



© Copyright 2012 Oregon State University. All Rights Reserved

College of Pharmacy

Drug Use Research & Management Program

Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079

Phone 503-947-5220 | Fax 503-947-2596



Drug Class Literature Scan: Tobacco Smoking Cessation

Date of Review: February 2021

Date of Last Review: September 2019

Literature Search: July 2019 – December 2020

Current Status of PDL Class:

See **Appendix 1**.

Purpose of Review:

- Provide new comparative effectiveness and safety evidence for smoking cessation therapeutic agents published since the last literature scan.
- Update Oregon Health Plan Fee-for-Service (OHP-FFS) prior authorization (PA) criteria to align with Health Evidence Review Commission (HERC) guidance.

Conclusions:

- Four systematic reviews and 2 clinical practice guidelines were identified which evaluated smoking cessation interventions in patients with tobacco dependence.
- The identified literature found no new current comparative evidence to demonstrate a difference in clinical efficacy or safety among FDA-approved pharmacological agents.
- No comparative evidence was found to favor the use of one specific smoking cessation intervention type over another to promote long term abstinence in any subpopulation.
- One American Thoracic Society (ATS) guideline recommended varenicline therapy over nicotine patch for initial treatment of adults with tobacco dependence as well as for adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder (strong recommendation, moderate certainty in the estimated effects).
- Prior Authorization Criteria for nicotine replacement therapy and bupropion HCl as smoking cessation treatments is supported by current federal and state policy but varenicline therapy requires an update to allow for two 12-week treatment regimens within 1 year for patients 17 years of age and older.

Recommendations:

- No changes were made to the current PDL based on new comparative evidence.
- After costs were evaluated in executive session, PA criteria and quantity limits were removed from all PDL preferred products. Age safety edit for varenicline was maintained.

Summary of Prior Reviews and Current Policy

High quality evidence identified from previous reviews demonstrated that combined pharmacotherapy and behavioral treatment were more effective than usual care, brief advice, or less intensive support in the treatment of tobacco dependence. The Health Evidence Review Commission (HERC) outlined tobacco cessation coverage benefits and standards for the OHP population which may currently be found on Line 5 of the Prioritized List. In January 2014 the Affordable Care Act (ACA) required health insurance plans to cover without cost sharing all preventive services that had received “A” or “B” ratings from the US Preventive Services Task Force.¹ In May 2014, the Department of Health and Human Services clarified what constitutes a comprehensive tobacco cessation benefit under the ACA.¹ In Oregon, the HERC requirements for tobacco cessation coverage under Medicaid are aligned with the ACA requirements.¹ According to these requirements, a group health plan or health insurance issuer must cover the following:

1. Screening for tobacco use
2. For those who use tobacco products, at least two tobacco cessation attempts per year, recognizing not everyone quits on their first try. For this purpose, covering a cessation attempt includes coverage for:
 - Four tobacco counseling sessions of at least 10 minutes each (including telephone, group and/or individual counseling)
 - All medications approved by the FDA as safe and effective for smoking cessation (including both prescription and over-the-counter medications) for a 90-day treatment regimen when prescribed by a health care provider
 - Plans should not require prior authorization to access these benefits
 - Cessation benefits shall be provided at no cost to the patient. No copays, coinsurance or deductibles should be charged

In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all FDA-approved smoking cessation agents are covered including varenicline, bupropion and all forms of nicotine replacement therapy. Current prior authorization (PA) policy requires a PA for non-preferred products; use of NRT beyond 6 months in the absence of behavioral counseling; and varenicline treatment for more than 12 weeks or for patients less than 17 years of age. In April through June of 2020, approximately 86% of the PA requests were initially approved, 6% had a paid claim within 30 days for either the requested agent or a similar agent, and only 8% did not have a paid claim after a denial mostly due lost eligibility or other insurance enrollment.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan 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:

A 2020 Cochrane Systematic Review evaluated the safety and efficacy of pharmacological interventions for smoking cessation during pregnancy.² The primary outcome was biochemically validated smoking cessation at the latest point in pregnancy (≥ 20 weeks gestation).² Eleven randomized controlled trials (N=2412)

with pregnant women were included in the review.² Nine of the trials investigated nicotine replacement therapy (NRT) and 2 of the trials studied bupropion, both of which were compared to either placebo or behavioral support.² Nine studies revealed low quality evidence that NRT increased the likelihood of smoking abstinence in late pregnancy compared to placebo or behavioral support alone (RR 1.37, 95% CI 1.08 to 1.74; $I^2 = 34\%$; N=2336).² The benefit was greater with NRT compared to behavioral therapy alone (Risk Ratio, (RR) 8.55, 95% CI 2.05 to 35.71; $I^2 = 0\%$, 3 studies, N=273) while there was unclear benefit in NRT compared to placebo (RR 1.21, 95% CI 0.95 to 1.55; $I^2 = 0\%$, 6 studies, N=2063).² There was no apparent statistically significant difference in effectiveness between fast acting NRT and patches (Test for subgroup differences: $\text{Chi}^2=3.13$, $\text{df}=1$ ($P=0.08$), $I^2=68.06\%$).² For safety, there was no evidence of differences between NRT and control groups in rates of caesarian section, birthweight, miscarriage, stillbirth, premature birth, neonatal intensive care admissions, congenital abnormalities, or neonatal death.² There was low-certainty evidence of no difference in smoking abstinence rates in later pregnancy for women treated with bupropion compared to placebo (RR 0.74, 95% CI 0.21 to 2.64; $I^2 = 0\%$, 2 studies, N=76) as well as no reported differences in safety outcomes.²

A systematic review with meta-analysis was conducted to evaluate the safety and efficacy of pharmacological interventions to achieve smoking abstinence in adults with schizophrenia/schizoaffective disorder and/or bipolar disorders.³ Most of the 28 RCTs identified (n=1947) measured biochemically validated abstinence rates at 3 and 6 months while a few assessed sustained abstinence from smoking at 52 weeks.³ A 5-study meta-analysis (n=214) of schizophrenia patients treated with bupropion alone or in combination with NRT reported a statistically significant smoking cessation benefit at 6 months compared to placebo (Risk Ratio (RR) 3.04 (95% CI, 1.14 to 8.09, $p=0.03$, $I^2=0\%$).³ However, pooled results of the 3 studies with bupropion monotherapy compared to placebo showed no effect at 6 months.³ Although pooled analysis of 2 studies (n=188) with varenicline reported a statistically significant difference smoking abstinence rates at 6 months compared with placebo (RR 3.69, 95% CI 1.08 to 12.60, $p=0.04$, $I^2=0\%$), no effect was observed in patients with bipolar disorder or schizophrenia.³ Neither bupropion or NRT was found to affect positive and negative symptoms, anxiety, or depressive symptoms, while analysis of varenicline studies showed a higher incidence of nausea and vomiting (RR 1.66 (1.23 to 2.24, $p=0.0009$).³ Evidence for the bupropion and varenicline studies was considered very low quality due to the overall poor methodology of included studies, placebo comparisons, limited population size, and short study durations.³ Estimates associated with the magnitude of benefit or risks associated with adverse effects for these therapies were uncertain.³

A meta-analysis was conducted to evaluate the efficacy and safety of varenicline combined with bupropion to achieve abstinence in nicotine-dependent adult smokers.⁴ Four RCTs (n=1230) compared the combination of varenicline plus bupropion to varenicline plus placebo.⁴ Abstinence rates were assessed and biochemically confirmed at the conclusion of treatment, at 6 months, and 12 months follow-up.⁴ All 4 trials were double blinded.⁴ Although the overall quality of the studies was considered high, only one trial described the methods of randomization clearly and two studies had unclear allocation concealment.⁴ Combination therapy with varenicline and bupropion were reported to show statistically significant rates of abstinence at the end of treatment compared to varenicline alone (RR 1.153, 95% CI 1.019 to 1.305, $P=0.024$; $I^2=42.2\%$, $P=0.158$).⁴ Abstinence rates at the 6 month follow-up (3 studies, n=1056) showed a benefit for combination therapy compared to varenicline alone (RR 1.23, 95% CI 1.02 to 1.50, $P=0.033$; $I^2=27.8\%$, $P=0.250$) but no benefit was observed at the 12 month follow-up assessment (2 studies, n=835) for varenicline plus bupropion combination therapy.⁴

A Cochrane systematic review of 63 studies (N = 41,509) reviewed efficacy and safety of various forms, delivery systems, doses, and durations of NRT to achieve long-term abstinence.⁵ Studies were at least 6 months duration and enrolled adult patients who typically smoked ≥ 15 cigarettes per day.⁵ Those studies with placebo comparators or a relatively short outcome follow-up (i.e. <6 months) were excluded.⁵ Based on data from 14 studies (n=11,356), there was high-certainty evidence of a higher rate of abstinence at 6 months with combination NRT (fast-acting formulation plus patch) compared to monotherapy (Risk Ratio (RR) 1.25, 95% CI 1.15 to 1.36; $I^2=4\%$).⁵ There was high-certainty evidence from 8 studies (n=3319) to indicate similar long-term quit rates for fast-acting NRT compared to nicotine patch (RR 0.90, 95%CI 0.77 to 1.05; $I^2=0\%$).⁵ One study (n=922) demonstrated significantly more withdrawals due to treatment for patients on nicotine nasal spray therapy compared to patch (RR 3.47, 95% CI 1.15 to 10.46), however, the findings were based on very low certainty evidence.⁵

Multiple systematic reviews, primarily Cochrane reviews, have been published to assess evidence for other smoking cessation strategies either used alone or in combination with pharmacotherapy to treat tobacco dependence or prevent relapse.^{6,7} Alternative smoking cessation strategies included reduction, instruction, behavioral support, and/or electronic-cigarettes compared to no treatment/advice or abrupt quit interventions.⁶ Evidence from these reviews was generally of insufficient to very low quality for clinical outcomes of interest upon comparison to placebo or other therapies.^{6,7} Quality of evidence was often limited by high or unclear risk of bias, limited population size, or small effect sizes.^{6,7} Estimates associated with the magnitude of benefit or risks associated with adverse effects for these therapies are uncertain.^{6,7}

After review, 9 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

The American Thoracic Society (ATS) released guidelines for initiation of pharmacologic treatment in tobacco-dependent adults.⁸ The guideline was intended to be an extension of the US Public Health Service (USPHS) smoking cessation guidelines which focused on the efficacy of various interventions.⁸ The ATS guideline goal was to provide more personalized, patient-centered recommendations for clinical questions of effectiveness in special populations and scenarios. Recommendations were based on the established Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria in terms of recommendation strength and certainty of estimated effects.⁸ The strength of recommendations considered the benefits and harms of therapy, patient values and preferences, resource issues, practicability, and impartiality of different recommendations which were rated on a continuum and referred to as strong or weak.⁸ The certainty of recommendations was graded as very low, low, moderate, or high quality based on risk of bias (including likelihood of publication bias), dose-effect, precision, consistency, and potential confounding.⁸

The guideline panel made 7 recommendations:

Strong Recommendations

- Use varenicline over a nicotine patch for initial treatment of adults with tobacco dependence (strong recommendation, moderate certainty in the estimated effects)⁸
- Use varenicline over bupropion for initial treatment of adults with tobacco dependence (strong recommendation, moderate certainty in the estimated effects)⁸
- Begin treatment with varenicline rather than wait until patients are ready to quit tobacco use in tobacco-dependent adults who are not ready to quit (strong recommendation, moderate certainty in the estimated effects)⁸
- Use varenicline over a nicotine patch for tobacco-dependent adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom tobacco cessation treatment is being initiated (strong recommendation, moderate certainty in the estimated effects)⁸
- Use extended-duration of therapy (>12 weeks) over standard duration (6–12 weeks) of therapy for tobacco-dependent adults for whom treatment is being initiated with a controller (strong recommendation, moderate certainty in the estimated effects)⁸

Conditional Recommendations

- Use varenicline plus a nicotine patch over varenicline alone for initial treatment of adults with tobacco dependence (conditional recommendation, low certainty in the estimated effects)⁸

-
- Use varenicline over electronic cigarettes for initial treatment of adults with tobacco dependence (conditional recommendation, very low certainty in the estimated effects)⁸

The ATS recommendations for tobacco dependence treatment of adults with comorbid psychiatric conditions did not compare varenicline with bupropion or other tobacco cessation agents.⁸ Many of the ATS guideline's lead authors received research funding and/or have served on advisory committees for the manufacturer.⁸

Additional Guidelines for Clinical Context:

The United States Preventative Services Task Force (USPSTF) released a recommendation statement for primary care interventions for prevention and cessation of tobacco use in children and adolescents.⁹ The recommendation was based on findings from an updated systematic review (n=44521) from primary care-relevant studies, randomized clinical trials, and nonrandomized controlled intervention studies that compared behavioral or pharmacological interventions to minimal/no care controls.^{9,10} The populations studied were children and adolescents up to 18 years of age for cessation and 25 years for prevention. The following main recommendations were provided by the USPSTF:

- For school-aged children and adolescents who have not started to use tobacco, primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents (Grade B, moderate certainty).⁹

The USPSTF determined current evidence was insufficient to assess the balance of benefits and harms of primary care-feasible interventions for the cessation of tobacco use among school-aged children and adolescents (Grade I, insufficient evidence).⁹ Due to relatively few studies with small sample sizes available for review, it was unclear if the lack of effect observed with behavioral counseling and pharmacotherapy interventions was the result of intervention failure or lack of statistical power.⁹

After review, one smoking cessation guideline was excluded due to methodological limitations/low quality.

New Formulations:

None identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts¹¹

| Generic Name | Brand Name | Month / Year of Change | Location of Change (Boxed Warning, Warnings, CI) | Addition or Change and Mitigation Principles (if applicable) |
|-------------------------|------------|------------------------|--|---|
| Nicotine | Nicotrol | 8/2019 | Warnings and Precautions | Care should be taken not to spray the eyes while administering NICOTROL NS; In a small clinical study of 33 subjects, use of NICOTROL NS by smokers with chronic rhinitis and sinusitis was associated with irritant effects with no significant impairment in nasal condition; Pharmacokinetic studies in patients with moderate to severe renal impairment or moderate to severe hepatic impairment have shown decreased nicotine clearance. Consider dose reduction and monitoring patients for adverse events (such as nausea or dizziness) associated with elevated levels of nicotine; [caution in patients with] esophagitis, [active] gastric or [peptic ulcers]; Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately; Adverse reactions identified during post-marketing experience with the nicotine nasal spray formulation: chest pain, anaphylactic reaction, dysphagia |
| Bupropion hydrochloride | Zyban | 7/2019 | Adverse Reactions | hyponatremia |

References:

1. Oregon Health Authority, Public Health and Health Systems Division Tobacco Cessation Coverage Standards. <https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCPREVENTION/Documents/> Published May 2014. Accessed November 30, 2020.
2. Claire R, Chamberlain C, Davey M-A, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. The Cochrane database of systematic reviews. 2020;3:CD010078.
3. Pearsall R, Smith DJ, Geddes JR. Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials. *BMJ open*. 2019;9(11):e027389.
4. Zhong Z, Zhao S, Zhao Y, Xia S. Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials. *Comprehensive psychiatry*. 2019;95:152125.
5. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. The Cochrane database of systematic reviews. 2019;4:CD013308.
6. Lindson N, Klemperer E, Hong B, Ordonez-Mena JM, Aveyard P. Smoking reduction interventions for smoking cessation. The Cochrane database of systematic reviews. 2019;9:CD013183.
7. Livingstone-Banks J, Norris E, Hartmann-Boyce J, et al. Relapse prevention interventions for smoking cessation. The Cochrane database of systematic reviews. 2019;2019(10).
8. Leone FT, Zhang Y, Evers-Casey S, et al. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*. 2020;202(2):e5-e31.
9. United States Preventative Services Task Force (USPSTF). Primary Care Interventions for Prevention and Cessation of Tobacco Use in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;323(16):1590-1598.
10. Selph S, Patnode C, Bailey SR, Pappas M, Stoner R, Chou R. Primary Care-Relevant Interventions for Tobacco and Nicotine Use Prevention and Cessation in Children and Adolescents: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama*. 2020;323(16):1599-1608.
11. Food and Drug Administration. Drug Safety Labeling Changes (SLC). <https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/>. Accessed 12/15/2020.

Appendix 1: Current Preferred Drug List

| <u>Generic</u> | <u>Brand</u> | <u>Form</u> | <u>Route</u> | <u>PDL</u> |
|----------------------|------------------|-------------|--------------|------------|
| bupropion HCl | BUPROPION HCL SR | TAB ER 12H | PO | Y |
| nicotine | NICOTINE PATCH | PATCH DYSQ | TD | Y |
| nicotine | NICOTINE PATCH | PATCH TD24 | TD | Y |
| nicotine polacrilex | NICOTINE GUM | GUM | BC | Y |
| nicotine polacrilex | NICOTINE LOZENGE | LOZENGE | BC | Y |
| nicotine polacrilex | NICOTINE LOZENGE | LOZNG MINI | BC | Y |
| varenicline tartrate | CHANTIX | TAB DS PK | PO | Y |
| varenicline tartrate | CHANTIX | TABLET | PO | Y |
| nicotine | NICOTROL | CARTRIDGE | IH | N |
| nicotine | NICOTROL NS | SPRAY | NS | N |

Appendix 2: New Comparative Clinical Trials

A total of 114 citations were manually reviewed from the initial literature search. After further review, all 114 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).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 30, 2020

- 1 *smoking cessation.mp. or Smoking Cessation/ 39815*
- 2 *"tobacco use disorder".mp. or "Tobacco Use Disorder"/ 11593*
- 3 *nicotine gum.mp. /687*
- 4 *nicotine lozenge.mp. or "Tobacco Use Cessation Devices"/ 1929*
- 5 *nicotine patch.mp. or "Tobacco Use Cessation Devices"/ 2639*
- 6 *nicoderm.mp. /29*
- 7 *nicotine spray.mp. /49*
- 8 *bupropion.mp. or Bupropion/ 5061*
- 9 *varenicline.mp. or Varenicline/1983*
- 10 *1 or 2 /46173*
- 11 *3 or 4 or 5 or 6 or 7 or 8 or 9 /8881*
- 12 *10 and 11 /4749*
- 13 *limit 12 to (english language and humans and yr="2019 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) /130*

Appendix 4: Key Inclusion Criteria

| | |
|---------------------|--|
| Population | Patients with tobacco use disorder |
| Intervention | Pharmacotherapy (nicotine replacement: patches, gum, lozenges, nasal spray, inhalation cartridges); bupropion, or varenicline with or without behavioral therapy |
| Comparator | Placebo or active comparator |
| Outcomes | Point prevalence abstinence/smoking cessation |
| Timing | Any study duration; literature search from August 2019 to November 2020 |
| Setting | Inpatient hospital or outpatient clinics; worldwide |

Smoking Cessation

Goal(s):

- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products

Length of Authorization:

- 6 months

Requires PA:

- Non-preferred drugs
- Varenicline for individuals younger than 17 years (safety edit)

Covered Alternatives:

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

| Approval Criteria | | |
|---|--|---|
| 1. What diagnosis is being treated? | Record ICD10 code | |
| 2. Is the diagnosis for tobacco dependence (ICD10 F17200)? | Yes: Go to #3 | No: Pass to RPh. Deny; medical appropriateness |
| 3. Will the prescriber change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. | Yes: Inform prescriber of covered alternatives in class | No: Go to #4 |

Approval Criteria

| | | |
|---|--|---|
| 4. Is the request for varenicline for a patient less than 17 years old? | Yes: Pass to RPh. Deny; medical appropriateness | No: Go to #5 |
| 5. Is the patient enrolled in a smoking cessation behavioral counseling program [e.g. Quit Line at: 800-QUIT-NOW (800-784-8669)]. | Yes: Approve NRT for 6 months | No: Pass to RPh. Deny; medical appropriateness |

P&T Review: 2/2021 (DE); 9/19; 7/16; 4/12
Implementation: 3/1/21; 11/1/19; 8/16, 7/23/12