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Class Update: Tobacco Cessation Products

Date of Review: July 2016 **Date of Last Review:** March 2014

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

Purpose for Class Update:
Smoking is a significant public health problem that can be associated with substantial health care costs and can cause many preventable diseases including cancers, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD). This review will evaluate current comparative effectiveness evidence to assist in establishing recommendations for the therapeutic agents indicated for smoking cessation.

Research Questions:
1. Is there new comparative evidence for differences in efficacy or effectiveness or safety of pharmacologic agents for the treatment of tobacco cessation?
2. Is there evidence that long term nicotine replacement therapy beyond 12 weeks is more effective in promoting tobacco abstinence?
3. Are there specific subpopulations based on severity of addiction or other disease characteristics that may benefit more from a specific drug or combination of drugs?

Conclusions:
- There is high quality evidence of a benefit of combined pharmacotherapy and behavioral treatment compared to usual care, brief advice, or less intensive support (RR 1.83; 95% CI 1.68 to 1.98).[1]
- There is high quality evidence that varenicline improves continuous or sustained abstinence compared to placebo (RR 2.24; 95% CI 2.06 to 2.43; NNT 11) and bupropion (RR 1.39; 95% CI 1.25 to 1.54), and moderate quality evidence compared to nicotine patches (RR RR 1.25; 95% CI 1.14 to 1.37).[2] There is also high quality evidence that compared to placebo, patients on varenicline experience more serious adverse events (RR 1.25; 95% CI 1.04 to 1.49).
- There is low quality and inconsistent evidence that the combination of varenicline and nicotine replacement therapy (NRT) is favorable on abstinence rates compared to varenicline alone (44% vs. 35.1%; OR 1.50; 95% CI 1.13 to 1.97).[3]
- There is evidence that increasing varenicline dose (up to 5 mg/day) in smokers with low response to standard dose (2 mg/day) does not improve smoking cessation at 12 weeks compared to standard dose (26% vs. 23%; OR 1.19; 95% CI 0.62-2.28) after the target quit date (TQD) and significantly increases nausea (80% vs. 18%; NNH 2) and vomiting (36% vs. 3%; NNH 3).[4]
- There is insufficient evidence that NRT improves prolonged abstinence rates in pregnant women who continue to smoke.[5,6] There is low quality evidence that infants born to mothers using nicotine replacement therapy (NRT) are more likely to have survived without any impairment than pregnant women who smoker on placebo (OR 1.40; 95% CI 1.05 to 1.86).[6]

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- There is low quality evidence that in certain patient populations, including those with serious mental illness, maintenance pharmacotherapy (52 weeks) with varenicline may improve prolonged tobacco abstinence rates at 52 weeks.[7] There is also low quality evidence based on one randomized controlled trial[8] that a "reduce-to-quit" approach with 24 weeks of varenicline may be more effective than placebo for continuous abstinence rates (RR 4.6; 95% CI 3.5 to 6.1) through 24 weeks. There is also low quality evidence that varenicline improves abstinence compared to placebo in patients who have had a prior quit attempt with varenicline (45% vs. 11.8%; OR 7.08; 95% CI 4.34 to 11.55).[9]
- There is moderate quality evidence that NRT, bupropion and varenicline are not associated with an increase in major adverse cardiovascular events (MACE) and an increase in minor events including palpitations and tachycardia with NRT (RR 1.89; 95% CI 1.31 to 2.73).[10]
- There is low quality evidence that there is no significant difference in neuropsychiatric adverse events between varenicline, placebo, bupropion or nicotine patches in both patients with and without a history of psychiatric disorders.[11] These results may not be generalizable to those with unstable or untreated psychiatric disorders.

Recommendations:

- No changes are warranted to current PDL based on new comparative evidence. Evaluate comparative costs in the executive session.

Previous Conclusions:

- No further review or research needed at this time; update PA criteria.

Previous Recommendations:

- Add Nicotine replacement therapy (NRT) products including the patch, gum and lozenges as preferred drugs on the PDL with a quantity limit for six months of treatment.
- Due to no differences in safety or efficacy between the NRT products, evaluate comparative costs for further decisions.
- Make bupropion sustained release (Zyban) a preferred drug.
- Make varenicline a preferred agent on the PDL with a quantity limit for twelve weeks of treatment within 6 months.
- Require prior authorization criteria for non-preferred products, NRT beyond 6 months in the absence of behavioral counseling, and varenicline beyond 12 weeks requiring the patient has quit for a second fill of varenicline and that the patient is enrolled in a smoking cessation behavioral counseling program in addition to medication therapy.

Background:

Tobacco use is a leading preventable cause of morbidity and premature death worldwide. [3] It is well confirmed that smoking increases risk of respiratory disease, CVD, diabetes mellitus, autoimmune disorders, reproductive system disorders, and many kinds of cancers.[3] Tobacco addiction is caused by the nicotine, which causes a release of dopamine stimulating a pleasurable effect from smoking.[12] There is strong and consistent evidence that tobacco dependence interventions, if delivered in a timely and effective way, can significantly reduce the user's risk of tobacco-related disease. [1] High quality evidence has demonstrated that the most effective method for smoking cessation is the combination of pharmacologic treatment and behavioral support.[13] Tobacco dependence is a chronic disease that often requires repeated interventions and multiple attempts to quit. Current guidelines recommend that clinicians strongly recommend the use of effective tobacco dependence counseling in combination with medication treatments to patients who use tobacco, and that health systems, insurers, and purchasers assist clinicians in making such effective treatments available.[14]

First-line medications for tobacco dependence include NRT, bupropion SR, and varenicline. [14] Bupropion blocks reuptake of dopamine, resulting in increased dopamine in the mesolimbic "reward center" that mimics nicotine. Varenicline is a partial nicotinic agonist that acts on $\alpha_4\beta_2$ nicotinic receptors.[4] Activation of this receptor reduces withdrawal symptoms and also affects the "reward center". All of these agents have shown to be effective in combination with behavioral interventions for achieving abstinence in patients willing and ready to quit, with similar effect sizes for a minimum of 12 weeks. [14] Patient preference, experience with certain agents, and side effects should be considered when choosing a specific pharmacologic regimen. The use of certain combinations of medications have also demonstrated efficacy in certain patients. Nicotine replacement therapy consists of short-acting agents (gum, lozenge and inhaler) that are titrated to control urges to smoke and other withdrawal symptoms and a long-acting agent, the nicotine patch.

The rate of smoking in people with psychiatric illness remains a difficult population to successfully treat. The rate of smoking in people with schizophrenia is estimated to be 2-4 times of that in the general population.[15] Most studies have excluded this population and so there are limited data on the effectiveness of smoking cessation therapies in those with psychiatric disorders. Smoking during pregnancy can be harmful to women and infants, but the safety and efficacy of smoking cessation medications in pregnancy is unknown. Behavioral support interventions as well as financial incentives appear to be effective in this population.[5] NRT appears to be cautiously accepted for use in pregnancy but there are no data to support the safety of bupropion or varenicline in this population.

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 use beyond 12 weeks. In 2015, approximately half of the PA requests were denied. The U.S. Public Health Service tobacco guideline recommends that health insurers include smoking cessation treatment as a covered service. One retrospective cohort analysis of pharmacy claims data found that about half of the patients did not fill any smoking cessation medication following a rejected varenicline claim.[16]

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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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 nicotine receptor partial agonists, including varenicline for smoking cessation.[2] RCTs comparing varenicline to placebo, bupropion and nicotine patches were included. Thirty-nine varenicline trials were included demonstrating high quality evidence for improved continuous or sustained abstinence at 6 months or longer of (RR 2.24; 95% CI 2.06 to 2.43) with a number needed to treat (NNT) of 11 (95% CI 9 to 13). [2] There was also high quality evidence from 5 trials that varenicline improved cessation rates compared to bupropion (RR 1.39; 95% CI 1.25 to 1.54) and moderate quality evidence compared to nicotine patches (RR 1.25; 95% CI 1.14 to 1.37; 8 trials). [2] Four trials evaluated varenicline beyond the standard 12-

week regimen and found it to be safe and well tolerated. Lastly, limited evidence suggests that varenicline may have a role in relapse prevention (RR 3.64; 95% CI 2.81 to 4.72). There was also high quality evidence that patients on varenicline experienced more serious adverse events than those on placebo (RR 1.25; 95% CI 1.04 to 1.49). This review included the recent EAGLES trial[11] which did not show significant difference in neuropsychiatric adverse events between varenicline and placebo, bupropion, or NRT. A pooled analysis of 4 trials found varenicline to be beneficial in smokers with a psychiatric disorder (RR 2.28; 95% CI 1.82 to 2.87). [2]

A systematic review and meta-analysis of RCTs was conducted to evaluate the efficacy and safety of varenicline combined with NRT to achieve abstinence.[3] There were 3 studies (n=904) that compared combination therapy with varenicline plus the nicotine patch versus varenicline alone that were included in the systematic review and meta-analysis. All 3 trials excluded subjects who were breastfeeding or pregnant, and who had current psychiatric illness. One study administered the trial patch 2 weeks before the targeted quit date, while the other 2 studies started the patch on the targeted quite date. None of the 3 studies took place in the U.S., and one study used a 15 mg/16 hours patch while the others used the more common dose of 21 mg/24 hours. Varenicline was titrated up to 2 mg daily and continued for 12 weeks and all studies provided concurrent behavioral counseling. Abstinence was confirmed using measured exhaled carbon monoxide. The overall quality of the included studies was deemed high. Overall, there was a favorable effect on early abstinence rates (4-12 weeks) with combination therapy versus varenicline alone (44.4% vs. 35.1%; OR 1.50; 95% CI 1.14 to 1.97). Two studies measured late abstinence (up to 24 weeks) and also showed a significant increase in the abstinence rate (32.4% vs. 23.1%; OR 1.62; 95% CI 1.18 to 2.23). In terms of safety, the combination therapy reported more nausea, insomnia, and abnormal dreams compared to varenicline; however, none of these differences reached statistical significance. The small number of trials in a non-US population limits the generalizability of the results. However, the methodology of the systematic review was strong.

Although the benefits of smoking cessation are widely known and supported by the literature, there has been a renewed concern that smoking cessation medications are associated with an increased risk of CVD. A meta-analysis was conducted to examine whether NRT, bupropion, and varenicline are associated with an increased risk in CVD.[10] There was no increased risk in CVD seen with bupropion (RR 0.98; 95% CI 0.54-1.74; 28 RCTs) or varenicline (RR 1.30; 95% CI 0.79 to 2.23; 18 RCTs), although there was an elevated risk associated with NRT (RR 2.29; 95% CI 1.39 to 3.82; 21 RCTs). These data were driven predominantly by less serious events (RR 1.89; 95% CI 1.31 to 2.73) with the most commonly reported adverse event being heart palpitations and tachycardia. There was no evidence of an increase in major adverse cardiovascular events (MACE) with NRT (RR 1.95; 95% CI 0.26 to 4.30), and bupropion appeared to protect against the risk of MACE relative to both NRT (RR 0.23; 95% CI 0.08 to 0.63) and varenicline (RR 0.33; 95% CI 0.16 to 0.87). There was also no significant increase risk in MACE with NRT in trials that only included high-risk CV patients (RR 1.53; 95% CI 0.38 to 6.24). However, overall rates of MACE were low, resulting in wide confidence intervals.

A Cochrane systematic review compared pharmacological interventions (including NRT, varenicline and bupropion) for smoking cessation during pregnancy.[5] A total of 9 trials (n=2210) of pregnant smokers were included. Eight trials included NRT (6 with the patch, one with gum, and one offered a choice) and one trialed bupropion as an adjunct to behavioral support. The bupropion trial had recruitment issues and was only able to recruit 11 subjects and was too small to make any conclusions regarding bupropion use. No trials evaluated the use of varenicline in pregnant subjects. The overall risk of bias was low. Compared to placebo and control groups, there was a decrease in smoking rates later in pregnancy with NRT (RR 1.41; 95% CI 1.03 to 1.93). However, a subgroup of only placebo-controlled trials did not demonstrate a benefit on smoking rates (RR 1.28; 95% CI 0.99 to 1.66) though heterogeneity between studies was substantially reduced. A subgroup with non-placebo controlled trials, however, demonstrated efficacy with NRT (RR 8.51; 95% CI 2.05 to 35.28) but with a wide confidence interval. Studies that reported adherence found that this was generally low and the majority of subjects did not use the NRT that was prescribed to them. A sensitivity analysis relating to adherence could not be done as trials reported adherence so differently. In addition, there was no evidence that NRT was effective in continued abstinence from smoking after childbirth (RR 1.15; 95% CI 0.75 to 1.77). There were no differences between NRT and control groups in

rates of miscarriage, stillbirth, premature birth, birthweight, low birthweight, admissions to neonatal intensive care, congenital abnormalities or neonatal death. The authors concluded that NRT used in pregnancy increase smoking cessation rates measured in late pregnancy by approximately 40% but there is evidence suggesting that when potentially biased, non-placebo RTCs are excluded, NRT is no more effective than placebo.

Another Cochrane systematic review from March 2016 evaluated the efficacy of combined pharmacotherapy and behavioral interventions compared to a minimal intervention or usual care for smoking cessation.[1] The primary outcome was abstinence from smoking after at least 6 months of follow up. Fifty-two studies (n=19,488) provided high quality evidence of a benefit of combined pharmacotherapy (most provided NRT) and behavioral treatment compared to usual care, brief advice, or less intensive support (RR 1.83; 95% CI 1.68 to 1.98) with moderate heterogeneity. Many of the trials were conducted in a healthcare setting (RR 1.97; 95% CI 1.79 to 2.18) and most counselling and support was provided by specialist cessation counsellors or trained personnel. How the intervention was delivered varied among the trials (telephone versus face to face, uptake of treatment optional versus required, etc.). There were no differences found in subgroups based on motivation to quit, treatment provider, number or duration of sessions, or take-up of treatment. The Lung Health Study was excluded from the meta-analysis due to the particularly intensive behavioral intervention provided to subjects. However, this type of intervention resulted in an even larger treatment effect for smoking cessation (RR 3.88; 95% CI 3.35 to 4.5). The authors concluded that interventions that combine pharmacotherapy and behavioral support increase smoking cessation success compared to a minimal intervention or usual care.

New Guidelines:
The U.S. Preventive Services Task Force (USPSTF) updated guidelines on interventions for tobacco smoking cessation in adults, including pregnant women. [17] The following main recommendations are provided:

- For all adults, behavioral interventions and FDA-approved pharmacotherapy should be offered for smoking cessation treatment (Grade A recommendation).
- For pregnant women, behavioral interventions should be provided for all pregnant women who continue to use tobacco (Grade A recommendation).
- The current evidence is insufficient to assess the benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women (Grade I statement).
- The current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. (Grade I statement)

New Safety Alerts:
The FDA made changes to the labeling of varenicline warning that it may react with alcohol and result in decreased tolerance, increased drunkenness or unusual aggressive behavior. The warning is based on 48 case reports. Rare reports of seizures were also reported, most of which occurred during the first month after starting varenicline. None of the cases involved excessive amounts of alcohol.[18] Patients should understand the risks of varenicline with alcohol before starting treatment.

Previous warning and precaution labeling for varenicline on the risk of neuropsychiatric side effects was also updated based on Pfizer data and observational studies that found adverse neuropsychiatric effects were not increased with use of varenicline.[18] However, the studies have inherent limitations preventing strong and reliable conclusions to be made. Since this FDA update, a recent RCT (n=8144) corroborated these findings and found no significant increase in neuropsychiatric adverse events from varenicline or buproprion compared to the nicotine patch or placebo.[11]

New Formulations or Indications:
None identified.

Randomized Controlled Trials:
A total of 188 citations were manually reviewed from the literature search. After further review, 176 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 12 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Hajek, et al.[4] DB, RCT, PC	1. Standard Dose Varenicline (2 mg/day) + placebo add on versus 2. varenicline add-on (up to 5 mg/day) started 21 days before their TQD	Varenicline nonresponders (no strong nausea, no clear reduction in smoking enjoyment, less than 50% reduction in their baseline smoking) (n=200)	Self-rated Smoking enjoyment	<u>12-week continued abstinence</u> 1. 23 (23%) 2. 26 (26%) OR 1.19; 95% CI 0.62-2.28); p=0.61 <u>Nausea</u> 1. 18 (18%) 2. 80 (80%) RR 4.4 (2.99-6.7); P<0.001 <u>Vomiting</u> 1. 3 (3%) 2. 36 (36%) RR 12 (95% CI 3.8-48.3); p<0.001
Schnoll, et al.[19] RCT,open-label	Standard (8 week) nicotine patch vs. extended (24 week) vs. maintenance (52 weeks) + behavioral counseling	Adults who smoke at least 10 cigarettes per day and interested in cessation (n=525)	7-day point prevalence abstinence, confirmed with CO levels	<u>24 week abstinence:</u> Standard: 21.7% Extended/Maintenance: 27.2% P=0.17 <u>Multivariate model controlled for covariates; abstinence rates</u> Extended/Maintenance versus standard: OR 1.70; 95% CI 1.02-2.81 <u>52 week abstinence:</u> Standard/extended: 23.8% Maintenance: 20.3% P=0.44; OR 1.17; 95% CI 0.69-1.90
Baker, et al.[20]	Nicotine patch (NRT)	Adult smokers (≥ 5 CPD),	7-day point prevalence	<u>26 week abstinence:</u>

RCT, OL	vs. varenicline vs. C-NRT (nicotine patch + nicotine lozenge)	desire to quit smoking but not engaged in treatment x 12 weeks (n=1086)	abstinence at 26 weeks, confirmed with CO levels	NRT 22.8% C-NRT: 26.8% RD -4.0%; (95% CI -10.8%-2.8%) NRT 22.8% Var: 23.6% RD -0.76%(95% CI -7.4%-5.9%)
Ebbert, et al.[8] RCT, DB, PC	Varenicline 1 mg BID x 24 weeks vs. placebo	Adult smokers who were not able to quit smoking now but willing to reduce (reduction in 50% by 4 weeks) and make a quit attempt within next 12 weeks (n=1510)	CO confirmed abstinence during weeks 15 through 24	<u>Continuous abstinence rates during weeks 15 through 24:</u> Var: 32.1% Pla: 6.9% RR 4.6; 95% CI 3.5-6.1 <u>Continuous abstinence rates during weeks 24 through 52:</u> Var: 27% Pla: 9.9% RR 2.7; 95% CI 2.1-3.5
Ramon, et al.[21] DB, PC, RCT	Varenicline + nicotine patch 21 mg versus varenicline + placebo patch x 12 weeks With background behavioral counseling	Smokers (≥20 cpd) (n=341)	Continuous abstinence for weeks 2 through 12	<u>Continuous abstinence:</u> Var + NRT: 32.8% VAR: 28.2% OR 1.17; 95% CI 0.4 to 1.9
SNAP[6] DB, PC, RCT	Nicotine patch vs. placebo over 2 years	Pregnant smokers (≥5 cpd currently/ ≥10 cpd prior to pregnancy) (n=1050)	Self-reported prolonged abstinence between TQD and childbirth	<u>Prolonged smoking cessation</u> NRT: 9.4% Pla: 7.6% OR 1.26; 95% CI 0.82 to 1.96 There was a significant improvement at 1 month with NRT that was not sustained until delivery <u>Infant outcomes at 2 years (no impairment):</u> NRT: 72.5% Pla: 65.5% OR 1.40; 95% CI 1.05 to 1.86
Gonzales, et al.[9] RCT, DB, PC	Varenicline vs placebo for 12 weeks	Adult smokers (≥10 cpd) with ≥ 1 prior quit attempt using varenicline and no quit	Continued abstinence rates	<u>Continued abstinence rates (weeks 9-12):</u> Var: 45% Pla: 11.8%

		attempts in ≤ 3 months (n=498)		OR 7.08; 95% CI 4.34 to 11.55 <u>Prolonged abstinence (weeks 9-52):</u> Var: 20.1% Pla: 3.3% OR 9.00; 95% CI 3.97 to 20.41
Chengappa, et al.[22] RCT, DB, PC	Varenicline vs. placebo x 12 weeks	Adults with bipolar disorder; smoking more than 10 CPD and a willingness to quit (n=60)	Abstinence at 12 weeks	<u>Abstinence at 12 weeks</u> Var: 15/31 (48.4%) Pla: 3/29 (10.3%) OR 8.13; 95% CI 2.03-32.53
Koegelenberg, et al.[23] DB, RCT, PC	Nicotine patch + varenicline vs. placebo patch + varenicline x 12 weeks	Adult smokers (n=446)	Continued abstinence weeks 9 to 12	<u>Continued abstinence weeks 9 to 12:</u> NRT + Var: 55.4% Pla + Var: 40.9% OR 1.85; 95% CI 1.19-2.89
Scherprof[24] DB, RCT	Nicotine patch versus placebo x 6-9 weeks	Adolescents aged 12-18 years who smoke at least 7 cpd (n=362)	Abstinence rates at 6 and 12 months	<u>Abstinence rates at 6 months</u> NRT: 8.1% Pla: 5.7% (p=NS) <u>Abstinence rates at 12 months</u> NRT: 8.1% Pla: 8.2% (p=NS)
Ebbert, et al.[25] RCT, DB, PC	Varenicline + bupropion SR vs. varenicline + placebo x 12 weeks	Adults smoking at least 10 cpd for at least 6 months and were motivated to quit (n=506)	Abstinence rates at week 12	<u>Abstinence rates at week 12</u> Var + bup: 53% Var + pla: 43.2% OR 1.49; 95% CI 1.05-2.12 <u>Abstinence rates at week 52</u> Var + bup: 30.9% Var + pla: 24.5% OR 1.39; 95% CI 0.93-2.07
Evins, et al.[7] RCT, DB, PC, PG	Continued varenicline vs. placebo from weeks 12 to 52	Smokers with schizophrenia or bipolar disease who had 2 weeks or more of continuous abstinence at week 12 after 12 weeks' open-label varenicline and behavioral therapy	7 day rate of continuous abstinence at study week 52	<u>Abstinence rates at week 52:</u> Var: (60%) Pla: (19%) OR 6.2; 95% CI 2.2-19.2

EAGLES trial[11] RCT, DB, PC	Varenicline and bupropion vs. nicotine patch or placebo for 12 weeks with 12-week non-treatment follow-up	Motivated to quit smokers with and without psychiatric disorders (n=8144)	Incidence of a composite measure of moderate to severe neuropsychiatric adverse events	<u>Non-psychiatric cohort:</u> Var: 13 (1.3%) Bup: 22 (2.2%) NRT: 25 (2.5%) Pla: 24 (2.4%) NS for all group comparisons	<u>Psychiatric cohort:</u> Var: 67 (6.5%) Bup: 68 (6.7%) NRT: 53 (5.2%) Pla: 50 (4.9%) NS for all group comparisons

Abbreviations: CO = carbon monoxide; CPD = cigarettes per day; DB = double blind; NRT = nicotine replacement therapy; C-NRT = combination nicotine replacement therapy; OL = open label; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; TQD = target quit date; RD = risk difference; Var = varenicline

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22. Chengappa KNR, Perkins KA, Brar JS, et al. Varenicline for smoking cessation in bipolar disorder: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*. 2014;75(7):765-772. doi:10.4088/JCP.13m08756.

23. Koegelenberg CFN, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA*. 2014;312(2):155-161. doi:10.1001/jama.2014.7195.

24. Scherphof CS, van den Eijnden RJJM, Engels RCME, Vollebergh WAM. Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. *Drug & Alcohol Dependence*. July 2014:217-220. doi:10.1016/j.drugalcdep.2014.04.007.

25. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA*. 2014;311(2):155-163. doi:10.1001/jama.2013.283185.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET ER	BUPROPION HCL SR	BUPROPION HCL	Y
ORAL	TABLET ER	ZYBAN	BUPROPION HCL	Y
BUCCAL	GUM	NICORELIEF	NICOTINE POLACRILEX	Y
BUCCAL	GUM	NICORETTE	NICOTINE POLACRILEX	Y
BUCCAL	GUM	NICOTINE GUM	NICOTINE POLACRILEX	Y
BUCCAL	LOZENGE	NICORETTE	NICOTINE POLACRILEX	Y
BUCCAL	LOZENGE	NICOTINE LOZENGE	NICOTINE POLACRILEX	Y
TRANSDERM	PATCH DYSQ	NICOTINE PATCH	NICOTINE	Y
TRANSDERM	PATCH TD24	NICODERM CQ	NICOTINE	Y
TRANSDERM	PATCH TD24	NICOTINE PATCH	NICOTINE	Y
ORAL	TAB DS PK	CHANTIX	VARENICLINE TARTRATE	Y
ORAL	TABLET	CHANTIX	VARENICLINE TARTRATE	Y
INHALATION	CARTRIDGE	NICOTROL	NICOTINE	Y
NASAL	SPRAY	NICOTROL NS	NICOTINE	Y

Appendix 2: Abstracts of Clinical Trials

1. Hajek P, McRobbie H, Myers Smith K, Phillips A, Cornwall D, Dhanji AR. Increasing varenicline dose in smokers who do not respond to the standard dosage: a randomized clinical trial. *JAMA Intern Med.* 2015 Feb;175(2):266-71.

IMPORTANCE: Standard varenicline tartrate dosing was formulated to avoid adverse effects (primarily nausea), but some patients may be underdosed. To our knowledge, no evidence-based guidance exists for physicians considering increasing varenicline dose if there is no response to the standard dosage.

OBJECTIVE: To determine whether increasing varenicline dose in patients showing no response to the standard dosage improves treatment efficacy.

DESIGN, SETTING, AND PARTICIPANTS: In a double-blind randomized placebo-controlled trial, 503 smokers attending a stop smoking clinic commenced varenicline use 3 weeks before their target quit date (TQD). Two hundred participants reporting no strong nausea, no clear reduction in smoking enjoyment, and less than 50% reduction in their baseline smoking on day 12 received additional tablets of varenicline or placebo.

INTERVENTIONS: All participants began standard varenicline tartrate dosing, gradually increasing to 2 mg/d. Dose increases of twice-daily varenicline (0.5 mg) or placebo took place on days 12, 15, and 18 (up to a maximum of 5 mg/d).

MAIN OUTCOMES AND MEASURES: Participants rated their smoking enjoyment during the prequit period and withdrawal symptoms weekly for the first 4 weeks after the TQD. Continuous validated abstinence rates were assessed at 1, 4, and 12 weeks after the TQD.

RESULTS: The dose increase reduced smoking enjoyment during the prequit period, with mean (SD) ratings of 1.7 (0.8) for varenicline vs 2.1 (0.7) for placebo (P = .001). It had no effect on the mean (SD) frequency of urges to smoke at 1 week after the TQD, their strength, or the severity of withdrawal symptoms: these ratings for varenicline vs placebo were 2.7 (1.1) vs 2.6 (0.9) (P = .90), 2.6 (1.1) vs 2.8 (1.0) (P = .36), and 1.5 (0.4) vs 1.6 (0.5) (P = .30), respectively. The dose increase also had no effect on smoking cessation rates for varenicline vs placebo at 1 week (37 [37.0%] vs 48 [48.0%], P = .14), 4 weeks (51 [51.0%] vs 59 [59.0%], P = .32), and 12 weeks (26 [26.0%] vs 23 [23.0%], P = .61) after the TQD. There was significantly more nausea (P < .001) and vomiting (P < .001) reported in the varenicline arm than in the placebo arm.

CONCLUSIONS AND RELEVANCE: Increasing varenicline dose in smokers with low response to the drug had no significant effect on tobacco withdrawal symptoms or smoking cessation. Physicians often consider increasing the medication dose if there is no response to the standard dosage. This approach may not work with varenicline.

2. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement therapy: a randomized clinical trial. JAMA Intern Med. 2015 Apr;175(4):504-11. doi: 10.1001/jamainternmed.2014.8313.

IMPORTANCE: The US Food and Drug Administration adopted labeling for nicotine patches to allow use beyond the standard 8 weeks. This decision was based in part on data showing increased efficacy for 24 weeks of treatment. Few studies have examined whether the use of nicotine patches beyond 24 weeks provides additional therapeutic benefit.

OBJECTIVE: To compare 8 (standard), 24 (extended), and 52 (maintenance) weeks of nicotine patch treatment for promoting tobacco abstinence.

DESIGN, SETTING, AND PARTICIPANTS: We recruited 525 treatment-seeking smokers for a randomized clinical trial conducted from June 22, 2009, through April 15, 2014, through 2 universities.

INTERVENTIONS: Smokers received 12 smoking cessation behavioral counseling sessions and were randomized to 8, 24, or 52 weeks of nicotine patch treatment.

MAIN OUTCOMES AND MEASURES: The primary outcome was 7-day point prevalence abstinence, confirmed with breath levels of carbon monoxide at 6 and 12 months (intention to treat).

RESULTS: At 24 weeks, 21.7% of participants in the standard treatment arm were abstinent, compared with 27.2% of participants in the extended and maintenance treatment arms ($\chi(2)(1) = 1.98$; P = .17). In a multivariate model controlled for covariates, participants in the extended and maintenance treatment arms reported significantly greater abstinence rates at 24 weeks compared with participants in the standard treatment arm (odds ratio [OR], 1.70 [95% CI, 1.03-2.81]; P = .04), had a longer duration of abstinence until relapse ($\beta = 21.30$ [95% CI, 10.30-32.25]; P < .001), reported smoking fewer cigarettes per day if not abstinent (mean [SD], 5.8 [5.3] vs 6.4 [5.1] cigarettes per day; $\beta = 0.43$ [95% CI, 0.06-0.82]; P = .02), and reported more abstinent days (mean [SD], 80.5 [38.1] vs 68.2 [43.7] days; OR, 1.55 [95% CI, 1.06-2.26]; P = .02). At 52 weeks, participants in the maintenance treatment arm did not report significantly greater abstinence rates compared with participants in the standard and extended treatment arms (20.3% vs 23.8%; OR, 1.17 [95% CI, 0.69-1.98]; P = .57). Similarly, we found no difference in week 52 abstinence rates between participants in the extended and standard treatment arms (26.0% vs 21.7%; OR, 1.33 [95% CI, 0.72-2.45]; P = .36). Treatment duration was not associated with any adverse effects or adherence to the counseling regimen, but participants in the maintenance treatment arm reported lower adherence to the nicotine patch regimen compared with those in the standard and extended treatment arms (mean [SD], 3.94 [2.5], 4.61 [2.0], and 4.7 [2.4] patches/wk, respectively; $F_{2,522} = 6.03$; P = .003).

CONCLUSIONS AND RELEVANCE: The findings support the safety of long-term use of nicotine patch treatment, although they do not support efficacy beyond 24 weeks of treatment in a broad group of smokers.

3. Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA*. 2016 Jan 26;315(4):371-9.

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.

4. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, Treadow J, Yu CR, Dutro MP, Park PW. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. JAMA. 2015 Feb 17;313(7):687-94.

IMPORTANCE: Some cigarette smokers may not be ready to quit immediately but may be willing to reduce cigarette consumption with the goal of quitting.

OBJECTIVE: To determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled, multinational clinical trial with a 24-week treatment period and 28-week follow-up conducted between July 2011 and July 2013 at 61 centers in 10 countries. The 1510 participants were cigarette smokers who were not willing or able to quit smoking within the next month but willing to reduce smoking and make a quit attempt within the next 3 months. Participants were recruited through advertising.

INTERVENTIONS: Twenty-four weeks of varenicline titrated to 1 mg twice daily or placebo with a reduction target of 50% or more in number of cigarettes smoked by 4 weeks, 75% or more by 8 weeks, and a quit attempt by 12 weeks.

MAIN OUTCOMES AND MEASURES: Primary efficacy end point was carbon monoxide-confirmed self-reported abstinence during weeks 15 through 24. Secondary outcomes were carbon monoxide-confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52.

RESULTS: The varenicline group (n = 760) had significantly higher continuous abstinence rates during weeks 15 through 24 vs the placebo group (n = 750) (32.1% for the varenicline group vs 6.9% for the placebo group; risk difference (RD), 25.2% [95% CI, 21.4%-29.0%]; relative risk (RR), 4.6 [95% CI, 3.5-6.1]). The varenicline group had significantly higher continuous abstinence rates vs the placebo group during weeks 21 through 24 (37.8% for the varenicline group vs 12.5% for the placebo group; RD, 25.2% [95% CI, 21.1%-29.4%]; RR, 3.0 [95% CI, 2.4-3.7]) and weeks 21 through 52 (27.0% for the varenicline group vs 9.9% for the placebo group; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]). Serious adverse events occurred in 3.7% of the varenicline group and 2.2% of the placebo group (P = .07).

CONCLUSIONS AND RELEVANCE: Among cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months, use of varenicline for 24 weeks compared with placebo significantly increased smoking cessation rates at the end of treatment, and also at 1 year. Varenicline offers a treatment option for smokers whose needs are not addressed by clinical guidelines recommending abrupt smoking cessation.

5. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. *BMC Med.* 2014 Oct 8;12:172.

BACKGROUND: Some smokers may benefit from a therapy that combines different nicotine replacement therapies (NRT) or drugs with different mechanisms of action. The aim of this study was to determine the efficacy of the combined therapy of varenicline and nicotine patches versus varenicline monotherapy.

METHODS: Three hundred forty-one smokers who smoked 20 or more cigarettes per day were recruited from a smoking cessation clinic between February 2012 and June 2013. The participants were randomized to receive a varenicline plus nicotine patch of 21 mg every 24 hours (170) or varenicline plus a placebo patch (171). All of the smokers received a standard 12-week course of varenicline and an 11-week course of either the placebo patch or the active patch after the

target quit day. Both groups received behavioral support. The primary outcome was continuous abstinence for weeks 2 through 12 confirmed by exhaled levels of carbon monoxide. Post hoc subgroup analyses were performed to evaluate the treatment effects for a specific endpoint in subgroups of smokers.

RESULTS: The combination of the nicotine patch with varenicline was not associated with higher rates of continuous abstinence at 12 weeks (39.1% versus 31.8%; odds ratio (OR) 1.24; 95% confidence interval (CI) 0.8 to 2.6) and 24 weeks (32.8% versus 28.2%; OR 1.17; 95% CI 0.4 to 1.9). When participants were analyzed by subgroups according to cigarette consumption, the abstinence rates among smokers who smoked more than 29 cigarettes per day at 12 weeks (OR 1.39; 95% CI 1.2 to 2.5) and 24 weeks (OR 1.46; 95% CI 1.2 to 2.8) were significantly higher in the combination group. Other post hoc analyses based on level of dependence and previous quit attempts did not show subgroup differences. No differences between the groups for the reported adverse events were observed ($\chi 2$ value 0.07; P 0.79).

CONCLUSIONS: The combination of varenicline with the nicotine patch does not improve abstinence rates at 12 and 24 weeks compared with varenicline used as monotherapy when all smokers were analyzed as a whole, independent of consumption level.

6. Cooper S, Lewis S, Thornton JG, Marlow N′ et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy--clinical effectiveness and safety until 2 years after delivery, with economic evaluation. *Health Technol Assess.* 2014 Aug;18(54):1-128.

BACKGROUND: Smoking during pregnancy causes many adverse pregnancy and birth outcomes. Nicotine replacement therapy (NRT) is effective for cessation outside pregnancy but efficacy and safety in pregnancy are unknown. We hypothesised that NRT would increase smoking cessation in pregnancy without adversely affecting infants.

OBJECTIVES: To compare (1) at delivery, the clinical effectiveness and cost-effectiveness for achieving biochemically validated smoking cessation of NRT patches with placebo patches in pregnancy and (2) in infants at 2 years of age, the effects of maternal NRT patch use with placebo patch use in pregnancy on behaviour, development and disability.

DESIGN: Randomised, placebo-controlled, parallel-group trial and economic evaluation with follow-up at 4 weeks after randomisation, delivery and until infants were 2 years old. Randomisation was stratified by centre and a computer-generated sequence was used to allocate participants using a 1 : 1 ratio. Participants, site pharmacies and all study staff were blind to treatment allocation.

SETTING: Seven antenatal hospitals in the Midlands and north-west England.

PARTICIPANTS: Women between 12 and 24 weeks' gestation who smoked ≥ 10 cigarettes a day before and ≥ 5 during pregnancy, with an exhaled carbon monoxide (CO) reading of ≥ 8 parts per million (p.p.m.).

INTERVENTIONS: NRT patches (15 mg per 16 hours) or matched placebo as an 8-week course issued in two equal batches. A second batch was dispensed at 4 weeks to those abstinent from smoking.

MAIN OUTCOME MEASURES: PARTICIPANTS: self-reported, prolonged abstinence from smoking between a quit date and childbirth, validated at delivery by CO measurement and/or salivary cotinine (COT) (primary outcome). Infants, at 2 years: absence of impairment, defined as no disability or problems with behavior and development. Economic: cost per 'quitter'.

RESULTS: One thousand and fifty women enrolled (521 NRT, 529 placebo). There were 1010 live singleton births and 12 participants had live twins, while there were 14 fetal deaths and no birth data for 14 participants. Numbers of adverse pregnancy and birth outcomes were similar in trial groups, except for a greater number of caesarean deliveries in the NRT group. Smoking: all participants were included in the intention-to-treat (ITT) analyses; those lost to follow-up (7% for primary outcome) were assumed to be smoking. At 1 month after randomisation, the validated cessation rate was higher in the NRT group {21.3% vs. 11.7%, odds ratio [OR], [95% confidence interval (CI)] for cessation with NRT, 2.05 [1.46 to 2.88]}. At delivery, there was no difference between groups' smoking cessation rates: 9.4% in the NRT and 7.6% in the placebo group [OR (95% CI), 1.26 (0.82 to 1.96)]. Infants: at 2 years, analyses were based on data from 888 out of 1010 (87.9%) singleton infants (including four postnatal infant deaths) [445/503 (88.5%) NRT, 443/507 (87.4%) placebo] and used multiple imputation. In the NRT group, 72.6% (323/445) had no impairment compared with 65.5% (290/443) in placebo (OR 1.40, 95% CI 1.05 to 1.86). The incremental cost-effectiveness ratio for NRT use was £4156 per quitter (£4926 including twins), but there was substantial uncertainty around these estimates.

CONCLUSIONS: Nicotine replacement therapy patches had no enduring, significant effect on smoking in pregnancy; however, 2-year-olds born to women who used NRT were more likely to have survived without any developmental impairment. Further studies should investigate the clinical effectiveness and safety of higher doses of NRT.

7. Gonzales D, Hajek P, Pliamm L, Nackaerts K, Tseng LJ, McRae TD, Treadow J. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. *Clin Pharmacol Ther*. 2014 Sep;96(3):390-6.

The efficacy and safety of retreatment with varenicline in smokers attempting to quit were evaluated in this randomized, double-blind, placebo-controlled, multicenter trial (Australia, Belgium, Canada, the Czech Republic, France, Germany, the United Kingdom, and the United States). Participants were generally healthy adult smokers (≥ 10 cigarettes/day) with ≥ 1 prior quit attempt (≥ 2 weeks) using varenicline and no quit attempts in ≤ 3 months; they were randomly assigned (1:1) to 12 weeks' varenicline (n = 251) or placebo (n = 247) treatment, with individual counseling, plus 40 weeks' nontreatment follow-up. The primary efficacy end point was the carbon monoxide-confirmed (≤ 10 ppm) continuous abstinence rate for weeks 9-12, which was 45.0% (varenicline; n = 249) vs. 11.8% (placebo; n = 245; odds ratio: 7.08; 95% confidence interval: 4.34, 11.55; P < 0.0001). Common varenicline group adverse events were nausea, abnormal dreams, and headache, with no reported suicidal behavior. Varenicline is efficacious and well tolerated in smokers who have previously taken it. Abstinence rates are comparable with rates reported for varenicline-naive smokers.

8. Chengappa KN, Perkins KA, Brar JS, Schlicht PJ, Turkin SR, Hetrick ML, Levine MD, George TP.Varenicline for smoking cessation in bipolar disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2014 Jul;75(7):765-72.

OBJECTIVE: Virtually no clinical trials for smoking cessation have been undertaken in bipolar disorder. Varenicline has shown efficacy for smoking cessation, but warnings about neuropsychiatric adverse events have been issued. We assessed the efficacy and safety of varenicline in euthymic bipolar subjects motivated to quit smoking.

METHOD: Clinically stable adult patients with DSM-IV bipolar disorder (n = 60) who smoked ≥ 10 cigarettes per day were randomized to a 3-month, double-blind, placebo-controlled varenicline trial and a 3-month follow-up. Study enrollment was completed from February 2010 through March 2013. Varenicline was dosed using standard titration, and smoking cessation counseling was provided to all patients. The primary outcome was defined as a 7-day point prevalence of self-reported no smoking verified by expired carbon monoxide level < 10 ppm at 12 weeks. Psychopathology and side-effects were assessed at each visit.

RESULTS: At 3 months (end of treatment), significantly more subjects quit smoking with varenicline (n/n = 15/31, 48.4%) than with placebo (n/n = 3/29, 10.3%) (OR = 8.1; 95% CI, 2.03-32.5; P < .002). At 6 months, 6 of 31 varenicline-treated subjects (19.4%) remained abstinent compared to 2 of 29 (6.90%) assigned to placebo (OR = 3.2; 95% CI, 0.60-17.6; P = .17). Psychopathology scores remained stable. Ten serious adverse events occurred (n = 6, varenicline; n = 4, placebo). Abnormal dreams occurred significantly more often in varenicline-treated subjects (n/n = 18/31, 61.3%) than in those receiving placebo (n/n = 9/29, 31%; Fisher exact test, P = .04). Eight varenicline-treated and 5 placebo-assigned subjects expressed fleeting suicidal ideation, a nonsignificant difference.

CONCLUSIONS: Varenicline shows efficacy for initiating smoking cessation in bipolar patients, but medication trials of longer duration are warranted for maintaining abstinence. Vigilance for neuropsychiatric adverse events is prudent when initiating varenicline for smoking cessation in this patient population.

9. Koegelenberg CF[1], Noor F[1], Bateman ED[2], Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA*. 2014 Jul;312(2):155-61.

IMPORTANCE: Behavioral approaches and pharmacotherapy are of proven benefit in assisting smokers to quit, but it is unclear whether combining nicotine replacement therapy (NRT) with varenicline to improve abstinence is effective and safe.

OBJECTIVE: To evaluate the efficacy and safety of combining varenicline and a nicotine patch vs varenicline alone in smoking cessation.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, blinded, placebo-controlled clinical trial with a 12-week treatment period and a further 12-week follow-up conducted in 7 centers in South Africa from April 2011 to October 2012. Four hundred forty-six generally healthy smokers were randomized (1:1); 435 were included in the efficacy and safety analyses.

INTERVENTIONS: Nicotine or placebo patch treatment began 2 weeks before a target quit date (TQD) and continued for a further 12 weeks. Varenicline was begun 1 week prior to TQD, continued for a further 12 weeks, and tapered off during week 13.

MAIN OUTCOMES AND MEASURES: Tobacco abstinence was established and confirmed by exhaled carbon monoxide measurements at TQD and at intervals thereafter up to 24 weeks. The primary end point was the 4-week exhaled carbon monoxide-confirmed continuous abstinence rate for weeks 9 through 12 of treatment, ie, the proportion of participants able to maintain complete abstinence from smoking for the last 4 weeks of treatment, as assessed using multiple

imputation analysis. Secondary end points included point prevalence abstinence at 6 months, continuous abstinence rate from weeks 9 through 24, and adverse events. Multiple imputation also was used to address loss to follow-up.

RESULTS: The combination treatment was associated with a higher continuous abstinence rate at 12 weeks (55.4% vs 40.9%; odds ratio [OR], 1.85; 95% CI, 1.19-2.89; P = .007) and 24 weeks (49.0% vs 32.6%; OR, 1.98; 95% CI, 1.25-3.14; P = .004) and point prevalence abstinence rate at 6 months (65.1% vs 46.7%; OR, 2.13; 95% CI, 1.32-3.43; P = .002). In the combination treatment group, there was a numerically greater incidence of nausea, sleep disturbance, skin reactions, constipation, and depression, with only skin reactions reaching statistical significance (14.4% vs 7.8%; P = .03); the varenicline-alone group experienced more abnormal dreams and headaches.

CONCLUSIONS AND RELEVANCE: Varenicline in combination with NRT was more effective than varenicline alone at achieving tobacco abstinence at 12 weeks (end of treatment) and at 6 months. Further studies are needed to assess long-term efficacy and safety.

10. Scherphof CS, van den Eijnden RJ, Engels RC, Vollebergh WA. Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. Drug Alcohol Depend. 2014 Jul 1;140:217-20.

BACKGROUND: A double-blind RCT on the short-term efficacy of nicotine patches compared to placebo patches among Dutch adolescents was conducted. The findings demonstrated that nicotine patches are efficacious for smoking cessation at end-of-treatment; however, only in highly compliant participants. We tested whether the effects of NRT also held in 6- (T7) and 12-month (T8) follow-up assessments.

METHODS: Adolescents aged 12-18 years, who smoked at least seven cigarettes a day and who were motivated to quit smoking were recruited at school yards and randomly assigned to either a nicotine patch (n=182) or a placebo patch (n=180) condition according to a computer generated list. Participants (N=257, age: 16.7 ± 1.13 years) attended an information meeting followed by a 6- or 9-week treatment. Smoking cessation, compliance, and potential covariates were measured by means of online questionnaires. Smoking cessation at T8 was biochemically validated by saliva cotinine.

RESULTS: At T7, 8.1% and 5.7% of participants were abstinent in the nicotine and placebo patch groups, respectively. At T8, abstinence was 4.4% and 6.6%, respectively. Intention-to-treat analyses showed no significant effects of NRT on abstinence rates at T7 (OR=1.54, 95% CI=0.57, 4.16) and validated abstinence rates at T8 (OR=0.64, 95% CI=0.21, 1.93) neither after considering compliance nor after adjusting for covariates.

CONCLUSIONS: NRT fails in helping adolescents quit smoking at 6- and 12-month follow-ups. This finding suggests that a more intensive approach is needed to assist youngsters in their quit attempts.

11. Ebbert JO, Hatsukami DK, Croghan IT, Schroeder DR, Allen SS, Hays JT, Hurt RD. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA.* 2014 Jan 8;311(2):155-63.

IMPORTANCE: Combining pharmacotherapies for tobacco-dependence treatment may increase smoking abstinence.

OBJECTIVE: To determine efficacy and safety of varenicline and bupropion sustained-release (SR; combination therapy) compared with varenicline (monotherapy) in cigarette smokers.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, blinded, placebo-controlled multicenter clinical trial with a 12-week treatment period and follow-up through week 52 conducted between October 2009 and April 2013 at 3 midwestern clinical research sites. Five hundred six adult (≥18 years) cigarette smokers were randomly assigned and 315 (62%) completed the study.

INTERVENTIONS: Twelve weeks of varenicline and bupropion SR or varenicline and placebo.

MAIN OUTCOMES AND MEASURES: Primary outcome was abstinence rates at week 12, defined as prolonged (no smoking from 2 weeks after the target quit date) abstinence and 7-day point-prevalence (no smoking past 7 days) abstinence. Secondary outcomes were prolonged and point-prevalence smoking abstinence rates at weeks 26 and 52. Outcomes were biochemically confirmed.

RESULTS: At 12 weeks, 53.0% of the combination therapy group achieved prolonged smoking abstinence and 56.2% achieved 7-day point-prevalence smoking abstinence compared with 43.2% and 48.6% in varenicline monotherapy (odds ratio [OR], 1.49; 95% CI, 1.05-2.12; P = .03 and OR, 1.36; 95% CI, 0.95-1.93; P = .09, respectively). At 26 weeks, 36.6% of the combination therapy group achieved prolonged and 38.2% achieved 7-day point-prevalence smoking abstinence compared with 27.6% and 31.9% in varenicline monotherapy (OR, 1.52; 95% CI, 1.04-2.22; P = .03 and OR, 1.32; 95% CI, 0.91-1.91; P = .14, respectively). At 52 weeks, 30.9% of the combination therapy group achieved prolonged and 36.6% achieved 7-day point-prevalence smoking abstinence compared with 24.5% and 29.2% in varenicline monotherapy (OR, 1.39; 95% CI, 0.93-2.07; P = .11 and OR, 1.40; 95% CI, 0.96-2.05; P = .08, respectively). Participants receiving combination therapy reported more anxiety (7.2% vs 3.1%; P = .04) and depressive symptoms (3.6% vs 0.8%; P = .03).

CONCLUSIONS AND RELEVANCE: Among cigarette smokers, combined use of varenicline and bupropion, compared with varenicline alone, increased prolonged abstinence but not 7-day point prevalence at 12 and 26 weeks. Neither outcome was significantly different at 52 weeks. Further research is required to determine the role of combination therapy in smoking cessation.

12. Eden Evins, MD, MPH; Corinne Cather, PhD; Sarah A. Pratt, PhD; et al. Maintenance Treatment With Varenicline for Smoking Cessation in Patients With Schizophrenia and Bipolar Disorder A Randomized Clinical Trial *JAMA.* 2014;311(2):145-154.

IMPORTANCE It is estimated that more than half of those with serious mental illness smoke tobacco regularly. Standard courses of pharmacotherapeutic cessation aids improve short-term abstinence, but most who attain abstinence relapse rapidly after discontinuation of pharmacotherapy.

OBJECTIVE To determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial conducted in 10 community mental-health centers. Of 247 smokers with schizophrenia or bipolar disease recruited from March 2008-April 2012, 203 received 12-weeks' open-label varenicline and cognitive behavioral therapy and 87 met abstinence criteria to enter the relapse prevention intervention.

INTERVENTIONS Participants who had 2 weeks or more of continuous abstinence at week 12 of open treatment were randomly assigned to receive cognitive behavioral therapy and double-blind varenicline (1 mg, 2 per day) or placebo from weeks 12 to 52. Participants then discontinued study treatment and were followed up to week 76.

MAIN OUTCOMES AND MEASURES Seven-day rate of continuous abstinence at study week 52, the end of the relapse-prevention phase, confirmed by exhaled carbon monoxide. Secondary outcomes were continuous abstinence rates for weeks 12 through 64 based on biochemically verified abstinence and weeks 12 through 76, based on self-reported smoking behavior.

RESULTS Sixty-one participants completed the relapse-prevention phase; 26 discontinued participation (7 varenicline, 19 placebo) and were considered to have relapsed for the analyses; 18 of these had relapsed prior to dropout. At week 52, point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) vs 19% (9 of 47) in the placebo group (odds ratio [OR], 6.2; 95% CI, 2.2-19.2; $P < .001$). From weeks 12 through 64, 45% (18 of 40) among those in the varenicline group vs 15% (7 of 47) in the placebo group were continuously abstinent (OR, 4.6; 95% CI, 1.5-15.7; $P = .004$), and from weeks 12 through 76, 30% (12 of 40) in the varenicline group vs 11% (5 of 47) in the placebo group were continuously abstinent (OR, 3.4; 95% CI, 1.02-13.6; $P = .03$). There were no significant treatment effects on psychiatric symptom ratings or psychiatric adverse events.

CONCLUSIONS AND RELEVANCE Among smokers with serious mental illness who attained initial abstinence with standard treatment, maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation.

13. Anthenelli RM, Benowitz, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *Lancet*. 2016 Apr 22.

BACKGROUND: Substantial concerns have been raised about the neuropsychiatric safety of the smoking cessation medications varenicline and bupropion. Their efficacy relative to nicotine patch largely relies on indirect comparisons, and there is limited information on safety and efficacy in smokers with psychiatric disorders. We compared the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders.

METHODS: We did a randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non-treatment follow-up done at 140 centres (clinical trial centres, academic centres, and outpatient clinics) in 16 countries between Nov 30, 2011, and Jan 13, 2015. Participants were motivated-to-quit smokers with and without psychiatric disorders who received brief cessation counselling at each visit. Randomisation was computer generated (1:1:1:1 ratio). Participants, investigators, and research personnel were masked to treatment assignments. The primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events. The main efficacy endpoint was biochemically confirmed continuous abstinence for weeks 9-12. All participants randomly assigned were included in the efficacy analysis and those who received treatment were included in the safety analysis. The trial is registered at ClinicalTrials.gov (number NCT01456936) and is now closed.

FINDINGS: 8144 participants were randomly assigned, 4116 to the psychiatric cohort (4074 included in the safety analysis) and 4028 to the non-psychiatric cohort (3984 included in the safety analysis). In the non-psychiatric cohort, 13 (1·3%) of 990 participants reported moderate and severe neuropsychiatric

adverse events in the varenicline group, 22 (2·2%) of 989 in the bupropion group, 25 (2·5%) of 1006 in the nicotine patch group, and 24 (2·4%) of 999 in the placebo group. The varenicline-placebo and bupropion-placebo risk differences (RDs) for moderate and severe neuropsychiatric adverse events were -1·28 (95% CI -2·40 to -0·15) and -0·08 (-1·37 to 1·21), respectively; the RDs for comparisons with nicotine patch were -1·07 (-2·21 to 0·08) and 0·13 (-1·19 to 1·45), respectively. In the psychiatric cohort, moderate and severe neuropsychiatric adverse events were reported in 67 (6·5%) of 1026 participants in the varenicline group, 68 (6·7%) of 1017 in the bupropion group, 53 (5·2%) of 1016 in the nicotine patch group, and 50 (4·9%) of 1015 in the placebo group. The varenicline-placebo and bupropion-placebo RDs were 1·59 (95% CI -0·42 to 3·59) and 1·78 (-0·24 to 3·81), respectively; the RDs versus nicotine patch were 1·22 (-0·81 to 3·25) and 1·42 (-0·63 to 3·46), respectively. Varenicline-treated participants achieved higher abstinence rates than those on placebo (odds ratio [OR] 3·61, 95% CI 3·07 to 4·24), nicotine patch (1·68, 1·46 to 1·93), and bupropion (1·75, 1·52 to 2·01). Those on bupropion and nicotine patch achieved higher abstinence rates than those on placebo (OR 2·07 [1·75 to 2·45] and 2·15 [1·82 to 2·54], respectively). Across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]). Efficacy treatment comparison did not differ by cohort.

INTERPRETATION: The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. Varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patch were more effective than placebo.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 2 2016
1 bupropion.mp or Bupropion/ 3210
2 venlafaxine.mp. or Vanlafaxine Hydrochloride/ 3048
3 Nicotinic Agonists/ or "Tobacco Use Cessation Products"/ or nicotine replacement.mp.
4 smoking cessation.mp or Smoking Cessation/ 24510
5 "Tobacco use Disorder"/ 7902
6 nicotine lozenge.mp. or "Tobacco Use Cessation Products"/ 987
7 nicotine gum.mp. 342
8 nicotine patch.mp. or "Tobacco Use Cessation Products"/ 1509
9 nicoderm.mp. 16
10 1 or 2 or 3 or 6 or 7 or 8 or 9 13732
11 4 or 5 28713
12 10 and 11
13 limit 12 to (English language and humans and yr="2014-Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)) 188
14 from 13 keep 10-12, 17, 19, 23-24, 27, 29…….. 20

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

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 #5	**No:** Go to #4
4. Is the request for varenicline?	**Yes:** Go to #5	**No:** Go to #7
5. Has patient quit?	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Go to #6

Approval Criteria		
6. 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
7. 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: *7/16 (MH); 4/12*
Implementation: *7/23/12*