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: September 2019

Date of Last Review: July 2016
Literature Search: June 2016 – June 2019

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

Purpose of Review:
The purpose of this literature scan is to provide new comparative effectiveness and safety evidence for therapeutic agents indicated for smoking cessation.

Conclusions:
- Seven systematic reviews, 9 randomized controlled trials, and 1 clinical practice guideline were identified which evaluated smoking cessation interventions in patients with tobacco dependence.
- The identified literature supports current policy and prior authorization (PA) criteria for smoking cessation as there is 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 including pharmacotherapy (NRT gum, lozenge, inhaler, and/or transdermal patch, varenicline or bupropion), behavioral counseling, or combination therapy in any subpopulation.
- Warnings about safety were added to the Chantix® (varenicline) label. Chantix® is not recommended for pediatric patients 16 years of age or younger because its efficacy in this population has not been demonstrated.

Recommendations:
- Recommend no changes to the current PDL based on new comparative evidence.
- Implement an age limit for varenicline and update PA criteria.
- After evaluation of comparative costs in the executive session, no PDL changes were recommended.

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. 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. Except for bupropion HCl, all covered products have associated quantity limits for utilization control. Use of varenicline beyond 12 weeks or preferred nicotine replacement therapy use beyond 6 months require prior authorization (PA) as do all of the nicotine cartridge and spray formulations. The PA criteria for these agents are listed in **Appendix 6**. The majority of utilization for smoking cessation agents include nicotine patch, varenicline, nicotine gum, and nicotine lozenges. Each quarter,

Author: Dave Engen, PharmD

there are approximately 800 paid claims for smoking cessation agents. The representative smoking cessation agents included on the Oregon PDL are presented in **Appendix 1**.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. The population, interventions, comparators, outcomes, timing, and setting for the included studies are listed in **Appendix 5**.

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 2016 Cochrane systematic review evaluated the efficacy of behavioral and/or pharmacological treatments for tobacco cessation in those with chronic obstructive pulmonary disease (COPD).[1] The primary outcome was percentage of participants with continuous or prolonged abstinence over a period of six months or longer. Sixteen randomized controlled trials (RCTs) were included in the review (N=13,123), 4 of which were used for meta-analysis.[1] Two studies (n=625) showed that nicotine sublingual tablet and varenicline were effective for increased quit rates versus placebo (14% vs 5%, respectively; RD 0.09 (95% CI 0.03 to 0.15) and 18.4% vs 5.5% RD of 0.13 (95% CI 0.07 to 0.18)).[1] Two studies (n=915) demonstrated that bupropion had a positive impact on tobacco quit rates versus placebo (pooled RD 0.09 (95% CI 0.03 to 0.15)). Pooled results from all four studies with low heterogeneity reported high-quality evidence of benefit with combined high-intensity behavioral support and medication intervention compared to behavioral support and placebo (RD 0.10 (95% CI 0.07 to 0.14; I^2=0%).[1] Nortriptyline did not demonstrate statistical significance in quit rate versus placebo. The authors were unable to effectively pool data for comparisons between different pharmacological treatments due to trial variability and overall high and unclear risk of bias.[1]

A Cochrane systematic review assessed the effects of different types of tobacco cessation interventions in adults treated for substance use disorders.[2] Interventions included pharmacotherapy (NRT gum, lozenge, inhaler, and/or transdermal patch, or non-NRT drugs such as varenicline or bupropion), behavioral counseling, or combination therapy.[2] Thirty-five RCTs (N=5796) of participants aged 15 or older with active treatment for, or recovery from, alcohol or drug dependence were included. Primary outcome was point prevalence abstinence biochemically verified.[2] Low quality evidence from 11 studies (N= 1808) suggested for people in treatment or recovery from alcohol or other drug dependency, tobacco abstinence at 8 weeks to 6 months improved with pharmacotherapy compared to placebo or usual care (RR 1.88 95% CI 1.37 to 2.57). Similarly, low quality evidence from 12 RCTs (N=2229) suggested that for people in alcohol or drug treatment/recovery, tobacco abstinence at 13 weeks to 18 months was more successful with combined pharmacotherapy and counseling versus usual care or placebo RR 1.74 (95% CI 1.39 to 2.18).[2] The studies did not address differences between the individual pharmacological agents and data on adverse effects were limited.[2]

Another Cochrane review evaluated the effectiveness of various pharmacologic and behavioral strategies to assist smoking cessation in individuals younger than 20 years of age.[3] The primary outcome of interest was individual-level smoking cessation at six-month follow-up or longer.[3] Forty-one RCTs (N>13,000) were selected for review of which 4 identified pharmacologic interventions with either nicotine patches, nicotine gum, or bupropion.[3] The majority of the studies were judged to have unclear or high risk of bias in at least one domain.[3] Pooled results of nicotine replacement therapy studies failed to demonstrate significant differences in smoking cessation outcomes compared to placebo.[3] The analysis failed to find a statistically significant benefit of standard dose bupropion versus placebo either alone or in combination with NRT. [3]

A systematic review evaluated the effectiveness of smoking cessation interventions in patients with substance use disorders.[4] The primary outcome measure was self-reported continuous abstinence rates at 6 and 12 months verified biochemically. [4] The review included seventeen RCTs (N=2966) which focused on smoking cessation interventions in adult patients who recently completed or were in active treatment for substance use disorder with at least a 6-months follow-up. [4] Trial quality varied as many of the required details used in evaluation were not reported. [4] Interventions included counseling, NRT, cognitive behavioral treatment (CBT), motivational interviewing, bupropion or varenicline either alone or in combination.[4] For smokers with a history of alcohol dependence, one small study of found 21-mg nicotine patches significantly increased continuous abstinence at 6 months follow-up compared to a placebo patch (24% vs 6% respectively; NNT=6, p<.05). [4] A combination of behavioral support and medication was found to be beneficial in two studies that included substance use dependent patients. For outpatient alcohol-dependent smokers, one study of intensive therapy with 16 CBT sessions plus 16 weeks of nicotine patches plus 26 weeks of nicotine lozenges demonstrated at 6-months post-treatment, there was a statistically significant difference in point prevalence abstinence compared to a smoking cessation clinic referral (ARD 15%, p=0.03) but there was no significant difference observed at 12 months. [4] In stimulant dependent smokers, treatment for substance use plus weekly individualized counseling and bupropion resulted in a significantly higher point prevalence abstinence at 6 months compared to substance use treatment alone (25.5% vs 2.2% respectively; P < .001). [4] Eight of the studies failed to report a difference between smoking cessation interventions in substance use dependent patients at the 6 or 12-month follow-up time period. [4]

A systematic review and meta-analysis evaluated the cardiovascular safety of varenicline in adult tobacco users.[5] Thirty-eight RCTs (N=12,706) of mostly 12-weeks in duration compared varenicline 1 mg twice daily to placebo. [5] Primary clinical outcomes included cardiovascular serious adverse events (SAEs) and/or all-cause mortality within treatment period or within 30 days of discontinuation. [5] Four of the studies examined CVD patients, 17 trials studied smokers from the general population, 5 evaluated smokers with mental disorders, 3 studied patients with opioid or cocaine dependency, 4 studied smokeless tobacco, and 5 trials studied other patient features. [5] Roughly one-third of studies had unclear bias in sequence generation, one-third were unclear to high risk of bias for incomplete outcome data, and half of the studies had unclear allocation concealment. [5] However, the authors reported a low risk of bias for the majority of included trials. Pooled analysis found no significant difference in cardiovascular SAEs compared to placebo (RR 1.03, 95% CI 0.72–1.49; I^2=0%, p=0.9327). [5] Similarly, no significant difference in all-cause mortality was found in varenicline-treated patients versus placebo (RR 0.88, 95% CI 0.50–1.52; I^2=10.4%, p=0.3411). [5] The authors did not report sources of support for the included studies.[5]

A systematic review and meta-analysis evaluated the effectiveness of smoking cessation strategies in severe mentally ill patients.[6] Twenty-six RCTs trials were included for qualitative analysis of which 18 were pooled for meta-analysis.[6] The primary clinical outcome was self-reported smoking cessation with biochemical verification at short-term follow-up (4 weeks or less), mid-term (up to 6 months), or long-term (>6 months).[6] The majority of studies included patients with a diagnosis of schizophrenia or schizoaffective disorder, and two included patients with bipolar disorder.[6] Requirements for clinically stable symptoms or steady doses of medications widely varied or were not reported in the studies. [6] Eight pooled trials of bupropion compared to placebo showed significantly improved quit rates in the medium term (26.2% vs 8.3%, RR = 2.93 (95% CI 1.61–5.34)) and long term (16.5% vs 5%, RR = 3.04 (95% CI 1.10–8.42)). [6] The majority of trials did not find significant changes in psychiatric symptoms however adverse events were not reported in a standardized manner. [6] The authors concluded that no

significant worsening was found after smoking cessation, but results should be interpreted with caution due to the authors assessment that the included trials had an overall high risk or unclear risk of bias.[6]

A systematic review and meta-analysis examined the effectiveness of psychological, pharmacological, and combined smoking cessation interventions in patients with current depression.[7] The primary outcome was 7-day point prevalence abstinence at short term (up to 3 months) and long-term (6 months or longer) follow-up.[7] The impact of smoking cessation treatment on depression symptoms was also explored.[7] Twenty RCTs were identified (N=5,061), 14 of which involved either bupropion, varenicline, fluoxetine, or NRT. Pooled data demonstrated an overall favorable effect of pharmacotherapy vs placebo at ≤3 month follow-up (24.7 vs 19.7%, respectively; RR = 1.53 (95% CI = 1.29–1.81)) as well as the ≥6-month follow-up (19.9% vs 17.4%, respectively; RR = 1.59 (95% CI = 1.23–2.05)).[7] One trial compared the efficacy of sequential fluoxetine treatment, standard fluoxetine treatment and transdermal nicotine patch monotherapy in which point prevalence abstinence rates at 26 weeks after quitting were 40% and 15.4% and 23.5%, respectively (p=NA).[7] Nineteen of the 20 trials failed to detect a statistically significant difference in depression scores with smoking cessation treatment.[7] Due to substantial study heterogeneity and that almost half the included studies were rated as weak methodological quality, the authors could not make firm conclusions regarding the optimal smoking cessation treatment model in this population.[7]

After review, 14 systematic reviews were excluded due to poor quality, wrong study design of included trials, comparator, or outcome studied.

New Guidelines:
The National Institute for Health and Care Excellence (NICE) updated their guidelines in 2018 for brief advice, behavioral support, and pharmacotherapies for commissioners and providers of stop smoking support.[8] The following recommendations of evidence-based smoking interventions were provided:

- Ensure individual or group behavioral support is available and provided by stop smoking staff trained to the National Center for Smoking Cessation and Training (NCSCT) Standard (individual behavioral counselling) and preferably hold an appropriate counselling qualification.
- Ensure very brief advice (<30 seconds) given by frontline healthcare staff is delivered according to the NCSCT training manual on very brief advice.
- For adult smokers, prescribe bupropion, combination of short- and long-acting nicotine replacement therapy (NRT), or varenicline before they stop smoking.
    - Agree to a quit date set within the first 2 weeks of bupropion treatment and within the first 1 to 2 weeks of varenicline treatment. Reassess the person shortly before the prescription ends.
    - Agree to a quit date if NRT is prescribed. Ensure that the person has NRT ready to start the day before the quit date.
- Consider NRT for young people over 12 who are smoking and dependent on nicotine.
    - If NRT prescribed, offer it with behavioral support
- Consider text messaging as an adjunct to behavioral support

New Formulations:
None identified.

New FDA Safety Alerts:

The FDA made changes to the labeling of varenicline warning that the drug is not recommended for pediatric patients 16 years of age or younger because its efficacy in this population has not been demonstrated. [9] The warning is based on results from a placebo-controlled study in pediatric patients that examined two weight-adjusted doses of varenicline in pediatric patients mostly 12-16 years that found its use did not significantly increase abstinence rates. [9] In addition, the FDA alert communicated that adverse effects identified during post-approval use of Chantix™ were updated on the label which included neuropsychiatric adverse events, seizures, accidental injury, cardiovascular events, somnambulism, angioedema, hypersensitivity reactions, and increased alcohol effects. [9]

A late 2016 FDA safety communication had removed black box warnings for both Chantix™ and Zyban™ labels regarding risk of serious side effects on mood, behavior, and thinking. [10] Although the risk of mental health side effects is still present, especially in those with past or current treatment for mental illness, the FDA determined that the benefits of smoking cessation outweigh the potential harms caused by the medications. [10] See **Table 1** for a summary of the FDA alerts.

Table 1. Description of New FDA Safety Alerts[9,10]

Generic Name	Brand Name	Month / Year of Change	Type of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
varenicline	Chantix™	2/2019	Product label update	Drug is not recommended for pediatric patients 16 years of age or younger because its efficacy in this population has not been demonstrated. Adverse effects identified during post-approval period included neuropsychiatric adverse events, seizures, accidental injury, cardiovascular events, somnambulism, angioedema, hypersensitivity reactions, and increased alcohol effects.
varenicline	Chantix™	12/16/2016	Removal of Boxed Warning and risk evaluation and mitigation strategy (REMS) requirement	Removed Boxed Warning for serious mental health side effects from the Chantix drug label. Removed risk evaluation and mitigation strategy (REMS) that formally required Medication Guide Added clarification that risk of serious mental health side effects is present but lower than previously suspected. Updated warning section on label that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial.

Bupropion SR	Zyban™	12/16/2016	Removed language from the Boxed Warning section and risk evaluation and mitigation strategy (REMS) that required Medication Guide	Removed language describing the serious mental health side effects seen in patients quitting smoking from the Boxed Warning section. Removed risk evaluation and mitigation strategy (REMS) that formally required Medication Guide. Added clarification that risk of serious mental health side effects is present but lower than previously suspected. Updated warning section on label that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial.

References:

1. van Eerd EA, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2016(8):CD010744.
2. Apollonio D, Philipps R, Bero L. Interventions for tobacco use cessation in people in treatment for or recovery from substance use disorders. *Cochrane Database Syst Rev.* 2016;11:CD010274.
3. Fanshawe TR, Halliwell W, Lindson N, Aveyard P, Livingstone-Banks J, Hartmann-Boyce J. Tobacco cessation interventions for young people. *The Cochrane database of systematic reviews.* 2017;11:CD003289.
4. Thurgood SL, McNeill A, Clark-Carter D, Brose LS. A Systematic Review of Smoking Cessation Interventions for Adults in Substance Abuse Treatment or Recovery. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2016;18(5):993-1001.
5. Sterling LH, Windle SB, Filion KB, Touma L, Eisenberg MJ. Varenicline and Adverse Cardiovascular Events: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2016;5(2).
6. Peckham E, Brabyn S, Cook L, Tew G, Gilbody S. Smoking cessation in severe mental ill health: what works? an updated systematic review and meta-analysis. *BMC psychiatry.* 2017;17(1):252.
7. Secades-Villa R, Gonzalez-Roz A, Garcia-Perez A, Becona E. Psychological, pharmacological, and combined smoking cessation interventions for smokers with current depression: A systematic review and meta-analysis. *PloS one.* 2017;12(12):e0188849.
8. National Institute for Health and Care Excellence (NICE). Stop smoking interventions and services. https://www.nice.org.uk/guidance/ng92/chapter/Recommendations. Published 2018, March. Accessed May 2, 2019.
9. United States Food and Drug Administration. FDA in Brief: FDA updates label for Chantix with data underscoring it's not effective in children 16 and younger. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-label-chantix-data-underscoring-its-not-effective-children-16-and-younger. Published 2019, February 22. Accessed May 2, 2019.

10. United States Food and Drug Administration. FDA Drug Safety Communication: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-description-mental-health-side-effects-stop-smoking. Published 2016, December 16. Accessed May 2, 2019.
11. Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA.* 2016;315(4):371-379.
12. Benowitz NL, Pipe A, West R, et al. Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial. *JAMA Intern Med.* 2018;178(5):622-631.
13. Eisenberg MJ, Windle SB, Roy N, et al. Varenicline for Smoking Cessation in Hospitalized Patients With Acute Coronary Syndrome. *Circulation.* 2016;133(1):21-30.
14. Nanovskaya TN, Oncken C, Fokina VM, et al. Bupropion sustained release for pregnant smokers: a randomized, placebo-controlled trial. *Am J Obstet Gynecol.* 2017;216(4):420 e421-420 e429.
15. Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. *BMC medicine.* 2016;14:80.
16. Smith RC, Amiaz R, Si T-M, et al. Varenicline Effects on Smoking, Cognition, and Psychiatric Symptoms in Schizophrenia: A Double-Blind Randomized Trial. *PloS one.* 2016;11(1):e0143490.
17. Rose JE, Behm FM. Combination Varenicline/Bupropion Treatment Benefits Highly Dependent Smokers in an Adaptive Smoking Cessation Paradigm. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2017;19(8):999-1002.
18. Foa EB, Asnaani A, Rosenfield D, Zandberg LJ, Gariti P, Imms P. Concurrent varenicline and prolonged exposure for patients with nicotine dependence and PTSD: A randomized controlled trial. *Journal of consulting and clinical psychology.* 2017;85(9):862-872.
19. Murphy CM, MacKillop J, Martin RA, Tidey JW, Colby SM, Rohsenow DJ. Effects of varenicline versus transdermal nicotine replacement therapy on cigarette demand on quit day in individuals with substance use disorders. *Psychopharmacology.* 2017;234(16):2443-2452.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	Route	PDL
bupropion HCl	BUPROPION HCL SR	TAB ER 12H	ORAL	Y
bupropion HCl	ZYBAN	TAB ER 12H	ORAL	Y
nicotine	NICOTINE PATCH	PATCH DYSQ	TRANSDERM	Y
nicotine	NICODERM CQ	PATCH TD24	TRANSDERM	Y
nicotine	NICOTINE	PATCH TD24	TRANSDERM	Y
nicotine	NICOTINE PATCH	PATCH TD24	TRANSDERM	Y
nicotine	NTS	PATCH TD24	TRANSDERM	Y
nicotine polacrilex	NICORELIEF	GUM	BUCCAL	Y
nicotine polacrilex	NICORETTE	GUM	BUCCAL	Y
nicotine polacrilex	NICOTINE GUM	GUM	BUCCAL	Y
nicotine polacrilex	QUIT 2	GUM	BUCCAL	Y
nicotine polacrilex	QUIT 4	GUM	BUCCAL	Y

nicotine polacrilex	COMMIT	LOZENGE	BUCCAL	Y
nicotine polacrilex	NICORETTE	LOZENGE	BUCCAL	Y
nicotine polacrilex	NICOTINE LOZENGE	LOZENGE	BUCCAL	Y
nicotine polacrilex	QUIT 2	LOZENGE	BUCCAL	Y
nicotine polacrilex	QUIT 4	LOZENGE	BUCCAL	Y
nicotine polacrilex	STOP SMOKING AID	LOZENGE	BUCCAL	Y
nicotine polacrilex	NICORETTE	LOZNG MINI	BUCCAL	Y
nicotine polacrilex	NICOTINE LOZENGE	LOZNG MINI	BUCCAL	Y
varenicline tartrate	CHANTIX	TAB DS PK	ORAL	Y
varenicline tartrate	CHANTIX	TABLET	ORAL	Y
nicotine	NICOTROL	CARTRIDGE	INHALATION	N
nicotine	NICOTROL NS	SPRAY	NASAL	N

Appendix 2: New Comparative Clinical Trials

A total of 17 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design, comparator, or outcome studied. The remaining 9 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Baker, et al. [11] OL, RCT	Varenicline vs C-NRT (nicotine patch + nicotine lozenges) vs nicotine patch	Adult smokers (≥ 5 cpd) (n=1086)	7-day point prevalence abstinence at 26 weeks, confirmed with CO levels	Abstinence rates at 26 weeks: varenicline: 23.6% C-NRT: 26.8% Nicotine Patch: 22.8% NS for all group comparisons
Benowitz, et al.[12] DB, PC, RCT	Varenicline and bupropion vs nicotine patch or placebo	Smokers, with or without established psychiatric diagnoses (n=8058)	Time to development of a major adverse cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) during 12-week treatment	Time to development of MACE over 12 weeks varenicline: hazard ratio, 0.29; 95% CI, 0.05-1.68 bupropion: hazard ratio, 0.50; 95% CI, 0.10-2.50 NS for time to onset of MACE for either varenicline or bupropion treatment vs placebo
Eisenberg, et al.[13] DB, PC, RCT	Varenicline vs placebo	Adult smokers hospitalized with acute	7-day point-prevalence smoking abstinence assessed at 24 weeks confirmed with CO levels	Abstinence rates at 24 weeks varenicline: 47.3% placebo: 32.5% RD 14.8; 95% CI 3.9 to 25.8; p=0.012

		coronary syndrome (n=302)		
Nanovskaya, et al.[14] DB, PC, RCT	Bupropion SR vs placebo	Adult pregnant female smokers (n=65)	7-day point-prevalence smoking abstinence assessed at 12 weeks and at end of pregnancy confirmed by CO levels; symptom relief during treatment	Abstinence rates at 12 weeks bupropion:17% placebo: 3% P=0.087 Abstinence rates at end of pregnancy bupropion:10% placebo: 3% P=0.328 NS findings between groups for total nicotine withdrawal symptoms and tobacco cravings (P=0.068 and 0.08, respectively)
Tulloch, et al. [15] OL, RCT	NRT (nicotine patches) vs. Extended NRT (high-dose nicotine patches plus nicotine gum or inhalers ad libitum) vs. varenicline	Adult smokers (≥10 cpd) (n=737)	Continuous abstinence rate during weeks 5–52 confirmed by CO levels	Abstinence rates for weeks 5-52 NRT: 10% Extended NRT: 12.4% varenicline: 15.3% P>0.025 NS for group comparisons
Smith, et al.[16] DB, PC, RCT	Varenicline vs. placebo	Adult smokers (≥6 cpd) with schizophrenia or schizoaffective disorder on antipsychotic therapy and RBANS scores <90 (n=91)	Change in cognitive performance as assessed by the MATRICS Consensus Cognitive Battery by week 8 of drug treatment.	Change from baseline in MATRICS Battery Scores by week 8: Varenicline: -0.19 +/- 2.14 Placebo: +1.67 +/- 1.86 NS (p=0.511)

Rose, et al.[17] DB, PC, RCT	Varenicline + bupropion vs. varenicline + placebo	Adult male smokers (CPD ≥10) stratified based on previous response to NRT (n=174)	Number of participants completing continuous 4-week smoking abstinence at weeks 8–11 after the target quit date confirmed by CO levels.	Overall abstinence rates at weeks 8-11 for NRT non-responders Varenicline + bupropion: 42% Varenicline + placebo: 41% p-value not reported Overall abstinence rates at weeks 8-11 for NRT responders Varenicline + bupropion: 56% Varenicline + placebo: 51% p-value not reported
Foa, et al.[18] RCT, DB, DP	Varenicline and smoking cessation counseling (VARCC) + prolonged exposure (PE) therapy vs VARCC only	Adults with nicotine dependence and PTSD (n=142)	7-day point prevalence abstinence post-treatment at 3 and 6 months verified by CO levels	Abstinence rates at 3 months: VARCC + PE: 20% VARCC only: 6% (p=NS) Abstinence rates at 6 months: VARCC + PE: 9.8% VARCC only: 1.8% (p=NS)
Murphy, et al.[19] RCT, QB, DP	NRT patch vs. varenicline for smoking cessation	Adult smokers with substance use disorder (SUD) (n=110)	7 -day smoking cessation at 1 and 3 months confirmed by expired alveolar CO levels of < 10 ppm or salivary cotinine < 16 ng/ml	Abstinence rates at 1 month: Varenicline: 10% NRT: 18% (NS) Abstinence rates at 3 months: Varenicline: 15% NRT: 4% (NS)

Abbreviations: CO=carbon monoxide; CPD=cigarettes per day; C-NRT=combination nicotine replacement therapy; DB=double blind; DP=Double Placebo; HIS=Heaviness of Smoking Index; MATRICS=Measurement and Treatment Research to Improve Cognition in Schizophrenia; NRT=nicotine replacement therapy; NS = Non-significant; OR=odds ratio; OL=open-label; PC=placebo controlled; PTSD=post-traumatic stress disorder; QB=quadruple blind; RCT=randomized clinical trial; RBANS=Repeatable Battery For The Assessment Of Neuropsychological Status; SUD=substance use disorder

Appendix 3: Abstracts of Comparative Clinical Trials

Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial
Baker TB, Piper, ME, Stein, JH, Smith, S, Bolt, DM, Fraser, DL, Fiore, MC.

IMPORTANCE: Smoking cessation medications are routinely used in health care; it is vital to identify medications that most effectively treat this leading cause of preventable mortality., OBJECTIVE: To compare the efficacies of varenicline, combination nicotine replacement therapy (C-NRT), and the nicotine patch for 26-week quit rates., DESIGN, SETTING, AND PARTICIPANTS: Three-group randomized intention-to-treat clinical trial occurring from May 2012 to November 2015 among smokers recruited in the Madison, Wisconsin, and Milwaukee, Wisconsin, communities; 65.5% of smokers offered the study (2687/4102) refused participation prior to randomization., INTERVENTIONS: Participants were randomized to one of three 12-week open-label smoking cessation pharmacotherapy groups: (1) nicotine patch only (n = 241); (2) varenicline only (including 1 prequit week; n = 424); and (3) C-NRT (nicotine patch + nicotine lozenge; n = 421). Six counseling sessions were offered., MAIN OUTCOMES AND MEASURES: The primary outcome was carbon monoxide-confirmed self-reported 7-day point-prevalence abstinence at 26 weeks. Secondary outcomes were carbon monoxide-confirmed self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at weeks 4, 12, and 52., RESULTS: Among 1086 smokers randomized (52% women; 67% white; mean age, 48 years; mean of 17 cigarettes smoked per day), 917 (84%) provided 12-month follow-up data. Treatments did not differ on any abstinence outcome measure at 26 or 52 weeks, including point-prevalence abstinence at 26 weeks (nicotine patch, 22.8% [55/241]; varenicline, 23.6% [100/424]; and C-NRT, 26.8% [113/421]) or at 52 weeks (nicotine patch, 20.8% [50/241]; varenicline, 19.1% [81/424]; and C-NRT, 20.2% [85/421]). At 26 weeks, the risk differences for abstinence were, for patch vs varenicline, -0.76% (95% CI, -7.4% to 5.9%); for patch vs C-NRT, -4.0% (95% CI, -10.8% to 2.8%); and for varenicline vs C-NRT, -3.3% (95% CI, -9.1% to 2.6%). All medications were well tolerated, but varenicline produced more frequent adverse events than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion., CONCLUSIONS AND RELEVANCE: Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 weeks. The results raise questions about the relative effectiveness of intense smoking pharmacotherapies.

Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial
Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM.

Importance: Quitting smoking is enhanced by the use of pharmacotherapies, but concerns have been raised regarding the cardiovascular safety of such medications. Objective: To compare the relative cardiovascular safety risk of smoking cessation treatments. Design, Setting, and Participants: A double-blind, randomized, triple-dummy, placebo- and active-controlled trial (Evaluating Adverse Events in a Global Smoking Cessation Study [EAGLES]) and its nontreatment extension trial was conducted at 140 multinational centers. Smokers, with or without established psychiatric diagnoses, who received at least 1 dose of study medication (n = 8058), as well as a subset of those who completed 12 weeks of treatment plus 12 weeks of follow up and agreed to be followed up for an additional 28 weeks (n = 4595), were included. Interventions: Varenicline, 1 mg twice daily; bupropion hydrochloride, 150 mg twice daily; and nicotine replacement therapy, 21-mg/d patch with tapering. Main Outcomes and Measures: The primary end point was the time to development of a major adverse cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) during treatment; secondary end points were the occurrence of MACE and other pertinent cardiovascular events (MACE+: MACE or new-onset or worsening peripheral vascular disease requiring intervention, coronary revascularization, or hospitalization for unstable angina). Results: Of the 8058 participants, 3553 (44.1%) were male (mean [SD] age, 46.5 [12.3] years). The incidence of cardiovascular events during treatment and follow-up was low (<0.5% for MACE; <0.8% for MACE+) and did not differ significantly by treatment.

No significant treatment differences were observed in time to cardiovascular events, blood pressure, or heart rate. There was no significant difference in time to onset of MACE for either varenicline or bupropion treatment vs placebo (varenicline: hazard ratio, 0.29; 95% CI, 0.05-1.68 and bupropion: hazard ratio, 0.50; 95% CI, 0.10-2.50). Conclusions and Relevance: No evidence that the use of smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment was observed. The findings of EAGLES and its extension trial provide further evidence that smoking cessation medications do not increase the risk of serious cardiovascular events in the general population of smokers.

Varenicline for Smoking Cessation in Hospitalized Patients With Acute Coronary Syndrome

Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, Cassavar D, Dion D, Haught H, Mehta SR, Baril JF, Lambert C, Madan M, Abramson BL, Dehghani P, Evita Investigators.

BACKGROUND: Less than one-third of smokers hospitalized with an acute coronary syndrome (ACS) remain abstinent following discharge. We assessed whether varenicline, begun in-hospital, is efficacious for smoking cessation following ACS. METHODS AND RESULTS: We conducted a multi-center, double-blind, randomized, placebo-controlled trial in which smokers hospitalized with an ACS were randomized to varenicline or placebo for 12 weeks. All patients received low-intensity counseling. The primary end point was point-prevalence smoking abstinence assessed at 24 weeks by 7-day recall and biochemical validation using expired carbon monoxide. A total of 302 patients were randomized (mean age 55+/-9 years; 75% male; 56% ST-segment elevation myocardial infarction; 38% non-ST-segment elevation myocardial infarction; 6% unstable angina). Patients smoked a mean of 21+/-11 cigarettes/d at the time of hospitalization and had been smoking for a mean of 36+/-12 years. At 24 weeks, patients randomized to varenicline had significantly higher rates of smoking abstinence and reduction than patients randomized to placebo. Point-prevalence abstinence rates were 47.3% in the varenicline group and 32.5% in the placebo group (P=0.012; number needed to treat=6.8). Continuous abstinence rates were 35.8% and 25.8%, respectively (P=0.081; number needed to treat=10.0), and rates of reduction >/=50% in daily cigarette consumption were 67.4% and 55.6%, respectively (P=0.05; number needed to treat=8.5). Adverse event rates within 30 days of study drug discontinuation were similar between groups (serious adverse events: varenicline 11.9%, placebo 11.3%; major adverse cardiovascular events: varenicline 4.0%, placebo 4.6%). CONCLUSIONS: Varenicline, initiated in-hospital following ACS, is efficacious for smoking cessation. Future studies are needed to establish safety in these patients.

Bupropion sustained release for pregnant smokers: a randomized, placebo-controlled trial
Nanovskaya TN, Oncken C, Fokina VM, Feinn RS, Clark SM, West H, Jain SK, Ahmed MS, Hankins GDV.

BACKGROUND: Bupropion is used to treat depression during pregnancy. However, its usefulness as a smoking cessation aid for pregnant women is not fully known. OBJECTIVE: The objective of the study was to evaluate the preliminary efficacy of bupropion sustained release for smoking cessation during pregnancy. STUDY DESIGN: We conducted a randomized, prospective, double-blind, placebo-controlled, pilot trial. Pregnant women who smoked daily received individualized behavior counseling and were randomly assigned to a 12 week, twice-a-day treatment with 150 mg bupropion sustained release or placebo. The primary study objectives were to determine whether bupropion sustained release reduces nicotine withdrawal symptoms on the quit date and during the treatment period compared with placebo and whether it increases 7 day point prevalence abstinence at the end of the treatment period and at the end of pregnancy. RESULTS: Subjects in the bupropion (n = 30) and placebo (n = 35) groups were comparable in age, smoking history, number of daily smoked cigarettes, and nicotine dependence. After controlling for maternal age and race, bupropion sustained release reduced cigarette cravings (1.5 +/- 1.1 vs 2.1 +/- 1.2, P = .02) and total nicotine withdrawal symptoms (3.8 +/- 4.3 vs 5.4 +/- 5.1, P = .028) during the treatment period. Administration of bupropion sustained release reduced tobacco exposure, as determined by levels of carbon monoxide in exhaled air (7.4 +/- 6.4 vs 9.1 +/- 5.8, P = .053) and concentrations of cotinine

in urine (348 +/- 384 ng/mL vs 831 +/- 727 ng/mL, P = .007) and increased overall abstinence rates during treatment (19% vs 2%, P = .003). However, there was no significant difference in 7 day point prevalence abstinence rates between the 2 groups at the end of medication treatment (17% vs 3%, P = .087) and at the end of pregnancy (10% vs 3%, P = .328). CONCLUSION: Individual smoking cessation counseling along with the twice-daily use of 150 mg bupropion sustained release increased smoking cessation rates and reduced cravings and total nicotine withdrawal symptoms during the treatment period. However, there was no significant difference in abstinence rates between groups at the end of medication treatment and at the end of pregnancy, likely because of the small sample size. A larger study is needed to confirm these findings and to examine the potential benefit/ risk ratio of bupropion sustained release for smoking cessation during pregnancy.

Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial
Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD.

BACKGROUND: Extended use of combined pharmacotherapies to treat tobacco dependence may increase smoking abstinence; few studies have examined their effectiveness. The objective of this study was to evaluate smoking abstinence with standard nicotine patch (NRT), extended use of combined formulations of nicotine replacement therapy (NRT+), or varenicline (VR)., METHODS: A total of 737 smokers, including those with medical and psychiatric comorbidities, were randomly assigned to one of the above three treatment conditions. The NRT group received 10 weeks of patches (21 mg daily maximum); the NRT+ group received patches (35 mg daily maximum) and gum or inhaler for up to 22 weeks; and the VR group received 1 mg twice daily for up to 24 weeks (22 weeks post target quit date). All participants also received six standardized 15-minute smoking cessation counseling sessions by nurses experienced in tobacco dependence treatment. The primary outcome was carbon monoxide-confirmed continuous abstinence rates (CAR) from weeks 5-52. Secondary outcomes were: CAR from weeks 5-10 and 5-22, and carbon monoxide-confirmed 7-day point prevalence (7PP) at weeks 10, 22, and 52. Adjusted and unadjusted logistic regression analyses were conducted using intention-to-treat procedures., RESULTS: The CARs for weeks 5-52 were 10.0 %, 12.4 %, and 15.3 % in the NRT, NRT+, and VR groups, respectively; no group differences were observed. Results with 7PP showed that VR was superior to NRT at week 52 (odds ratio (OR), 1.84; 97.5 % Confidence Interval (CI), 1.04-3.26) in the adjusted intention-to-treat analysis. Those in the VR group had higher CAR at weeks 5-22 (OR, 2.01; CI, 1.20-3.36) than those in the NRT group. Results with 7PP revealed that both NRT+ (OR, 1.72; CI, 1.04-2.85) and VR (OR, 1.96; CI, 1.20-3.23) were more effective than NRT at 22 weeks. As compared to NRT monotherapy, NRT+ and VR produced significant increases in CAR for weeks 5-10 (OR, 1.52; CI, 1.00-2.30 and OR, 1.58; CI, 1.04-2.39, respectively); results were similar, but somewhat stronger, when 7PP was used at 10 weeks (OR, 1.57; CI, 1.03-2.41 and OR, 1.79; CI, 1.17-2.73, respectively). All medications were well tolerated, but participants in the VR group experienced more fatigue, digestive symptoms (e.g., nausea, diarrhea), and sleep-related concerns (e.g., abnormal dreams, insomnia), but less dermatologic symptoms than those in the NRT or NRT+ groups. The frequency of serious adverse events did not differ between groups., CONCLUSIONS: Flexible and combination NRT and varenicline enhance success in the early phases of quitting. Varenicline improves abstinence in the medium term; however, there is no clear evidence that either varenicline or flexible, dual-form NRT increase quit rates in the long-term when compared to NRT monotherapy.

Varenicline Effects on Smoking, Cognition, and Psychiatric Symptoms in Schizophrenia: A Double-Blind Randomized Trial
Smith RC, Amiaz R, Si TM, Maayan L, Jin H, Boules S, Sershen H, Li C, Ren J, Liu Y, Youseff M, Lajtha A, Guidotti A, Weiser M, Davis, JM.

Schizophrenic patients have a high rate of smoking and cognitive deficits which may be related to a decreased number or responsiveness of nicotinic receptors in their brains. Varenicline is a partial nicotinic agonist which is effective as an antismoking drug in cigarette smokers, although concerns have been raised about potential psychiatric side-effects. We conducted a double-blind placebo controlled study in 87 schizophrenic smokers to evaluate the effects of varenicline (2 mg/day) on measures of smoking, cognition, psychiatric symptoms, and side-effects in schizophrenic patients who were cigarette smokers. Varenicline

significantly decreased cotinine levels (P<0.001), and other objective and subjective measures of smoking (P < .01), and responses on a smoking urges scale (P = .02), more than placebo. Varenicline did not improve scores on a cognitive battery designed to test the effect of drugs on cognitive performance in schizophrenia (the MATRICS battery), either in overall MATRICS battery Composite or individual Domain scores, more than placebo. There were no significant differences between varenicline vs. placebo effects on total symptom scores on psychiatric rating scales, PANSS, SANS, or Calgary Depression scales, and there were no significant drug effects in any of these scales sub-scores when we used Benjamin-Hochberg corrected significance levels (alpha = .05). Varenicline patients did not show greater side-effects than placebo treated patients at any time point when controlled for baseline side-effect scores. Our study supports the use of varenicline as a safe drug for smoking reduction in schizophrenia but not as a cognitive enhancer.

Combination Varenicline/Bupropion Treatment Benefits Highly Dependent Smokers in an Adaptive Smoking Cessation Paradigm
Rose JE, Behm FM.

Introduction: This study replicated and extended results of a previous trial, which found that combination varenicline/bupropion treatment increased smoking abstinence in smokers who were male, highly dependent, and who did not respond to prequit nicotine patch treatment with a >50% reduction in expired-air carbon monoxide in the first week., Methods: One hundred and twenty-two male nicotine patch nonresponders and 52 responders were identified. Smokers in each group were randomized to receive 12 weeks of varenicline plus bupropion treatment versus varenicline plus placebo. The primary outcome was continuous smoking abstinence at weeks 8-11 after the target quit date., Results: For smokers with a high level of dependence, judged by having a baseline Fagerstrom Test for Nicotine Dependence (FTND) score >= 6 and cigarette consumption >= 20/d, combination varenicline/bupropion treatment increased the abstinence rate relative to varenicline alone: 71.0% versus 43.8% (odds ratio = 3.14; 95% confidence interval = 1.11-8.92, p [one tailed] = .016). In contrast, less dependent smokers did not show a benefit of combination treatment relative to varenicline (abstinence rates of 32.1% vs. 45.6%, respectively); there was a significant interaction of treatment and dependence level. Patch nonresponders tended to benefit the most from combination treatment, which was well tolerated overall., Conclusions: Combination varenicline/bupropion treatment proved significantly more efficacious than varenicline alone among highly dependent male smokers. These results, together with prior studies, support an adaptive treatment paradigm that assigns smoking cessation treatment according to baseline smoker characteristics and initial response to nicotine patch treatment., Implications: This study replicated, in a prospective manner, an important and surprising retrospective finding from a previous clinical trial, which showed that a specific subpopulation of smokers benefited substantially from receiving a combination treatment of varenicline plus bupropion, relative to varenicline plus placebo. Specifically, male smokers having high baseline nicotine dependence (FTND score >= 6 and cigarette consumption >= 20/d), showed a marked increase in smoking abstinence rate on combination pharmacotherapy. The present study likewise found an enhancement in end-of-treatment abstinence rate in this subgroup, from 43.8% to 71.0%. The adaptive treatment paradigm, which classifies smokers based on initial dependence level and response to prequit nicotine patch treatment, may be used to identify target populations of smokers whose success can be enhanced by intervening with combination pharmacotherapy before the quit-smoking date.

Concurrent varenicline and prolonged exposure for patients with nicotine dependence and PTSD: A randomized controlled trial
Foa EB, Asnaani A, Rosenfield D, Zandberg LJ, Gariti P, Imms P.

BACKGROUND: Prevalence of smoking among individuals with posttraumatic stress disorder (PTSD) is disproportionately high, and PTSD is associated with especially poor response to smoking cessation treatment., OBJECTIVE: The current study examined whether integrating treatments for smoking cessation (varenicline plus smoking cessation counseling; VARCC) and PTSD (prolonged exposure therapy; PE) enhances smoking outcomes among smokers diagnosed with PTSD., METHOD: 142 adults with nicotine dependence (ND) and PTSD were randomized to a treatment program consisting of varenicline, smoking cessation counseling, and PE (VARCC + PE) or to VARCC only. Seven-day point prevalence abstinence (PPA) at posttreatment (3-months postquit day) and follow-up (6-

months postquit day), verified by serum cotinine levels and exhaled carbon monoxide, was the primary smoking outcome. Psychological outcomes were PTSD and depression severity. Mixed effects models included baseline PTSD severity as a moderator of treatment condition effects., RESULTS: Overall, VARCC + PE participants did not show greater PPA than VARCC participants. However, treatment effects were moderated by baseline PTSD severity. For participants with moderate and high PTSD severity, VARCC + PE led to significantly higher PPA than VARCC alone (ps<.05). No differences between treatment conditions emerged for participants with low baseline PTSD severity. Participants who received PE showed significantly greater reduction of PTSD and depression symptoms than those who did not receive PE., CONCLUSIONS: Integrating psychological treatment for PTSD and smoking cessation treatment enhances smoking cessation for participants with moderate or severe PTSD symptom severity, but does not enhance smoking cessation for participants with low baseline PTSD severity.

Effects of varenicline versus transdermal nicotine replacement therapy on cigarette demand on quit day in individuals with substance use disorders
Murphy CM, MacKillop J, Martin RA,Tidey JW, Colby SM, Rohsenow DJ.

RATIONALE: Cigarette demand is a behavioral economic measure of the relative value of cigarettes. Decreasing the value of cigarette reinforcement may help with quitting smoking., OBJECTIVES: This study aimed to evaluate the effects of initial use of varenicline (VAR) versus nicotine replacement therapy (NRT) on demand for cigarettes on quit day among smokers with substance use disorders (SUD) and to determine whether reduced demand was associated with subsequent abstinence from smoking at 1 and 3 months., METHODS: Participants (N = 110) were randomized to double-blind, double-placebo conditions: VAR with placebo NRT or NRT with placebo capsules. The cigarette purchase task (CPT) was used to assess demand for cigarettes at baseline and on quit day, following a 1-week medication dose run-up/placebo capsule lead-in and first day use of the patch., RESULTS: Demand for cigarettes decreased from baseline to quit day without significant differences between medications. Reductions in CPT intensity (number of cigarettes that would be smoked if they were free) and CPT breakpoint (lowest price at which no cigarettes would be purchased) predicted greater likelihood of abstaining on quit day. Reduced intensity predicted length of abstinence at 1 and 3 months while reduced breakpoint predicted only 1 month length of abstinence., CONCLUSIONS: Initial therapeutic doses of VAR and NRT resulted in similar reductions in cigarette reinforcement. Larger initial reductions in demand on quit day were associated with early success with abstaining from cigarettes. Behavioral economic approaches may be useful for identifying individuals who benefit less from pharmacotherapy and may need additional treatment resources.,

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 5 2019

1 nicotinic agonists.mp. or Nicotinic Agonists/7477
2 tobacco cessation products.mp./7
3 nicotine replacement.mp./2815
4 smoking cessation.mp. or Smoking Cessation/33408
5 "tobacco use disorder".mp. or "Tobacco Use Disorder"/10776
6 nicotine gum.mp./638
7 nicotine lozenge.mp. or "Tobacco Use Cessation Devices"/1633
8 nicotine patch.mp. or "Tobacco Use Cessation Devices"/2268
9 nicoderm.mp./25
10 nicotine spray.mp./39
11 bupropion.mp. or Bupropion/4289
12 varenicline.mp. or Varenicline/1527

13 1 or 2 or 3 or 6 or 7 or 8 or 9 or 10 or 11 or 12/14687
14 4 or 5/39341
15 13 and 14/5943
16 limit 15 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) 297
17 from 16 keep 1, 5, 8, 16-17, 33, 35.../62
18 from 17 keep 1-2, 4-7, 11, 13-21, 24-25, 27-33.../45
19 from 18 keep 1-2, 4-7, 9-36, 38-45 /42
20 from 19 keep 1-4, 6-14, 16-19, 21-27, 29-42 /38
21 nicotinic agonists.mp. or Nicotinic Agonists/7477
22 tobacco cessation products.mp. /7
23 nicotine replacement.mp./ 2815
24 smoking cessation.mp. or Smoking Cessation/33408
25 "tobacco use disorder".mp. or "Tobacco Use Disorder"/10776
26 nicotine gum.mp. /638
27 nicotine lozenge.mp. or "Tobacco Use Cessation Devices"/1633
28 nicotine patch.mp. or "Tobacco Use Cessation Devices"/2268
29 nicoderm.mp./25
30 nicotine spray.mp./39
31 bupropion.mp. or Bupropion/4289
32 varenicline.mp. or Varenicline/ 1527
33 21 or 22 or 23 or 26 or 27 or 28 or 29 or 30 or 31 or 32/14687
34 24 or 25/39341
35 33 and 34/5943
36 limit 35 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))/297
37 from 36 keep 1, 5, 8, 16-17, 33, 35.../62
38 from 37 keep 1-2, 4-7, 11, 13-21, 24-25, 27-33.../45
39 from 38 keep 1-2, 4-7, 9-36, 38-45 /42
40 from 39 keep 1-4, 6-14, 16-17, 19-27, 29-42 /38

Appendix 5: 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 July 2016 to July 2019
Setting	Inpatient hospital or outpatient clinics; worldwide

Appendix 6: Prior Authorization Criteria

Smoking Cessation

Goal(s):

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

Length of Authorization:

- 3-6 months

Requires PA:

- Non-preferred drugs
- Nicotine replacement therapy (NRT) for more than 6 months in the absence of behavioral counseling
- Varenicline treatment for more than 12 weeks or for patients less than 17 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 diagnosis for tobacco dependence (ICD10 F17200)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for a preferred NRT product?	**Yes:** Go to #6	**No:** Go to #4
4. Is the request for varenicline?	**Yes:** Go to #5	**No:** Go to #8
5. Is the patient at least 17 years of age?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Has patient quit?	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Go to #7
7. 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 additional months or approve varenicline for 12 additional weeks	**No:** Pass to RPh. Deny; medical appropriateness
8. Will the prescriber change to a preferred product? Message: • Preferred products do not require a PA for initial treatment. • 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:** Approve treatment for up to 6 months

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