% / 50	4.8% / 21
CV Death	NS	NS	NS	0.9% / 112
Death from any cause	NS	0.6% / 167	NS	NS
Myocardial infarction	1.2% /84	1% / 100	1.7% / 59	2.3% / 44
Stroke	0.4% / 250	0.4% / 250	NS	0.8% / 125

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: not significant

Inclisiran (Leqvio®) was FDA approved in December 2021. It is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits hepatic production of PCSK9, resulting in decreased circulating LDL-C levels.[13] Reduction in intrahepatic PCSK9 levels leads to increased recycling and expression of the LDL-C receptor (LDLR) on the hepatocyte cell surface, which in turn increases LDL-C uptake, thus reducing circulating LDL-C.[14] It has only been used as add-on therapy to

background maximally tolerated statin therapy with or without ezetimibe. Inclisiran is given as a subcutaneous (SC) injection on day 1, day 90 and every 6 months after that.[15] Initial phase II studies demonstrated reductions in LDL-C and PCSK9 levels in patients with homozygous familial hypercholesterolemia (HoFH) and showed no added benefit beyond the 300 mg dose.[16,17]

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

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

Systematic Reviews:
After review, 6 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses)[13,18-20], wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[21,22].

A systematic review was done to evaluate the effects of alirocumab on cardiovascular events and all-cause mortality.[23] There were a total of 13 studies identified with an overall low risk of bias. Consistent with findings from previous high quality systematic reviews, there was high quality evidence of a reduction in CV event with alirocumab compared to placebo (10.9% versus 13.4%; relative risk [RR] 0.89; 95% confidence interval [CI] 0.83 to 0.95) with no significant difference in CV mortality (2.3% vs. 2.7%; RR 0.87; 95% CI 0.74 to 1.04). [23] This review did find a reduction in all-cause mortality with alirocumab compared to placebo (1.6% vs. 2.1%; RR 0.80; 95% CI 0.66 to 0.96). Although this is likely from non-CV mortality, it is uncertain whether alirocumab will lower all-cause mortality.

New Guidelines:
No High-Quality Guidelines identified.

After review, 1 guideline was excluded due to poor quality which was based on weak recommendations and largely on expert opinion and shared decision making.[24]

New Formulations or Indications:
None

New FDA Safety Alerts:
None

Randomized Controlled Trials:

A total of 15 citations were manually reviewed from the initial literature search and 7 RCTs were identified after initial evaluation. After further review, 5 citations were excluded because of wrong study design (e.g., observational)[25-28], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[29]. The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Furtado, et al[30]	Evolocumab vs. placebo	Adults with stable ASCVD, LDL ≥ 70 mg/dl (n=17,073)	MACE (Composite of cardiovascular death, MI, stroke, unstable angina, or coronary revascularization) with or without prior PCI	<u>MACE: Prior PCI</u> Evolocumab: 951 (11.2%) Placebo: 1128 (13.2%) HR 0.84; 95 % CI 0.77-0.91 <u>MACE: No Prior PCI</u> Evolocumab: 391 (7.4%) Placebo: 434 (8.3%) HR 0.88; 95 % CI 0.77-1.01 P for interaction: 0.51*	Pre-specified subgroup analysis from FOURIER trial Differences in populations at baseline *There was no difference in the reduction in MACE with evolocumab in those with or without prior PCI
Deedwania, et al[31]	Evolocumab vs. placebo	Adults with stable ASCVD, LDL ≥ 70 mg/dl stratified by MetS (n=17,073)	MACE (Composite of cardiovascular death, MI, stroke, unstable angina, or coronary revascularization) with or without MetS	<u>MACE: MetS</u> Evolocumab: 13.5% Placebo: 15.8% HR 0.83; 95 % CI 0.76-0.91 <u>MACE: No Prior PCI</u> Evolocumab: 11.2% Placebo: 12.9% HR 0.89; 95 % CI 0.79-1.01 P for interaction: 0.39*	Pre-specified subgroup analysis from FOURIER trial *There was no difference in the reduction in MACE with evolocumab in those with or without MetS
Abbreviation: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HR = hazard ratio; LDL = low density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MetS = metabolic syndrome; MI = myocardial infarction; PCI = percutaneous coronary intervention					

NEW DRUG EVALUATION:

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

Clinical Efficacy:
Inclisiran is an siRNA directed at PCSK9 mRNA indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD, who require additional lowering of LDL-C.[15]

Approval was based on 3 similarly designed RCTs (ORION-9, ORION-10, and ORION-11) evaluating the efficacy of four subcutaneous (SC) injections of inclisiran 300 mg over 18 months in patients with HeFH, established ASCVD, and high risk for ASCVD who all required additional LDL-C lowering.[1,2] Each was a double-blind, placebo-controlled RCT including patients with LDL-C ≥ 70 mg/dl or 100 mg/dl, depending on risk category, despite maximally tolerated LDL-C lowering therapy. The primary endpoint in each trial was change in LDL-C from baseline to day 510. More details on study design and risk of bias are included in **Table 6**.

ORION-9 included patients with HeFH based on genetic confirmation or the phenotypic Simon Broome criteria (LDL-C > 190 mg/dl plus physical finding of tendon xanthomas or DNA based evidence of LDL-receptor mutation) who had an LDL-C of ≥ 100 mg/dl on maximally tolerated statin therapy with or without ezetimibe.[1] The study population was primarily white (94%) and 90% were on statin therapy, including 75% who were receiving high-intensity statin therapy. Overall, there was a significant difference in percent reduction in LDL-C from baseline (difference -47.9%; 95% CI -52.5% to -42.3%) with inclisiran compared to placebo and more patients in the inclisran group who achieved goal LDL-C levels of < 100 mg/dl and < 70 mg/dl.[1] Subgroup analysis showed similar LDL reductions in all subgroups evaluated.

There was unclear selection bias due to minor differences in baseline characteristics. More patients in the placebo group had ASCVD (30.4% vs. 24.4%) and diabetes (11.7% vs. 8.3%) compared to the inclisiran group. More patients in the inclisiran group were on high-intensity statin (76.4% vs. 71.2%) and ezetimibe (55.8% vs. 50%) compared to the placebo group. The primary outcome was measured at month 17 compared to the more traditional month 3 to allow for steady state concentrations to be achieved of inclisran. The FDA reviewer notes missing data as a result from measuring the primary outcome this late.[13] This may also increase the risk of unblinding if a patient had an LDL-C drawn in the meantime. Lastly, 94% of the study population was white and there is limited applicability to non-white patients.

ORION-10 and ORION-11 were similarly designed but ORION-10 included patients with clinical ASCVD and LDL-C ≥ 70 mg/dl and ORION-11 included patients with ASCVD and LDL ≥ 70 mg/dl or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or 10-year ASCVD risk ≥ 20%), and LDL ≥ 100 mg/dl.[2] In both populations, inclisiran significantly lowered LDL-C from baseline compared to placebo with a difference of -52.3% (95% CI -55.7% to -48.8%) and -49.9% (95% CI -53.1% to -46.6%), respectively.[2] There were also significant reductions in non-HDL and apolipoprotein B (Apo-B). Results were similar across subgroups, and there was a trend toward increased magnitude of effect with lower baseline LDL-C in both trials and a trend towards greater treatment effect in patients on statin compared to not on a statin in ORION-11.[13]

Most patients in ORION-11 had ASCVD (87.5%) making the two study populations relatively similar and limiting generalizability to patients with an ASCVD risk equivalent. Thirty-three percent of the screened patients in ORION-10 did not meet randomization criteria, limiting applicability to the general population. The

most common criteria not met were LDL ≥ 70 mg/dl and having “any condition that interferes with the study”. It is unclear what specific conditions this included. Similarly, 32% of screened patients in ORION-11 did not meet randomization criteria.

In all studies, use of PCSK9 inhibitors were excluded and the safety and efficacy of use of inclisiran in addition to a PCSK9 inhibitor remains unknown. The majority of patients in all studies were on background high-intensity statins, but there were few patients on ezetimibe (<10%). There are no data evaluating the effects of inclisiran on CV events or CV mortality.

Clinical Safety:

From the primary 3 RCTs submitted for FDA approval (n=3655), there were very few discontinuations 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] The most common adverse event that occurred more frequently than placebo was injection site reactions (8.2% vs. 1.8%, respectively). This was also the most common reason for withdrawal of treatment. Other adverse effects occurring more commonly than placebo are included in **Table 4.** There were slightly more serious adverse events in the placebo arm (23%) compared to inclisiran (20%) and most were well balanced between groups. The most commonly reported serious adverse events were cardiac disorders which is likely a reflection of the high-risk cardiovascular population. There was no significant difference in changes in creatine kinase between inclisiran and placebo, with a 1% increase in incidence of arthralgia with inclisran and 0.7% increase in pain in extremity. Long term safety beyond 18 months remains uknown.

Table 4: Adverse Reactions Occurring in >3% of Patients and Greater than Placebo[15]

Reactions	Placebo (N = 1822) %	Inclisiran (N = 1833) %
Injection site reaction	1.8%	8.2%
Arthralgia	4%	5%
Urinary Tract Infection	3.6%	4.4%
Diarrhea	3.5%	3.9%
Bronchitis	2.7%	4.3%
Pain in extremity	2.6%	3.3%
Dyspnea	2.6%	3.2%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Cardiovascular mortality
2) Non-fatal cardiovascular events
3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percent change in LDL-C from baseline to day 510

Table 5. Pharmacology and Pharmacokinetic Properties.[15]

Parameter	
Mechanism of Action	Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA). In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.
Oral Bioavailability	N/A (subcutaneous injection)
Distribution and Protein Binding	87% protein bound; volume of distribution 500 L with high uptake in the liver
Elimination	16% cleared through the kidney
Half-Life	9 hours
Metabolism	Primarily metabolized by nuclease; no CYP450 metabolism

Abbreviations: L = liters, LDL-C = low density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilsin-kexin type 9; N/A = not applicable; RNA = ribonucleaic acid.

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. ORION-9[1,13] Phase III, PC, DB, RCT	1. inclisiran 300 mg SC 2. placebo On days 1, 90, 270 and 450	Demographics: mean age 56 y/o 47% men 94% white Mean LDL-C 153 mg/dl 90% on statins; 75% on high-intensity 25% ASCVD Key Inclusion Criteria: • Adults with HeFH • LDL-C ≥ 100 mg/dl • TG < 400 mg/dl • eGFR > 30 ml/min • maximally tolerated statin Key Exclusion Criteria: • NYHA class IV HF • EF < 25% • SBP > 180 mmHg • active liver disease • uncontrolled or serious disease • alcohol and/or drug abuse in last 5 years	ITT: 242 240 PP: 230 234 Attrition: 9 (3.8%) 7 (2.9%)	Primary Endpoint: Percent change in LDL-C from baseline: 1. -39.7% 2. + 8.2% Difference -47.9%; 95% CI -52.5% to -42.3%; P<0.001 Exploratory Endpoints: Reduction from baseline in mean LDL-C of ≥ 50%: 1. 92 (38%) 2. 2 (0.8%) P<0.001*	NA ARR 38% / NNT 3	Discontinue due to adverse events: 1. 0 2. 0 p-values not reported	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; randomization via automated interactive response technology; some minor differences in baseline characteristics. Performance Bias: low, double-blinded using appropriate blinding techniques and blinded syringes. Unblinding due to lower LDL-C possible prior to day 510. Detection Bias: unclear; no details about blinding of outcome assessors Attrition Bias: low; low overall attrition in both groups. ITT analysis performed. Reporting Bias: low; results for all pre-specified outcomes were reported Other Bias: unclear; funded by the Medicines Company which was acquired by the manufacturer of inclisran **Applicability**: Patient: limited representation of non-white patients, limited generalizability to Medicaid population Intervention: Dose regimen selected based on phase I and II dose ranging studies Comparator: placebo comparator Outcomes: surrogate outcome Setting: 46 sites in 8 countries (37% South Africa, 17% Spain, 13% US, 10% Denmark)

2. ORION-10 [2,13] Phase 3, PC, DB, PG, RCT	1. inclisiran 300 mg SC 2. placebo On days 1, 90, 270 and 450	Demographics: Male 69.4% Mean age 66 y/o 85.6% white 12.6% black Mean LDL-C 105 Key Inclusion Criteria: • Adults with ASCVD • LCD-C ≥ 70 mg/dl, • background lipid lowering therapy • TG < 400 mg/dl • eGFR > 30ml/min Key Exclusion Criteria: See above	ITT: 781 780 PP: 729 715 Attrition: 60 (7.7%) 86 (11%)	Primary Endpoint: Percent change in LDL-C from baseline: 1. -51.3% 2. + 1% Difference -52.3%; 95% CI -55.7% to -48.8%; P<0.001 Exploratory Endpoints: Reduction from baseline in mean LDL-C of ≥ 50%: 1. 503 (72.8%) 2. 17 (2.6%) OR 67.1; 95% CI 41.8 to 107.6 P<0.001	NA ARR 70.2%/ NNT 2	Discontinue due to adverse events: 1. 8 (1.0%) 2. 5 (0.6%) p-values not reported	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization via automated interactive response technology; groups balanced at baseline Performance Bias: low, double-blinded using appropriate blinding techniques and blinded syringes. Unblinding possible due to lower LDL-C prior to day 510. Detection Bias: unclear; no details about blinding of outcome assessors Attrition Bias: low; low overall attrition in both groups. ITT analysis performed. Reporting Bias: low; results for all pre-specified outcomes were reported Other Bias: unclear; funded by the Medicines Company which was acquired by the manufacturer of inclisran **Applicability**: Patient: 33% of screened patients did not meet randomization criteria. Patients with relevant comorbidities included (HTN, DM). Limited representation from Asian or American Indian groups. Intervention: Dose regimen selected based on phase I and II dose ranging studies Comparator: placebo comparator Outcomes: surrogate outcome Setting: 146 sites in the US
3. ORION-11 [2] Phase 3, PC, DB, PG, RCT	1. inclisiran 300 mg SC 2. placebo On days 1, 90, 270 and 450	Demographics: 71.7% male Mean age 64.8 y/o 98.1% white 87.5 ASCVD Key Inclusion Criteria: • Adults with ASCVD or • ASCVD risk equivalent (T2DM, FH, or 10-year ASCVD risk ≥ 20%) • LDL ≥ 70 mg/dl • background lipid lowering therapy • TG < 400 mg/dl • eGFR > 30ml/min Key Exclusion Criteria: See above	ITT: 810 807 PP: 782 779 Attrition: 38 (4.7%) 37 (4.6%)	Primary Endpoint: Percent change in LDL-C from baseline: 1. -45.8% 2. + 4% Difference -49.9%; 95% CI -53.1% to -46.6% P<0.001 Exploratory Endpoints: Reduction from baseline in mean LDL-C of ≥ 50%: 1. 418 (57.7%) 2. 17 (2.3%) OR 49.3; 95% CI 30.3 to 80.3 P<0.001	NA ARR 55.4%/ NNT 2	Discontinue due to adverse events: 1. 4 (0.5%) 2. 0 p-values not reported	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization via automated interactive response technology; groups balanced at baseline Performance Bias: low, double-blinded using appropriate blinding techniques and blinded syringes. Unblinding due to lower LDL-C possible prior to day 510. Detection Bias: unclear; no details about blinding of outcome assessors Attrition Bias: low; low overall attrition in both groups. ITT analysis performed. Reporting Bias: low; results for all pre-specified outcomes were reported Other Bias: unclear; funded by the Medicines Company which was acquired by the manufacturer of inclisran **Applicability**: Patient: 32% of screened patients did not meet randomization criteria; limited representation of non-white patients, limited generalizability to Medicaid population Intervention: Dose regimen selected based on phase I and II dose ranging studies Comparator: placebo comparator Outcomes: surrogate outcome Setting: 72 centers in 8 countries (Europe and South Africa)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HF = heart failure; HTN = hypertension; ITT = intention to treat; LDL-C = low density lipoprotein cholesterol; N = number of subjects; MC = multicenter; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = new York heart association; OR = odds ratio; PC = placebo controlled; PCSK9 = proprotein convertase subtilsin-kexin type 9; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SBP = systolic blood pressure; SC = subcutaneous; T2DM = type 2 diabetes; TG = triglyceride; y/o = years old.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWD PACK	Y
cholestyramine/aspartame	PREVALITE	ORAL	POWD PACK	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWDER	Y
cholestyramine/aspartame	PREVALITE	ORAL	POWDER	Y
cholestyramine/aspartame	QUESTRAN LIGHT	ORAL	POWDER	Y
evolocumab	REPATHA SURECLICK	SUBCUT	PEN INJCTR	Y
evolocumab	REPATHA SYRINGE	SUBCUT	SYRINGE	Y
evolocumab	REPATHA PUSHTRONEX	SUBCUT	WEAR INJCT	Y
ezetimibe	EZETIMIBE	ORAL	TABLET	Y
ezetimibe	ZETIA	ORAL	TABLET	Y
fenofibrate	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	TRICOR	ORAL	TABLET	Y
fenofibrate,micronized	ANTARA	ORAL	CAPSULE	Y
fenofibrate,micronized	FENOFIBRATE	ORAL	CAPSULE	Y
fenofibric acid (choline)	FENOFIBRIC ACID	ORAL	CAPSULE DR	Y
fenofibric acid (choline)	TRILIPIX	ORAL	CAPSULE DR	Y
omega-3 acid ethyl esters	LOVAZA	ORAL	CAPSULE	Y
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	ORAL	CAPSULE	Y
alirocumab	PRALUENT PEN	SUBCUT	PEN INJCTR	N
bempedoic acid	NEXLETOL	ORAL	TABLET	N
bempedoic acid/ezetimibe	NEXLIZET	ORAL	TABLET	N
colesevelam HCl	COLESEVELAM HCL	ORAL	POWD PACK	N
colesevelam HCl	WELCHOL	ORAL	POWD PACK	N
colesevelam HCl	COLESEVELAM HCL	ORAL	TABLET	N
colesevelam HCl	WELCHOL	ORAL	TABLET	N
colestipol HCl	COLESTID	ORAL	GRANULES	N
colestipol HCl	COLESTIPOL HCL	ORAL	GRANULES	N
colestipol HCl	COLESTID	ORAL	PACKET	N
colestipol HCl	COLESTIPOL HCL	ORAL	PACKET	N
colestipol HCl	COLESTID	ORAL	TABLET	N
colestipol HCl	COLESTIPOL HCL	ORAL	TABLET	N
evinacumab-dgnb	EVKEEZA	INTRAVEN	VIAL	N
fenofibrate	FENOFIBRATE	ORAL	CAPSULE	N
fenofibrate	LIPOFEN	ORAL	CAPSULE	N

fenofibrate	FENOFIBRATE	ORAL	TABLET	N
fenofibrate	FENOGLIDE	ORAL	TABLET	N
fenofibric acid	FENOFIBRIC ACID	ORAL	TABLET	N
gemfibrozil	GEMFIBROZIL	ORAL	TABLET	N
gemfibrozil	LOPID	ORAL	TABLET	N
icosapent ethyl	ICOSAPENT ETHYL	ORAL	CAPSULE	N
icosapent ethyl	VASCEPA	ORAL	CAPSULE	N
inclisiran sodium	LEQVIO	SUBCUT	SYRINGE	N
inositol	INOSITOL	ORAL	TABLET	N
lomitapide mesylate	JUXTAPID	ORAL	CAPSULE	N
niacin	NIACIN	ORAL	CAPSULE ER	N
niacin	NIACIN ER	ORAL	TAB ER 24H	N
niacin	NIASPAN	ORAL	TAB ER 24H	N
niacin	NIACIN	ORAL	TABLET	N
choline	CHOLINE	ORAL	TABLET	N
niacin	NIACIN	ORAL	TABLET ER	N
niacin	NIADELAY	ORAL	TABLET ER	N
niacinamide	NIACINAMIDE	ORAL	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

1. Furtado R., Aurelio Fagundes A., Oyama K. et al. Effect of Evolocumab in Patients With Prior Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2022 Mar;15(3):e011382. doi: 10.1161/CIRCINTERVENTIONS.121.011382. Epub 2022 Feb 25.

Background: Patients with prior percutaneous coronary intervention (PCI) are at high residual risk for multiple types of coronary events within and beyond the stented lesion. This risk might be mitigated by more intensive LDL-C (low-density lipoprotein cholesterol)-lowering beyond just with statin therapy.

Methods: FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) randomized 27 564 patients with stable atherosclerotic disease on statin to the PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor evolocumab or placebo with a median follow-up of 2.2 years. The end points of interest were major adverse cardiovascular events (MACE; a composite of cardiovascular death, myocardial infarction, stroke, unstable angina or coronary revascularization), and major coronary events (a composite of coronary heart death, myocardial infarction, or coronary revascularization). We compared the risk of MACE and the magnitude of relative and absolute risk reductions with evolocumab in patients with and without prior PCI.

Results: Seventeen thousand seventy-three patients had prior PCI. In the placebo arm, those with prior PCI had higher rates of MACE (13.2% versus 8.3%; hazard ratio [HR]adj 1.61 [95% CI, 1.42-1.84]; P<0.0001) and major coronary events (11.5% versus 6.0%; HRadj, 1.72 [95% CI, 1.49-1.99]; P<0.0001). Relative risk reductions with evolocumab were similar in patients with and without prior PCI (MACE: HR, 0.84 [0.77-0.91] versus HR, 0.88 [0.77-1.01]; Pinteraction 0.51; major coronary events: HR, 0.82 [0.75-0.90] versus HR, 0.88 [0.75-1.04]; Pinteraction 0.42). Absolute risk reductions for MACE were 2.0% versus 0.9% (Pinteraction 0.14) and for major coronary events 2.0% versus 0.7% (Pinteraction 0.045). In those with prior PCI, the effect of evolocumab on coronary revascularization (HR, 0.76 [0.69-0.85]) was directionally consistent across types of revascularization procedures: coronary artery bypass grafting (HR, 0.71 [0.54-0.94]); any PCI (HR, 0.77 [0.69-0.86]); PCI for de novo lesions (HR, 0.76 [0.66-0.88]); and PCI for stent failure or graft lesions (HR, 0.76 [0.63-0.91]).

Conclusions: Evolocumab reduces the risk of MACE in patients with prior PCI including the risk of coronary revascularization, with directionally consistent effects across several types of revascularization procedures, including coronary artery bypass grafting and PCI for stent or graft failure.

2. Deedwania P, Murphy SA, Scheen A, Badariene J, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR, Sabatine MS, Giugliano RP. Efficacy and Safety of PCSK9 Inhibition With Evolocumab in Reducing Cardiovascular Events in Patients With Metabolic Syndrome Receiving Statin Therapy: Secondary Analysis From the FOURIER Randomized Clinical Trial. *JAMA Cardiol.* 2021 Feb 1;6(2):139-147. doi: 10.1001/jamacardio.2020.3151.

Objective: To investigate outcomes with evolocumab in patients with and without MetS.

Design, setting, and participants: The FOURIER trial randomized patients worldwide with stable atherosclerotic cardiovascular disease receiving statin to evolocumab vs placebo with follow-up for a median of 2.2 years. Data were collected February 2013 to November 2016. For this prespecified analysis, patients with the requisite data were stratified based on the National Cholesterol Education Program Adult Treatment Panel III MetS criteria; in secondary analyses, patients were further substratified by diabetes at baseline. Analysis was intention to treat. Analysis began March 2018 and ended April 2020.

Interventions: Patients were randomized to evolocumab or placebo.

Main outcomes and measures: The primary end point was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was cardiovascular death, myocardial infarction, or stroke.

Results: Of 27 342 patients (mean [SD] age, 63 [9] years; 20 623 men [75.4%]) included in this analysis, 16 361 (59.8%) with baseline MetS were, when compared with patients without MetS, at higher risk of cardiovascular events (adjusted hazard ratio [95% CI], 1.31 [1.18-1.46]; P < .001 for the primary and 1.38 [1.20-1.57]; P < .001 for the key secondary end point). Evolocumab reduced low-density lipoprotein cholesterol similarly in patients with MetS (median [interquartile range], 92 [79-109] mg/dL vs 30 [19-48] mg/dL; P < .001) and without MetS (median [interquartile range], 92 [81-108] mg/dL vs 29 [18-44] mg/dl; P < .001). For the primary end point, the hazard ratios (95% CI) with evolocumab vs placebo were 0.83 (0.76-0.91) and 0.89 (0.79-1.01) in patients with and without MetS (P for interaction = .39). For the key secondary end point, the corresponding hazard ratios (95% CIs) were 0.76 (0.68-0.86) and 0.86 (0.74-1.01) (P for interaction = .23), respectively. Evolocumab did not increase the risk of new-onset diabetes or other major safety outcomes including worsening glycemic control, compared with placebo in patients with MetS.

Conclusions and relevance: Patients with atherosclerotic cardiovascular disease and MetS have substantial residual risk of cardiovascular events despite statin therapy. Evolocumab significantly reduced low-density lipoprotein cholesterol and cardiovascular risk in patients with MetS without increasing new-onset diabetes, worsening glycemic control, or other major safety events. These data suggest the addition of evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease and MetS is safe and efficacious to reduce residual cardiovascular risk.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to May 18, 2022>

1	evolocumab.mp.	909
2	alirocumab.mp.	817
3	PCSK9 inhibitors.mp. or PCSK9 Inhibitors/	1709
4	inclisiran.mp.	164
5	cardiovascular events.mp.	41853
6	cardiovascular mortality.mp.	15671
7	Mortality/ or mortality.mp.	1318953
8	Myocardial Infarction/ or Cardiovascular Diseases/ or major adverse cardiovascular events.mp.	340307
9	1 or 2 or 3 or 4	2459
10	5 or 6 or 7 or 8	1596548
11	9 and 10	979
12	limit 11 to (english language and humans and yr="2021 -Current" and (clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review"))	22
13	from 12 keep 1-3,6-11,13,15-18,22	15

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

LEQVIO® (inclisiran) injection, for subcutaneous use
Initial U.S. Approval: 2021

----------**INDICATIONS AND USAGE**----------
LEQVIO is a small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). (1)

Limitations of Use:
The effect of LEQVIO on cardiovascular morbidity and mortality has not been determined. (1)

----------**DOSAGE AND ADMINISTRATION**----------
- The recommended dosage of LEQVIO, in combination with maximally tolerated statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months. (2.1)
- LEQVIO should be administered by a healthcare professional. (2.2)
- Inject LEQVIO subcutaneously into the abdomen, upper arm, or thigh. (2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------
Injection: 284 mg/1.5 mL (189 mg/mL) in a single-dose prefilled syringe. (3)

----------**CONTRAINDICATIONS**----------
None. (4)

----------**ADVERSE REACTIONS**----------
Common adverse reactions in clinical trials (≥ 3%): injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, and dyspnea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2021

Appendix 5: Key Inclusion Criteria

Population	Individuals with cardiovascular disease or high-risk cardiovascular disease
Intervention	PCSK9 modulator
Comparator	Placebo or active control
Outcomes	Cardiovascular events, all-cause mortality, cardiovascular mortality
Timing	At least 12 weeks
Setting	Outpatient or inpatient after acute coronary syndrome

PCSK9 Modulators

Goal(s):

- Promote use of PCSK9 modulators that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 modulators (pharmacy and provider 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. Is this a request for the renewal of a previously approved prior authorization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

Approval Criteria		
3. Does the patient have very high-risk clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of multiple major ASCVD events **OR** one major ASCVD event and multiple high-risk conditions (See below) <u>Major ASCVD events</u> • Recent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease <u>High-Risk Conditions:</u> • Age ≥ 65 • Heterozygous familial hypercholesterolemia • History of prior CABG or PCI • Diabetes Mellitus • Hypertension • Chronic Kidney Disease • Current smoking • Persistently elevated LDL-C ≥ 100 despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 3 months with a LDL-C still ≥ 70 mg/dl? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C	**Yes:** Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Recent LDL-C _____ mg/dL Date:_____	**No:** Go to #6
5. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
6. Does the patient have: • A history of rhabdomyolysis caused by a statin; or alternatively, • a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin; or • Intolerable statin-associated side effects that have been re-challenged with ≥ 2 statins Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Go to #8	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe?	**Yes:** Go to #9 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
9. Is the request for inclisiran?	**Yes:** Go to #10	**No:** Approve for up to 12 months

Approval Criteria		
~~9.~~10. Has the patient tried and failed a PCSK9 inhibitor with evidence of a reduction in cardiovascular events (i.e., evolocumab or alirocumab) or have a contraindication to one of these agents? *Failure of a PCSK9 inhibitor includes adherence to PCSK9 inhibitor for at least 12 weeks with an LDL-C that remains > 70 mg/dl with evidence of clinical atherosclerotic cardiovascular disease (ASCVD)	**Yes:** Go to #11	**No:** Pass to RPh; deny for medical appropriateness.
~~10.~~11. Is the patient currently still receiving a PCSK9 inhibitor (alirocumab or evolocumab)?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Approve for up to 12 months. Note: Any current PA approvals for PCSK9 inhibitors will be end-dated.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2	
2. Has the patient experienced and maintained a reduction in LDL-C compared to baseline labs (prior to initiating PCSK9 modulator)?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Is the patient adherent with PCSK9 modulator therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	Moderate-intensity Statins (30 to <50% LDL-C Reduction)

Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Rosuvastatin 5-10 mg Pravastatin 40-80 mg Simvastatin 20-40 mg

P&T / DUR Review: *8/22 (MH) 8/21; 8/20; 5/19; 1/18; 11/16; 11/15*
Implementation: *TBD; 7/1/2019; 3/1/18; 1/1/1*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Drug Class Review: Oral Thyroid Hormone

Date of Review: August 2022 **End Date of Literature Search:** 05/06/2022

Plain Language Summary:

- Thyroid hormones are medicines used to treat thyroid conditions like low thyroid levels and thyroid growths called nodules. Low thyroid is a condition in which the body does not make enough thyroid hormone. Levothyroxine is the name of the most common medicine used to treat low thyroid. It is not helpful to use thyroid hormone in people whose lab levels may show early signs of low thyroid but who have no symptoms of low thyroid because it does not usually improve how a person feels. In people with thyroid nodules, thyroid hormone may reduce the size of the growth.
- Use of thyroid hormone may lower risk of early childbirth compared to no treatment in pregnant people who have antibodies against thyroid tissue with normal thyroid levels, but more research is needed.
- There is no difference between different types of levothyroxine. A lower dose of thyroid hormone is usually needed for people who are older or who have heart disease.
- The Drug Use Research Management program recommends that thyroid hormones have a designated policy for this group of medicines. The recommendation is that all thyroid hormones have a formulation available that is paid for by Fee-for-service (FFS) Medicaid.

Purpose for Class Review: The purpose of this review is to create a class for oral thyroid products based on high quality evidence from a recent literature search.

Research Questions:

1. What is the high-quality comparative evidence on the efficacy and harms between thyroid hormone therapies?
2. Is there evidence regarding subgroups of patients based on demographics (i.e., age, race, ethnicity, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), for which a specific thyroid therapy is more effective or associated with fewer harms?

Conclusions:

- There were three systematic reviews and meta-analyses and two high-quality clinical practice guidelines that were included in this class review.
- There is moderate quality of evidence that levothyroxine reduces nodule volume of 50% or more when compared to placebo or no treatment (relative risk [RR] 1.57; confidence interval [CI] 1.04 to 2.38).[1] Nodule reduction can be associated with less symptoms of pain due to pressure and for cosmetic reasons. There was insufficient evidence to draw conclusions on important health outcomes, such as incidence of thyroid cancer, health-related quality of life and adverse events.

Author: Kathy Sentena, PharmD

- A Cochrane review found low quality evidence that the treatment of people who were euthyroid, who had thyroid peroxidase antibodies (TPOAb), during pregnancy was beneficial in reducing the risk of preterm birth compared to no treatment (RR 0.28; 95% CI, 0.10 to 0.80; absolute risk reduction [ARR] 19%/number needed to treat [NNT] 5/treatment duration of 30 weeks).[2]
- Treating individuals with subclinical hypothyroidism (baseline thyroid stimulating hormone [TSH] 4.4 to 12.8 mIU/L) with thyroid replacement, compared to placebo, did not improve health-related quality of life or hypothyroid symptoms based on a high-quality systematic review and meta-analysis (high quality evidence).[3] Treatment of subclinical hypothyroidism is not recommended for most patients based on recommendations from high-quality guidelines (strong recommendation based on high-quality evidence).[5] Treatment of subclinical hypothyroidism in some patients with serum TSH levels exceeding 10 mIU/L may prevent progression to overt hypothyroidism and is recommended by some guidelines.[4]
- A guideline published by the National Institute for Health and Care Excellence (NICE) recommends the use of levothyroxine first-line for the treatment of hypothyroidism.[4]
- There was insufficient evidence to recommend the use of a specific formulation of levothyroxine in preference to another.
- There is evidence for the use of lower doses of levothyroxine in patients who are elderly or in those with a history of cardiovascular (CV) disease.[4] Women and children should follow specific dosing recommendations per labeling instructions.[6,7]

Recommendations:
- Recommend at least one formulation of levothyroxine, liothyronine and desiccated thyroid be available as preferred products.
- Evaluate drug costs in the executive session.

Background:
Hypothyroidism affects approximately one in every 300 persons in the United States (US).[8] Women receive a diagnosis of hypothyroid 5-10 times more than men. Low levels of thyroid are most commonly a result of iodine deficiency worldwide; however, in the U.S. autoimmune thyroiditis (e.g. Hashimoto's thyroiditis) is the primary etiology of hypothyroidism.[9] Thyroid hormones play an important role in regulating metabolism, and brain, heart, muscle and digestive function. Untreated hypothyroidism may result in increased risk of heart failure, CV mortality and adversely affect serum lipid levels.[9] Symptoms of hypothyroid vary by age but commonly include fatigue, hair loss, depression and temperature intolerance.[10] Screening and diagnosis is predominately done by measuring TSH, with treatment of patients with serum TSH levels above 10 mIU/L. Primary hypothyroidism is defined as high serum TSH concentrations and low levels of serum free thyroxine (T4).[10] A less common etiology is central hypothyroidism which occurs as a result of hypothalamic or pituitary disease with resulting low serum T4 concentrations and a serum TSH concentration that is not appropriately elevated in response. Another type of thyroid disorder is subclinical hypothyroidism. It is associated with high serum TSH levels, normal free T4 concentrations and symptoms of hypothyroidism (e.g., tiredness, constipation, and weight gain).[9] Guidelines recommend the use of thyroid hormones to treat subclinical hypothyroidism in individuals with serum TSH values exceeding 10 mIU/L. The treatment of patients with levels of 4.5 to 10 mIU/L is controversial and has not consistently demonstrated benefit or improved outcomes.[3]

In most people, hypothyroidism is chronic and requires lifelong supplementation of thyroid hormones to reach a euthyroid state (TSH levels of 0.5 to 5.0 mIU/L). Levothyroxine (tablets, soft gels, or liquid) is synthetic thyroxine and a preferred thyroid hormone used to normalize TSH levels. Levothyroxine is converted to triiodothyronine (T3), the active thyroid hormone, in the peripheral tissues.[10] Levothyroxine is dosed at 1.6 mcg/kg per day. Individuals who are older or those with coronary heart disease should have levothyroxine initiated at a lower 25-50 mcg daily dose. Those with subclinical hypothyroidism usually require less supplementation and doses of 25-75 mcg daily are often sufficient.[9] Levothyroxine should be given on an empty stomach with water, 30-60 minutes before the first meal of the day or 2 hours after the last meal of the day.[10] Use of branded levothyroxine over generic products may be preferred by some clinicians, but the

general consensus is to use a consistent formulation of levothyroxine to reduce risk of variable patient response.[9] Desiccated thyroid can be derived from porcine or bovine sources and is most commonly available as Armour® Thyroid. Desiccated thyroid has not been extensively studied and is not commonly used but remains an option for certain patients who do not respond to other types of thyroid; however, not recommended by some guidelines.[9] Liothyronine (T3) is also used in patients who remain symptomatic on levothyroxine. Serum TSH should be reevaluated at 4-6 weeks after initiating thyroid hormone therapy. There is no high-quality evidence that supports thyroid hormone supplementation in euthyroid individuals.[10] There is insufficient evidence to support combination therapy with levothyroxine and L-triiodothyronine.[9]

Outcome measures used to determine the efficacy of thyroid replacement are normalization of elevated serum TSH levels and/or T4 levels.[11] Quality of life assessments are also used, especially in the treatment of subclinical hypothyroidism. The Thyroid-Related Quality-of-Life Patient-Reported Outcome Measure (ThyPRO) is a 4-item scale with a range of 0-100, with higher scores indicative of more hypothyroid symptoms.[3] Another tool measures quality of life via an 18-item underactive thyroid-dependent quality of life (ThyDQoL) tool, comprised of a range of -9 to 3 with higher scores indicating a better quality of life.[3]

There were 823 fee-for-service (FFS) patients who received thyroid hormones last quarter. Ninety-two percent of the claims were for levothyroxine. Thyroid hormones represent a small portion of health care costs to the Oregon Health Authority (OHA).

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

Table 1. Indications and Dosing.

Generic Drug Name	Indication(s)	Strength/Route	Dose and Frequency+
Levothyroxine capsules, tablets and solution[10]	Hypothyroidism and pituitary thyrotropin suppression	13 - 200 mcg oral tablets and capsules (brand dependent) Oral solution 13-200 mcg/mL	Dose titrated to effect once daily (TSH levels)
Liothyronine tablets[10]	Hypothyroidism, pituitary thyrotropin suppression and thyroid suppression test	5, 25, and 50 mcg oral tablets	Dose titrated to effect once daily (TSH levels and T3 levels)
Thyroid, pork tablets*	As a replacement supplement for patients with hypothyroidism of any etiology except for transient hypothyroidism during the recovery phase of acute thyroiditis.	15-300 mg oral tablets	Starting dose of 30 mg once daily and titrated to effect

Key: * Labeling has not been approved by FDA; + TSH should be monitored every 4-6 weeks during dose titration
Abbreviations: mcg – microgram; mg – milligram; mL – milliliter; T3 – triiodothyronine; TSH – thyroid stimulating hormone

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence

(NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:

Cochrane – Levothyroxine or Minimally Invasive Therapies for Benign Thyroid Nodules

The focus of a 2014 Cochrane review evaluated the use of levothyroxine, or other treatments, for reducing the size of benign thyroid nodules.[1] Thyroid nodules are common and rarely cancerous. Nodules are problematic due to pressure symptoms or because of cosmetic concerns. The use of levothyroxine for nodule reduction was compared to placebo, or to no therapy, as well as the use of other minimally invasive therapies. Thirty-one studies (n=2083) were identified. All patients were euthyroid and most were female. Participant ages ranged from 18 to 69 years. Sixteen studies, lasting 6 months to 5 years, evaluated levothyroxine specifically. Six studies compared levothyroxine to no therapy and eight studies were placebo comparisons. Doses of levothyroxine ranged from 1 mcg/kg/day to 3 mcg/kg/day. Goal TSH levels were less than 0.01 mIU/L to 0.2 to 0.8 mIU/L (.[1]

There was insufficient evidence to draw strong conclusions on the effect of levothyroxine on the incidence of thyroid cancer, health-related quality of life and adverse events. Nodule reduction (greater than 50%) was greater with levothyroxine compared to no treatment or placebo, 16% vs. 10% (RR 1.57; CI 1.04 to 2.38; $p<0.05$), based on moderate evidence.[1]

Cochrane – Interventions for Clinical and Subclinical Hypothyroidism Pre-pregnancy and During Pregnancy

Management of clinical and subclinical hypothyroidism throughout pregnancy was the focus of a 2013 Cochrane review.[2] Studies evaluating the use of levothyroxine compared to placebo or active treatment were eligible for inclusion. Four trials with 362 women who were pregnant and euthyroid with TPOAb were included in the review. Trials were found to have moderate risk of bias.[2] Outcomes of interest were pre-eclampsia, premature birth, miscarriages and cognitive delay in newborns.

One trial (n=115) found treatment with levothyroxine, compared to no treatment did not significantly reduce the risk of pre-eclampsia in women who were euthyroid but had thyroid peroxidase antibodies (RR 0.61; 95% CI, 0.11 to 3.48).[2] Preterm birth was reduced more in with levothyroxine treatment compared to placebo in this population by 72% (RR 0.28; 95% CI, 0.10 to 0.80) (low quality of evidence).[2] There was insufficient evidence to determine the effect of levothyroxine on other outcomes.

Feller, et al – Association of Thyroid Hormone Therapy with Quality of Life and Thyroid-Related Symptoms in Patients with Subclinical Hypothyroidism

A 2018 systematic review and meta-analysis evaluated the role of treating subclinical hypothyroidism.[3] Twenty-one randomized controlled trials (RCTs) (n=2192), durations lasting from 3-18 months, met inclusion criteria. Comparisons were between thyroid hormone therapy and placebo, or no therapy, in participants who were not pregnant and had a diagnosis of subclinical hypothyroidism. Mean ages ranged from 32-74 years with women representing 46-100% of participants.[3] Mean TSH levels at baseline were 4.4 to 12.8 mIU/L and participants reported symptoms ranging from mild to moderate.[3] The primary outcomes of interest

were quality of life and thyroid-related quality of life/hypothyroid symptoms. Quality of life was scores were based on several different assessments including general health Questionnaire (GHQ-30), 18-Item ThyDQoL, and ThyPRO.

Treatment with thyroid hormone resulted in normalization in thyrotropin values (0.5-3.7 mIU/L) compared to placebo (4.6-14.7 mIU/L).[3] There was no difference between groups in general quality of life (standard mean difference [SMD] -0.11; 95% CI, -0.25 to 0.03, I^2= 66.7%).[3] Thyroid-related quality of life/hypothyroid symptoms scores were also similar between groups with a SMD of 0.01 (95% CI, -0.12 to 0.14; I^2 = 0%).[3] There was no strong evidence that thyroid replacement resulted in improved outcomes in patients with subclinical hypothyroidism.

After review, 17 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[12–17,17–28]

Guidelines:
High Quality Guidelines:

<u>NICE – Thyroid Disease: Assessment and Management</u>
NICE updated their guidance in 2019 for the use of levothyroxine in the management of thyroid disease.[4] Treatment with levothyroxine is recommended for individuals with hypothyroidism. Obtaining goal TSH levels may take up to 6 months in individuals with very high levels at initiation. TSH should be measured every 3 months until levels have stabilized and then checked annually.[4] Patients that remain symptomatic after starting levothyroxine may benefit from measurement of free T4 as well as TSH levels.[4] Measurement of free T4 and TSH can be valuable for children ages 2 years and older and young people. Testing should be done every 6 to 12 weeks until TSH levels have normalized and then every 4 to 6 months till after puberty. After puberty, testing is recommended annually.[4] For children under the age of 2 years, the recommendation is to measure free T4 and TSH levels every 4 to 8 weeks until normalization, then every 2 to 3 months during the first year of life and every 3 to 4 months during the second year of life.[4]

NICE treatment recommendations for hypothyroidism are as follows:
- Levothyroxine is recommended first-line for adults, children and young people with primary hypothyroidism.
    - Initiate levothyroxine at a dose of 1.6 mcg/kg (round to nearest 25 micrograms) for adults under 65 years old with primary hypothyroidism and no history of CV disease.[4]
    - For adult patients with history of CV disease and are 65 years and older, consider starting levothyroxine at 25 to 50 mcg per day with titration.[4]
- Liothyronine is not routinely recommended because there has been no evidence of benefit over levothyroxine and long-term harms are unknown.
- Natural thyroid is not recommended due to lack of evidence.
- Levothyroxine can be considered for all adults with subclinical hypothyroidism (TSH of 10 mIU/L or higher on 2 separate occasions 3 months apart). Dosing should follow the same recommendations as those for hypothyroidism.[4]
- Levothyroxine can also be considered for adults under 65 years with subclinical hypothyroidism with a TSH above the reference range but lower than 10 mIU/L on 2 separate occasions 3 months apart and symptoms of hypothyroidism.
- Children and young people over the age of 2 years may also be treated with levothyroxine for subclinical hypothyroidism. Considerations should be for children with the following: TSH level of 20 mIU/L or higher, TSH between 10 and 20 mIU/L on 2 separate occasions 3 months apart or TSH between 5 and 10 mIU/L on 2 separate occasions 3 months apart with thyroid dysgenesis or signs and symptoms of thyroid dysfunction.
- Children under that age of 2 years with TSH levels of 10 mIU/L or higher with subclinical hypothyroidism are also candidates for levothyroxine.

Bekkering, et al – Thyroid Hormones Treatment for Subclinical Hypothyroidism: A Clinical Practice Guideline

A 2019 practice guideline on the treatment of subclinical hypothyroidism was developed by the British Medical Journal and the MAGIC group, who uses GRADE methodology to develop web-based guidelines. Recommendations and guidance was based off of a high-quality systematic review and meta-analysis by Feller, et al (described above).[5] Recommendations were based on the GRADE approach. No authors had conflicts with industry. Guidance pertains to individuals with subclinical hypothyroidism; defined as elevated TSH levels with normal T4 levels.

There is a strong recommendation against the use of thyroid hormone to treat subclinical hypothyroidism.[5] This recommendation is based on high-quality evidence that there was no difference between thyroid hormone supplementation and no treatment, in patients 65 years and older with subclinical hypothyroidism for the following outcomes: general quality of life, thyroid-related symptoms, fatigue/tiredness, depressive symptoms and cognitive symptoms.[5] There was low quality of evidence that there was no difference between treatment and no treatment for the outcomes of mortality and CV event. For individuals 65 years and younger, there is moderate to high quality evidence that there was no important difference between thyroid hormone and no treatment benefit for the following outcomes: general quality of life, thyroid-related symptoms, fatigue/tiredness and depressive symptoms.[5]

Additional Guidelines for Clinical Context:

ATA/AACE – Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association

In 2012 the American Thyroid Association (ATA)/American Association of Clinical Endocrinologists (AACE) released new guidance on the management of hypothyroidism.[9] The literature search and evidence evaluation was consistent with the AACE Protocol for Standardized Production of Clinical Guidelines. The evidence was graded using grades A to D, with A representing high-quality evidence and D representing expert opinion. The strength of the recommendation were also given a "best evidence" rating level (BEL) ranging from 1-4, with a level 1 recommendation being based on prospective RCTs and a level 4 determined by expert opinion.[9] Two authors had conflicts of interest. Specifics on how the systematic review was conducted was not described, and therefore, the guidelines will be used for context only.

Treatment of hypothyroidism is recommended for individuals with TSH levels greater than or equal to 10 mIU/L (Grade B, BEL 1).[9] Target TSH ranges, for non-pregnant patients, are dependent on testing and should be within the normal range of a third-generation TSH assay. In general, a range of 0.45-4.12 mIU/L should be targeted if an upper limit of normal range of a third generation TSH assay is not available (Grade B, BEL 2).[9] Patients who qualify for treatment should be initiated on levothyroxine monotherapy (Grade A, BEL 1). Levothyroxine 50 mcg daily is recommended for patients 50 to 60 years without evidence of coronary heart disease (Grade D, BEL 4).[9] Individuals with subclinical hypothyroidism should be considered for levothyroxine 25 to 75 mcg daily (Grade B, BEL 2).[9] Levothyroxine should be taken 30-60 minutes before breakfast or at bedtime 4 hours after the last meal. There is insufficient evidence to recommend the use of combination therapy with levothyroxine and L-triiodothyronine (Grade B, BEL 1). Desiccated thyroid is not recommended for the treatment of hypothyroidism (Grade D, BEL 4).[9] Interruptions in therapy lasting less than 6 weeks can be restarted at previous dose of levothyroxine, with the exception of patients with a cardiac event or marked weight loss (Grade D, BEL 4). In patients with central hypothyroidism, serum free T4 should be used to guide therapy, and levothyroxine should be titrated to increase serum T4 to mid-normal range for the assay (Grade B, BEL 3).[9] Serum TSH should be reevaluated every 4-8 weeks upon initiation of levothyroxine, to obtain TSH values within the normal range (Grade A, BEL 1).[9]

Target TSH levels for people who are pregnant should be based on trimester and are the following upper-normal reference ranges : 1st trimester, 2.5 mIU/L; second trimester 3.0 mIU/L; third trimester 3.0 mIU/L (Grade C, BEL 2).[9] Women of childbearing age should be treated with levothyroxine if they have TSH levels between 2.5 mIU/L and the upper limit of normal if they are planning on becoming pregnant or in the first trimester of pregnancy. Levothyroxine is recommended for people in the second trimester of pregnancy with a TSH between 3.0 mIU/L and the upper limit of normal or in the third trimester of pregnancy with a TSH between 3.5 mIU/L and the upper limit of normal (Grade B, BEL 2).[9] People that have positive serum TPOAb levels and are pregnant or planning on becoming pregnant should be considered for levothyroxine treatment, especially if there is a history of hypothyroidism or miscarriage (Grade B, BEL 2).[9] Levothyroxine is also recommended for people who are pregnant or planning on becoming pregnant who have positive levels of TPOAb and a TSH more than 2.5 mIU/L (Grade B, BEL 2).[9]

American Thyroid Association – Guidelines for the Treatment of Hypothyroidism

ATA released guidance on treating hypothyroidism in 2014.[11] The task force systematically reviewed the literature and graded the evidence. Grading of the evidence was done via the American College of Physicians' Guideline Grading System, with quality of evidence rated as low, medium or high. The strength of the evidence recommendation was used to assign a clinical recommendation ranging from strong to weak or no recommendation if there was insufficient evidence.[11] Two of the nine authors had industry relations. Specific methodology related to the systematic review was not described, and details on included evidence were lacking. Therefore, the guideline will be considered for clinical context only.

Table 2. ATA Recommendations for the Treatment of Hypothyroidism.[11]

Recommendation	Strength or Recommendation	Quality of Supporting Evidence
Levothyroxine is the preferred treatment for hypothyroidism.	Strong	Moderate
Clinical goals of levothyroxine therapy are resolution of hypothyroid symptoms, normalization of serum TSH and avoidance of overtreatment.	Strong	Moderate
Adherence to either brand or the same generic formulations of levothyroxine is advised to avoid variability in dose.	Weak for general population Strong for frail patients, high-risk thyroid cancer patients, and pregnant patients Strong for early childhood hypothyroidism	Low Low Moderate
Levothyroxine should be taken either 60 minutes before breakfast or at bedtime 3 or more hours after the evening meal for optimal, consistent absorption.	Weak	Moderate
Levothyroxine should be separated from medications and supplements (e.g., calcium carbonate and ferrous sulfate) that may interact by 4 hours.	Weak	Weak
Initial levothyroxine doses should be based on patient characteristics such as pregnancy, presence of cardiac disease, weight, lean body mass, etiology of hypothyroidism, degree of TSH elevation, and age.	Strong	Moderate

Serum TSH levels should be evaluated 4-6 weeks after any dosage change. Titration of levothyroxine dose should be gradual.	Strong	Moderate
Higher serum TSH levels may be targeted in elderly patients (e.g., those over 65 years).	Strong	Moderate
Women who are pregnant should receive levothyroxine with doses titrated to the appropriate level according to trimester of pregnancy. Serum TSH levels should be evaluated every 4 weeks during the first half of pregnancy. For women already taking levothyroxine, two additional doses per week of current dose may be started after confirmation of pregnancy.	Strong	Moderate
Levothyroxine 10-15 mcg/kg/day should be initiated in newborns who test positive for overt hypothyroidism with a goal of normalizing serum thyroxine in 2-4 weeks. Surveillance testing of serum TSH and T4 should occur every 1-2 months during the first year of life once the proper dose is determined. All children with overt hypothyroidism should be treated with levothyroxine.	Strong	High
Patients with secondary hypothyroidism should have a treatment goal of maintaining serum free T4 values in the upper half of the reference range.	Strong	Moderate
The use of levothyroxine to treat individuals with nonspecific symptoms and normal biochemical studies is not recommended.	Strong	High
Levothyroxine is not recommended for patients with depression who are euthyroid.	Weak	Low
Levothyroxine should not be used to treat obesity in individuals who are euthyroid.	Strong	Moderate
The treatment of urticaria with levothyroxine in euthyroid patients is not recommended.	Strong	Moderate
Levothyroxine is recommended over thyroid extracts for patients with primary hypothyroidism.	Strong	Moderate
Combination treatment with levothyroxine and liothyronine is not recommended for primary hypothyroidism.	Weak	Moderate

After review, seven guidelines were excluded due to poor quality or updated high quality guidance available.[9,11,29–33]

Randomized Controlled Trials:
A total of 1783 citations were manually reviewed from the initial literature search. After further review, all randomized controlled trial citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Specific Drug Information

Generic	Brand	Form
levothyroxine sodium	LEVOTHYROXINE	CAPSULE
levothyroxine sodium	TIROSINT	CAPSULE
levothyroxine sodium	THYQUIDITY	SOLUTION
levothyroxine sodium	TIROSINT-SOL	SOLUTION
levothyroxine sodium	EUTHYROX	TABLET
levothyroxine sodium	LEVO-T	TABLET
levothyroxine sodium	LEVOTHYROXINE SODIUM	TABLET
levothyroxine sodium	LEVOXYL	TABLET
levothyroxine sodium	SYNTHROID	TABLET
levothyroxine sodium	UNITHROID	TABLET
liothyronine sodium	CYTOMEL	TABLET
liothyronine sodium	LIOTHYRONINE SODIUM	TABLET
thyroid, pork	ARMOUR THYROID	TABLET
thyroid, pork	NP THYROID	TABLET

Table 3. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Levothyroxine (T4)[6]	Levothyroxine is synthetic T4 that exerts the same physiological effect as endogenous T4. Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.	Gastrointestinal 40-80% (T4 absorption is increased by fasting)	Metabolism is by sequential deiodination predominately via the liver and via conjugation with glucuronides and sulfates. Elimination is primarily via the kidneys (80%).	• Half-life: 6-7 days • Cmax: Not reported • AUC: Not reported • Vd: 99.96% protein bound
Liothyronine (T3)[7]	Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.	95% absorbed within 4 hours	Metabolism is by sequential deiodination predominately. Around 80% of circulating T3 is derived from peripheral T4 monodeiodination. Conjugation is responsible for a small amount of metabolism.	• Half-life: 2.5 days • Cmax: Not reported • AUC: Not reported • Vd: 99.5% protein bound

Thyroid, pork (T3 and T4)[34]	Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.	95% absorbed within 4 hours	Deiodination in the liver, kidney and other tissues	• Half-life: 2.5 days • Cmax: Not reported • AUC: Not reported • Vd: 99% protein bound

Use in Specific Populations:

Drug Safety:

Use in Specific Populations[6,7]:

- Elderly: initiate thyroid hormone at reduced doses, 12.5 to 25 mcg per day.
- Underlying cardiac disease: initiate thyroid hormone at reduced doses, 12.5 to 25 mcg per day.
- Pediatrics: thyroid doses should be dosed on body weight. Newborns at risk for cardiac failure and children at risk for hyperactivity should receive a lower starting dose.
- Pregnancy: thyroid doses may need to be increased during pregnancy based on serum TSH and free T4 levels.

Drug Interactions:[6,35]

- Oral anticoagulants
- Midodrine or drugs that increase blood pressure
- Drugs that may decrease T4 absorption: phosphate binders, orlistat, bile acid sequestrants, proton pump inhibitors, sucralfate, antacids.
- Drugs that may alter T4 and T3 serum transport without affecting free T4 concentrations: clofibrate, estrogen containing oral contraceptives, estrogen, heroin, methadone, 5-flourouracil, mitotane, tamoxifen , androgens, asparaginase, glucocorticoids, and slow-release nicotinic acid.
- Drugs that may transiently increase free T4: salicylates, carbamazepine, furosemide, heparin, hydantoins, non-steroidal anti-inflammatory drugs and fenamates.
- Drugs that may alter hepatic metabolism: phenobarbital and rifampin.
- Drugs that may decrease conversion of T4 to T3: beta-adrenergic antagonists, glucocorticoids and amiodarone.
- Thyroid hormones may decrease the effect of digitalis glycosides.

Boxed Warnings:
There is a FDA black box warning against the use of levothyroxine for the treatment of obesity or weight loss. Doses exceeding daily hormonal requirements may result in serious or life-threatening manifestations of toxicity.[6,7,35]

Risk Evaluation Mitigation Strategy (REMS) Programs:
There are no REMS programs for thyroid hormones.

Contraindications:
Levothyroxine should not be used in individuals with uncorrected adrenal insufficiency and in untreated thyrotoxicosis.[6,7,35]

Table 4. Summary of Warnings and Precautions.

Warning/Precaution	Levothyroxine[6]	Liothyronine[7]	Thyroid, pork[35]
Increased risk of cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease	X	X	X
Oral products should not be used to treat myxedema coma	X	X	X
In individuals with acute adrenal crisis and concomitant adrenal insufficiency, replacement glucocorticoids should be used as initial treatment before initiation of thyroid hormone treatment	X	X	X
Worsening of glycemic control	X	X	X
Decreased bone mineral density associated with thyroid hormone over-replacement	X	X	X
Prevention of hyperthyroidism or incomplete treatment of hypothyroidism by proper dose titration and ongoing monitoring due to a narrow therapeutic index. Close monitoring is recommended.	X	X	X

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 06, 2022

Search Strategy:

#	Searches	Results
1	levothyroxine.mp. or Thyroxine/	40489
2	liothyronine.mp. or Triiodothyronine/	26163
3	thyroid.mp. or Thyroid Gland/	229285
4	hypothyroid.mp.	9689
5	1 or 2 or 3 or 4	249664
6	limit 5 to (english language and humans and yr="2012 -Current")	50111
7	limit 6 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	1783

Appendix 3: Key Inclusion Criteria

Population	Individuals with hypothyroidism
Intervention	Thyroid hormone
Comparator	Placebo or active treatment
Outcomes	Normalization of thyroid activity and symptom reduction
Timing	NA
Setting	Outpatient

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Drug Class Update: Beta Blockers, Oral

Date of Review: August 2022

Date of Last Review: May 2015
Dates of Literature Search: 01/01/2015-05/02/2022

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

Purpose for Class Update:
To review and evaluate recent evidence and guideline recommendations for beta blockers approved for the treatment of hypertension, angina, heart failure, left ventricular dysfunction after myocardial infarction, arrhythmias, infantile hemangiomas, esophageal varices, or for migraine prophylaxis.

Research Questions:
1. For adult patients with hypertension, angina, recent myocardial infarction, heart failure, arrhythmias, bleeding esophageal varices, or migraines, do beta blocker drugs differ in efficacy or effectiveness?
2. For adult patients with hypertension, angina, recent myocardial infarction, heart failure, arrhythmias, bleeding esophageal varices, or migraines, do beta blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographic characteristics (i.e., age, race, ethnicity, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

Conclusions:
- Since the previous beta blocker literature scan, 5 high-quality systematic reviews have been published which assess the comparative safety and efficacy of beta blockers in hypertension, heart failure, migraine prophylaxis, and infantile hemangiomas.[1-5] Seven guidelines addressing the therapeutic use of beta blockers in hypertension, chronic coronary disease, gestational hypertension, heart failure, atrial fibrillation, ascites in patients with cirrhosis, and infantile angioma have been published or updated.[6-12]

Systematic Reviews
- A 2017 systematic review evaluated treatment of hypertension to assist in the update of an American College of Cardiology (ACC)/American Heart Association (AHA) clinical practice guideline.[1] No class of medications including angiotensin converting enzyme inhibitor (ACEIs), angiotensin-II receptor blocker (ARBs), calcium channel blocker (CCBs) or beta blockers, was significantly better than thiazide diuretics as a first-line therapy for any outcome related to hypertension.[1] Compared to beta-blockers, thiazides were associated with a lower risk of stroke, all-cause mortality, cardiovascular mortality, and cardiovascular events.[1]

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- A 2021 Cochrane review assessed the safety and efficacy of beta blockers in patients without heart failure in the non-acute phase after myocardial infarction (MI).[2] The meta-analyses show that beta blockers compared with placebo or no intervention probably reduce risk of all-cause mortality (risk ratio [RR] 0.81, 97.5% confidence interval [CI] 0.73 to 0.90; moderate-certainty evidence) and MI (RR 0.76, 98% CI 0.69 to 0.88; moderate-certainty evidence) in this population.[2] Beta blockers compared with placebo or no intervention may reduce the risks of major cardiovascular events (RR 0.72, 97.5% CI 0.69 to 0.84; low-certainty evidence) and cardiovascular mortality (RR 0.73, 98% CI 0.68 to 0.85; I^2 = 47%; low-certainty evidence).[2]
- A 2021 Cochrane review assessed the effects of beta blockers, ACEIs, ARBs, angiotensin receptor neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs) in people with heart failure with preserved ejection fraction (HFpEF).[3] A possible reduction in cardiovascular mortality was observed with beta blockers (RR 0.78, 95% CI 0.62 to 0.99; low-certainty evidence).[3] There may be little to no effect on all-cause mortality (RR 0.82, 95% CI 0.67 to 1.00; low-certainty evidence).[3] Based on low quality evidence, the effects of beta blockers on heart failure hospitalization, and quality of life in patients with HFpEF remain uncertain.[3]
- A 2019 systematic review and meta-analysis assessed the efficacy of beta blockers in preventing migraine and tension-type headaches.[4] High-quality evidence shows propranolol 160 mg to 240 mg once daily is effective in reducing episodic migraine frequency compared to placebo.[4] At 8 weeks patients with migraine headaches experienced an average reduction of 1.5 headaches per month (95% CI -2.3 to -0.65) with propranolol compared with placebo.[4] In 3 trials, metoprolol also reduced headache frequency, though the reduction was less than 1 headache a month.[4] Conclusions regarding the efficacy of other beta blockers is less certain, as most were studied in only one trial.[4] Atenolol, bisoprolol and timolol have weak evidence of benefit.[4] Acebutolol and nadolol appear to be ineffective in migraine prophylaxis.[4]
- A 2018 Cochrane review assessed the effects of oral propranolol versus topical timolol versus placebo and for the management of infantile hemangiomas in children.[5] There is moderate-quality evidence that, when compared with placebo, oral propranolol is probably beneficial in terms of complete or almost complete clearance and probably reduces hemangioma volume more than placebo.[5] There is low-quality evidence which assessed a difference in short- or long-term adverse events between oral propranolol and placebo, which made definitive conclusions difficult.[5] Low-quality evidence indicates that topical timolol may reduce infantile hemangioma redness more than placebo, with possibly no accompanying cardiovascular events, although no other safety data were assessed for this comparison.[5] There was no evidence of a difference between oral propranolol and topical timolol maleate in their ability to generate a 50% or greater reduction in infantile hemangioma size, based on low-quality evidence.[5] Very low-quality evidence about adverse events made it difficult to draw conclusions about the comparative safety of oral propranolol versus topical timolol in managing infantile hemangioma.[5]

Clinical Practice Guidelines

- The 2020 International Society of Hypertension (IHS) guideline was developed to provide recommendations for the management of hypertension in adults, aged 18 years and older.[6] In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's systolic blood pressure (SBP) in the office or clinic is 140 mmHg or higher and/or their diastolic blood pressure (DBP) is 90 mmHg or higher, following repeated examination.[6] Beta blockers should be considered to manage hypertension when there is a specific indication for their use (e.g. heart failure, angina, post-MI, atrial fibrillation, or in hypertensive patients planning pregnancy or currently pregnant).[6]
- The 2020 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin addressed optimal antihypertensive treatment for patients with gestational hypertension or preeclampsia.[7] Antihypertensive treatment should be initiated for severe hypertension (SBP of 160 mm Hg or more or DBP of 110 mm Hg or more, or both) that is confirmed as persistent.[7] Oral labetalol and CCBs have been commonly used.[7] One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/day).[7]
- The 2019 European Society of Cardiology (ESC) guidance for management of chronic coronary syndromes updated 2013 guidance focused on management of stable coronary artery disease (CAD).[8]

- First-line treatment for angina/ischemia relief is with beta blockers or non-dihydropyrine CCBs that control heart rate and symptoms (Class 1 recommendation; high-quality evidence).[8]

- The 2021 ESC guidance on heart failure includes recommendations regarding the use of beta blockers to treat different heart failure stages and co-morbidities associated with heart failure as follows:
  - A beta blocker may be considered in patients with mild heart failure and reduced ejection fraction (HFrEF) (e.g. patients with an ejection fraction 40% to 49%) to reduce the risk of heart failure hospitalization and death (Class 2B recommendation; low-quality evidence).[9]
  - A beta blocker is recommended for patients with stable heart failure with reduced ejection fraction (HFrEF) to reduce the risk of heart failure hospitalization and death (Class 1 recommendation: high-quality evidence).[9]
  - Beta blockers should be considered for short- and long-term rate control in patients with heart failure and atrial fibrillation (Class 2A recommendation: moderate-quality evidence).[9]
- The 2020 Canadian Cardiovascular Society (CCS) and Canadian Heart Rhythm Society (CHRS) guideline on management of atrial fibrillation is an update of 2010 guidance.[10] Beta blockers are preferred in patients with acute coronary syndrome who require acute rate control.[10] Intravenous rate control agents might be initially considered if the patient is not hemodynamically stable.[10]
  - Either beta blockers or non-dihydropyridine CCBs (diltiazem or verapamil) are first-line agents for atrial fibrillation rate control in patients without significant left ventricular (LV) dysfunction (e.g., patients with an ejection fraction greater than 40%). (strong recommendation; moderate-quality evidence).[10]
  - Beta blockers bisoprolol, carvedilol and metoprolol are first-line agents for rate control of hemodynamically stable atrial fibrillation in the acute care setting in patients with significant LV dysfunction (e.g., patients with an ejection fraction 40% or less). (strong recommendation; moderate-quality evidence).[10]
- In 2021 the British Society of Gastroenterology in collaboration with British Association for the Study of the Liver updated 2007 guidance on the management of ascites in cirrhosis.[11] The use of beta blockers in ascites is a very small component of the overall management strategies. The portal pressure-lowering effects of non-selective beta blockers have been known to be beneficial in patients with ascites for three decades.[11] Until randomized high-quality data are available, the current evidence supports the use of non-selective beta blockers when indicated in patients with refractory ascites, unless alternative markers of circulatory failure, such as hypotension or reduced glomerular filtration rate, are present.[11]
  - Refractory ascites should not be viewed as a contraindication to a non-selective beta blocker. (strong recommendation; moderate-quality evidence).[11]
  - Patients with refractory ascites who are taking a non-selective beta-blocker should be monitored closely, and dose reduction or discontinuation may be appropriate in those who develop hypotension or acute/progressive renal dysfunction. (strong recommendation; moderate-quality evidence).[11]
- In 2019, the American Academy of Pediatrics (AAP) published clinical practice guidelines on the management of infantile hemangioma.[12] Pharmacotherapy recommendations are as follows:
  - Use propranolol as the first-line agent for infantile hemangioma requiring systemic treatment (strong recommendation; high-quality evidence).[12]
  - May prescribe oral prednisolone or prednisone to treat infantile hemangioma if there are contraindications or inadequate response to oral propranolol (moderate recommendation; moderate-quality evidence).[12]
  - May prescribe topical timolol maleate as a therapy for thin and/or superficial infantile hemangioma (moderate recommendation; moderate-quality evidence).[12]

- No subgroups of patients based on demographic characteristics (i.e., age, race, ethnicity, gender), other medications (drug-drug interactions) have been identified for which one beta-blocker is more effective or associated with fewer adverse effects. However, beta blockers are only appropriate first-line agents in hypertension when treating specific, compelling indications including stable ischemic heart disease, atrial fibrillation, or heart failure.[8,9] Three beta blockers, bisoprolol, carvedilol, and extended-release metoprolol succinate, have been shown to reduce mortality and morbidity in patients with HFrEF.[9] A beta blocker without intrinsic sympathomimetic activity such as extended-release metoprolol succinate, bisoprolol, or carvedilol, should be initiated in the setting of an acute MI to manage atrial fibrillation.[10] Acebutolol is no longer included as an appropriate beta blocker to initiate after MI. Labetalol is the preferred oral beta-blocker for managing gestational hypertension.[13] Finally, propranolol has demonstrated efficacy in migraine prophylaxis[4] and treatment of infantile hemangioma.[5,12] Topical timolol is also effective in treatment of thin (less than 1 mm), superficial infantile hemangioma.[12]

Recommendations:

- Based on current evidence, make acebutolol non-preferred and at least one form of extended-release propranolol and propranolol oral solution preferred on the PDL.
- Review drug costs in the executive session.

Summary of Prior Reviews and Current Policy:

- The beta blocker drug class was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the May 2015 meeting. A Drug Effectiveness Review Project (DERP) scan was used to identify any new comparative research. All of the beta blockers reviewed were effective in the treatment of hypertension, but there was no evidence of differences between beta blockers for blood pressure control, survival, or quality of life.
- Based on previous recommendations, at least one of the following drugs with evidence of effectiveness in moderate to severe chronic heart failure should be preferred on the Preferred Drug List (PDL): carvedilol or metoprolol succinate. In addition, based on previous recommendations, at least one of the following drugs with evidence of effectiveness in recent myocardial infarction (MI) should be preferred on the PDL: acebutolol, carvedilol, metoprolol tartrate, propranolol or timolol. Finally, based on previous recommendations, at least one of the following drugs with evidence of effectiveness for reducing esophageal variceal bleeds should be preferred on the PDL: atenolol, nadolol, propranolol or extended-release propranolol.
- **Appendix 1** summarizes the current preferred beta blocker status on the PDL which includes: acebutolol, atenolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, and propranolol.
- In the first quarter of 2022, 97% of the beta blocker utilization was for preferred agents (e.g., propranolol, metoprolol succinate, carvedilol, metoprolol tartrate, atenolol, and labetalol). The remainder of the utilization was for non-preferred agents including sotalol, bisoprolol, nadolol, extended-release propranolol, and propranolol solution.

Background:

Adrenergic beta antagonists, commonly called beta blockers, refer to a group of drugs with diverse pharmacodynamic and pharmacokinetic properties.[14] Beta blockers competitively inhibit beta receptors and thus modulate sympathetic nervous system activity.[15] They act via multiple pathways, limiting the effects of catecholamine excess, affecting inotropy and chronotropy, providing anti-arrhythmic and anti-ischemic effects and inhibiting renin release.[16] The primary therapeutic uses of beta blockers include: hypertension, angina, post-MI, arrhythmias, and heart failure.[17] Beta blockers can be distinguished by the following properties: selectivity for beta-1 and beta-2 receptors; intrinsic sympathomimetic activity; blockade of alpha receptors; differences in lipid solubility; capacity to induce vasodilation; and pharmacokinetic parameters.[18] Beta adrenergic receptors are present in many body systems including the heart, blood vessels, lungs, kidneys, and nervous system. There are 3 main classes of beta-receptors: beta-1, beta-2, and beta-3. Beta-1 selective (cardioselective) receptor blockers act

mainly on the myocardium with less of an effect on the bronchial or vascular smooth muscle tissues, where beta-2 receptors are present.[17] In patients with bronchospastic reactive airway disease requiring a beta blocker, a cardioselective agent (e.g., atenolol, betaxolol, bisoprolol, metoprolol) is preferred.[19] Beta-1 selective receptor blockers have no intrinsic sympathomimetic activity or alpha-blocking effects. Non-selective beta blockers may decrease cardiac output due to a decrease in cardiac contractility, heart rate and slight increase in peripheral resistance.[17] Beta blockers with partial beta-agonistic activity (e.g., pindolol, acebutolol) or those possessing some alpha-blocking activity (e.g., carvedilol, labetalol) can lower peripheral vascular resistance.[17]

On the basis of their pharmacokinetic properties, beta blockers can be classified into two broad categories: those eliminated by hepatic metabolism and those excreted unchanged by the kidney.[20] Hepatically metabolized drugs such as propranolol and metoprolol, are lipid-soluble, almost completely absorbed by the small intestine, and largely metabolized by the liver.[20] They enter the central nervous system (CNS) in high concentrations, possibly resulting in an increased incidence of CNS side effects.[20] In contrast, renally eliminated beta blockers, such as atenolol and sotalol, are more water soluble, incompletely absorbed through the gut, eliminated unchanged by the kidney, and do not as readily enter the CNS.[20,21] Renally eliminated beta blockers show less variance in bioavailability and have longer plasma half-lives.[21] A pharmacodynamic and pharmacokinetic comparison of oral beta blockers is presented in **Table 1.**

Table 1. Beta Blocker Pharmacokinetic and Pharmacodynamic Comparisons[22,23]

Drug Name	Indications	Primary Site of Metabolism	Mixed Alpha- and Beta-Blocker	Cardioselective (Beta-1 selective)	ISA
Acebutolol	Hypertension; arrhythmias	Hepatic		X	X
Atenolol	Angina; hypertension	Renal		X	
Betaxolol	Hypertension	Renal		X	
Bisoprolol	Hypertension, heart failure, post-MI	Hepatic/Renal		X	
Carvedilol	Heart failure; hypertension; post-MI	Hepatic	X		
Labetalol	Hypertension	Hepatic	X		
Metoprolol	Angina; heart failure; hypertension; post-MI	Hepatic		X	
Nadolol	Angina pectoris; hypertension	Renal			
Nebivolol	Hypertension	Hepatic		X	
Pindolol	Hypertension	Hepatic			X
Propranolol	Angina; infantile hemangioma; arrhythmias; essential tremor; hypertension; migraine prophylaxis; pheochromocytoma, post-MI	Hepatic			
Sotalol	Arrhythmias	Renal			
Timolol	Hypertension, post-MI	Hepatic			

Abbreviations: ISA = intrinsic sympathomimetic activity; MI = myocardial infarction

For patients with hypertension but without compelling indications, a beta blocker should not be used as the initial first-line agent.[19] Clinical trial data and meta-analyses suggest that hypertension treatment with a beta blocker may reduce cardiovascular events better than placebo, but not to the extent that an ACEI, ARB, CCB, or thiazide diuretic can achieve.[19] A beta blocker is only an appropriate first-line agent in hypertension when treating specific, compelling indications such as stable ischemic heart disease or heart failure.[8,9]

Beta blockers should be used for the treatment of hypertension in patients with stable ischemic heart disease who have reduced left ventricular ejection fraction (LVEF) after MI.[19] In these patients, beta blockers decrease myocardial ischemia, reinfarction, and the frequency of complex ventricular dysrhythmias.[24] In randomized long-term trials, use of beta blockers after MI reduced all-cause mortality by 23%.[19] The protective benefit in asymptomatic patients with depressed LVEF without a history of MI is less well established and lacks placebo-controlled trials.[25] A beta blocker without intrinsic sympathomimetic activity such as extended-release metoprolol succinate, bisoprolol, or carvedilol, should be initiated in the setting of an acute MI.[24]

Hypertension in pregnancy is a condition affecting 5–10% of pregnancies worldwide.[6] Hypertension in pregnancy includes the following conditions: persistent BP greater than 140/90 mmHg in gestational hypertension; pre-existing hypertension with superimposed gestational hypertension; and hypertension with subclinical hypertension mediated organ damage at any time during pregnancy.[6] Maternal risks include placental abruption, stroke, multiple organ failure (liver, kidney), and disseminated vascular coagulation.[6] Fetal risks include intrauterine growth retardation, preterm birth, and intrauterine death.[6] When antihypertensive drug therapy should be initiated varies by guideline. ACOG recommends starting drug therapy when blood pressure is 160/110 mm Hg or greater.[7] International societies recommend beginning drug treatment when blood pressure is greater than 140/90 mm Hg.[6] However, the benefit from normalization of blood pressure treatment for pregnant women, coupled with theoretical concerns for fetal well-being from a reduction *in utero* placental perfusion and *in utero* exposure to antihypertensive medication has some controversy in clinical practice.[26] Initial drug therapy is monotherapy with labetalol or methyldopa.[26] Some, but not all, clinical guidelines support the use of oral nifedipine as initial therapy.[26] These therapeutic options are based on small individual trials and are advocated by national and international clinical practice guidelines.[26] Some observational studies have associated beta blocker treatment, including labetalol, with an increased risk for birthing small-for-gestational-age infants, although the study investigators did not adjust for treatment indication and severity of maternal disease.[26] Metoprolol and pindolol are considered acceptable alternatives to labetalol based on limited data in pregnant patients.[27] Propranolol and other non-elective beta blockers should be avoided as they may promote uterine irritability through beta-2 receptor blockade.[27] Atenolol has been associated with slightly lower placental and fetal weight at delivery when used early in pregnancy and should be avoided if an effective drug with a better safety profile is available.[28,29]

Beta blockers are one of the main classes of medications used for treating patients with HFrEF, defined as LVEF of 40% or less. Patients with heart failure with no or minimal evidence of volume overload should be treated with one of the following beta blockers with established clinical benefits in randomized trials: carvedilol, extended release metoprolol succinate, or bisoprolol.[17] In patients with HFrEF, these 3 beta-blockers have been shown to reduce morbidity and mortality from cardiovascular disease, reduce hospitalization rates, and improve symptoms.[30] The favorable findings with these 3 beta blockers should not be considered a beta blocker class effect in HFrEF.[31] Other beta blockers are not recommended for use in patients with HFrEF.[31] Clinical trials have shown that beta blockers should be prescribed to all patients when HFrEF is diagnosed, including in-hospital, unless contraindicated or not tolerated.[31] The benefits of beta blockers were observed in patients with or without CAD, and in patients with or without diabetes, older patients, as well as in women and across racial and ethnic groups but not in patients with atrial fibrillation.[31] Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major cardiovascular events.[31]

The use of beta blockers in ascites is a very small component of the overall management strategies. The portal pressure-lowering effects of non-selective beta blockers (e.g., carvedilol, propranolol, nadolol) have been known to be beneficial in patients with ascites for three decades.[11] A 1991 meta-analysis of trial data demonstrated that non-selective beta blockers reduce the likelihood of first variceal hemorrhage in the ascites subgroup, while in Child's Pugh B and C cirrhosis the addition of non-selective beta blockers to band ligation results in less variceal rebleeding and superior survival.[11] Proven hemodynamic response to non-selective beta blockers (drop in hepatic venous pressure gradient (HVPG) of 10 to 20% or more from baseline, or to less than 12 mm Hg) has been linked with a lower probability of the development of ascites; and in patients already with ascites, a lower probability of refractory ascites and hepatorenal syndrome.[11] However, it remains possible that non-response in this context is simply a surrogate marker for disease severity.[11] Until randomized high-quality data are available, the current evidence supports the use of non-selective beta blockers when indicated in patients with refractory ascites, unless alternative markers of circulatory failure, such as hypotension or reduced glomerular filtration rate, are present.[11]

Infantile hemangiomas (previously known as strawberry birthmarks) are the most common vascular tumors among children, occurring in 3% to 10% of infants.[5] These benign vascular tumors are usually uncomplicated and tend to regress spontaneously.[5] However, when hemangiomas occur in high-risk areas, such as near the eyes, throat, or nose, impairing their function, or when complications develop, intervention may be necessary.[5] The skin covering hemangiomas may become ulcerated, exposing the underlying blood vessels and making them more liable to bleed from minor trauma and become infected.[5] Although most hemangiomas are self-limited and do not need treatment, some indications for treatment include the following: high-output cardiac failure, bleeding, ulceration, risk of permanent disfigurement, or airway or visual obstruction.[5] Infantile hemangiomas appear more commonly among White persons, being evident in up to 12% of all White children.[5] Infantile hemangiomas affect females in a ratio of 3:1.[5] Sixty per cent of infantile hemangiomas are located in the head and neck area, whereas 25% occur on the trunk and 15% on the extremities.[5] A chance observation of an antiproliferative effect of propranolol on infantile hemangioma was described in 2015.[5] This drug has showed a highly effective profile with tolerable adverse events, in comparison with previous recommended interventions used for infantile hemangioma (e.g. steroids, interferon, chemotherapy).[5] Minimal side effects were reported with propranolol, and the response rate approached 100%.[5] Propranolol is now the first-line treatment for infantile hemangioma and has been approved for this indication.[5]

Most adverse drug reactions experienced with the use of beta blockers are an extension of their pharmacologic activity.[15] Beta blockers can cause bradycardia, atrioventricular block and symptomatic hypotension, especially in patients with sinus or atrioventricular node dysfunction, and are contraindicated in severe asthma because of the risk of life-threatening bronchospasm.[16] Central nervous system adverse drug effects like fatigue, depression, insomnia, and general malaise are usually mild but are among the most common reasons for treatment discontinuation.[15] In addition, most beta blockers negatively influence glucose or lipid metabolism.[32] Beta blockers are absolutely contraindicated in patients with pre-existing bradycardia, second or third-degree atrioventricular block, a history of uncontrolled reactive airway disease (e.g., severe asthma), severe peripheral arterial disease (e.g., critical limb ischemia), hypotension, HFrEF with unstable fluid status, and patients with diabetes who have frequent episodes of hypoglycemia.[15] If beta blocker therapy needs to be discontinued, doses should be slowly tapered over 2 to 3 weeks to prevent abrupt withdrawal.[15]

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:

American College of Cardiology/American Heart Association Task Force: Hypertension Treatment

A 2017 systematic review evaluated literature focused on detection, evaluation, and treatment of hypertension to assist in the update of an ACC/AHA clinical practice guideline.[1] The research question most pertinent for the current beta blocker class update addresses how various antihypertensive drug classes differ in their benefits and harms compared with each other as first line-therapy for adults with hypertension.[1] Literature was searched through 2015.[1] Study population criteria required that study participants be adults 18 years of age and older with primary hypertension or hypertension due to chronic kidney disease.[1] The study interventions must have used thiazides, ACEIs, ARBs, CCBs, or beta blockers.[1] Comparators were the same as described for the interventions as long as they represented a different class of antihypertensive medication than the intervention.[1] There were 8 outcome criteria evaluated in the review: all-cause mortality, cardiovascular mortality, congestive heart failure (CHF), stroke, MI, composite cardiovascular events, major adverse cardiac events, and renal outcomes.[1] Fifty-eight RCTs (n=152,379 with 3.5 years of follow-up) met inclusion criteria.[1] Fourteen trials included a thiazide arm, 25 RCTs had an ACEI arm, 9 RCTs had an ARB arm, 28 RCTs had a CCB arm, and 10 RCTs had a beta-blocker arm.[1] The mean age of enrolled populations ranged from 47 to 69 years, and approximately 50% of participants were women.[1] Overall, the studies included in the analyses showed low or unclear risk of bias.[1] There appeared to be publication bias against studies with longer follow-up and null findings.[1] The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) trial contributed the largest number of participants randomized to beta-blockers for assessment of all-cause mortality, cardiovascular mortality, MI, and heart failure.[1]

Random-effects Bayesian network meta-analyses were conducted to compare multiple antihypertensive treatments within the same statistical model.[1] Compared with thiazides, the relative risks of all-cause mortality were 1.0 (95% CI 0.95 to 1.1) for ACEIs; 0.99 (95% CI 0.88 to 1.1) for ARBs; 1.1 (95% CI 0.98 to 1.2) for beta-blockers; and 0.97 (95% CI 0.90 to 1.1) for CCBs.[1] Compared with thiazides, the relative risks of cardiovascular mortality were 1.1 (95% CI 0.92 to 1.3) for ACEIs; 1.1 (95% CI 0.87 to 1.5) for ARBs; 1.2 (95% CI 0.98 to 1.4) for beta-blockers; and 1.0 (95% CI 0.86 to 1.2) for CCBs.[1 1] Also, the risk of cardiovascular mortality was higher (but not statistically significant) for beta blockers compared with CCBs (RR 1.2; 95% CI 0.98 to 1.4).[1] Compared with thiazides, the relative risks of stroke were 1.1 (95% CI 0.98 to 1.4) for ACEIs; 1.1 (95% CI 0.88 to 1.4) for ARBs; 1.3 (95% CI 1.1 to 1.6) for beta-blockers; and 0.96 (95% CI 0.83 to 1.2) for CCBs.[1] There was also an increased, but not statistically significant risk of stroke for ACEIs and beta-blockers compared with CCBs (RR 1.2; 95% CI 1.0 to 1.4 and RR 1.4; 95% C 1.1 to 1.7, respectively).[1] Compared with thiazides, the relative risks of cardiovascular events were 1.1 (95% CI 0.96 to 1.3) for ACEIs; 1 (95% CI 0.89 to 1.2) for ARBs; 1.2 (95% CI 1.0 to 1.4) for beta blockers; and 1.1 (95% CI 0.98 to 1.2) for CCBs.[1] The risk of cardiovascular events was reduced (but not statistically significant) for ARBs compared with beta blockers (RR 0.88; 95% CI 0.78 to 1.0).[1] There were also no statistically significant differences between drug classes in risk of adverse renal outcomes.[1]

To investigate whether these results were consistent by race, the authors conducted stratified analyses among studies with predominantly Black study participants (defined as studies reporting subgroup analysis in Blacks or having populations with at least 85% Black participants) or which published race-specific analyses.[1] No significant differences were observed in all-cause mortality, cardiovascular mortality, MI, CHF, cardiovascular events, or renal outcomes among Blacks between any of the drug classes.[1] Effects by multiple subgroups of interest including age, race, sex, and diabetes mellitus status were also assessed.[1] No significant effects were identified, likely due to the relatively few studies for each class-to-class comparison with published data available for these analyses.[1] Therefore, these findings should be interpreted with caution.[1]

In summary, SBP lowering to a target of less than 130 mm Hg may reduce the risk of several important outcomes including risk of stroke, CHF, major cardiovascular events, and mortality.[1] No other class of antihypertensives (i.e., ACEIs, ARBs, CCBs, or beta blockers) was significantly better than thiazide diuretics as a first-line therapy for any outcome related to hypertension.[1] Compared to beta blockers, thiazides were associated with a lower risk of stroke and cardiovascular events.[1]

Cochrane: Beta Blockers In Patients Without Heart Failure After Myocardial Infarction

A 2021 Cochrane review assessed the safety and efficacy of beta blockers in patients without heart failure in the non-acute phase after MI.[2] Literature was searched through February 2021 to identify all RCTs assessing effects of beta blockers versus control (placebo or no treatment) in patients without heart failure after MI.[2] Primary outcomes were all-cause mortality, serious adverse events (SAEs), and major cardiovascular events (composite of cardiovascular mortality and non-fatal MI).[2] Secondary outcomes were quality of life, angina, cardiovascular mortality, and MI during follow-up.[2] Twenty-five RCTs (n=22,423) met inclusion criteria.[2] All trials and outcomes were at high risk of bias.[2]

The meta-analyses show that beta blockers compared with placebo or no intervention probably reduce the risks of all-cause mortality (RR 0.81, 97.5% CI 0.73 to 0.90; I^2 = 15%; 22,085 participants, 21 trials; moderate-certainty evidence) and MI (RR 0.76, 98% CI 0.69 to 0.88; I^2 = 0%; 19,606 participants, 19 trials; moderate-certainty evidence).[2] Beta blockers compared with placebo or no intervention may reduce the risks of major cardiovascular events (RR 0.72, 97.5% CI 0.69 to 0.84; 14,994 participants, 15 trials; low-certainty evidence) and cardiovascular mortality (RR 0.73, 98% CI 0.68 to 0.85; I^2 = 47%; 21,763 participants, 19 trials; low-certainty evidence).[2] Evidence seems to suggest that beta blockers versus placebo or no treatment may result in a minimum reduction of 10% in RR for risks of all-cause mortality, major cardiovascular events, cardiovascular mortality, and MI.[2] However, beta blockers compared with placebo or no intervention may not affect the risk of angina (RR 1.04, 98% CI 0.93 to 1.13; I^2 = 0%; 7115 participants, 5 trials; low-certainty evidence).[2] No trials provided data on SAEs or quality of life.[2]

Cochrane: Beta Blockers And Inhibitors Of The Renin-Angiotensin-Aldosterone System For Chronic Heart Failure With Preserved Ejection Fraction

A 2021 Cochrane review assessed the effects of beta blockers, ACEIs, ARBs, ARNIs, and MRAs in people with HFpEF.[3] Literature was searched through May 2020 to identify RCTs with a parallel group design which enrolled adults with HFpEF, defined by LVEF greater than 40%.[3] Forty-one RCTs met inclusion criteria.[3] The risk of bias in trials was frequently unclear and only five studies had a low risk of bias in all domains.[3]

For the purposes of this drug class update, the focus will be on the 10 trials (n=3087) which evaluated beta blockers.[3] Five studies used a placebo comparator and in 5 RCTs, the comparator was usual care.[3] The mean age of participants ranged from 30 years to 81 years.[3] A possible reduction in cardiovascular mortality was observed with beta blockers (RR 0.78, 95% CI 0.62 to 0.99; number needed to treat (NNT) 25; 1046 participants; 3 studies); however, the certainty of evidence was low due to the small trial sizes and uncertainty about the study methodology.[3] There may be little to no effect on all-cause mortality (RR 0.82, 95% CI 0.67 to 1.00; 1105 participants; 4 studies; low-certainty evidence).[3] The effects of beta blockers on heart failure hospitalization and quality of life in patients with HFpEF remain uncertain.[3]

Beta Blockers For The Prevention Of Headache In Adults

The purpose of a 2019 systematic review and meta-analysis was to assess the efficacy of beta blockers in preventing migraine and tension-type headache.[4] Literature was searched through August 2018.[4] One hundred eight RCTs ranging from 4 to 64 weeks in duration met inclusion criteria.[4] Fifty RCTs were placebo-controlled and 58 RCTs were comparative effectiveness trials.[4] The average age of patients was 37 years and 77% of participants were women.[4] Ten different beta blockers were studied. Propranolol 80 mg to 240 mg per day (n=74) and metoprolol 100 mg to 200 mg per day (n=21) were the most commonly evaluated beta

blockers.[4] Atenolol, nadolol, pindolol and timolol had 2 studies each.[4] Compared to placebo, propranolol reduced episodic migraine headaches by 1.5 headaches per month at 8 weeks (95% CI -2.3 to -0.65) and was more likely to reduce headaches by 50% (RR 1.4, 95% CI 1.1 to 1.7).[22] Studies had a number of quality issues including high drop-out rates (16%), lack of intention to treat analysis (76%), inadequate sequence generation (83%), lack of evidence of concealed allocation (90%) and inadequate blinding (60%).[4] Trials comparing beta blockers to other interventions were largely single trials.[4]

The primary outcome of interest was number of headaches per month.[4] Among patients with episodic migraines, the average number of headaches at baseline was 4.9 headaches per month.[4] The most studied beta blocker was propranolol, which was more effective than placebo at 8 and 12 weeks (8 weeks: -1.5 headaches/month, 95% CI -2.3 to -0.65); 12 weeks: -1.2 headaches/month, 95% CI -1.8 to -0.60).[4] Propranolol outcomes at 8 and 12 weeks were both graded as high-quality evidence.[4] The recommended dose of propranolol extended release for migraine prophylaxis is an initial dose of 80 mg once daily, and gradually increased to the usual effective dose of 160 mg to 240 mg once daily.[33] The propranolol immediate release formulation may also be used, but the daily dose must be administered in 3 to 4 divided doses per day.[34] Propranolol was comparable to other medications known to be effective in migraine prophylaxis including topiramate and valproate.[4] Other beta blockers that were more effective than placebo at 8 weeks included bisoprolol (-0.70 headaches/month, 95% CI -1.4 to -0.05, low quality), metoprolol (-0.86 headaches/month, 95% CI -1.4 to -0.34, moderate quality) and timolol (-0.77 headaches/month, 95% CI -1.4 to -0.12, moderate quality).[4] Two beta blockers, acebutolol and bisoprolol, did not significantly reduce headache frequency in single trials.[4]

There were 4 trials that evaluated propranolol to an active comparator (e.g., nortriptyline, topiramate, and valproic acid) for chronic migraine headaches.[4] Propranolol was more likely to reduce chronic migraine headaches by at least 50% (RR 2.0, 95% CI 1.0 to 4.3).[4] There was only one trial of beta blockers for tension-type headache, comparing the combination of pindolol and amitriptyline to placebo and to amitriptyline alone.[4] The combination of pindolol and amitriptyline was more effective than placebo at reducing headache frequency at 4 and 8 weeks and in reducing headaches by at least 50% (RR 3.8, 95% CI 1.5 to 9.3), but equally effective with amitriptyline.[4]

Participants on beta blockers were more likely to experience side effects than those on placebo (RR 1.2, 95% CI 1.0 to 1.4), though they were not more likely to withdraw from therapy (RR 0.99, 95% CI 0.83 to 1.2).[4] Specific side effects more common with beta blockers included dizziness (RR 1.5, 95% CI 1.0 to 2.3) and fatigue (RR 1.5, 95% CI 1.2 to 2.0).[4]

In summary, there is high quality evidence that compared to placebo, propranolol was effective in reducing episodic migraine frequency.[4] Other comparisons were rated as low-quality based on only including single trials, which made definitive conclusions about comparative effectiveness impossible.[4] There were relatively few trials examining beta blocker effectiveness for chronic migraine or tension-type headache though there was limited evidence of benefit.[4] Conclusions regarding the efficacy of other beta blockers is less certain, as most were studied in just one trial each.[4] Atenolol, bisoprolol and timolol had weak evidence of benefit.[4] Acebutolol and nadolol appeared to be ineffective in migraine prophylaxis.[4]

Cochrane: Interventions For Infantile Hemangiomas

A 2018 Cochrane review updated a 2011 review which assessed the effects of interventions for the management of infantile hemangiomas in children.[5] The literature search for RCTs of all types of interventions in children with single or multiple infantile hemangiomas was competed in February 2017.[5] Twenty-eight RCTs, with a total of 1728 participants, assessing 12 different interventions, including lasers, beta blockers (e.g. propranolol, timolol maleate), radiation therapy, and steroids (oral prednisolone) were identified.[5] Comparators included placebo, an active monitoring approach, sham radiation, and interventions given alone or in combination.[5] Studies were conducted in a number of countries, including Canada, China, Egypt, France, and Australia.[5] Primary outcomes included clearance of the hemangioma, as assessed by the clinician at any follow-up: proportion of children with lesions completely cleared or with minimal residual signs

(defined as faint macular erythema with no palpable component) from baseline to six-moth follow-up, and adverse events.[5] Participant age ranged from 12 weeks to 13.4 years.[5] Most studies (23/28) included a majority of females and different types of infantile hemangiomas.[5] Duration of follow-up ranged from 7 days to 72 months.[5] Most of the trials were at low risk of randomization s, attritions, or selective reporting bias.[5] The domains of allocation concealment and blinding were not clearly reported in general.[5] Evidence was downgraded for issues related to risk of bias and imprecision.[5] The 3 most important comparisons were: 1) oral propranolol versus placebo; 2) topical timolol versus placebo; and 3) oral propranolol versus topical timolol.

1) Oral Propranolol Versus Placebo

Compared with placebo, oral propranolol 3 mg/kg/day divided into 2 doses and administered for 6 months, probably improves clinician-assessed clearance (RR 16.61, 95% CI 4.22 to 65.34; 1 study; 156 children; moderate-quality evidence) and probably leads to a clinician-assessed reduction in mean hemangioma volume of 45.9% (95% CI 11.60% to 80.20%; 1 study; 40 children; moderate-quality evidence).[5] No differences were identified in terms of short- or long-term SAEs (RR 1.05, 95% CI 0.33 to 3.39; 3 studies; 509 children; low-quality evidence), bronchospasm, hypoglycemia, or serious cardiovascular adverse events.[5] There is moderate-quality evidence that, when compared with placebo, oral propranolol is probably beneficial in terms of complete or almost complete clearance and probably reduces hemangioma volume more than placebo.[5] There is insufficient evidence to determine a difference in terms of short- or long-term adverse events between the groups (low-quality evidence).[5] The single study was industry sponsored. [5]

2) Topical Timolol Maleate Versus Placebo

Topical timolol maleate is available in a 0.25% and 0.5% ophthalmic solution, as well as an extended release 0.5% gel-forming solution. Frequency and method of application have varied from once daily under occlusion to twice daily without occlusion; 1 to 2 drops have typically been used and are usually given for 2 to 6 months.[5] The chance of reduction of redness, as a measure of clinician-assessed resolution, may be improved with topical timolol maleate 0.5% gel applied twice daily when compared with placebo (RR 8.11, 95% CI 1.09 to 60.09; 1 study; 41 children; low-quality evidence).[5] Regarding short- or long-term serious cardiovascular events, no instances of bradycardia or hypotension were reported in either group (1 study; 41 children; low-quality evidence).[5] No other safety data were assessed, and clearance was not measured.[5] Low-quality evidence indicates that topical timolol maleate may reduce infantile hemangioma redness more than placebo, with possibly no accompanying cardiovascular events, although no other safety data were assessed for this comparison.[5]

3) Oral Propranolol Versus Topical Timolol Maleate

When topical timolol maleate (0.5% eye drops applied twice daily) was compared with oral propranolol (via a tablet taken once per day, at a 1.0 mg/kg dose), there was no evidence of a difference in hemangioma size (as a measure of resolution) when measured by the proportion of patients with a clinician-assessed reduction of 50% or greater (RR 1.13, 95% CI 0.64 to 1.97; 1 study; 26 participants; low-quality evidence).[5] Although there were more short- or long-term general adverse effects (such as severe diarrhea, lethargy, and loss of appetite) in the oral propranolol group, there was no evidence of a difference between groups (RR 7.00, 95% CI 0.40 to 123.35; 1 study; 26 participants; very low-quality evidence).[5] This comparison did not measure clearance.[5] There was no evidence of a difference between oral propranolol and topical timolol maleate in their ability to generate a 50% or greater reduction in infantile hemangioma size, based on low-quality evidence.[5] Very low-quality evidence about adverse events made it difficult to draw conclusions about the comparative safety of oral propranolol versus topical timolol in managing infantile hemangioma.[5]

In summary, there is limited evidence for the treatment of infantile hemangiomas as a large number of interventions and outcomes have not been assessed in RCTs.[5] Key results from the 28 RCTs indicate that in the management of infantile hemangioma in children, oral propranolol and topical timolol maleate are more beneficial than placebo in terms of clearance or other measures of resolution, or both, without an increase in harms.[5] No evidence of a difference between oral propranolol and topical timolol maleate was identified with regard to reducing hemangioma size, but it is uncertain if there is a difference in safety.[5] However, these results are based on moderate- to very low-quality evidence.[5]

After review, 15 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).[35-50]

New Guidelines

High Quality Guidelines:

International Society of Hypertension

The 2020 IHS guideline was developed to provide recommendations for the management of hypertension in adults, aged 18 years and older.[6] Despite several initiatives, the prevalence of raised blood pressure and adverse impact on cardiovascular morbidity and mortality are increasing globally, irrespective of income.[6] In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's SBP in the office or clinic is 140 mmHg or higher and/or their diastolic blood pressure (DBP) is 90 mmHg or higher, following repeated examination.[6] Beta blockers should be considered when there is a specific indication for their use, such as with heart failure, angina, post-MI, atrial fibrillation, or in hypertensive women planning pregnancy or currently pregnant.[6] In patients with hypertension and heart failure, renin-angiotensin-system (RAS) blockers, beta-blockers, and MRAs are all effective in improving clinical outcome in patients with established HFrEF, whereas for diuretics, evidence is limited to symptomatic improvement.[6] Recommended first-line oral pharmacotherapy options in gestational hypertension include methyldopa, labetalol, and nifedipine.[6] Contraindicated therapies include RAS blockers (e.g., ACEI, ARB, and direct renin inhibitors) because of adverse fetal and neonatal outcomes.[6]

American College of Obstetricians and Gynecologists: Gestational Hypertension and Preeclampsia

A 2020 ACOG Practice Bulletin summary addressed optimal antihypertensive treatment for women with gestational hypertension or preeclampsia.[7] Antihypertensive treatment should be initiated for severe hypertension (SBP of 160 mm Hg or more or DBP of 110 mm Hg or more, or both) that is confirmed as persistent.[7] Parenteral antihypertensive therapy may be needed initially for acute control of blood pressure, however, oral medications can be used as expectant management is continued.[7] Oral labetalol and calcium channel blockers have been commonly used.[7] One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/day).[7] If the maximum dose is inadequate to achieve the desired blood pressure goal, or the dosage is limited by adverse effect, then short-acting oral nifedipine can be added gradually.[7]

European Society of Cardiology: Management of Chronic Coronary Syndromes

The 2019 ESC guidance for management of chronic coronary syndromes updated 2013 guidance focused on management of stable CAD.[8] Coronary artery disease is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive.[8] The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion.[8] The dynamic nature of the CAD process results in various clinical presentations, which can be categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes.[8] The most frequently encountered clinical scenarios in patients with suspected or established chronic coronary syndrome are: 1) patients with suspected CAD and stable anginal symptoms or dyspnea; 2) patients with new onset of heart failure or left ventricular dysfunction and suspected CAD; 3) asymptomatic and symptomatic patients with stabilized symptoms less than 1 year after an ACS event, or patients with recent revascularization; 4) asymptomatic and symptomatic patients 1 year or longer after initial diagnosis or revascularization; 5) patients with angina and suspected vasospastic or microvascular disease; and 6) asymptomatic subjects in whom CAD is detected at screening.[8] All of these scenarios are classified as a chronic coronary syndrome, but involve different risks for future cardiovascular events (e.g. death or MI) and the risk may change over time.[8]

Beta blockers can be combined with dihydropyridine (DHP) CCBs (e.g., long-acting nifedipine or amlodipine) to reduce DHP-induced tachycardia, but with uncertain incremental clinical value.[8] Caution is warranted when a beta blocker is combined with non-dihydropyridine CCBs (e.g., verapamil or diltiazem) due to

the potential for developing worsening of heart failure, excessive bradycardia, or atrioventricular block.[8] The ESC recommendation on anti-ischemic drugs in patients with chronic coronary syndrome is as follows:

- First-line treatment is indicated for angina/ischemia relief with beta blockers or non-dihydropyridine CCBs to control heart rate and symptoms (Class I recommendation: evidence that a given treatment is beneficial, useful, and effective. Class A level of evidence: data is derived from multiple RCTs or meta-analyses).[8]

In certain patients with recent MI and those with chronic HFrEF, beta blockers have been associated with a significant reduction in mortality and/or cardiovascular events, but the protective benefit in patients with CAD without prior MI or heart failure is less well established and lacks placebo-controlled trials.[8] A retrospective analysis of 21,860 matched patients from the REACH (Reduction of Atherothrombosis for Continued Health) Registry showed no reduction in cardiovascular mortality with beta-blockers in patients with either CAD with risk factors only, known prior MI, or known CAD without MI.[8] In a retrospective national registry of 755,215 patients aged 65 years and older with a history of CAD without prior MI or heart failure with reduced ejection fraction undergoing elective percutaneous coronary intervention (PCI), beta blocker use at discharge was not associated with any reduction in cardiovascular morbidity or mortality at 30-day and 3-year follow-up.[8] However, in patients with or without previous MI undergoing coronary artery bypass grafting (CABG), beta-blockers were associated with lower risk of long-term mortality and adverse cardiovascular events.[8] Other observational studies and meta-analyses have questioned the benefit of long-term (greater than 1 year) beta blocker therapy in patients with a previous MI.[8] This is still a matter for debate, and uncertainties remain on the comparative role of beta blockers and ACEIs/ARBs.[8]

European Society of Cardiology: Treatment of Heart Failure

The aim of the 2021 ESC Guideline is to help health professionals manage people with heart failure according to the best available evidence.[9] In the updated publication, each phenotype of heart failure, based on LVEF, is addressed separately in terms of diagnosis and management.[9] The diagnosis of mild HFrEF requires the presence of symptoms or signs of heart failure, and a mildly reduced ejection fraction (41 to 49%).[9] There is a substantial overlap of clinical characteristics, risk factors, patterns of cardiac remodeling, and outcomes among the LVEF categories in heart failure.[9] Patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF, in that they are more commonly men, younger, and are more likely to have CAD (50 to 60% prevalence), and less likely to have AF and non-cardiac comorbidities.[9] However, ambulatory patients with HFmrEF have a lower mortality than those with HFrEF, more akin to those with HFpEF.[9] There is no specific trial of beta-blockade in HFmrEF.[9] Since many patients with HFmrEF may have another cardiovascular indication for a beta blocker (e.g., atrial fibrillation or angina), treatment with beta blockers may be considered in patients with HFmrEF.[9]

The diagnosis of HFpEF requires objective evidence of cardiac structural, or functional abnormalities as well as elevated plasma natriuretic peptide concentrations consistent with the presence of LV diastolic dysfunction and raised LV filling pressures.[9] A diastolic stress test is recommended when these markers are equivocal.[9] Heart failure with preserved ejection fraction of 50% or more differs from HFrEF and HFmrEF in that HFpEF patients are older and more often female.[9] Atrial fibrillation, chronic kidney failure, and non-cardiovascular comorbidities are more common in patients with HFpEF than in those with HFrEF.[9] To date, no treatment has been shown to reduce mortality and morbidity in patients with HFpEF.[9] Despite the lack of evidence for specific disease-modifying therapies in HFpEF, as the vast majority of HFpEF patients have underlying hypertension and/or CAD, many are already treated with ACE-I/ARB, beta-blockers, or MRAs.[9]

There are 3 major goals of treatment for patients with HFrEF: 1) reduction in mortality, 2) prevention of recurrent hospitalizations due to worsening HF, and 3) improvement in clinical status, functional capacity, and quality of life.[9] The triad of an ACEI or ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for patients with HFrEF, unless the drugs are contraindicated or not tolerated.[9] The dose should be titrated up to the doses used in the clinical trials (or

to maximally tolerated doses if that is not possible).[9] **Table 2** provides specific, evidence-based, beta blocker dose recommendations.[9] Specific beta blockers (**Table 2**) have been shown to reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACEI and diuretic.[9] They also improve heart failure symptoms.[9] There is consensus that ACEI and beta blockers can be started together as soon as the diagnosis of symptomatic HFrEF is established.[9] There is no evidence favoring the initiation of a beta blocker before an ACEI and vice versa.[9] Beta blockers should be initiated in clinically stable, euvolemic, patients at a low dose and gradually up titrated to the maximum tolerated dose.[9] In patients admitted with acute heart failure, beta blockers should be cautiously initiated in the hospital, once the patient is hemodynamically stabilized.[9]

Table 2. Evidence-based doses of disease-modifying beta-blockers in patients with heart failure with reduced ejection fraction[9]

Beta blocker	Starting Dose	Target Dose
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily*
Metoprolol Succinate (extended-release)	12.5 to 25 mg once daily	200 mg once daily
*A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg		

Specific recommendations regarding the use of beta blockers to treat different stages of heart failure and the quality of evidence supporting the recommendation are:

- A beta blocker may be considered in patients with mild HFrEF to reduce the risk of heart failure hospitalization and death. (Class 2B recommendation; efficacy is less well established by evidence. Class C level of evidence: consensus of opinion of experts or small studies, retrospective studies, and registries).[9]
- A beta blocker is recommended for patients with stable HFrEF to reduce the risk of heart failure hospitalization and death. (Class I recommendation: evidence that a given treatment is beneficial, useful, and effective. Class A level of evidence: data derived from multiple RCTs or meta-analyses).[9]

Atrial fibrillations and heart failure frequently coexist.[9] They can cause or exacerbate each other through mechanisms such as structural cardiac remodeling, activation of neurohormonal systems, and rate-related LV impairment.[9] The proportion of patients with heart failure who develop atrial fibrillation increases with age and heart failure severity.[9] When atrial fibrillation causes heart failure, the clinical course seems more favorable than with other causes of HF.[9] In contrast, development of atrial fibrillations in patients with chronic heart failure is associated with worse prognosis, including stroke and increased mortality.[9] Beta-blockers can be used for rate control in patients with HFrEF or mild HFrEF because of their established safety in these patients.[9] Recommendations for management of patients with heart failure and atrial fibrillation includes beta blocker therapy. For HFpEF, there is a paucity of evidence to demonstrate efficacy of any agent. There is insufficient evidence in favor of a strategy of rhythm control with antiarrhythmic drugs versus rate control in patients with heart failure and atrial fibrillation.[9]

Recommendation:

- Beta blockers should be considered for short- and long-term rate control in patients with heart failure and atrial fibrillation. (Class 2A recommendation: weight of evidence is on favor of efficacy. Class B level of evidence: data derived from a single RCT or large non-randomized studies).[9]

Canadian Cardiovascular Society/Canadian Heart Rhythm Society: Management of Atrial Fibrillation

The 2020 Canadian Cardiovascular Society(CCS)/Canadian Heart Rhythm Society guideline on management of atrial fibrillation is an update of 2010 guidance.[10] Atrial fibrillation, the most common sustained cardiac arrhythmia, is associated with reduced quality of life, functional status, cardiac performance, and survival.[10] The management of atrial fibrillation is centered on symptomatic improvement, decreasing morbidity outcomes and mortality , and reduction in atrial

fibrillation-related emergency department (ED) visits or hospitalizations.[10] In the setting of recent onset atrial fibrillation, the rate control agent and the formulation chosen will be influenced by clinical circumstance (e.g., the presence of heart failure or hypotension) and patient comorbidities (e.g., known LV dysfunction, reactive airways disease, hypotension, history of MI, or angina).[10] Options include oral or intravenous beta blockers, oral or intravenous non-dihydropyridine CCBs, intravenous digoxin, and intravenous amiodarone (recognizing that the latter is also a rhythm control agent).[10] Beta blockers are preferred in patients with acute coronary syndrome who require acute rate control.[10] Intravenous rate control agents might be initially considered in patients who are not hemodynamically stable.[10]

Recommendations:

- Either beta blockers or non-dihydropyridine CCBs (diltiazem or verapamil) are first-line agents for atrial fibrillation rate control in patients without significant LV dysfunction (e.g., patients with an LVEF greater than 40%) (strong recommendation; moderate-quality evidence).[10]
- Beta blockers bisoprolol, carvedilol and metoprolol are preferred for rate control of hemodynamically stable atrial fibrillation in the acute care setting in patients with significant LV dysfunction (e.g., patients with an LVEF 40% or less) (strong recommendation; moderate-quality evidence).[10]

Pharmacotherapy for long-term atrial fibrillation rate control revolves around agents with negative dromotropic properties such as beta blockers and non-dihydropyridine CCBs verapamil and diltiazem.[10] The choice of a specific rate-controlling regimen should be based on patient characteristics and the drug's efficacy and side effect profile.[10] In patients without significant LV dysfunction (LVEF less than 40%), beta blockers and non-dihydropyridine CCBs are first-line options.[10] There are no randomized long-term data to support choosing a beta blocker over an non-dihydropyridine CCB. Several retrospective studies of atrial fibrillation patients have shown conflicting results when rates of hospital admission were compared after using beta-blockers versus CCBs: one showed no difference whereas another showed that use of CCBs was associated with a higher rate of hospitalization compared with beta blocker use.[10] Beta blockers might be more effective long-term at slowing ventricular rates at rest and during exercise; however, their use is associated with a higher risk of adverse effects like fatigue and exercise intolerance.[10] Moreover, there is emerging evidence suggesting that CCBs might have favorable dose-response characteristics for atrial fibrillation rate control versus beta blockers, such that they might be preferred in patients with a preserved LVEF and without another indication for a beta blocker.[10] Specific patient characteristics might favor the use of one pharmacological class (e.g., non-dihydropyridine CCBs with hypertension or reactive airway disease versus beta-blockers with CAD).[10] Caution should be used when beta-blockers are used with verapamil or diltiazem.[10]

Recommendations:

- Beta-blockers or non-dihydropyridine CCBs (diltiazem or verapamil) are first-line agents for rate control of atrial fibrillation in patients without significant LV dysfunction (strong recommendation; moderate-quality evidence).[10]
- Evidence-based beta blockers (bisoprolol, carvedilol, metoprolol) are first-line agents for rate control of atrial fibrillation in patients with significant LV dysfunction (strong recommendation; moderate-quality evidence).[10]

British Society Of Gastroenterology/British Association For The Study Of The Liver: Management Of Ascites In Cirrhosis[11]

In 2021 the British Society of Gastroenterology in collaboration with British Association for the Study of the Liver updated 2007 guidance on the management of ascites in cirrhosis.[11] In recent years, there has been increasing recognition that the benefits of non-selective beta blockers in patients with cirrhosis may not be exclusively explained by the reduction in portal pressure.[11] Non-selective beta blockers reduce markers of intestinal permeability, bacterial translocation, systemic inflammation and the incidence of spontaneous bacterial peritonitis independently of hemodynamic response, suggesting a direct effect, potentially via intestinal transit time or on the bowel mucosal integrity.[11] Given the mounting evidence that bacterial translocation and the systemic inflammatory response contribute to the downward spiral of circulatory dysfunction in cirrhosis, it follows that non-selective beta blockers may also reduce non-bleeding related mortality.[11] Until randomized high-quality data are available, the current evidence supports the use of non-selective beta blockers when indicated in patients with refractory ascites, unless alternative markers of circulatory failure, such as hypotension or reduced glomerular filtration rate, are present.[11]

Recommendations:

- Refractory ascites should not be viewed as a contraindication to non-selective beta blockers (strong recommendation; moderate-quality evidence).[11]
- Patients with refractory ascites who are taking non-selective beta blockers should be monitored closely, and dose reduction or discontinuation may be appropriate in those who develop hypotension or acute/progressive renal dysfunction (strong recommendation; moderate-quality evidence).[11]

American Academy of Pediatrics: Management of Infantile Hemangiomas

In 2019, the AAP published a clinical practice guideline on the management of infantile hemangioma.[12] Systemic therapy with corticosteroids was considered the standard of care for several decades before being replaced by oral propranolol.[12] Oral propranolol is now recommended over oral corticosteroids to avoid the adverse effects associated with corticosteroid therapy.[12] Caution is advised for the use of propranolol in infants less than 5 weeks of age or postconceptional age of less than 48 weeks.[12] As other beta blockers, use of propranolol should be avoided in patients with cardiogenic shock or heart failure, sinus bradycardia, heart block greater than first degree, presence or risk of coarctation of the aorta and cerebrovascular anomalies, or asthma.[12] Treatment of infantile angioma with topical application of ophthalmic timolol maleate 0.5% gel has shown modest benefit in clearing small (less than 1 mm thick), superficial lesions (expected clearance 62%).[12] The adverse effects associated with topical timolol are low, but include a possible risk of local irritation, sleep disturbance, cold extremities, bronchospasm, and bradycardia.[12] Additional caution is advised in preterm infants and those without intact skin (i.e., ulceration).[12]

The pharmacotherapy recommendations are as follows:

- Use propranolol as the first-line agent for infantile hemangioma requiring systemic treatment (strong recommendation; high-quality evidence).[12]
- Dose propranolol between 2 and 3 mg/kg per day unless there are comorbidities or adverse effects (e.g., sleep disturbance) that necessitate a lower dose (strong recommendation; moderate-quality evidence).[12]
- May prescribe oral prednisolone or prednisone to treat infantile hemangioma if there are contraindications or inadequate response to oral propranolol (moderate recommendation; moderate-quality evidence).[12]
- May prescribe topical timolol maleate as a therapy for thin and/or superficial infantile hemangioma (moderate recommendation; moderate-quality evidence).[12]

After review, 2 guidelines were excluded due to poor quality.[51,52]

New Formulations or Indications:

A new dosage form of metoprolol succinate received Food and Drug Administration (FDA) approval on 1/26/18. Metoprolol succinate extended-release capsules (KAPSPARGO SPRINKLE) are formulated for once daily administration.[53] It is approved for treatment of hypertension, angina pectoris, and heart failure. The capsule should be swallowed whole, but for patient unable to swallow an intact capsule, alternative administration options are available.[53] The capsule can be opened and the contents sprinkled over soft food.[53] The contents of the capsules should be swallowed along with a small amount (teaspoonful) of soft food such as applesauce, pudding or yogurt.[53] The drug/food mixture should be swallowed within 60 minutes and not stored for future use.[53] The contents of the capsule can also be diluted in 15 mL of water and administered via a nasogastric tube.[53]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[54]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Metoprolol Succinate	TOPROL-XL	1/12/2022	Boxed Warning Warnings and Precautions	New section on bradycardia added: *Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of TOPROL-XL. Patients with first-degree atrioventricular block, sinus node dysfunction, conduction disorders (including Wolff- Parkinson-White) or on concomitant drugs that cause bradycardia, may be at increased risk. Monitor heart rate in patients receiving TOPROL-XL. If severe bradycardia develops, reduce or stop TOPROL-XL.*
Propranolol	HEMANGEOL	6/22/2021	Warnings and Precautions	Hypoglycemia section revised (additions are underlined) HEMANGEOL prevents the response of endogenous catecholamines to correct hypoglycemia and masks the adrenergic warning signs of hypoglycemia, particularly tachycardia, palpitations and sweating. HEMANGEOL can cause hypoglycemia, <u>at any time during treatment. Risk is increased during a fasting period (e.g., poor oral food intake, infection, vomiting) or</u> when <u>glucose demands</u> are <u>increased (e.g., cold, stress</u>, infections). Withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. <u>Discontinue HEMANGEOL if hypoglycemia develops and treat appropriately</u>.
Propranolol	HEMANGEOL	4/2/2020	Adverse Reactions	Skin and subcutaneous tissues disorders: dermatitis psoriasiform added to this section.

Randomized Controlled Trials:

A total of 797 citations were manually reviewed from the initial literature search. After further review, 794 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 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Kim, SG et al[55] OL, MC, RCT Duration: 6 weeks	1. Carvedilol 6.25 mg to 12.5 mg po daily dose (mean dose = 11.25 mg)* Vs. 2. Propranolol 40 to 320 po daily dose (mean dose = 153 mg)* *Titrated to HR decreased by 25% or 55 beats/min and SBP > 90 mm Hg	Adults aged 20-70 yo with cirrhosis and esophageal varies with baseline HVPG > 12 mm Hg N=110	Decrease in mean HVPG by 20% compared with baseline or less than 12 mm Hg at 6 weeks	Decrease in mean HVPG at 6 weeks 1. -3.5 $\pm$ 4.8 mm Hg 2. -2.0 $\pm$ 5.5 mm Hg Difference: -1.5 mm Hg CI NR P=0.163	Open label study design Small population size
Kim, HG et al[56] NI, RCT Duration: 16 weeks	1. Propranolol 2 mg/kg/day po (n=17) Vs. 2. Prednisolone 2 mg/kg/day po (n=17)	Children aged 0 to 9 mo (mean age: 3.3 mo) with and IH, IH-related organ dysfunction and IH-related aesthetic issue N=34	Hemangioma volume change from baseline to 16 weeks NI margin: -20%	Hemangioma Volume Reduction at 16 weeks 1. 55.87% 2. 46.52% Difference: 9.35 CI NR P=0.27	NI study design Small population size
Kalambokis GN, et al.[57] SC, RCT	1. Carvedilol 12.5 mg per day (n=58) Vs. 2. Propranolol 75 mg per day (n=32)	Adults 18 to 75 yo with cirrhosis and ascites, treated with propranolol for esophageal variceal bleeding prophylaxis N=96	Primary endpoints: liver-related mortality; and occurrence of new decompensating events (reappearance of ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding) within a 2-year follow-up	Liver-related Death 1. 12% 2. 37.5% P=0.02 CI NR Frequency of Decompensating Events 1. 10.3% 2. 37.5% P=0.002 CI NR	-Small patient population -Selection bias due to strict inclusion criteria and exclusion of patients not responding or intolerant to carvedilol

Abbreviations: CI = confidence interval; HR = heart rate; HVPG = hepatic venous pressure gradient; IH = infantile hemangioma; kg = kilogram; mg = milligrams; MC = multicenter; mo = months; NI = noninferiority; NR = not reported; PC = placebo controlled; po = oral; RCT = randomized clinical trial; SBP = systolic blood pressure: SC = single center; yo = years old.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
acebutolol HCl	ACEBUTOLOL HCL	ORAL	CAPSULE	Y
atenolol	ATENOLOL	ORAL	TABLET	Y
atenolol	TENORMIN	ORAL	TABLET	Y
carvedilol	CARVEDILOL	ORAL	TABLET	Y
carvedilol	COREG	ORAL	TABLET	Y
labetalol HCl	LABETALOL HCL	ORAL	TABLET	Y
metoprolol succinate	METOPROLOL SUCCINATE	ORAL	TAB ER 24H	Y
metoprolol succinate	TOPROL XL	ORAL	TAB ER 24H	Y
metoprolol tartrate	LOPRESSOR	ORAL	TABLET	Y
metoprolol tartrate	METOPROLOL TARTRATE	ORAL	TABLET	Y
propranolol HCl	PROPRANOLOL HCL	ORAL	TABLET	Y
betaxolol HCl	BETAXOLOL HCL	ORAL	TABLET	N
bisoprolol fumarate	BISOPROLOL FUMARATE	ORAL	TABLET	N
carvedilol phosphate	CARVEDILOL ER	ORAL	CPMP 24HR	N
carvedilol phosphate	COREG CR	ORAL	CPMP 24HR	N
metoprolol succinate	KAPSPARGO SPRINKLE	ORAL	CAP SPR 24	N
nadolol	CORGARD	ORAL	TABLET	N
nadolol	NADOLOL	ORAL	TABLET	N
nebivolol HCl	BYSTOLIC	ORAL	TABLET	N
nebivolol HCl	NEBIVOLOL HCL	ORAL	TABLET	N
pindolol	PINDOLOL	ORAL	TABLET	N
propranolol HCl	INDERAL XL	ORAL	CAP ER 24H	N
propranolol HCl	INNOPRAN XL	ORAL	CAP ER 24H	N
propranolol HCl	INDERAL LA	ORAL	CAP SA 24H	N
propranolol HCl	PROPRANOLOL HCL ER	ORAL	CAP SA 24H	N
propranolol HCl	HEMANGEOL	ORAL	SOLUTION	N
propranolol HCl	PROPRANOLOL HCL	ORAL	SOLUTION	N
sotalol HCl	SOTYLIZE	ORAL	SOLUTION	N
sotalol HCl	BETAPACE	ORAL	TABLET	N
sotalol HCl	BETAPACE AF	ORAL	TABLET	N
sotalol HCl	SORINE	ORAL	TABLET	N
sotalol HCl	SOTALOL	ORAL	TABLET	N
sotalol HCl	SOTALOL AF	ORAL	TABLET	N
timolol maleate	BLOCADREN	ORAL	TABLET	N
timolol maleate	TIMOLOL MALEATE	ORAL	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

A Randomized, Multi-Center, Open-Label Study to Evaluate the Efficacy of Carvedilol vs. Propranolol to Reduce Portal Pressure in Patients With Liver Cirrhosis[55]

Objectives: Propranolol has been used as prophylaxis for variceal bleeding in patients with cirrhosis. More recent data suggest that carvedilol may be more effective for reducing the hepatic venous pressure gradient (HVPG) than propranolol. The primary aim of this study was to evaluate the hemodynamic response to carvedilol compared with propranolol.

Methods: A total of 110 patients with a baseline HVPG value >12 mm Hg were allocated randomly to receive either carvedilol or propranolol. The HVPG measurement was repeated after 6 weeks of daily medication. The primary end point was a ≥20% fall in HVPG compared with baseline or <12 mm Hg.

Results: The difference in the proportion of responders in the carvedilol (49.1%) vs. propranolol (30.9%) groups did not reach statistical significance in the intention-to-treat analysis (P=0.08). However, among patients with a model for end-stage liver disease (MELD) score ≥15, carvedilol resulted in a significantly greater response than that of propranolol (7/12, 58.3% vs. 0/10, 0%; P=0.005). Similarly, carvedilol was superior to propranolol in patients with Child-Pugh score ≥9 (46.2 vs. 0%; P=0.046). The presence of ascites also had a significant influence on the response rate (51.5 vs. 24.2%; P=0.042). A MELD score ≥15 was the only significant predictor of response among these post hoc groups after adjusting for multiple comparisons (P=0.005). Severe adverse events were higher in the carvedilol group although drug-associated adverse events were not different.

Conclusions: Overall, carvedilol offered no clear advantage over propranolol but it may be more effective in advanced cirrhotic patients with a MELD score≥15 in reducing the portal pressure gradient. However, this potential benefit may come with a cost of increased risk of side-effects and outcome data over a longer term is needed to understand the relative risk benefit.

Comparison of Efficacy and Safety Between Propranolol and Steroid for Infantile Hemangioma[56]

Objective: To determine the efficacy and safety of propranolol compared with steroid as a first-line treatment for infantile hemangioma (IH).

Design, Setting, and Participants: This randomized clinical noninferiority trial tested the efficacy and safety of propranolol vs steroid treatment for IH at a single academic hospital. All participants were diagnosed with IH between June 2013 and October 2014, had normal heart function, and had not been previously treated for IH.

Interventions: The participants were randomly assigned to either the propranolol group or the steroid group. In the propranolol group, the patients were admitted, observed for adverse effects for 3 days after treatment initiation, and then released and treated as outpatients for 16 weeks (2 mg/kg/d). In the steroid group, the patients were seen as outpatients from the beginning and were also treated for 16 weeks (2 mg/kg/d).

Main Outcomes and Measures: The primary efficacy variable was the response to treatment at 16 weeks, which was evaluated by the hemangioma volume using magnetic resonance imaging before and at 16 weeks after treatment initiation. While comparing the effect of medication between the groups, we monitored the adverse effects of both drugs.

Results: A total of 34 patients (15 boys, 19 girls; mean age, 3.3 months; range, 0.3-8.2 months) were randomized to receive either propranolol or steroid treatment (17 in each treatment group). Guardians for 2 patients in the steroid group withdrew their consent, and 1 patient in the propranolol group did not complete the efficacy test. The intention-to-treat analysis, applying multiple imputations, found the treatment response rate in the propranolol group to be 95.65%, and that of the steroid group was 91.94%. Because the difference in response rate between the groups was 3.71%, propranolol was considered noninferior. We found that there was no difference between the groups in safety outcomes.

Conclusions and Relevance: Our trial demonstrated that propranolol was not inferior to steroid with respect to therapeutic effects in IH.

Conversion of Propranolol to Carvedilol Improves Renal Perfusion and Outcome in Patients With Cirrhosis and Ascites[57]

Background: In recent years, concerns have been raised on the potential adverse effects of nonselective beta-blockers, and particularly carvedilol, on renal perfusion and survival in decompensated cirrhosis with ascites. We investigated the long-term impact of converting propranolol to carvedilol on systemic hemodynamics and renal function, and on the outcome of patients with stable cirrhosis and grade II/III nonrefractory ascites.

Patients and Methods: Ninety-six patients treated with propranolol for esophageal varices' bleeding prophylaxis were prospectively evaluated. These patients were randomized in a 2:1 ratio to switch to carvedilol at 12.5 mg/d (CARVE group; n=64) or continue propranolol (PROPRA group; n=32). Systemic vascular resistance, vasoactive factors, glomerular filtration rate, and renal blood flow were evaluated at baseline before switching to carvedilol and after 6 and 12 months. Further decompensation and survival were evaluated at 2 years.

Results: During a 12-month follow-up, carvedilol induced an ongoing improvement of systemic vascular resistance (1372±34 vs. 1254±33 dynes/c/cm^5; *P*=0.02) along with significant decreases in plasma renin activity (4.05±0.66 vs. 6.57±0.98 ng/mL/h; *P*=0.01) and serum noradrenaline (76.7±8.2 vs. 101.9±10.5 pg/mL; *P*=0.03) and significant improvement of glomerular filtration rate (87.3±2.7 vs. 78.7±2.3 mL/min; *P*=0.03) and renal blood flow (703±17 vs. 631±12 mL/min; *P*=0.03); no significant effects were noted in the PROPRA group. The 2-year occurrence of further decompensation was significantly lower in the CARVE group than in the PROPRA group (10.5% vs. 35.9%; *P*=0.003); survival at 2 years was significantly higher in the CARVE group (86% vs. 64.1%; *P*=0.01, respectively).

Conclusion: Carvedilol at the dose of 12.5 mg/d should be the nonselective beta-blocker treatment of choice in patients with cirrhosis and nonrefractory ascites, as it improves renal perfusion and outcome.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1996 to May Week 1, 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to May 16, 2022

1	exp Acebutolol/	857
2	exp Atenolol/	5258
3	exp Carvedilol/	2813
4	exp Labetalol/	1881
5	exp Metoprolol/	5627
6	exp Betaxolol/	669
7	exp Bisoprolol/	1182
8	exp Nadolol/	822
9	exp Nebivolol/	842
10	exp Pindolol/	3711
11	exp Propranolol/	32757
12	exp Sotalol/	2109
13	Timolol/	3810
14	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	56140
15	limit 15 to (english language and humans and yr=2015-current) and clinical trial, comparative study, controlled clinical trial, guideline, meta-analysis, practice guideline, randomized clinical trial or systematic review	797

Appendix 4: Key Inclusion Criteria

Population	Adults
Intervention	Oral Beta-blockers
Comparator	Placebo, other antihypertensives
Outcomes	All cause-mortality, cardiovascular mortality, myocardial infarction, or stroke
Timing	1 year
Setting	Outpatient

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Drug Class Update: Nasal Allergy Inhalers

Date of Review: August 2022

Date of Last Review: July 2015
Dates of Literature Search: 05/31/2015 – 05/25/2022

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

Purpose for Class Update:
Prior authorization (PA) with clinical criteria has been in place for intranasal corticosteroids, antihistamines and mast cell stabilizers since 2002. However, these criteria have not been reviewed by the P&T committee since 2015. These drugs have received Food and Drug Administration (FDA) approval for use in seasonal and/or perennial allergic rhinitis, which is not currently funded by the Oregon Health Plan (OHP), unless the patient has a co-morbidity such as asthma.

Research Questions:
- For adults and children, which conditions have nasal inhalers been studied and FDA-approved to treat?
- Do nasal corticosteroids, antihistamines or mast cell stabilizers differ in effectiveness when used to treat FDA-approved conditions?
- Do nasal corticosteroids, antihistamines or mast cell stabilizers differ in safety when used to treat FDA-approved conditions?
- Are there subgroups of patients based on demographics (e.g., age, race, gender), concomitant comorbidities and medications, or pregnancy status, for which one nasal inhaler is more effective or associated with fewer harms?

Conclusions:
- Intranasal antihistamines and intranasal corticosteroids are FDA-approved to manage symptoms associated with seasonal and perennial allergic rhinitis.[1,2] The legend status and approved administration age varies by product (see **Table 1**). Intranasal cromolyn is available over-the-counter (OTC) and approved to manage allergic rhinitis in people 2 years of age and older.[1,2] Intranasal ipratropium is available only by prescription and is approved to manage rhinorrhea associated with seasonal and perennial allergic rhinitis and nonallergic rhinitis in patients 5 years of age and older.[1,2]
- Since the previous Pharmacy and Therapeutics Committee review in 2015, 3 high-quality systematic reviews have been published regarding the use of intranasal corticosteroids for management of chronic rhinosinusitis,[3] nonallergic rhinitis,[4] and allergic rhinitis.[5] Two high quality guideline focused on rhinitis and sinusitis management were updated in 2020 and 2015.[6,7]
- A 2016 Cochrane review assessed the effects of different types of intranasal corticosteroids in people with chronic rhinosinusitis and found insufficient evidence to suggest that one type of intranasal corticosteroid is more effective than another in patients with chronic rhinosinusitis.[3] It is unclear if higher doses result in better symptom improvements (low quality evidence), but there was moderate quality evidence of an increased risk of epistaxis as an adverse effect of treatment when higher doses of intranasal corticosteroids were used.[3]

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- A 2019 Cochrane review assessed the effects of intranasal corticosteroids in the management of nonallergic rhinitis.[4] It is unclear whether intranasal corticosteroids reduce patient-reported disease severity in nonallergic rhinitis patients compared with placebo when therapy was continued up to 3 months (very low- to low-quality evidence).[4] However, intranasal corticosteroids probably have a higher risk of epistaxis compared with placebo (moderate-quality evidence).[4]
- A 2019 systematic review and meta-analysis examined existing literature to determine efficacy in treating allergic rhinitis with combination azelastine/fluticasone compared to monotherapy with azelastine or fluticasone.[5] Meta-analysis of high-quality studies revealed superiority of combination therapy in reducing Total Nasal Symptom 4 question (TNS-4) score compared to placebo (mean change from baseline: −2.41; 95% confidence interval (CI), −2.82 to −1.99; P<0.001; I^2 = 60%), azelastine (mean change from baseline: −1.40; 95% CI, −1.82 to −0.98; P<0.001; I^2 = 0%), and fluticasone (mean change from baseline: −0.74; 95% CI, −1.17 to −0.31; P<0.001; I^2 = 12%).[5] The minimal clinically important difference (MCID) for change in the TNS-4 score is 0.28 points.[8] The results of this meta-analysis support the recommendations from International Consensus Statement on Allergy and Rhinology[9] and the American Academy of Otolaryngology–Head and Neck Surgery Foundation[10] for combination azelastine/fluticasone therapy as second-line treatment for patients with allergic rhinitis that is not controlled with monotherapy.[5]
- The American Academy of Allergy, Asthma and Immunology (AAAAI) 2020 rhinitis guideline updated a previously published 2008 guideline on diagnosis and management of allergic and non-allergic rhinitis.[6] Strong recommendations based on moderate- to high-quality evidence are as follows:
    - Clinicians should offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis and nonallergic rhinitis (strength of recommendation: strong; high-quality evidence).[6]
    - When choosing monotherapy for persistent allergic rhinitis, intranasal corticosteroids are the preferred medication (strength of recommendation: strong; high-quality evidence).[6]
    - For the initial treatment of moderate- to severe-seasonal allergic rhinitis in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over a leukotriene antagonist (strength of recommendation: strong; high-quality evidence).[6]
    - Initial treatment with intranasal corticosteroid monotherapy in patients 12 years of age and older with symptoms of seasonal allergic rhinitis is preferred over combination therapy with an oral antihistamine and an intranasal corticosteroid (strength of recommendation: strong; moderate-quality evidence).[6]
- The American Academy of Otolaryngology-Head and Neck Foundation updated clinical practice guidance for adult sinusitis in 2015.[7] Only one strong recommendation is included in the guidance regarding the use of intranasal corticosteroids:
    - Clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of chronic rhinosinusitis (strength of recommendation: strong; high-quality evidence).[7]
- The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents who are 21 years of age and younger enrolled in Medicaid.[11] The goal of this benefit is to ensure that children receive age-appropriate screening, preventive services, and treatment services that are medically necessary to correct or ameliorate any identified conditions.[11] Management of allergic rhinitis symptoms when it impacts the ability to grow, develop or participate in school falls under this benefit.
- No subgroups of patients based on demographics (e.g., age, race, gender), concomitant comorbidities and medications, or pregnancy status were identified for which one nasal inhaler was more effective or associated with fewer harms.

Recommendations:

- No changes to the Preferred Drug List (PDL) for intranasal allergy medications are recommended based on review of recent evidence.

- Remove prior authorization (PA) criteria for intranasal allergy products in children and adolescents 21 years of age and younger with rhinitis to enhance the ability to grow, develop, or participate in school per the EPSDT Medicaid benefit.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy:

- The 2015 class update on allergic rhinitis identified moderate quality evidence that intranasal corticosteroids are effective in managing asthma-related outcomes in patients who are not concurrently receiving an orally inhaled corticosteroid.[12] There is low quality evidence that intranasal corticosteroids reduce apneas and hypopneas, without improving nadir oxygen saturation, by demonstration of improvement in the Apnea Hypopnea Index (AHI) following short-term therapy in children and adults with obstructive sleep apnea (OSA).[12] There is moderate quality evidence that patients receiving intranasal corticosteroids are more likely to experience resolution or improvement in symptoms of acute sinusitis at 21 days of treatment compared to placebo.[12] There is moderate quality evidence that when compared to placebo, intranasal corticosteroids improve symptom scores in patients with chronic rhinosinusitis.[12]
- Evidence is insufficient to draw any conclusions about comparative effectiveness, efficacy, or safety between intranasal corticosteroid formulations for management of asthma-related outcomes, obstructive sleep apnea, acute sinusitis and chronic rhinosinusitis.[12]
- Evidence is insufficient for the intranasal use of antihistamines or mast cell stabilizers for any indication other than allergic rhinitis.[12]
- There is moderate quality evidence that intranasal corticosteroids, antihistamines and mast cell stabilizers are not associated with increased serious harms compared to placebo. However, use of intranasal corticosteroids in growing children may be associated with increased risk for growth suppression.[12]
- All intranasal products require prior authorization (PA) for OHP funded indications. Fluticasone propionate is the only preferred drug on the preferred drug list (PDL) and all other intranasal corticosteroids non-preferred (**Appendix 1**). Non-steroid intranasal allergy drugs are non-preferred due to lack of evidence for OHP-funded conditions. Use of non-preferred intranasal corticosteroids for OHP-funded conditions is restricted as outlined in the PA criteria in **Appendix 3**.

Background:

Allergic rhinitis is an immunoglobulin (Ig) E-mediated disease that occurs after exposure to indoor or outdoor allergens, such as dust mites, insects, animal dander, molds, and pollen.[13] Symptoms include rhinorrhea, sneezing, nasal congestion, and pruritus.[9] Allergic rhinitis affects up to 60 million people in the United States annually, can have a major impact on quality of life, and poses a substantial economic burden on society.[6] Self-reported rates of allergic rhinitis are 10% to 30% of adults and as many as 40% of children in the United States.[6] A report from the AAAAI estimates that about 19 million employed adults suffer from allergic rhinitis, and that approximately $4.5 billion in direct costs and 3.8 million lost work and school days are attributable to this disease annually.[14] Rhinitis is also a significant cause of decreased work productivity/presenteeism (work interference) and school performance.[6] Allergic rhinitis can, by itself, introduce significant inattention, impairment of cognition, and decreased daytime school performance.[6] Quality of life issues associated with rhinitis include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits.[6] The EPSDT benefit provides comprehensive and preventive health care services for children under age 21 who are enrolled in Medicaid.[11] The goal of this benefit is to ensure that children receive age-appropriate screening, preventive services, and treatment services that are medically necessary to correct or ameliorate any identified conditions.[11] It is important that children and adolescents enrolled in Medicaid receive all recommended preventive services and any medical treatment needed to promote healthy growth and development.[11] Management of allergic rhinitis symptoms to enhance attention and learning in school falls under this benefit.

Validated clinical surveys for allergic rhinitis often include questions about congestion, rhinorrhea and/or sneezing and may either be representative of current symptoms or reflective of a period of days or weeks.[15] One patient reported outcome measure is the Total Nasal Symptom (TNS-4) score, which is typically administered as an instantaneous daily survey comprised of 4 questions about runny nose, nasal itching, sneezing, and congestion.[15] The TNS-4 score is the sum of scores for each of the 4 symptoms, measured on an ordinal scale of 0, 1, 2 or 3 representing no symptoms, mild, moderate, or severe symptoms respectively for a maximum score of 12.[16] The TNS-4 is the most accepted primary efficacy variable that is rated for drug approval in allergic rhinitis by the Food and Drug Administration (FDA).[17] Relatively few articles have calculated MCID scores for allergic rhinitis outcome measures, and those that have suggest widely different approaches.[18] The Agency for Healthcare Research and Quality (AHRQ) recommended the MICD be equal to 30% of the maximum TNS-4 score (i.e., ±3.6 points on a 12 point scale).[18] However, when this threshold was applied, the AHRQ panel could not demonstrate any differences in effectiveness between the various therapeutic classes, which they mostly attributed to insufficient evidence to support the superiority of one treatment over another.[18] Although the lack of good comparative data for some of the comparisons contributed to the outcomes, of greater concern was that the AHRQ method was flawed in 2 important ways.[18] First, using the fixed number of ±3.6 points (on a 12-point scale) based on 30% of the maximum TNS-4 could ultimately negate milder levels of allergic rhinitis from being clinically relevant.[18] Second, although the 30% criterion could be relevant for an individual patient response, there was no indication of how it could be applied to a comparison of differences in population means.[18] A 2010 analysis of 9 RCTS in intermittent and persistent allergic rhinitis patients (n=204) utilized anchor- and distribution based approaches to calculate MCIDs for subjective and objective outcome measures in allergic rhinitis using regression and meta-analysis techniques.[16] Based on the authors' calculations from pooled data, the MCID for the TNS-4 was estimated as 0.23 or 0.28 points depending on whether regression or meta-analytical methods, respectively, were applied.[16] The 12-hour reflective total nasal symptoms score (rTNSS) was also been reported in clinical studies evaluating efficacy of intranasal products.[18] Both morning and evening assessments are added together so the rTNSS can range from 0 to 24 points.[18] For the rTNSS scale of 0 to 24 points, the comparable MCID thresholds would be 0.46 points (by regression analysis) or 0.56 points (by meta-analysis).[18] Despite the very small change in scoring, which calls into question significant clinical benefit, there are no other validated methods to determine MCID for clinical trials of allergic rhinitis medications.[18]

Symptoms of rhinitis are classified based on the temporal pattern (seasonal, perennial, or episodic), frequency, and severity.[13] Mild rhinitis severity is present when symptoms are not interfering with quality of life such as impairment of daily activities, work or school performance, leisure activities, and sleep.[6] Moderate or severe rhinitis is present when symptoms are troublesome or there is negative impact on any of these quality of life parameters.[6] Symptom frequency has been divided into intermittent (less than 4 days per week or less than 4 consecutive weeks per year) and persistent (4 or more days per week and 4 or more consecutive weeks per year).[6] Allergic rhinitis may also be classified by the temporal pattern of environmental exposure to a triggering allergen: 1) seasonal (e.g., from pollens); 2) perennial (year-round, e.g., dust mites); or 3) from episodic allergen exposures not normally encountered in the patient's environment, such as visiting a home with pets.[6] In the United States, allergic rhinitis has traditionally been viewed as either seasonal or perennial, and it is this classification system that the FDA uses when approving new medications for allergic rhinitis.[6] Symptoms of acute infectious bacterial rhinosinusitis include nasal congestion, mucopurulent nasal discharge, pain and pressure, headache, olfactory disturbance, postnasal drainage, and cough.[6] While these symptoms may overlap and mimic those of allergic rhinitis, the presence of a recurrent seasonal pattern of symptoms, the presence of an obvious allergic trigger, and symptoms of nasal or ocular pruritus strongly suggest the diagnosis of allergic rhinitis.[6] This diagnostic distinction is important to avoid inappropriate treatment of allergic rhinitis with antibiotics.[6] The leukotriene antagonist, montelukast, should only be used for allergic rhinitis treatment if there has been an inadequate response or intolerance to alternative first-line therapies, which are discussed below.[6] Nonallergic rhinitis is defined as rhinitis that is independent of an IgE-mediated mechanism that includes vasomotor rhinitis (sometimes referred to as nonallergic rhinopathy or idiopathic rhinitis), infectious rhinitis, food-induced rhinitis, hormonal rhinitis (associated with estrogen/progesterone changes observed in pregnancy, menopause or puberty), drug-induced rhinitis, nonallergic occupational rhinitis, atrophic rhinitis, non-allergic rhinitis with eosinophilia syndrome and rhinitis of the elderly.[6]

Intranasal pharmacologic options for the treatment of rhinitis include corticosteroids, antihistamines, mast cell stabilizers, and anticholinergics (see **Table 1**). Intranasal corticosteroids are the mainstay of treatment for allergic rhinitis.[9] Specific intranasal corticosteroid agents include beclomethasone, flunisolide, budesonide, fluticasone propionate, mometasone, fluticasone furoate, triamcinolone, and ciclesonide.[19] Mometasone, fluticasone furoate, ciclesonide, and triamcinolone are approved by the Food and Drug Administration (FDA) for use in children 2 years of age and older.[19] They act by decreasing the influx of inflammatory cells and inhibiting the release of cytokines, thereby reducing inflammation of the nasal mucosa.[9] Intranasal corticosteroids also help reduce symptoms of sneezing, itching, rhinorrhea, and congestion.[6] Limited data suggest that intranasal corticosteroids can also reduce allergic eye symptoms, such as itching, tearing, redness, and puffiness.[6] In comparative studies, intranasal corticosteroids have shown superior efficacy to oral antihistamines and leukotriene inhibitors in controlling nasal symptoms, with no significant difference in the relief of ocular symptoms.[10] There is no evidence that one intranasal corticosteroid is superior over another product.[9] Onset of action for intranasal corticosteroids starts at time points ranging from 3 to 5 hours to 60 hours after first dosing.[10] Patients with known seasonal allergic rhinitis should start prophylactic treatment with intranasal corticosteroids several days before the pollen season with an evaluation of the patient's response in 2 weeks.[10]

The most common local adverse effects of intranasal corticosteroids include nasal dryness, throat irritation, burning, hoarseness, sneezing, and bitter aftertaste.[20] The effect of intranasal corticosteroids on growth in children has been investigated in controlled studies using both knemometry in short-term studies (2 to 4 weeks) and stadiometry in long-term (12 months) studies.[10] A meta-analysis of 8 randomized controlled trials (n=755) with appropriate controls showed that, compared to children using placebo, mean growth was significantly lower among children using intranasal corticosteroids in trials using knemometry (n = 4) and that there was no significant growth difference in studies using stadiometry (n = 4).[21] The data suggests that intranasal corticosteroids might have deleterious effects on short-term growth in children, but the heterogeneity in the stadiometry studies makes the effects on long-term growth suppression unclear.[10] All intranasal corticosteroids carry a warning that long-term use may restrict growth in children, so using the lowest effective dose is advised to avoid negative growth effects.[22]

Two intranasal antihistamines, azelastine and olopatadine, are FDA-approved for the treatment of rhinitis. Intranasal antihistamines have a rapid onset, are more effective for nasal congestion than oral antihistamines, are more effective for ocular symptoms than intranasal corticosteroids, and show consistent reduction in symptoms and improvement in quality of life in randomized controlled trials (RCTs) compared to placebo.[10] They are less effective for nasal congestion than intranasal corticosteroids.[10] Adverse effects observed with intranasal antihistamines include a bitter aftertaste, headache, nasal irritation, epistaxis, and sedation.[13] Although intranasal antihistamines are an option if symptoms do not improve with nonsedating oral antihistamines, their use as first- or second-line therapy is limited by adverse effects and twice daily dosing.[23] Either intranasal antihistamines or intranasal corticosteroids may be offered as first-line monotherapy for nonallergic rhinitis.[6]

Intranasal cromolyn is available over the counter and is thought to inhibit the degranulation of mast cells, thereby preventing histamine release.[13] Although safe for general use, it is not considered first-line therapy for allergic rhinitis because it is less effective than intranasal corticosteroids and is administered three or four times daily.[24] Although evidence supports the use of intranasal ipratropium, an anticholinergic, for severe rhinorrhea, it is not effective for other nasal symptoms.[25] Adverse effects of ipratropium include dryness of the nasal mucosa, epistaxis, and headache.[13] The recommended administration is two to three times daily.[13]

Allergic rhinitis also is often associated with and can potentially impact asthma, allergic conjunctivitis, atopic dermatitis, rhinosinusitis, and sleep apnea.[6] Allergic rhinitis, notably present in about 75% to 80% of all patients with asthma and in nearly 100% with allergic asthma, is associated with increased asthma-related hospitalizations and higher total annual medical costs.[6] Intranasal use of antihistamines and mast cell stabilizers has not been adequately studied in conditions

outside of allergic rhinitis.[12] However, intranasal corticosteroids have been studied and used for several other conditions that are currently funded by the Oregon Health Plan (OHP).[12] For example, allergic rhinitis and asthma are often comorbid diseases. An epidemiologic association between allergic rhinitis and asthma has been consistently demonstrated across patient populations.[12] Given the association, it is hypothesized that reducing inflammation in the upper airway with an intranasal corticosteroid may improve asthma symptoms.[26] Attempts have also been made to reduce frequency of episodes of obstructive sleep apnea by changing the characteristics of the upper airway using therapies such as intranasal corticosteroids.[27] Acute sinusitis is frequently caused by a viral infection and is a common reason for primary care visits. Inflammation of nasal mucosa plays an essential role in the development of sinusitis. In addition to treating seasonal and perennial rhinitis, corticosteroids might be beneficial in reducing inflammation in the treatment of sinusitis.[28] Lastly, chronic rhinosinusitis (CRS) is a group of disorders characterized by chronic inflammation of the mucosa of the nose and paranasal sinuses, with symptoms that persist for more than 12 weeks without complete resolution of symptoms.[29] It is most commonly classified as CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). The use of corticosteroids for the management of CRS is supported by a high level of evidence, with particularly strong evidence for CRSwNP.[29]

Table 1. Nasal Allergy Medications: Indications and Age Ranges.[1,2]

Drug Name (Trade Name)	FDA Indication(s)	Formulation	OTC
Intranasal Antihistamines			
Azelastine (ASTEPRO ALLERGY, generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥6 yo	205.5mcg/spray	YES
Azelastine (ASTEPRO)	Seasonal Allergic Rhinitis; ≥ 2 yo to 6 yo Perennial Allergic Rhinitis; ≥ 6 months to 6 yo	137 mcg/spray	NO
Olopatadine (PATANSASE, generic)	Seasonal Allergic Rhinitis ≥6 yo	665 mcg/spray	NO
Combination Intranasal Antihistamine/Corticosteroids			
Azelastine-Fluticasone propionate (DYMISTA, generic)	Seasonal Allergic Rhinitis ≥6 yo	137 mcg-50 mcg/spray	NO
Olopatadine-Mometasone (RYALTRIS)	Seasonal Allergic Rhinitis ≥12 yo	665 mcg-25mcg/spray	NO
Intranasal Corticosteroids			
Beclomethasone dipropionate (BECONASE AQ)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis; Nonallergic Rhinitis; Nasal Polyps ≥6 yo	42 mcg/spray	NO
Beclomethasone (QNASL)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥4 yo	40 mcg and 80 mcg/spray	NO
Budesonide (RHINOCORT ALLERGY, generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥6 yo	32 mcg/spray	YES
Ciclesonide (OMNARIS)	Seasonal Allergic Rhinitis ≥6 yo Perennial Allergic Rhinitis ≥12 yo	50 mcg/spray	NO
Ciclesonide (ZETONNA)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥12 yo	37 mcg/spray	NO
Flunisolide (generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥6 yo	25 mcg/spray	NO
Fluticasone furoate (FLONASE SENSIMIST)	Allergic Rhinitis ≥2 yo	27.5 mcg/spray	YES

Fluticasone propionate (FLONSASE ALLERGY RELIEF, generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis; Nonallergic Rhinitis ≥4 yo	50 mcg/spray	YES
Fluticasone propionate (EXHANCE)	Nasal polyps ≥ 18 yo	93 mcg/spray	NO
Mometasone (NASONEX, generic)	Seasonal Allergic Rhinitis ≥2 yo	50 mcg/spray	YES
Triamcinolone (NASACORT ALLERGY 24 HOUR, generic)	Allergic Rhinitis ≥2 yo	50 mcg/spray	YES
Intranasal Mast Cell Stabilizer			
Cromolyn (generic)	Allergic Rhinitis ≥2 yo	5200 mcg/spray	YES
Intranasal Anticholinergics			
Ipratropium (generic)	Rhinorrhea associated with Perennial Allergic Rhinitis; Seasonal Allergic Rhinitis; and Nonallergic Rhinitis ≥5 yo	21 mcg and 42 mcg/spray	NO
Abbreviations: FDA = Food and Drug Administration; mcg = micrograms; mg = milligrams; OTC = over the counter; yo = years old			

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:
Cochrane: Intranasal Corticosteroids For Chronic Rhinosinusitis
The objective of this 2016 review was to assess the effects of different types of intranasal corticosteroids in people with chronic rhinosinusitis.[3] The literature search for the systematic review was conducted through August 2015.[3] Randomized controlled trials with a follow-up period of at least 3 months comparing first-generation intranasal corticosteroids (beclomethasone dipropionate, triamcinolone, flunisolide, and budesonide) with second-generation intranasal corticosteroids (ciclesonide, fluticasone furoate, fluticasone propionate, mometasone, and betamethasone sodium phosphate), or sprays versus drops, or low-dose versus high-dose intranasal corticosteroids were included in the selection critiera.[3] Primary outcomes included disease-specific health-related quality of life (HRQL), patient-reported disease severity and the most common adverse event associated with nasal corticosteroids, epistaxis.[3] Nine RCTs (n=911) met inclusion criteria, including 4 different comparisons.[3] The studies varied in size: some were small, with as few as 20 patients, while others included over 200 participants.[3] Most studies recruited adult patients, while only one study included children.[3] In the majority of the adult studies, most participants were male (72% to 79%).[3] In all studies, the participants had chronic rhinosinusitis with nasal polyps.[3] None of the studies evaluated the first primary outcome measure, disease-specific HRQL.[3]

Two very low quality RCTs (n=56) compared fluticasone propionate with beclomethasone dipropionate to evaluate disease severity and epistaxis and found no differences between the 2 steroids.[3] One very low quality study (n=100) evaluated disease severity (nasal symptom scores) in a comparison of fluticasone propionate versus mometasone and reported no differences.[3] Five studies compared high dose versus low dose steroids (n=663) in participants with nasal polyps.[3] Three RCTs used mometasone (400 µg versus 200 µg in adults and older children, 200 µg versus 100 µg in younger children) and 2 RCTs used fluticasone propionate drops (800 µg versus 400 µg).[3] Evaluations of disease severity and nasal polyp size were similar between the high-dose and low-dose groups based on low quality evidence.[3] Although all studies reported more improvement in polyp scores in the high-dose group, the significance of this is unclear due to the small size of the improvements.[3] The primary adverse effect, epistaxis, was more common when higher doses were used (risk ratio [RR] 2.06, 95% CI 1.20 to 3.54, 637 participants, moderate quality evidence).[3] Most of the studies that contributed data to this outcome used a broad definition of epistaxis, which ranged from frank bleeding to bloody nasal discharge to flecks of blood in the mucus.[3]

In summary, there is insufficient evidence to suggest that one type of intranasal corticosteroid is more effective than another in patients with chronic rhinosinusitis, nor that the effectiveness of a spray differs from an aerosol.[3] No studies that compared drops with spray were identified.[3] It is unclear if higher doses result in better symptom improvements (low quality evidence), but there was moderate quality evidence of an increased risk of epistaxis as an adverse effect of treatment when higher doses of intranasal corticosteroids were used.[3]

Cochrane: Intranasal Corticosteroids For Nonallergic Rhinitis

Nonallergic rhinitis is defined as dysfunction and non-infectious inflammation of the nasal mucosa that is caused by provoking agents other than allergens or microbes.[4] Several subgroups of nonallergic rhinitis can be distinguished, depending on the trigger responsible for symptoms; these include occupation, cigarette smoke, hormones, medication, food and age.[4] This systematic review evaluated literature through July 2019.[4] Selection criteria included RCTs comparing intranasal corticosteroids, delivered by any means and in any volume, with (a) placebo or no intervention or (b) other active treatments in adults and children (aged 12 years and older).[4] The primary outcomes were patient-reported disease severity and a significant adverse effect, epistaxis.[4] Thirteen studies provided data for the main comparison, intranasal corticosteroids versus placebo.[4] The participants were mainly defined as patients with perennial rhinitis symptoms and negative allergy tests.[4] No studies reported outcomes beyond three months of follow-up.[4] Fluticasone propionate was the most commonly used intranasal corticosteroid and was the main intervention in 10 studies, beclomethasone dipropionate was used in 7 studies, flunisolide nasal spray was used in 6 studies, budesonide was used in 5 studies, fluticasone furoate was used in 2 studies, and mometasone and triamcinolone were included in 1 study each.[4]

Thirty-four studies (n=4452) met inclusion criteria; however only 13 RCTs (n=2045) provided data for the main comparison, intranasal corticosteroids versus placebo.[4] The studies used different scoring systems for patient-reported disease severity, ranging from one symptom to a total nasal symptom score or an overall disease severity score, so data was pooled in each analysis using the standardized mean difference (SMD).[4] Intranasal corticosteroid treatment may improve patient-reported disease severity as measured by total nasal symptom score compared with placebo at up to 4 weeks (SMD -0.74, 95% CI -1.15 to -0.33; 4 studies; 131 participants; I^2 = 22%; low-certainty evidence).[4] However, between 4 weeks and 3 months the improvement in disease severity is very uncertain with no difference from placebo (SMD -0.24, 95% CI -0.67 to 0.20; 3 studies; 85 participants; I^2 = 0%; very low-certainty evidence).[4]

All 4 studies evaluating the risk of epistaxis showed that there is probably a higher risk in the intranasal corticosteroids group (RR 2.10, 95% CI 1.24 to 3.57; 4 studies; 1174 participants; I^2 = 0%; moderate-certainty evidence).[4] The absolute risk difference was 4% with a number needed to harm (NNH) of 25 (95% CI 16.7 to 100).[4] Intranasal corticosteroids probably resulted in little or no difference in the risk of other adverse events compared to placebo (RR 0.99, 95% CI 0.87 to 1.12; 3 studies; 1130 participants; I^2 = 0%; moderate-certainty evidence).[4]

Overall, the certainty of the evidence for most outcomes in this review was low or very low.[4] It is unclear whether intranasal corticosteroids reduce patient-reported disease severity in nonallergic rhinitis patients compared with placebo when measured up to 3 months.[4] However, intranasal corticosteroids probably have a higher risk of epistaxis compared with placebo.[4]

Intranasal Azelastine and Fluticasone as Combination Therapy for Allergic Rhinitis

A 2019 systematic review and meta-analysis examined existing literature to determine efficacy in treating allergic rhinitis with combination azelastine/fluticasone compared to monotherapy with azelastine or fluticasone.[5] Literature was searched through January 2018.[5] Eight articles with a low risk of bias met inclusion criteria.[5] All studies exhibited a greater decrease in patient-reported symptom scores in patients treated with combination therapy compared to monotherapy or placebo.[5] Meta-analysis revealed superiority of combination therapy in reducing Total Nasal Symptom Score (TNSS) compared to placebo (mean change from baseline: −2.41; 95% CI, −2.82 to −1.99; P<0.001; I^2 = 60%), azelastine (mean change from baseline: −1.40; 95% CI, −1.82 to −0.98; P<0.001; I^2 = 0%), and fluticasone (mean change from baseline: −0.74; 95% CI, −1.17 to −0.31; P<0.001; I^2 = 12%).[5] The International Consensus Statement on Allergy and Rhinology and the American Academy of Otolaryngology–Head and Neck Surgery Foundation Clinical Practice Guideline for Allergic Rhinitis both recommend a first-line treatment of intranasal corticosteroid spray and suggest clinicians may offer combination therapy in patients with persistent symptoms.[9,10] The results of this meta-analysis support the recommendations presented in these 2 guidelines. Azelastine/fluticasone combination therapy should be considered as second-line treatment for patients with allergic rhinitis that is not controlled with monotherapy.[5]

After review, one systematic review was excluded due to poor quality (e.g., failure to meet AMSTAR criteria).[30]

New Guidelines:

High Quality Guidelines:

The American Academy of Allergy, Asthma and Immunology: Rhinitis

The AAAAI 2020 rhinitis guideline updated a previously published 2008 guideline on diagnosis and management of allergic and non-allergic rhinitis.[6] Recommendations were systematically developed to optimize care of adult and adolescent patients (≥ 12 to 15 years of age) and to assist health care practitioners and patients to make decisions regarding diagnosis and therapy for rhinitis.[6] Assessment of rhinitis by severity, frequency, and exposure can assist the clinician in developing the most appropriate treatment strategies for an individual patient.[6]

For relief of nasal symptoms of seasonal allergic rhinitis, intranasal antihistamines (e.g., azelastine, olopatadine) are equal to or superior to oral antihistamines and may benefit patients for whom oral antihistamine treatment fails.[31] Azelastine is also approved for the treatment of perennial allergic rhinitis and vasomotor rhinitis.[6] Intranasal antihistamines have a more rapid onset of action than intranasal corticosteroids and oral antihistamines, are more effective than oral antihistamines in the control of nasal congestion, and provide a favorable safety profile.[6] Comparisons of intranasal corticosteroids versus intranasal antihistamines for reduction of nasal symptoms are conflicting, with some showing equality and some showing superiority of intranasal corticosteroids.[6,10] In a 2002 systematic review of intranasal corticosteroids and intranasal antihistamines, intranasal antihistamines provided comparable relief of allergic eye symptoms.[32] The recommendation and strength of evidence regarding the use of intranasal antihistamines in rhinitis is as follows:

- Clinicians should offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis and nonallergic rhinitis (strength of recommendation: strong; high-quality evidence).[6]

Intranasal corticosteroids remain the most effective monotherapy for allergic rhinitis and are therefore recommended as preferred monotherapy for moderate and severe allergic rhinitis that have negative impact on quality of life.[33-35] Other guidelines from 2010 and 2015 support this recommendation.[9,36] Not only are these agents effective in controlling nasal symptoms in patients with allergic rhinitis, but they have also been shown to be effective in the control of allergic ocular symptoms.[6] When given in recommended doses, intranasal corticosteroids are not generally associated with clinically significant systemic side effects.[33] A meta-analysis of relevant trials relating to growth in children suggests that short-term use of intranasal corticosteroids may decrease short-term growth velocity (but there was no such effect on longer-term growth velocity).[6] Therefore, when using intranasal corticosteroids in children, it is prudent to use the lowest effective dose and monitor growth carefully.[6] Strong recommendations and associated strength of evidence regarding the use of intranasal corticosteroids in various rhinitis types are as follows:

- When choosing monotherapy for persistent allergic rhinitis, intranasal corticosteroids are the preferred medication (strength of recommendation: strong; high-quality evidence).[6]
- For the initial treatment of moderate- to severe-seasonal allergic rhinitis in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over a leukotriene antagonist (strength of recommendation: strong; high-quality evidence).[6]
- Initial treatment with intranasal corticosteroid monotherapy in patients 12 years of age and older with symptoms of seasonal allergic rhinitis is preferred over combination therapy with an oral antihistamine and an intranasal corticosteroid (strength of the recommendation: strong; moderate-quality evidence).[6]

Ipratropium either as the 0.03% or 0.06% concentration is safe, well-tolerated, and is effective for the treatment of rhinorrhea related to perennial allergic rhinitis (0.03%) and non-allergic rhinitis (0.03%), as well as for the common cold (0.06%).[6] While ipratropium bromide 0.06% is FDA-approved for the treatment of seasonal allergic rhinitis in both children and adults, no randomized controlled trials have been completed to study its effectiveness.[6] The efficacy of ipratropium appears to especially benefit rhinorrhea.[6] Ipratropium has not been shown to be of significant value when postnasal drainage is the dominant complaint.[6] The most common adverse effects reported with ipratropium are nasal dryness and epistaxis, although these are usually mild and rarely lead to discontinuation of treatment.[6] The conditional recommendations for the use of ipratropium are based on moderate- to low-quality evidence depending on the type of rhinitis as follows:

- Patients with perennial allergic rhinitis and non-allergic rhinitis who have rhinorrhea as their main nasal symptom should be offered intranasal ipratropium (strength of recommendation: conditional; low-quality evidence for perennial allergic rhinitis and moderate-quality evidence for non-allergic rhinitis).[6]
- For patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium (strength of recommendation: conditional; moderate-quality evidence).[6]

The primary benefit of cromolyn sodium is to stabilize mast cells and thus inhibit the release of mast cell mediators that promote IgE-mediated allergic rhinitis.[6] Intranasal administration of cromolyn sodium, compared with placebo, improves symptoms of seasonal allergic rhinitis.[6] In perennial allergic rhinitis, with marked skin test responses, benefit has been found in some but not all studies of patients with perennial allergic rhinitis.[6] Intranasal cromolyn may reduce nasal eosinophils in patients with allergic rhinitis.[6] The AAAAI recommendation for use of intranasal cromolyn in rhinitis is as follows:

- Intranasal cromolyn may be offered as an option to be taken just prior to allergen exposure to reduce symptoms of allergic rhinitis from episodic allergen exposures (strength of recommendation: conditional; very low-quality evidence).[6]

The AAAAI conditional recommendation to initiate combination intranasal corticosteroid/intranasal antihistamine therapy is based on high quality evidence as follows:

- Clinicians may consider the combination of an intranasal corticosteroid and intranasal antihistamine for the initial treatment of moderate/severe nasal symptoms of seasonal allergic rhinitis in patients 12 years of age and older (strength of recommendation: conditional; high-quality evidence).[6]

The American Academy of Otolaryngology-Head and Neck Foundation

The American Academy of Otolaryngology-Head and Neck Foundation updated clinical practice guidance for adult sinusitis in 2015.[7] Inflammation is considered the pathological basis for chronic rhinosinusitis, and therefore corticosteroids are widely recommended.[7] The efficacy of topical steroid therapy for reducing symptoms of chronic rhinosinusitis is supported by systematic reviews of randomized controlled trials from Cochrane authors that show benefits with excellent safety and minimal adverse events.[37] The benefits are symptomatic relief, promoting awareness of effective over-the-counter interventions, discouraging improper and ineffective usage, and avoiding adverse events from systemic therapies.[7] The risks include intranasal discomfort, burning, stinging and epistaxis.[7]

- Strong recommendation that clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of chronic rhinosinusitis. (aggregate evidence quality grade A: systematic review of RCTs; high-quality evidence).[7]

Intranasal steroids may have a role in managing viral rhinosinusitis, even though they do not have a FDA indication for this purpose.[7] A systematic review found that topical nasal steroids relieved facial pain and nasal congestion in patients with rhinitis and acute sinusitis, even though many patients likely had viral illness.[38] The magnitude of effect, however, was small: 66% of patients improved with placebo at 14 to 21 days, rising to 73% with steroid therapy.[38] The benefit may be a reduction in symptoms and avoidance of unnecessary antibiotics.[7] The harms include the adverse effects of topical corticosteroids.[7]

- Optional recommendation that clinicians may recommend topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of viral rhinosinusitis (aggregate evidence quality grade B and C: RCTs with limitations and cohort studies; moderate-quality evidence).[7]

A Cochrane review, which included 4 RCTs of topical intranasal steroid versus placebo or no intervention as monotherapy for acute bacterial rhinosinusitis, found that steroids increased the rate of symptom improvement from 66% to 73% after 15 to 21 days (risk ratio, 1.10; 95% CI, 1.02-1.18). The studies had low risk of bias, and only minor adverse events were reported, which included epistaxis, headache, and nasal itching.[39] The benefit may be a modest increase in symptom relief from topical nasal corticosteroids (number needed to treat 14). The harms include the adverse effects of topical corticosteroids.[7]

- Optional recommendation that clinicians may recommend topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of acute bacterial rhinosinusitis (aggregate evidence quality grade A: systematic review of RCTs; moderate-quality evidence).[7]

After review, 1 guideline was excluded due to poor quality.[40]

New Formulations or Indications:

- A new formulation of fluticasone propionate nasal spray (XHANCE) received FDA approval September 2017.[41] This device delivers fluticasone into the nose by actuating the pump spray into one nostril while simultaneously blowing into the mouthpiece of the inhaler, which improves deposition of fluticasone throughout the nasal cavity.[42] XHANCE is FDA-approved for the treatment of nasal polyps in patients 18 years of age and older.[41] The recommended dose is one spray (93 mcg) per nostril twice daily (total daily dose of 372 mcg).[41] Three studies were submitted to the FDA for approval of this product. Two safety and efficacy double-blind, placebo-controlled RCTs (Study 3101 and Study 3102) were conducted over 16 weeks in patients with bilateral nasal polyps and 1 open-label safety trial was conducted over 12 months in patients with chronic sinusitis with or without nasal polyps.[43] The large majority of patients enrolled were White, 88% and 94% for Studies 3101 and 3102, respectively.[43] For Study 3101, 50% of the patients were male

with 44% of the patients were enrolled from US sites.[43] For Study 3102, 58% of patients were male with 41% enrolled from US sites.[43] Patients received placebo, fluticasone 93 mcg, 186 mg, or 372 mcg intranasally twice daily.[43]

The 2 co-primary efficacy variables were reduction of nasal congestion and obstruction symptoms at Week 4 and reduction in the nasal polyp grade at Week 16.[43] The reduction of nasal congestion/obstruction symptoms at Week 4 was defined as the change from baseline in instantaneous morning diary symptom scores to the Week 4 visit.[43] Symptoms graded on a scale of 0 (no symptoms) to 3 (severe symptoms) included nasal congestion/obstruction, rhinorrhea, facial pain or pressure symptoms, and sense of smell.[43] In study 3101, reduction of nasal congestion was improved with fluticasone for all of the twice daily doses compared to placebo (93 mcg least square mean [LSM] difference = -0.25; 95% CI -0.43 to -0.06; p= 0.01; 186 mcg LSM difference = -0.30; 95% CI -0.48 to -0.11; p=0.002); 372 mcg LSM difference = -0.39; 95% CI -0.57 to -0.19; p<0.001).[43] Similar results in reduction of nasal congestion with fluticasone compared with placebo were observed in Study 3102.[43] The reduction in nasal polyp grade at Week 16 was defined as the change from the screening baseline in the total polyp grade (sum of scores from both nasal cavities) at the Week 16 assessment. Polyp grade of each nasal cavity was determined on a four-point polyp grading scale (0 – no polyps, 1- mild polyposis, 2 - moderate polyposis, 3 - severe polyposis) using nasoendoscopy at monthly screenings.[43] In Study 3101, the change from baseline in bilateral nasal polyp grade at week 16 was improved for the twice daily fluticasone 186 mcg dose (LSM difference = -0.59; 95% CI -0.93 to -0.24) and 372 mcg dose (LSM difference = -0.62; 95% CI -0.96 to -0.27) compared to placebo.[43] Similar improvements in nasal polyp grade were observed in Study 3012.[43] Serious adverse effects and study discontinuations due to adverse effects were uncommon in the 16-week RCTs.[43] Epistaxis occurred relatively frequently, in about 20% of patients on active treatment compared with 6% of those receiving placebo.[43]

- A combination nasal spray of the antihistamine, olopatadine, and corticosteroid, mometasone, (RYALTRIS) received FDA-approval in January 2022.[44] RYALTRIS is indicated for the treatment of symptoms of seasonal allergic rhinitis in patients 12 years of age and older.[44] The efficacy of RYALTRIS was evaluated in 2 multi-center, double-blind, placebo and active-comparator (e.g., olopatadine or mometasone) RCTs of 2-week duration in 2,352 subjects 12 years of age and older with seasonal allergic rhinitis.[44] In both studies, 2-week treatment with RYALTRIS resulted in a statistically significant improvement in rTNSS compared to olopatadine hydrochloride (LSM difference: -0.4 points; 95% CI -0.8 to -0.1; p<0.5) and to mometasone furoate (LSM difference: -0.5 points ; 95% CI -0.9 to -0.1; p<0.5) as well as to placebo (LSM difference: -1.1 points; 95% CI -1.5 to -0.7; p<0.5).[44] The MCID for this score is 0.46 points,[8] so clinical significance is was only observed when combination therapy was compared to placebo and mometasone. Adverse reactions observed in clinical trials included dysgeusia (bitter taste), epistaxis, and nasal discomfort.[44]

- Azelastine (ASTEPRO ALLERGY) 0.15% nasal spray received a partial over-the-counter (OTC) status as of June 2021 for treatment of seasonal and perennial allergic rhinitis in people six years of age and older.[45] The 0.1% strength, which includes the perennial allergy indication for children 6 months to 6 years old and seasonal allergy indication for children 2 to 6 years old, will remain prescription based.[45]

- Mometasone (NASONEX 24HR ALLERGY) received FDA approval March 2022 for OTC status.[46]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[47]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Beclomethasone Dipropionate	QNASL	7/2017	Warnings and Precautions	Additions are underlined Use of intranasal and inhaled corticosteroids may result in the development of increased intraocular pressure, blurred vision, glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts.

Randomized Controlled Trials:

A total of 111 citations were manually reviewed from the initial literature search. After further review, 111 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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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL	OTC
fluticasone propionate	FLUTICASONE PROPIONATE	NASAL	SPRAY SUSP	Y	F
azelastine HCl	AZELASTINE HCL	NASAL	SPRAY/PUMP	N	F
azelastine/fluticasone	AZELASTINE-FLUTICASONE	NASAL	SPRAY/PUMP	N	F
azelastine/fluticasone	DYMISTA	NASAL	SPRAY/PUMP	N	F
beclomethasone dipropionate	QNASL	NASAL	HFA AER AD	N	F
beclomethasone dipropionate	QNASL CHILDREN	NASAL	HFA AER AD	N	F
beclomethasone dipropionate	BECONASE AQ	NASAL	SPRAY	N	F
budesonide	BUDESONIDE	NASAL	SPRAY/PUMP	N	O
ciclesonide	ZETONNA	NASAL	HFA AER AD	N	F
ciclesonide	OMNARIS	NASAL	SPRAY/PUMP	N	F
cromolyn sodium	CROMOLYN SODIUM	NASAL	SPRAY/PUMP	N	O
cromolyn sodium	NASAL ALLERGY CONTROL	NASAL	SPRAY/PUMP	N	O
cromolyn sodium	NASAL ALLERGY SPRAY	NASAL	SPRAY/PUMP	N	O
flunisolide	FLUNISOLIDE	NASAL	SPRAY	N	F
flunisolide	NASALIDE	NASAL	SPRAY	N	F
fluticasone propionate	XHANCE	NASAL	AER BR.ACT	N	F
fluticasone propionate	ALLERGY RELIEF	NASAL	SPRAY SUSP	N	O
fluticasone propionate	FLUTICASONE PROPIONATE	NASAL	SPRAY SUSP	N	O
ipratropium bromide	IPRATROPIUM BROMIDE	NASAL	SPRAY	N	F
mometasone furoate	MOMETASONE FUROATE	NASAL	SPRAY/PUMP	N	F
olopatadine HCl	OLOPATADINE HCL	NASAL	SPRAY/PUMP	N	F
olopatadine HCl	PATANASE	NASAL	SPRAY/PUMP	N	F
triamcinolone acetonide	24 HOUR NASAL ALLERGY	NASAL	SPRAY	N	O
triamcinolone acetonide	NASAL ALLERGY	NASAL	SPRAY	N	O
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	NASAL	SPRAY	N	O

F= Federal Legend (Prescription)
O=Over-The-Counter (OTC)

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2022, Ovid MEDLINE(R) In-Process & In-Data Review Citations 1946 to May 25, 2022

1	exp Beclomethasone/	1694
2	exp Budesonide/	4268
3	ciclesonide.mp.	393
4	flunisolide.mp.	214
5	exp Fluticasone/	3231
6	Exp Mometasone/	846
7	exp Triamcinolone Acetonide/ or exp Triamcinolone/	5391
8	exp Nasal Absorption/ or exp Administration, Intranasal/	12660
9	1 or 2 or 3 or 4 or 5 or 6 or 7	14689
10	8 and 9	734
11	exp Asthma/	90139
12	exp Sleep Apnea Syndromes	35765
13	exp Sinusitis/	14950
14	exp Rhinitis, Allergic/	22977
15	11 or 12 or 13 or 14	215337
16	10 and 15	700
17	Limit 16 to (english language and humans and yr="2015-Current"	88

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2022, Ovid MEDLINE(R) In-Process & In-Data Review Citations 1946 to May 25, 2022

1	azelastine.mp.	773
2	exp Olopatadine	296
3	exp Ipratropium	1901
4	exp Cromolyn Sodium/	4106
5	exp Nasal Absorption/ or exp Administration, Intranasal/	15986
6	1 or 2 or 3 or 4	6937
7	5 and 6	334
8	exp Sleep Apnea Syndromes/	40793
9	exp Sinusitis/	22447
10	exp Asthma/	13770
11	exp Rhinitis, Allergic/	22950
12	8 or 9 or 10 or 11	214895
13	7 and 12	226
14	Limit 13 to (english language and humans and yr="2015-Current"	23

Intranasal Allergy Drugs

Goals:

- Restrict use of intranasal allergy inhalers for conditions funded by the OHP and where there is evidence of benefit.
- Treatment for allergic or non-allergic rhinitis is funded by the OHP only if it complicates asthma, sinusitis or obstructive sleep apnea. Only intranasal corticosteroids have evidence of benefit for these conditions.
- The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents 21 years of age and younger who are enrolled in Medicaid.[1] Management of allergic rhinitis symptoms falls under this benefit when it impacts the ability to grow, develop or participate in school.

Length of Authorization:

- 30 days to ~~6~~12 months

Requires PA:

- Preferred intranasal corticosteroids without prior claims evidence of asthma for adults over 21 years of age.
- Preferred intranasal antihistamines for adults over 21 years of age.
- Non-preferred intranasal corticosteroids
- Non-preferred intranasal antihistamines
- Intranasal ipratropium
- Intranasal cromolyn sodium

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/
- Preferred intranasal corticosteroids, preferred antihistamines DO NOT require prior authorization for children and adolescents 21 years of age and younger.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the prescribed drug intranasal ipratropium or cromolyn~~corticosteroid~~?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Go to #3

Approval Criteria		
3. Does patient have co-morbid conditions funded by the OHP? • Chronic Sinusitis (J320-J329) • Acute Sinusitis (J0100; J0110; J0120; J0130; J0140; J0190) • Sleep Apnea (G4730; G4731; G4733; G4739)	**Yes:** Document ICD10 code(s) and approve for up to 12~~6~~ months for chronic sinusitis or sleep apnea and approve for no more than 30 days for acute sinusitis	**No:** Go to #4
4. Is there a diagnosis of asthma or reactive airway disease in the past 1 year (J4520-J4522; J45901-45998)?	**Yes:** Go to #5	**No:** Go to #6
5. Is there a claim for an *orally* inhaled corticosteroid in the past 90 days? Note: Asthma-related outcomes are not improved by the addition of an intranasal corticosteroid to an orally inhaled corticosteroid.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 6 months
6. Is the prescribed drug a preferred product?	**Yes:** Go to #8	**No:** Go to #7
7. Will the prescriber consider switching to a preferred product? Note: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives. Go to #8	**No:** Go to #8
~~7.~~8. Is the patient 21 years of age or younger AND is there documentation or provider attestation that the therapy is expected to improve the patient's ability to grow, develop or participate in school?	**Yes:** Approve for 6 months	**No:** Go to # 9

Approval Criteria		
~~8.~~9. RPh only: Is the diagnosis funded by the OHP?	**Funded:** Deny; medical appropriateness. (eg, COPD; Obstructive Chronic Bronchitis; or other Chronic Bronchitis [J449; J40; J410-418; J42; J440-449] Use clinical judgment to APPROVE for 1 month starting today to allow time for appeal. Message: "The request has been denied because it is considered medically inappropriate; however, it has been APPROVED for 1 month to allow time for appeal."	**Not Funded:** Deny; not funded by the OHP. (eg, allergic rhinitis (J300-J309); chronic rhinitis (J310-312); allergic conjunctivitis (H1045); upper respiratory infection (J069); acute nasopharyngitis (common cold) (J00); urticaria (L500-L509); etc.)

P&T / DUR Review: *8/22 (DM);11/15 (AG); 7/15; 9/08; 2/06; 9/04; 5/04; 5/02*
Implementation: *TBD; 10/13/16; 1/1/16; 8/25/15; 8/09; 9/06; 3/06; 5/05; 10/04; 8/02*

1. Medicaid Early Periodic Screening, Diagnostic, and Treatment benefit. https://www.medicaid.gov/medicaid/benefits/early-and-periodic-screening-diagnostic-and-treatment/index.html. Accessed June 9, 2022

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Drug Class Update with New Drug Evaluation: Sedatives

Date of Review: August 2022

Date of Last Review: December 2020
Dates of Literature Search: 04/01/2020 – 03/14/2022
Brand Name (Manufacturer): Quviviq (Idorsia Pharmaceuticals US Inc.)
Dossier Received: no

Generic Name: daridorexant

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

Plain Language Summary

- Is there any new evidence that would change the current policy for medicines to treat sleep disorders?
- The American Academy of Sleep Medicine and the European Sleep Research Society recommend cognitive behavioral therapy (CBT) for sleep disorders:
  - that make it difficult to fall asleep or stay asleep *and*
  - where lack of sleep creates difficulty doing activities during the day.
- Providers can prescribe medicines for sleep disorders when cognitive behavioral therapy does not improve patient sleep.
  - Many medicines are used for sleep disorders.
  - Studies show that, when used for less than 3 months, these medicines likely have the same benefits and risks.
  - When patients use these medicines for more than 3 months, the risk of bone fracture and dementia may increase.
  - Risk of side effects may increase as people get older, particularly if over 65 years of age.
- Daridorexant is a new medicine the Food and Drug Administration (FDA) approved for sleep disorders in adults. Two 3-month studies showed that the medicine helped people fall asleep about 8-12 minutes faster than without medicine. And, if patients woke up during the night, the medicine reduced how long they stayed wake by about 10-18 minutes.
- Providers must explain to the Oregon Health Authority why someone needs a sedative before Medicaid will pay for it. This process is called prior authorization.
- Medicaid Open Card will pay for melatonin when prescribed for children but does not require prior authorization. Melatonin is not covered for adults.
- The Mental Health Clinical Advisory Group (MHCAG) recently posted guidance on how to stop taking benzodiazepines safely. The Drug Use Research Management program recommends policy updates to match this guidance.

Purpose for Class Update:
To evaluate new updated evidence for the sedative class and place in therapy for a new drug, daridorexant (Quviviq), recently approved by the Food and Drug Administration (FDA).

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Research Questions:

1. What is the comparative evidence of efficacy or harms between sedatives when used for treatment of sleep disorders?
2. Are sedatives more effective or associated with more harms than no treatment when used to treat sleep disorders?
3. Are there subgroups of patients based on specific demographics, co-morbidities or other factors (e.g., age, co-morbid behavioral or mental disorders, concomitant medications, etc.) in which one sedative is more effective or associated with fewer adverse events than another sedative?

Conclusions:

- Two high-quality systematic reviews, one expanded indication, and one new drug approval were identified since the last drug class update.
- A systematic review evaluating use of melatonin for sleep disorders in adults who are blind found insufficient evidence for efficacy and safety of melatonin.[1]
- A systematic review evaluating sleep disturbances in patients with dementia identified low quality evidence that trazodone 50 mg may improve sleep efficiency and total sleep time (mean difference [MD] 42.46 minutes, 95% confidence interval [CI] 0.9 to 84.0) with short-term treatment (2 weeks).[2] Orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (based on moderate quality evidence).[2] Other sleep outcomes demonstrated no difference from placebo. Ramelteon and melatonin did not demonstrate any change in sleep outcomes based on low quality evidence.[2] No studies evaluated other commonly prescribed therapies such as benzodiazepines or benzodiazepine receptor agonists (e.g., eszopiclone, zolpidem, zaleplon).
- Daridorexant, an orexin receptor antagonist, was FDA approved in January 2022 for the treatment of insomnia in adults. Treatment was evaluated over 3 months in 2 phase 3 RCTs which demonstrated improvement in time awake after sleep onset (WASO) and latency to persistent sleep (LPS) compared to placebo (moderate quality evidence).[3] At 3 months, WASO improved by an average of 18 minutes compared to placebo with a 50 mg dose and 10-12 minutes with a 25 mg dose.[3] LPS improved by about 12 minutes with a 50 mg dose and 8-9 minutes with a 25 mg dose.[3] Though population level averages cannot be directly applied to individual patients, these changes likely represent only a marginal clinical improvement for many patients based values of minimum clinically important differences (MCIDs) referenced in the literature (WASO of 20 minutes, LPS of 10 minutes). Patients with comorbid disorders were excluded from these studies and patient demographics other than White patients were underrepresented. Subgroup analyses based on age and gender demonstrated similar direction of effect.[3]
- There is insufficient evidence comparing daridorexant to other drugs for insomnia. Direct comparative data includes only a small phase 2 trial.[4]
- Tasimelteon oral suspension, was FDA approved in December 2020 for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age based on results from one small, crossover, placebo-controlled trial (n=25).[5]
- Patient and provider resources describing best practices for benzodiazepine tapers were recently published by the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG).[6] Guidance recommends that taper schedules be individualized, and many patients may benefit in switching to a longer-acting benzodiazepine like diazepam before tapering.[6]

Recommendations:

- No policy changes recommended based on clinical evidence. Evaluate costs in executive session.
- Update prior authorization (PA) criteria to facilitate benzodiazepine tapers as described in recent guidance from the mental health clinical advisory group.

Summary of Prior Reviews and Current Policy

- There is insufficient comparative evidence that assesses differences in efficacy or effectiveness between sedative classes or between individual sedative agents. Similar improvement in total sleep time was found with short-term use of benzodiazepines, non-benzodiazepine sedatives, and sedating antidepressants compared to placebo based on moderate-quality evidence.[7]
- In elderly patients over 65 years of age, there is evidence supporting use of eszopiclone to improve total sleep time and wake time after sleep onset, use of zolpidem and ramelteon to improve sleep onset latency, and doxepin to improve insomnia symptoms.
- There is insufficient evidence to assess efficacy or safety of long-term use of sedatives.[7]
    - Few randomized control trials for non-benzodiazepine sedatives examine outcomes beyond 3 months, and study durations of benzodiazepines beyond 14 days were rare.
    - Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. The risk of fracture may depended on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.[7] FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.
- There is also insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.
- Cognitive Behavioral Therapy (CBT) is highly recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine[8] and the European Sleep Research Society[9] based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[8,9] Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon are all weakly recommended to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.[8] However, long-term treatment of chronic insomnia with a sedative is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.[9] Trazodone, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.[8]
- Uncomplicated sleep disorders (including insomnia) are unfunded conditions on the prioritized list unless the sleep disorder exacerbates or worsens a concomitant funded condition. All drugs currently require prior authorization for this class except melatonin in children. Melatonin coverage for patients less than or equal to 18 years of age was added as a preferred agent in October 2021. The current prior authorization policy restricts use of concomitant use of benzodiazepines, opioids or sedatives.

Background:

Sleep disorders encompass a wide variety of conditions including insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders.[10] This review will focus primarily medications listed in the Sedative PDL class (see **Appendix 1**) for treatment of insomnia, one of the most common sleep disorders. Other disorders are discussed only briefly. Drugs not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants or atypical antipsychotics. Some of these medications are addressed in other class reviews and are covered with other PA criteria. For example, lorazepam is included in PA criteria for the benzodiazepine class, and current PA criteria restrict use of low-dose quetiapine for insomnia.

Insomnia is defined as the subjective perception of difficulty with sleep which occurs despite adequate opportunity for sleep and causes functional impairment during the day.[8,11] Insomnia is often classified as short-term (typically <3 months in duration with an identifiable stressor), long-term (occurring ≥3 times per

week for >3 months) or other (if criteria for short- and long-term criteria are not met). Diagnosis is primarily based on sleep history.[10,11] It is estimated that up to 30-50% of the population experience insomnia symptoms, and chronic insomnia is diagnosed in approximately 5-10% of patients.[8] Insomnia is more common in elderly, females, individuals who are divorced or separated, those with shift work, and patients with lower socioeconomic status.[12] Insomnia symptoms have been associated with reduced health-related quality of life and cognitive decline in patients over 65 years of age.[12] Insomnia can also worsen outcomes for patients with comorbid conditions including cardiovascular disease, post-traumatic stress disorder, and depression.[12] Insomnia may also be associated with a wide variety of comorbid conditions, both medical and psychological. Identification and treatment of contributing factors and comorbid conditions (such as medical conditions, substance misuse and psychiatric conditions) is important for the management of insomnia symptoms.[11]

Cognitive Behavioral Therapy (CBT) is recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine[8] and the European Sleep Research Society[9] based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[8,9] Evidence supports efficacy of both brief CBT interventions and longer therapy.[9] Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon all have weak recommendations to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.[8] However, long-term treatment of chronic insomnia with a sedative (≥12 weeks) is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.[9] FDA labeling for most sedative drugs indicated for insomnia recommends re-evaluation of comorbid diagnoses which could be contributing to symptoms if insomnia persists for more than 7-10 days of treatment. Trazodone, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.[8]

Common adverse effects associated with sedative medications include dizziness, daytime drowsiness, and somnolence. Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. The risk of fracture may depended on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.[7] FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions. Risk for daytime impairment may be higher in women or elderly who metabolize and eliminate sedative medications more slowly from the body.[13] The FDA warns that high levels of a sedative in the bloodstream can result in impairment even if patients feel fully awake.[13] Benzodiazepine sedatives are also associated with physical dependence and a taper plan is usually recommended to minimize withdrawal symptoms and facilitate discontinuation after routine, long-term use. Provider resources and best practices for benzodiazepine tapers were recently published by the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG).[6] Taper schedules be individualized based on patient circumstances, diagnoses, dose, and length of benzodiazepine use. Many patients may benefit in switching, or cross-tapering, to a longer-acting benzodiazepine like diazepam before reducing their total benzodiazepine dose.[6]

Improvement in symptom severity is typically measured by patient-reported improvement in severity, sleep symptoms, and quality of life. However, differences in efficacy are often difficult to evaluate due to a strong placebo response which is apparent with both subjective and objective measures of efficacy. One systematic review examining effect size of the placebo response in RCTs of sedative drugs for treatment of primary insomnia determined that approximately 64% of drug response could be attributed to a placebo effect.[14] Sleep outcomes which are commonly reported in trials include subjective change in sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Change in these outcome measures compared to placebo which may represent clinically meaningful improvement have been proposed by the American Academy of Sleep Medicine (**Table 1**). Other assessment scales include the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI) which document overall symptom severity.[15]

Table 1. Clinically Meaningful Outcomes for Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).[8]

Outcome (units)	Minimum Clinically Important Difference Versus Placebo^		
	Polysomnography (PSG)	Actigraphy	Subjective
Sleep Onset Latency (min)	10	10	20
Total Sleep Time (min)	20	20	30
Wake After Sleep Onset (min)	20	20	30
Quality of Sleep (varies*)	Varies	Varies	Varies
Sleep Efficiency (%)	5	5	10
Number of Awakenings (n)	2	2	0.5

^Clinical significance was judged to be present when a specific agent led to a mean change in the outcome of this magnitude, compared to placebo.
*For standardized mean difference (SMD), an effect size of 0.5 is considered clinically significant.

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

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

Systematic Reviews:
Pharmacotherapies for sleep disturbances in dementia
A Cochrane systematic review on pharmacotherapy for sleep disturbances in patients with dementia was published in 2020.[2] Identified trials evaluated treatment with melatonin (n=222), trazodone (n=30), ramelteon (n=74), or an orexin receptor antagonist (suvorexant or lemborexant; n=323). Primary outcomes included objective sleep measures evaluated by polysomnography or actigraphy (such as total sleep time, sleep latency, nocturnal awakenings, etc) and were evaluated over short-term (≤ 6weeks) and long-term therapy (> 6 weeks).[2] For patients with moderate to severe Alzheimer's dementia, trazodone 50 mg may improve sleep efficiency (MD 8.53%, 95% CI 1.9 to 15.1) and total sleep time (MD 42.46 minutes, 95% CI 0.9 to 84.0) over 2 weeks compared to placebo (low quality evidence).[2] Other sleep outcomes and outcomes for cognitive function failed to achieve statistical significance and were limited by significant imprecision.[2] In patients with mild to moderate Alzheimer's dementia, orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (moderate quality evidence).[2] There was no difference in number of nocturnal awakenings, change in cognitive function, or caregiver distress based on moderate quality evidence. Ramelteon did not improve sleep outcomes in one phase 2 trial in patients with mild to moderate Alzheimer's dementia (low quality evidence).[2] Trials evaluating up to 10 mg of melatonin were mostly conducted in patients with moderate to severe Alzheimer's dementia and identified no improvement in total sleep time or the ratio of day-time to night-time sleep (low quality evidence).[2] Similarly, there was no difference on sleep efficiency, time awake after sleep onset, number of night-time awakenings, cognitive function, or caregiver burden (low quality evidence).[2] Serious adverse events were rarely reported for all treatments.

Melatonin for treating sleep disorders in adults who are blind

An evidence review was developed by NICE 2021 evaluating use of melatonin for treatment of sleep disorders in adults who are blind.[1] Only one RCT was included in the analysis; other identified trials were crossover studies without adequately reported randomization methods which may increase risk of bias.[1] All studies were small (with the largest enrolling 13 participants) and were likely underpowered to determine differences between groups.[1] All identified studies were of short duration (maximum 12 weeks) with long-term efficacy and safety unknown.[1] Overall, 2 studies (n=20) found no significant improvement in total sleep time with 2mg or 10mg of melatonin. One study reported a statistically significant improvement in total sleep time of 0.65 hours (about 40 minutes) with use of melatonin 0.5 mg compared to placebo.[1] Two studies reported melatonin decreased the time spent awake after sleep onset by 0.56 hours with melatonin 0.5mg and 1.3 hours with melatonin 10 mg.[1] No studies identified a difference with melatonin compared to placebo for sleep latency or quality of life. Overall, authors concluded that evidence is insufficient to determine efficacy and safety for use of melatonin in adults who are blind.[1]

After review, 11 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses),[16-27] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[23,25,26] or outcome studied (e.g., non-clinical).

New Guidelines:

No high-quality guidelines were identified.

New Formulations or Indications:

A new formulation of tasimelteon (Hetlioz LQ™), an oral suspension, was FDA approved in December 2020.[5] Tasimelteon was previously available as a capsule for non-24 hour sleep-wake cycle disorder. Tasimelteon also received an expanded indication for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age.[5] Smith-Magenis Syndrome is a rare developmental disorder which affects multiple organ systems and is often associated with multiple behavioral health conditions including intellectual disability, speech and motor delays, sleep disturbances, and self-injurious behaviors.[28] It is most commonly caused by a deletion in chromosome 17 and is estimated to affect 1 in 15,000-25,000 patients.[28] The recommended dose in pediatric patients less than 28 kg is weight based at 0.7 mg/kg one hour before bedtime.[5] Approval was based on a single 9-week double-blind, placebo-controlled, crossover RCT including 25 patients (age 3-39 years) with Smith-Magenis Syndrome and sleep disturbances.[5] Patients were randomized to receive tasimelteon or placebo for 4 weeks, had a 1 week washout period, then received the alternative medication for 4 weeks. The primary outcomes were subjective total sleep time and nighttime sleep quality (reported by the patient's parent/guardian) for the 50% of nights with the worst sleep.[5] Sleep quality was rated on a 5 point scale from excellent (5) to poor (1). Compared to placebo, tasimelteon treatment resulted in improved sleep quality for the 50% of nights with the worst sleep quality though magnitude of benefit was small (2.8 vs. 2.4; least square mean difference 0.4 [95% CI 0.1 to 0.7]).[5] The difference from placebo in total sleep time for the 50% of nights with the worst sleep was not statistically improved with tasimelteon (7 vs. 6.7 hours; least square mean difference 0.3 [95% CI -0.0 to 0.6]).[5]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month/Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Zolpidem[29]	Ambien®	2/2022	Warnings/Precautions	**Abnormal Thinking and Behavioral Changes:** Addition of delirium to warning/precautions of zolpidem based on post-marketing reports. **Respiratory Depression:** Strengthen warnings to emphasize risk with concomitant use of opioids or other central nervous system depressants

Temazepam[30]	Restoril™	2/2021	Box Warning Warnings/Precautions	Language in labeling revised to emphasize risk of abuse, misuse, addiction, dependence, and withdrawal symptoms. Use of benzodiazepines exposes patients to risk of abuse, misuse, and addiction. Before and throughout prescribing, assess a patient's risk for abuse or misuse. Long-term use can increase risk of physical dependence with risk of withdrawal symptoms upon discontinuation or with rapid tapering. Gradual tapers may decrease risk of withdrawal symptoms.

Randomized Controlled Trials:
A total of 93 citations were manually reviewed from the initial literature search. After further review, all but 2 RCTs 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). Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Castro, et al. 2020.[31] N=67 DB, double-dummy, RCT Duration: 3 months	1. Oral zolpidem 10 mg, nightly 2. Sublingual zolpidem 5mg nightly with 5mg as needed	Adults with insomnia diagnosis and self-reported nocturnal awakenings	Sleep onset latency, Nights with middle of the night awakenings	Change in sleep onset latency 1. +10 minutes (SD 29) 2. -14 minutes (SD 42) P=0.03 Other sleep outcomes including total sleep time, number of nights with middle of the night awakenings, wake after sleep onset time, sleep quality indices, and sleep severity indices were no different between groups	Randomization methods not reported and there were differences in baseline sleep onset latency (78 vs. 51 min; p=0.03). High attrition (31%) and use of LOCF for missing data increases risk of bias. 17 patients (25%) discontinued due to AEs and 10 (15%) discontinued based on medical advice.
Morin, et al, 2020.[32] Sequential, multiple assignment, single-blind; RCT N=211	Step 1 (6 weeks) 1. Behavioral therapy (BT) 2. Zolpidem 5-10mg nightly Step 2 (for patients without remission) 1. Medication (zolpidem or trazodone 50-	Adults with chronic insomnia disorder	Response to therapy and remission after step 1 (at 6 weeks) and after step 2 (at 12 weeks) Response was defined based on reduction in the ISI of at least 8 points. Remission	<u>Step 1</u> Response to therapy 1. 45.5% 2. 49.7% OR 1.18; 95% CI 0.60-2.33 Remission 1. 38.03% 2. 30.3% OR 1.41; 95% CI 0.75-2.65 <u>Step 2 (n=108)</u> Change in proportion of patients with response 1. BT+zolpidem: 40.6% to 62.7%	High attrition rates (step 1: 15% vs. 25%; step 2: 25%) with higher attrition rates in patients initiating zolpidem treatment which may increase risk of bias. Response and remission rates were highest in patients randomized to initial BT followed by either zolpidem or CBT. In a subgroup of patients with a psychiatric comorbidity, response and remission rates were highest in

Setting: Canada and Colorado Duration: 12 months	150mg nightly) 2. Psychological therapy (BT or CBT) Patients who did not remit in step 1 were randomized to therapies in step 2		was defined as a total ISI score of less than 8.	OR 2.46; 95% CI 1.14-5.30 2. BT+CBT: 50.6% to 68.2% OR 2.09; 95% CI 1.01-4.35 3. Zolpidem+trazodone: 46.4% to 55.7%; P=NS 4. Zolpidem+BT: 52.9% to 47.9%; P = NS Change in proportion of patients with remission 1. BT+zolpidem: 38.1% to 55.9% OR 2.06; 95% CI 1.04-4.11 2. BT+CBT: 38.0% to 45.2%; P = NS 3. Zolpidem+trazodone: 31.4% to 49.4%; p=NS 4. Zolpidem+BT: 29.2% to 36.2%; P = NS	patients randomized to CBT or trazodone.

Abbreviations: AE = adverse events; BT = behavioral therapy; CBT = cognitive behavioral therapy; DB = double blind; ISI = insomnia severity index; LOCF = last observation carried forward; NS = non-significant; OR = odds ratio; PC = placebo controlled; RCT = randomized controlled trial; SD = standard deviation

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Daridorexant 25 mg or 50 mg daily was FDA approved for treatment of insomnia in 2022 based on two phase 3, double-blind, placebo-controlled, RCTs. Trials were identically designed, though one study evaluated a lower dose of 10 mg. FDA approval was also supported by evidence from a phase 2 trial[4] and several small, short-term, RCTs evaluating safety of daridorexant in patients at least 65 years of age,[33] patients with obstructive sleep apnea,[34] patients with chronic obstructive pulmonary disease (COPD),[35] and patients with sedative drug use disorder.[36]

Overall, the phase 3 studies were well designed in order to minimize risk of bias (**Table 4**). However, both trials had extensive exclusion criteria which limit applicability to the general population. Patients who had psychiatric comorbidities, other sleep-wake disorders, alcohol or drug misuse, 15 or more apnea or hypopnea events per hour, or oxygen saturation less than 80% were excluded from the study.[3] As a method to control for and minimize the placebo effect, a patient-blinded placebo run-in period (13-24 days) was also required before randomization. Patients were required to meet baseline eligibility criteria for disturbed sleep and polysomnography during both screening and run-in periods. Treatment for insomnia has historically been associated with a very large placebo effect, and of the patients included in the run-in period, 50-54% of patients were excluded because they did not meet baseline inclusion criteria.[3] The primary reasons for exclusion were for apnea/hypopnea, oxygen saturation, or failure to meet subjective or objective baseline sleep disturbance criteria or polysomnography sleep parameters. Screening failure rate was slightly higher among patients identifying as Black compared to patients identifying as White which may result in a disproportionately larger population of White patients included in the study compared to the general population of patients who experience insomnia.[3]Other racial and ethnic subgroups were underrepresented in the studies.

Overall, only 25-28% of patients screened were included in these trials. Included patients were predominately female (64-69%) with an average age of 55-57 years, had been diagnosed with insomnia for approximately 10-11 years.[3] Additional required sleep parameters included an insomnia severity index of at least

15, wake after sleep onset (WASO) time of at least 30 minutes, latency to persistent sleep (LPS) of at least 20 minutes, and total sleep time (TST) of less than 7 hours.[3] Average values for the population are listed in **Table 4** are overall representative of a population with moderate to severe chronic insomnia.

Outcomes evaluated in these trials included both subjective and objective sleep parameters. Primary outcomes included WASO and LPS evaluated by polysomnography after 1 and 3 months of treatment. Magnitude of effect was generally comparable at 1 and 3 months for most outcomes. At 3 months, there was a least square mean difference from placebo in WASO time of 18 minutes with 50 mg nightly and 10-12 minutes with 25 mg nightly.[3] Compared to placebo, LPS improved by about 12 minutes with a 50 mg dose and 8-9 minutes with a 25 mg dose.[3] In Study 2, outcomes for 10 mg dose were not significantly improved compared to placebo.[3] While these results were statistically significant compared to placebo, it is unclear whether a mean improvement of less than 20 minutes in sleep maintenance time or less than 10 minutes in sleep latency would be clinically significant for most patients.

The two pre-specified secondary outcomes included total sleep time and change in the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleep domain score. The IDSIQ evaluates patient-reported impact of sleep on daytime symptoms and is divided into 3 domains of sleepiness, mood, and alert/cognition. The sleep domain is comprised of 4 items each rated 0-10 (max score of 40) with higher scores indicating more severe disease burden.[3] A within-person difference of 4 points was pre-specified as a clinically significant improvement on the sleep domain score.[3] In study 1, total sleep time improved by about 22 minutes at 1 month and 58 minutes at 3 months with a dose of 50 mg nightly compared to placebo.[3] For the 25 mg dose, the magnitude of benefit differed between the studies for self-reported total sleep time. Upon comparison of a 25 mg dose to placebo, self-reported total sleep time improved by 47.8 minutes (95% CI 41.3 to 54.3) in study 1 and 19.1 minutes (95% CI 10.1 to 28.0) in study 2 at 3 months.[3] With a 50 mg dose, IDSIQ sleep domain score was reduced (i.e., improved) by an average of -1.8 (95% CI -2.5 to -1.0) and -1.9 points (95% CI -2.9 to -0.9) compared to placebo at 1 and 3 months, respectively.[3] There was no difference in the IDSIQ sleep domain score with a 25mg dose compared to placebo in study 1, and study 2 found a statistically significant improvement of −1.3 points (95% CI −2.2 to −0.3) at 3 months compared to placebo.[3] Subgroup analyses for outcomes by age, sex, or center location demonstrated a similar direction of effect.[3]

There are currently no large trials comparing efficacy of daridorexant to other sleep medications. One small phase 2 trial for daridorexant did include an active comparison to zolpidem.[4] The primary goal of the trial was to evaluate dose response with daridorexant over a one month period, and statistical analyses compared to zolpidem were not performed. However, improvement in objective and subjective outcomes of WASO, LPS and total sleep time after 1 month had a similar magnitude of effect between zolpidem 10 mg and daridorexant 25-50 mg.[4]

These trials have limited applicability due to extensive exclusion criteria, and the magnitude of benefit and safety in patients with comorbid conditions is unknown. Due to stringent baseline insomnia criteria, the population studied is representative of those with moderate to severe insomnia, and the average time since the first insomnia diagnosis was over 10 years. The magnitude of benefit in patients with less severe disease is unknown. Despite use of a run-in period to minimize the placebo effect, patients randomized to placebo still had a significant improvement in sleep parameters. A long-term extension study evaluating maintenance of efficacy and long-term safety of daridorexant was recently completed but is not yet published.

Clinical Safety:

The safety profile of daridorexant is overall consistent with other orexin receptor antagonists used for the treatment of insomnia. Safety data was primarily derived from two phase 3 trials and a long-term extension study. The safety population included approximately 1232 patients who were exposed to 10-50 mg of daridorexant.[37] About 40% of these patients were older than 65 years of age and 46% were on therapy for more than 6 months.[37] Common adverse events associated with treatment included central nervous system (CNS) disorders such as headache (6-7% vs. 5% with placebo), somnolence/fatigue (5-6% vs. 4% with

placebo) and dizziness (2-3% vs. 2% with placebo).[37] Adverse events were slightly more common with higher doses. Nausea was also more common with daridorexant 50 mg compared to placebo (3% vs. 2%). Incidence of somnolence and fatigue increased with age, which may increase risk of falls in this population.[37]

Similar to other sedative drugs for insomnia, rare but serious adverse events are included in the labeling for daridorexant. These include parasomnias (e.g., sleep paralysis, hallucinations and narcolepsy/cataplexy-like symptoms), complex sleep behaviors (e.g., sleepwalking, sleep-driving, etc), worsening of depression and suicidal ideation, abuse/dependence, rebound insomnia, and respiratory depression.[37] Daridorexant is a central nervous system depressant and can cause impaired daytime functioning and wakefulness. Co-administration with other CNS depressants may have additive effects and patients with concomitant use of CNS depressants were excluded from clinical trials. Similarly, patients with underlying respiratory conditions resulting in sleep apnea, hypopnea or decreased oxygen saturation were excluded from clinical trials and risks of respiratory depression in these populations cannot be ruled out. Patients with comorbid psychiatric conditions were also excluded from clinical trials. Patients with psychiatric conditions, including insomnia, may be at increased risk of suicide, and there have been post-marketing reports of worsening depression, suicidal thoughts, and suicide attempts in patients treated with sedative hypnotics.[37] Daridorexant is undergoing evaluation by the DEA for controlled substance schedule and patients with history of substance use disorders were excluded from phase 3 trials. Close monitoring is recommended for patients with risk for substance abuse.[37] Physical dependence and withdrawal symptoms were not observed upon discontinuation of FDA-approved doses in phase 3 trials, but an abuse potential study documented similar "drug liking" ratings with use of daridorexant 100mg, zolpidem 30 mg and suvorexant 150mg.[37]

Because daridorexant is extensively metabolized by CYP enzymes, use is not recommended in conjunction with strong CYP3A4 inhibitors or inducers. A reduced dose (max 25 mg) is recommended if used in conjunction with moderate CYP3A4 inhibitors and in patients with moderate hepatic impairment.[37]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Daytime function
2) Quality of life
3) Sleep onset and maintenance
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:
1) Wake time after sleep onset (WASO) at 1 and 3 months (sleep maintenance)
2) Latency to persistent sleep (LPS) at 1 and 3 months (sleep onset)

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Orexin receptor antagonists which blocks binding of orexin A and orexin B to receptors in order to suppress wakefulness
Oral Bioavailability	62%; onset of 30 to 40 minutes
Distribution and Protein Binding	Volume of distribution = 31L 99.7% plasma protein binding
Elimination	57% feces, 28% urine (primarily as metabolites)
Half-Life	8 hours
Metabolism	89% via CYP3A4

Table 4. Comparative Evidence Table.

<table>
<tr><th>Ref./ Study Design</th><th>Drug Regimens/ Duration</th><th>Patient Population</th><th>N</th><th>Efficacy Endpoints</th><th>ARR/ NNT</th><th>Safety Outcomes</th><th>ARR/ NNH</th><th>Risk of Bias/ Applicability</th></tr>
<tr>
<td>1. Mignot, et al. 2022.[3]

MC, DB, PC, PG</td>
<td>1. daridorexant 50 mg every evening

2. daridorexant 25 mg every evening

3. placebo

Duration: 3 months randomized treatment period

- Screening period: 7-18 days
- Run-in period: 13-24 days
- Run-out period: 7 days
- Safety follow-up: 23 days

Patients could enroll in an optional extension period (9 months)</td>
<td><u>Demographics</u>:
- Female: 64-69%
- Mean age 55 years (SD 15)
- Age ≥65 years: 39%
- Race: White 88-93%
Black 6-10%
- Mean BMI: 26 kg/m^2
- Time since diagnosis:10-11 yrs
- WASO: 95-102 min
- LPS: 63-37 min
- Self-reported TST: 309-315 min
- Total sleep time: 318-328 min
- ISI: 19 (SD 4)
- IDSIQ sleep domain: 22 (SD 7)

<u>Key Inclusion Criteria</u>:
- Adults ≥ 18 years
- Insomnia diagnosis (DSM-5)
- Insomnia Severity Index ≥ 15
- Patient-reported history of disturbed sleep* for ≥3 months
- Patient-reported disturbed sleep* during baseline screening
- Baseline polysomnography: LPS ≥ 20 min, WASO ≥ 30 min, & mean total sleep time <7 hrs

<u>Key Exclusion Criteria</u>:
- Daytime napping ≥1 hr on ≥3 days per week
- History of suicidal ideation, suicide attempt, uncontrolled acute or chronic psychiatric conditions, severe depression
- Alcohol or drug misuse (including ≥ 1 pack per day of tobacco use)
- Apnea or hypopnea index of ≥15 events/hr or O_2 sat <80%</td>
<td><u>ITT</u>:
1. 310
2. 310
3. 310

<u>Attrition</u>:
1. 24 (8%)
2. 22 (7%)
3. 28 (9%)</td>
<td><u>Primary Endpoints</u>:
Change in WASO (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>-29.0</td><td>−29.4</td></tr>
<tr><td>2</td><td>-18.4</td><td>−23.0</td></tr>
<tr><td>3</td><td>-6.2</td><td>−11.1</td></tr>
</table>
LSMD At 1 month
1 vs. 3: -22.8; 95% CI -28.0 to -17.6, p<0.0001
2 vs. 3: -12.2; 95% CI -17.4 to -7.0, p<0.0001
LSMD At 3 months
1 vs. 3: -18.3; 95% CI -23.9 to -12.7, p<0.0001
2 vs. 3: −11.9; 95% CI -17.5 to -6.2, p<0.0001

Change in LPS (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>-31.2</td><td>-34.8</td></tr>
<tr><td>2</td><td>-28.2</td><td>-30.7</td></tr>
<tr><td>3</td><td>-19.9</td><td>-23.1</td></tr>
</table>
LSMD at 1 month
1 vs. 3: -11.4; 95% CI -16.0 to -6.7, p<0.0001
2 vs. 3: -8.3; 95% CI -13.0 to -3.6; p=0.0005
LSMD at 3 months
1 vs. 3: −11.7; 95% CI −16.3 to −7.0, p<0.0001
2 vs.3: -7.6; 95% CI -12.3 to -2.9, p<0.0001

<u>Secondary Endpoints</u>:
Change in Self-reported TST (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>43.6</td><td>57.7</td></tr>
<tr><td>2</td><td>34.2</td><td>47.8</td></tr>
<tr><td>3</td><td>21.6</td><td>37.9</td></tr>
</table>
At 1 month
1 vs. 3: 22.1; 95% CI 14.4 to 29.7; p<0.0001
2 vs. 3: 12.6; 95% CI 5.0 to 20.3; p=0.0013
At 3 months
1 vs. 3: 57.7; 95% CI 51.2 to 64.2, p<0.0001
2 vs. 3: 47.8; 95% CI 41.3 to 54.3, p=0.033</td>
<td>NA for all</td>
<td><u>DC due to AE</u>:
1. 3 (1%)
2. 2 (1%)
3. 7 (2%)

<u>SAE</u>
1. 3 (1%)
2. 2 (1%)
3. 7 (2%)

<u>Accidental overdose</u>
1. 8 (3%)
2. 4 (1%)
3. 5 (2%)

<u>Fall</u>
1. 1 (<1%)
2. 1 (<1%)
3. 8 (3%)

<u>Sleep paralysis</u>
1. 1 (<1%)
2. 1 (<1%)
3. 0 (0%)

<u>Suicidal ideation or self-injury</u>
None</td>
<td>NA for all</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. Randomized via interactive response technology system with allocation concealment. Baseline characteristics balanced.
<u>Performance Bias</u>: Low. Blinded with use of matching placebo for 3 month treatment period. Investigators not blinded for run-in period. Blinded safety board adjudicated AEs.
<u>Detection Bias</u>: Low. Investigators and patients blinded with use of matching placebo.
<u>Attrition Bias</u>: Low. ITT analysis used. About 9.4% missing data for all endpoints and treatment groups. Missing data was comparable between groups. Linear MMRM was used for each analysis and missing data was assumed to be comparable to other participants in the same treatment group. Sensitivity analysis evaluating various imputation methods resulted in comparable magnitude of effect.
<u>Reporting Bias</u>: Low. Outcomes reported as prespecified. Gatekeeping procedure used to adjust for multiplicity.
<u>Other Bias:</u> Unclear. Study sponsor was involved in study design, data collection, data analysis, data interpretation, & report writing.

Applicability:
<u>Patient</u>: About 28% of patients screened were included. Screening failure rate was slightly higher among Black individuals. Patients were most commonly excluded for apnea or hypopnea index ≥ 15 events/hr, O_2 Sat <80%, failure to meet subjective patient-reported sleep disturbance criteria, or failure to meet objective baseline polysomnography criteria. Due to stringent baseline insomnia criteria, population is representative of those with moderate to severe insomnia. Patients with comorbidities were excluded.
<u>Intervention</u>: Despite recommended use as a first-line treatment, few patients had prior CBT for insomnia. Dose range appropriate based on</td>
</tr>
</table>

		- Other sleep-wake disorders (restless leg syndrome, shift work. circadian rhythm disorder, rapid-eye-movement behavior disorder, narcolepsy) - Unstable medical condition, significant medical disorder or acute illness, ECG, or abnormal lab results within prior 1 month which could affect the patients safety or interfere with study assessments		**Change in IDSIQ - sleep domain score** 1: 1 month -3.8; 3 months -5.7 2: 1 month -2.8; 3 months -4.8 3: 1 month -2.0; 3 months -3.8 **At 1 month** 1 vs. 3: -1.8; 95% CI -2.5 to -1.0, p<0.0001 2 vs. 3: -0.8; 95% CI -1.5 to 0.01; p=0.055 (NS) **At 3 months** 1 vs. 3: -1.9; 95% CI -2.9 to -0.9; p=0.0002 2 vs. 3: -1.0; 95% CI -2.0 to 0.01; p=0.053 (NS)				phase 2 studies that demonstrated a dose response relationship for outcomes of WASO and LPS. Near maximal effect on sleep latency was observed at 10 mg but had no plateau effect on WASO when dosed up to 50 mg. Comparator: Placebo appropriate to determine efficacy. No active comparator, which could have informed place in therapy. Outcomes: Relatively large placebo effect, but both subjective and objective sleep measures had the same direction of effect. Setting: 75 sites in 10 countries from June 4, 2018 and Feb 25, 2020 (Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland, and the USA). US patients represented 31-34%.
2. Mignot, et al. 2022.[3] MC, DB, PC, PG	1. daridorexant 25 mg every evening 2. daridorexant 10 mg every evening 3. placebo Duration: see above	Demographics: - Female: 69% - Mean age 56-57 years (SD 14) - Age ≥65 years: 39% - Race: White 87-89% Black 5-9% - Mean BMI: 26 kg/m^2 - Time since diagnosis:10-12 yrs - WASO: 104-108 min - LPS: 67-72 min - Self-reported TST:307-308 min - Total sleep time: 307-316 min - ISI: 20 (SD 4) - IDSIQ sleep domain: 22 (SD 6) Key Inclusion Criteria: - See above Key Exclusion Criteria: - See above	ITT: 1. 309 2. 307 3. 308 Attrition: 1. 23 (7%) 2. 23 (7%) 3. 18 (6%)	Primary Endpoints: **Change in WASO (min)** 1: 1 month −24.2; 3 months -24.3 2: 1 month -15.3; 3 months -16.0 3: 1 month -12.6; 3 months -12.6 **LSMD At 1 month** 1 vs. 3: −11.6 (95% CI −17.6 to −5.6); p=0.0001 2 vs. 3: −2.7 (95% CI −8.7 to 3.2); p=0.37 (NS) **LSMD At 3 months** 1 vs. 3: -10.3 (95% CI -17.0 to −3.5); p=0.0028 2 vs. 3: −2.0 (95% CI −8.7 to 4.8); p=0.57 (NS) **Change in LPS (min)** 1: 1 month -26.5; 3 months -28.9 2: 1 month -22.6; 3 months -23.1 3: 1 month -20.0; 3 months -19.9 **LSMD at 1 month** 1 vs. 3: −6.5 (95% CI −12.3 to −0.6); p=0.030 2 vs. 3: −2.6 (95% CI −8.4 to 3.2); p=0.38 (NS) **LSMD at 3 months** 1 vs. 3: −9.0 (95% CI −15.3 to −2.7); p=0.0053 2 vs. 3: −3.2 (95% CI −9.5 to 3.1); p=0.32 (NS)	NA for all	DC due to AE: 1. 4 (1%) 2. 6 (2%) 3. 7 (2%) SAE: 1. 3 (1%) 2. 3 (1%) 3. 4 (1%) Accidental overdose 1. 4 (1%) 2. 4 (1%) 3. 1 (<1%) Fall 1. 3 (1%) 2. 4 (1%) 3. 3 (1%) Sleep paralysis 1. 2 (1%) 2. 0 (0%) 3. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low; see above. Placebo group had slightly more severe sleep variables (TST, WASO, LPS) at baseline compared to treatment groups but differences were small (difference of about 5 min TST, 2 min WASO; 4 min LPS). Performance Bias: Low; see above. Detection Bias: Low; see above. Attrition Bias: Low; see above. Reporting Bias: Low; see above. Other Bias: Unclear; see above. **Applicability**: Patient: About 25% of patients screened were included. See above. Intervention: See above. Comparator: See above. Outcomes: See above. Setting: 81 sites in 11 countries from May 29, 2018, and May 14, 2020 (Belgium, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hungary, South Korea, Sweden, and the USA). US patients represented 35-37%.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary Endpoints (at 3 months):
Change in Self-reported TST (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>43.8</td><td>56.2</td></tr>
<tr><td>2</td><td>41.0</td><td>50.7</td></tr>
<tr><td>3</td><td>27.6</td><td>37.1</td></tr>
</table>
At 3 months
1 vs. 3: 19.1 (95% CI 10.1 to 28.0); p<0.0001
2 vs. 3: 13.6 (95 % CI 4.7 to 22.5); p =0.0028

Change in IDSIQ - sleep domain score
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>-3.5</td><td>-5.3</td></tr>
<tr><td>2</td><td>-3.2</td><td>-4.8</td></tr>
<tr><td>3</td><td>-2.8</td><td>-4.0</td></tr>
</table>
At 3 months
1 vs. 3: −1.3 (95% CI −2.2 to −0.3); p=0.012
2 vs. 3: −0.7 (95% CI −1.7 to 0.2); p=0.14 (NS)</td>
<td></td>
<td>Suicidal ideation or self-injury
1. 1 (<1%)
2. 1 (<1%)
3. 0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="8">Abbreviations: AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CBT = cognitive behavioral therapy; CI = confidence interval; DB = double-blind; DC = discontinuation; ECG = electrocardiogram; DC = discontinue; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition ; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; ISI = insomnia severity index; ITT = intention to treat; LPS = latency to persistent sleep; LSMD = least squares mean difference; MC = multi-center; mITT = modified intention to treat; MMRM = mixed-effects model for repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PC = placebo controlled; PG = parallel group ; PP = per protocol; SAE = severe adverse event; SD = standard deviation; TST = total sleep time; WASO = awake after sleep onset
* Disturbed sleep defined as all the following ≥ 30 min to fall asleep, ≥ 30 min awake during sleep time & total sleep time ≤ 6.5 hrs for ≥ 3 nights per week</td>
</tr>
</table>

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
melatonin	MELATONIN	TABLET	Y
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
diphenhydramine HCl	NIGHTTIME SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP TIME	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
tasimelteon	HETLIOZ LQ	ORAL SUSP	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N
chloral hydrate	CHLORAL HYDRATE	SYRUP	
melatonin/pyridoxine HCl (B6)	MELATONIN-VITAMIN B6	TABLET	

Castro LS, Otuyama LJ, Fumo-Dos-Santos C, Tufik S, Poyares D. Sublingual and oral zolpidem for insomnia disorder: a 3-month randomized trial. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). 2020;42(2):175-184.

OBJECTIVE: To evaluate the safety and efficacy of a 5 mg sublingual dose of zolpidem, compared to a 10 mg oral dose, at bedtime and "as needed" following middle-of-the-night awakenings.

METHODS: Participants were randomized into an oral group (oral zolpidem 10 mg and sublingual placebo at bedtime and "as-needed") and a sublingual group (oral placebo and sublingual zolpidem 5 mg at bedtime and "as-needed"). Participants underwent medical evaluation, polysomnography, the psychomotor vigilance test, and completed questionnaires.

RESULTS: Of 85 patients, 67 met the criteria for insomnia (48+/-10 years; 79% women) and were randomized. Of these, 46 completed 92+/-5 days of treatment. Mild-to-moderate adverse events were reported by 25% of the participants, including headache, sleepiness, and dizziness. Both treatments decreased middle-of-the-night awakenings by an average of -3.1+/-2.3 days/week and increased total sleep time by 1.5 hours. Changes in sleep quality and insomnia severity scores were also favorable and comparable between groups: variation depended on continuation of treatment. Regarding PSG findings, sleep latency decreased more in the sublingual group than the oral group (-14+/-42 vs. 10+/-29 min; p = 0.03). The psychomotor vigilance test showed minor residual effects 30 minutes after awakening, which reversed after 2 hours.

CONCLUSIONS: The safety and efficacy of both zolpidem formulations are comparable. The sublingual 5 mg dose induced sleep more rapidly., CLINICAL TRIAL REGISTRATION: NCT01896336.

Morin CM, Edinger JD, Beaulieu-Bonneau S, et al. Effectiveness of Sequential Psychological and Medication Therapies for Insomnia Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2020;77(11):1107-1115.

Importance: Despite evidence of efficacious psychological and pharmacologic therapies for insomnia, there is little information about what first-line treatment should be and how best to proceed when initial treatment fails., Objective: To evaluate the comparative efficacy of 4 treatment sequences involving psychological and medication therapies for insomnia and examine the moderating effect of psychiatric disorders on insomnia outcomes.

Design, Setting, and Participants: In a sequential multiple-assignment randomized trial, patients were assigned to first-stage therapy involving either behavioral therapy (BT; n = 104) or zolpidem (zolpidem; n = 107), and patients who did not remit received a second treatment involving either medication (zolpidem or trazodone) or psychological therapy (BT or cognitive therapy [CT]). The study took place at Institut Universitaire en Sante Mentale de Quebec, Universite Laval, Quebec City, Quebec, Canada, and at National Jewish Health, Denver, Colorado, and enrollment of patients took place from August 2012 through July 2017.

Main Outcomes and Measures: The primary end points were the treatment response and remission rates, defined by the Insomnia Severity Index total score.

Results: Patients included 211 adults (132 women; mean [SD] age, 45.6 [14.9] years) with a chronic insomnia disorder, including 74 patients with a comorbid anxiety or mood disorder. First-stage therapy with BT or zolpidem produced equivalent weighted percentages of responders (BT, 45.5%; zolpidem, 49.7%; OR, 1.18; 95% CI, 0.60-2.33) and remitters (BT, 38.03%; zolpidem, 30.3%; OR, 1.41; 95% CI, 0.75-2.65). Second-stage therapy produced significant increases in responders for the 2 conditions, starting with BT (BT to zolpidem, 40.6% to 62.7%; OR, 2.46; 95% CI, 1.14-5.30; BT to CT, 50.1% to 68.2%; OR, 2.09; 95% CI, 1.01-4.35) but no significant change following zolpidem treatment. Significant increase in percentage of remitters was observed in 2 of 4 therapy sequences (BT to zolpidem, 38.1% to 55.9%; OR, 2.06; 95% CI, 1.04-4.11; zolpidem to trazodone, 31.4% to 49.4%; OR, 2.13; 95% CI, 0.91-5.00). Although response/remission rates were lower among patients with psychiatric comorbidity, treatment sequences that involved BT followed by CT or zolpidem followed by trazodone yielded better outcomes for patients with comorbid insomnia. Response and remission rates were well sustained through the 12-month follow-up.

Conclusions and Relevance: Behavioral therapy and zolpidem medication produced equivalent response and remission rates. Adding a second treatment produced an added value for those whose insomnia failed to remit with initial therapies., Trial Registration: ClinicalTrials.gov Identifier: NCT01651442.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to March 14, 2022

Searches		Results	Type
1	exp Melatonin/		21698
2	exp Zolpidem/		1700
3	exp Diphenhydramine/		4475
4	exp Doxepin/		841
5	exp Doxylamine/		390
6	exp Estazolam/		111
7	exp Eszopiclone/		131
8	exp Flurazepam/		781
9	exp Orexin Receptor Antagonists/		467
10	lemborexant.mp.		64
11	exp Midazolam/		9374
12	ramelteon.mp.		458
13	suvorexant.mp.		316
14	tasimelteon.mp.		87
15	exp Temazepam/		674
16	exp Triazolam/		1239
17	zaleplon.mp.		430
18	exp Sleep Aids, Pharmaceutical/		8896
19	exp Benzodiazepines/		67755
20	daridorexant.mp.		27
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20		98736
22	exp "Sleep Initiation and Maintenance Disorders"/		15525
23	exp Sleep Wake Disorders/		100918
24	22 or 23		100918
25	21 and 24		4919
26	limit 25 to yr="2020 -Current"		352
27	limit 26 to (english language and humans)		312
28	limit 27 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")		93

Appendix 4: Prescribing Information Highlights

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

QUVIVIQ (daridorexant) tablets, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

----------INDICATIONS AND USAGE----------
QUVIVIQ is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage is 25 mg to 50 mg once per night, taken orally within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening. (2.1)
- Time to sleep onset may be delayed if taken with or soon after a meal. (2.1)
- Hepatic Impairment: (2.3)
  - Moderate hepatic impairment: Maximum recommended dosage is 25 mg no more than once per night.
  - Severe hepatic impairment: Not recommended.

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 25 mg, 50 mg. (3)

----------CONTRAINDICATIONS----------
QUVIVIQ is contraindicated in patients with narcolepsy. (4)

----------WARNINGS AND PRECAUTIONS----------
- CNS-Depressant Effects and Daytime Impairment: Impairs alertness and motor coordination including morning impairment. Risk increases when used with other central nervous system (CNS) depressants. For patients taking QUVIVIQ, caution against next-day driving and other activities requiring complete mental alertness. (5.1)
- Worsening of Depression/Suicidal Ideation: Worsening of depression or suicidal thinking may occur. (5.2)
- Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms: May occur with use of QUVIVIQ. (5.3)
- Complex Sleep Behaviors: Behaviors including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur. Discontinue immediately if complex sleep behavior occurs. (5.4)
- Compromised Respiratory Function: Effect on respiratory function should be considered. (5.5, 8.7)
- Need to Evaluate for Co-morbid Diagnoses: Reevaluate if insomnia persists after 7 to 10 days. (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reactions (reported in ≥ 5% of patients treated with QUVIVIQ and at an incidence ≥ than placebo) were headache and somnolence or fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Idorsia Pharmaceuticals Ltd at toll-free phone 1-833-400-9611 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 7.1)
- Moderate CYP3A4 inhibitors: Maximum recommended dose is 25 mg. (2.2, 7.1)
- Moderate or Strong CYP3A4 inducers: Avoid concomitant use. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2022

Appendix 5: Key Inclusion Criteria

Population	Patients with insomnia
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1 or placebo
Outcomes	Outcomes Sleep latency (SL) Total sleep time (TST) Wake after sleep onset (WASO) Quality of sleep (QOS) Sleep efficiency (SE) Number of awakenings (NOA)
Timing	At least 4 weeks
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives (e.g., sedative hypnotics, hypnotics-melatonin agonists) except melatonin in children and adolescents. Melatonin is not covered for adults over 18 years of age.

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/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class. Go to #5	**No:** Go to #5
5. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for lifetime.	**No:** Go to #6
6. Has the patient been treated with a different~~nother~~ non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #7	**No:** Go to #9~~8~~
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #9 Document reason for switch and approve duplication for 30 days.	**No:** Go to #8~~Pass to RPh. Deny; medical appropriateness.~~

Approval Criteria		
8. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~9. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #10~~9~~	**No:** Go to #11~~0~~
~~9.~~10. Is patient on CPAP?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.
~~10.~~11. Is the patient being treated for co-morbid: • Depression; • Anxiety or panic disorder; or • Bipolar disorder? **AND** Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Go to #12~~1~~

Approval Criteria		
~~11.~~12. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Go to #13~~2~~
13. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?	**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.	**No:** Deny; medical appropriateness

P&T/DUR Review: *6/22 (SS); 12/20 (AG); 7/18 (JP); 3/17; 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Benzodiazepines

Goal(s):

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

Length of Authorization:

- 1 month to 12 months (criteria-specific)

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Does the patient have a seizure disorder diagnosis or is the patient enrolled in a program for short-term outpatient management of alcohol withdrawal syndrome? Note: benzodiazepines are not indicated for alcohol dependence.	**Yes:** Approve for 12 months for seizure disorder or up to 1 month for alcohol withdrawal	**No:** Go to #5
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber evaluated the PDMP at least once in the past 3 months for this patient?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7

Approval Criteria		
7. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #9	**No:** Go to #10
9. Is the medication prescribed by or in consultation with a prescribing mental health specialist OR does the patient have a documented trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including antidepressants AND psychotherapy (e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing)? Note: An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
10. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #11	**No:** Go to #12

Approval Criteria		
11. Is the medication prescribed by or in consultation with a prescribing mental health specialist OR does the patient have an adequate trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including second-generation antipsychotics AND psychotherapy (e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation)? Note: For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
12. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Go to #13~~Pass to RPh. Deny; medical appropriateness.~~	**No:** Go to #14~~3~~

Approval Criteria		
13. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
~~13.~~14. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #2

Renewal Criteria		
2. Is the request for an increase in dose?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #4	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
4. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.

P&T Review: *3/19 (SS); 9/18, 3/14*
Implementation: *5/1/19; 11/1/2018; 5/1/16*