Drug Use Research & Management Program
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Month/Year of Review: March 2014
PDL Classes: Tobacco Cessation Products

Date of Last Review: April 2012
Source Document: Abbreviated Class Review: Tobacco Cessation Products

Current Status of PDL Class:

- Preferred Agents: BUPROPION HCL TABLET SR, NICOTINE PATCH DYSQ, NICOTINE PATCH TD24, NICOTINE POLACRILEX GUM, NICOTINE POLACRILEX LOZENGE, VARENICLINE TARTRATE (CHANTIX®)
- Nonpreferred Agents: NICOTINE NASAL SPRAY (NICOTROL®), NICOTINE INHALER (NICOTROL®)

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 (generic 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.

PA Criteria: Prior authorization criteria are currently in place for nonpreferred nicotine replacement therapy. In addition, requests for greater than 12 weeks of varenicline or six months of nicotine replacement therapy require a PA (Appendix 1).

Conclusions and Recommendations:

- No further review or research needed at this time; update PA criteria.
- Evaluate comparative costs in executive session.

Methods:

A Medline OVID search was conducted with the following search terms: tobacco use disorder, tobacco use cessation, smoking, smoking cessation, tobacco abstinence, tobacco cessation products, nicotine, nicotine replacement agents, nicotine patch, nicotine gum, nicotine lozenge, nicotine inhaler, nicotine nasal spray, bupropion, varenicline, Chantix, clonidine, and nortriptyline. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to January week one 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

The Cochrane Collaboration published a systematic review and meta-analysis on smoking cessation agents to assess comparative efficacy and safety. Varenicline, bupropion and nicotine replacement therapy (NRT) agents were the primary focus although many off-label agents were included (i.e. clonidine, nortriptyline). The primary outcome measured was continuous abstinence for at least six months from the start of treatment. Comparative safety was evaluated through the incidence of serious adverse events associated with treatment. Twelve treatment-specific Cochrane reviews were included with 267 trials (n=101,804). When compared with placebo, NRT (OR 1.84; 95% CI 1.71

to 1.99; 119 studies), varenicline (OR 2.88; 95% CI 2.40 to 3.47; 15 studies) and bupropion (OR 1.82; 95% CI 1.60 to 2.06; 36 studies) patients were significantly more likely to remain tobacco free. No difference was seen between treatment with NRT (patch, gum, lozenge, spray or inhaler) or bupropion (OR 0.99; 95% CI 0.86 to 1.13; 9 studies) when compared directly for tobacco abstinence. When compared with NRT (patch, gum, lozenge, spray or inhaler), varenicline was found to be more effective (OR 1.57; 95% 1.29 to 1.91). Varenicline measured against single agents was more effective no matter the NRT formulation: vs. patch (OR 1.51; 95% CI 1.22 to 1.87); vs. gum (OR 1.72; 95% CI 1.38 to 2.13); or vs. 'other' NRT (lozenges, spray, or inhaler) (OR 1.42; 95% CI 1.13 to 1.79). Varenicline was found to be more effective than bupropion (OR 1.59; 95% CI 1.29 to 1.96; 3 studies). When compared with combination NRT, varenicline was not more effective for tobacco abstinence (OR 1.06; 95% CI 0.75 to 1.48). No single NRT treatment was significantly more effective than any other. In safety analysis, rates of serious adverse events were found to be similar between varenicline and placebo (RR 1.06; 95% CI 0.72 to 1.55; 14 trials). Rates of cardiac events were also similar between varenicline and placebo (RR 1.26; 95% CI 0.62 to 2.56); as were rates of neuropsychiatric events (RR 0.53; 95% CI 0.17 to 1.67). Compared with placebo, bupropion also showed no significant difference in cardiac events (RR 0.77; 95% CI 0.37 to 1.59) or neuropsychiatric events (RR 0.88; 95% CI 0.31 to 2.50). Seizures occurred six times in bupropion patients versus no occurrence for placebo patients; this is a rate of 0.07%. The authors conclude that varenicline, bupropion and NRT all improve the likelihood of sustained tobacco abstinence with a low risk of severe adverse events. This meta-analysis was based on several systematic reviews rated as high quality based on AMSTAR ratings. Individual trial quality was not reported within this analysis, although the authors acknowledge that quality varied considerably; 81% of varenicline trials were considered high quality, while only 21% of NRT trials were given this rating.[1]

The Cochrane Collaboration updated their systematic review evaluating the efficacy of nicotine replacement treatment (NRT) for tobacco abstinence. The primary outcome was sustained quit rates after at least six months after treatment. One hundred and seventeen trials were included in the review with 51,265 trial participants. Patients on any type of NRT were more likely to remain tobacco abstinent than placebo or control subjects (RR 1.60; 95% CI 1.53 to 1.68). Individual NRT products were also all more effective than placebo for tobacco abstinence: gum (RR 1.49; 95% CI 1.40 to 1.60; 53 trials), nicotine patch (RR 1.64; 95% CI 1.52 to 1.78; 43 trials), lozenges (RR 1.95; 1.61 to 2.36; 6 trials), inhaler (RR 1.90; 95% CI 1.36 to 2.67; 4 trials), and nasal spray (RR 2.02; 95% CI 1.49 to 2. 73; 4 trials). Combination treatment with the patch and a second NRT product was more effective than any NRT alone (RR 1.34; 95% CI 1.18 to 1.51; 9 trials). NRT (any type) compared with bupropion was similar in efficacy (RR 1.01; 95% CI 0.87 to 1.18; 5 trials); although combination treatment bupropion and an NRT product was more effective than bupropion alone (RR 1.24; 95% CI 1.06 to 1.45; 4 trials). Individual study quality was evaluated for randomization, allocation concealment, blinding, incomplete outcomes data and other biases. Most trials were considered fair to low quality with only 19 trials rated as having adequately reported blinding, allocation concealment and randomization methodology.[2]

The Cochrane Collaboration published an updated systematic review on the effectiveness of nicotine receptor partial agonists for smoking cessation. The authors included 19 trials (n= 12,223) which compared varenicline to either placebo, bupropion or nicotine replacement therapy (NRT). The primary outcome measured was continued tobacco abstinence at least six months after treatment ends. Compared with placebo, varenicline treated subjects were more likely to remain tobacco free after six months or longer post-trial end (RR 2.27; 95% CI 2.02 to 2.55; 14 trials). Four trials compared varenicline at lower than standard dosing (< 1 mg BID) with placebo. The varenicline patients were again more likely to remain tobacco abstinent than the placebo cohort (RR 1.09; 95% CI 1.56 to 2.78). Three trials had a direct comparison between varenicline and bupropion for continued tobacco abstinence measured one year after the end of treatment. Again the varenicline subjects were more likely to remain tobacco free than their counterparts in the bupropion group (RR 1.52; 95% CI 1.22 to 1.88). Comparison, however, with NRT at six months was statistically insignificant (RR 1.13; 95% CI 0.94 to 1.35; 2 trials). Secondary outcomes examined were related to the safety of varenicline. Seventeen trails measured serious adverse events which occurred either during or after the trial. Varenicline patients were found to more likely have had a serious adverse event than their placebo or active comparator comparators (RR 1.36; 95% CI 1.04 to 1.79). The authors found little evidence in their review of any increase in psychiatric or cardiac adverse events with varenicline treatment. Individual study quality was evaluated for

randomization, allocation concealment, blinding, incomplete outcomes data and other biases. Of the 19 trials included in the varenicline analysis, 13 were judged to have provided adequate information randomization, allocation concealment and blinding and were considered to have minimal risk of bias.[3]

Mills et al conducted a systematic review to compare the efficacy of high dose nicotine replacement therapy (NRT) or combination NRT with standard dose NRT, varenicline or bupropion for sustained tobacco abstinence. The primary outcome was measured at four different time points: short term (< four weeks, three months, six months and twelve months; 146 randomized controlled trials were included. Trials were included if a placebo or active control was used and the analysis for all treatments employed a random-effects pairwise meta-analysis and a Bayesian multiple treatment comparison. All treatments except combination NRT were statistically superior for patients remaining tobacco abstinent for all time points when compared with placebo. Combination NRT was not significantly different than treatment with placebo for tobacco abstinence at three months (RR 1.29; 95% CI 0.73 to 2.07) and 12 months post treatment (RR 1.34; 95% CI 0.96 to 1.84). For all time points, standard dose NRT patch showed similar efficacy to both combination NRT and bupropion treatment. High dose NRT (>22 mg nicotine patch per day) was only significantly superior to standard dose NRT in the short term (RR 1.14; 95% CI 1.07 to 1.21) and six months after treatment (RR 1.32; 95% CI 1.11 to 1.57). Varenicline was more efficacious at all time points when compared with standard dose NRT (short term RR 1.43, 95% CI 1.26 to 1.60; three months RR 1.48, 95% CI 1.23 to 1.75; six months RR 1.38, 95% CI 1.15 to 1.64; and at 12 months RR 1.65, 95% CI 1.29 to 2.07). Varenicline was also more efficacious at most time points when compared with high dose NRT (short term RR 1.29, 95% CI 1.12 to 1.46; three months RR 1.40, 95% CI 1.05 to 1.80; six months RR 1.05, 95% CI 0.80 to 1.36; and 12 months RR 1.47, 95% CI 1.06 to 2.01); when compared with combination NRT (short term RR 1.28, 95% CI 1.02 to 1.53; three months RR 1.85, 95% CI 1.15 to 2.65; six months RR 1.31, 95% CI 0.95 to 1.75; and 12 months RR 1.78, 95% CI 1.25 to 2.41); and when compared with bupropion (short term RR 1.29, 95% CI 1.12 to 1.45; three months RR 1.43, 95% CI 1.24 to 1.63; six months RR 1.34, 95% CI 1.13 to 1.57; and 12 months RR 1.61, 95% CI 1.32 to 1.93). Bupropion treatment had similar efficacy to both combination and high dose NRT at all time points. Individual trial quality was not evaluated for this meta-analysis making it difficult to measure the overall strength of evidence of the conclusions.[4]

Guidelines:

The American College of Chest Physicians updated their guidelines for the treatment of tobacco use in lung cancer published in CHEST in May 2013. Recommendations used are based on the GRADE Working Group classifications. The formulation of recommendations considered the balance between the desirable and undesirable consequences of an intervention; the quality of evidence; the variability in patient values and preferences; and, on occasion, resource use issues. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "The expert panel recommends" and labeled “1”. Recommendations were graded as weak when desirable effects were not clearly greater or less great than undesirable effects. Weak recommendations were worded as "The expert panel suggests" and labeled “2”. The rating of the quality of the evidence—high, A; moderate, B; or low, C—is provided with the strength of each recommendation.[5]

- We recommend that current smokers undergoing low-dose CT screening be provided with cessation interventions that include counseling and pharmacotherapy (Grade 1B)
- Among lung cancer patients undergoing surgery, we recommend perioperative cessation pharmacotherapy as a method for improving abstinence rates (Grade 1B)
- For lung cancer patients attempting cessation in conjunction with surgical interventions, we recommend initiating counseling and pharmacotherapy at the outset of surgical intervention (Grade 1B)
- Among lung cancer patients undergoing chemotherapy, we recommend cessation interventions that include counseling and pharmacotherapy to improve abstinence rates (Grade 1B)
- Among lung cancer patients with depressive symptoms, we suggest cessation pharmacotherapy with bupropion as a method to improve abstinence rates, depressive symptoms, and quality of life (Grade 2B)

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The Global Initiative for Chronic Obstructive Lung Disease updated their guidelines for their strategy for diagnosis, management, and prevention of COPD in 2013. Recommendations were given a grade of A, B, C, or D based the level of evidence for the recommendation. Grade A recommendations were based on evidence from endpoints of well-designed randomized control trials (RCTs) and require a substantial numbers of studies involving substantial numbers of participants. Grade B recommendations were based on evidence from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B recommendations were made when few randomized trials existed, were small in size, were undertaken in a population that differs from the target population of the recommendation, or when the results were somewhat inconsistent. Grade C recommendations were from the outcomes of uncontrolled, nonrandomized trials, or from observational studies. Grade D recommendations were used only in cases where some guidance was needed but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. Grade D recommendations were made by Panel Consensus and were based on clinical experience or knowledge that does not meet the above-listed criteria. [6]

Smoking cessation recommendations were not graded.

- In patients who smoke, smoking cessation is very important. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- First-line pharmacotherapies for tobacco dependence—varenicline, bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch—are effective and at least one of these medications should be prescribed in the absence of contraindications.

New drugs:

None

New Formulations/Indications:

None

New FDA safety alerts:

The FDA updated their recent safety alert concerning the use of varenicline and major adverse cardiovascular events (MACE). In June 2011, the FDA cautioned the public about the possibility of a connection between MACE and varenicline use; the evidence for the caution was based on a single study. Because of this, the FDA asked the manufacturer of varenicline to conduct a meta-analysis to determine any extent of MACE with varenicline use. This current safety alert from December 2012 reports the results of the meta-analysis which included 15 trial and 7,002 subjects. The meta-analysis found there was an overall low incidence of MACE during treatment or within 30 days post treatment (0.31% varenicline subjects vs. 0.21% placebo subjects) and the difference between treatment groups was not statistically significant (hazard ratio 1.95; 95% CI 0.79 to 4.82). Therefore, the FDA advises health care professionals to weigh the risks of varenicline against the benefits of its use; be aware that smoking is a major risk factor for cardiovascular disease; and that varenicline is effective at helping patients quit smoking and remain abstinent for as long as one year.[7]

New Trials (Appendix 1):

A total of 213 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

Cinciripini et al conducted a twelve week randomized control trial comparing the efficacy of varenicline, bupropion sustained release (SR) and placebo on smoking abstinence. Patients (n=294) were randomized to one of the three treatment cohorts; all patients also received intensive counseling on smoking cessation over 10 sessions for a total of 240 minutes of counseling over the duration of the clinical trial. The study's primary outcome was long-term abstinence

from smoking measured at three and six months post quit date. Abstinence rates were significantly higher for bupropion SR versus placebo patients at the end of treatment (OR 2.77; 95% CI 1.48 to 5.20) and at three months (OR 2.90; 95% CI 1.52 to 5.54), but not at six months (OR 1.77; 95% CI 0.86 to 3.62). Patients on varenicline were significantly more likely to remain tobacco abstinent than those on placebo at the end of treatment (OR 3.92; 95% CI 2.06 to 7.47), at three months (OR 3.69; 95% CI 1.90 to 7.16), and at six months (OR 2.35; 95% CI 1.1 to 4.83). There was no significant difference between rates of tobacco abstinence between varenicline and bupropion SR patients at the end of treatment (OR 1.41; 95% CI 0.79 to 2.42), three months (OR 1.27; 95% CI 0.71 to 2.28), or six months (OR 1.33; 95% CI 0.68 to 2.58). Overall rates of adverse events were similar between treatment groups: varenicline 86.1%, bupropion 80.4%, and placebo 79.0%. No significant group differences were reported for any of the psychiatric or neurological adverse events, including anxiety, irritability, depression, emotional lability, and disturbances in attention. Cardiovascular adverse events were highest in the placebo group. This was a high quality study.[8]

Ferkitech et al conducted a twelve week trial comparing tobacco abstinence rates for varenicline versus combination patch and gum nicotine replacement therapy (NRT). Patients with HIV and a tobacco habit were directed to treatment with varenicline (n=118) or NRT (n=110) dependent on patient preference or psychiatric history; patients with comorbid psychiatric illness were given NRT. All patients received 12 weeks of telephone smoking cessations counseling. The primary endpoint was tobacco abstinence at three months after the end of the trial. Abstinence was counted by measuring salivary cotinine and expired air carbon monoxide. Patients on varenicline were significantly more likely to remain tobacco abstinent at the end of three months than the NRT patients (OR 2.72; 95% CI 1.50 to 4.94). Adverse events were higher in the varenicline cohort than the NRT group. Discontinuations due to adverse events were much higher for varenicline versus NRT patients (14.4% vs 1.8%). This was a low quality trial with many opportunities for bias to compromise the results. No randomization, blinding or allocation concealment was conducted. Trial conductors had a more favorable view of varenicline efficacy over NRT which was made evident by their encouraging patients to use varenicline over NRT.[9]

References:

1. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. In: The Cochrane Collaboration, Cahill K, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013. Available at: http://doi.wiley.com/10.1002/14651858.CD009329.pub2. Accessed January 12, 2014.

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8. Cinciripini PM, Robinson JD, Karam-Hage M, et al. Effects of Varenicline and Bupropion Sustained-Release Use Plus Intensive Smoking Cessation Counseling on Prolonged Abstinence From Smoking and on Depression, Negative Affect, and Other Symptoms of Nicotine Withdrawal. *JAMA Psychiatry*. 2013;70(5):522. doi:10.1001/jamapsychiatry.2013.678.

9. Ferketich AK, Diaz P, Browning KK, et al. Safety of Varenicline Among Smokers Enrolled in the Lung HIV Study. *Nicotine & Tobacco Research*. 2012;15(1):247–254. doi:10.1093/ntr/nts121.

Date: March 2014

Appendix 1: Smoking cessation PA

Smoking Cessation

Goal(s):

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

Requires PA: Non-preferred products
NRT beyond 6 month in the absence of behavioral counseling
Varenicline beyond 12 weeks

Length of Authorization: 3-6 months

Approval Criteria : Nicotine Replacement Therapy (NRT)		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis for tobacco dependence? (ICD-9 305.1)?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the request for a preferred NRT?	**Yes:** Go to #6	**No:** Go to #4
4. Is the request for varenicline?	**Yes:** Go to #5.	**No:** Go to #7
5. Has patient quit?	**Yes:** Approve varenicline x 12 additional weeks.	**No:** Go to #6
6. Is the patient enrolled in a smoking cessation behavioral counseling program (e.g. Quit Line at: 800 – xxx-xxxx).	**Yes:** Approve NRT x 6 additional months or Approve varenicline x 12 additional weeks.	**No:** Pass to RPH; Deny (medical appropriateness)
7. Will the prescriber consider a 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. Reports are available at: http://pharmacy.oregonstate.edu/drug_policy/reviews	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml	**No:** Go back to #6

P&T Action: 4-26-2012
Revision(s): 3-27-2014 (MH)
Initiated:

Appendix 2: Abstracts of Randomized Control Trials

Cinciripini PM, Robinson JD, Karam-Hage M, et al. Effects of Varenicline and Bupropion Sustained-Release Use Plus Intensive Smoking Cessation Counseling on Prolonged Abstinence From Smoking and on Depression, Negative Affect, and Other Symptoms of Nicotine Withdrawal. *JAMA Psychiatry*. 2013;70(5):522.

Importance: Given the actions of varenicline tartrate and bupropion hydrochloride sustained-release (SR) on neurobiological targets related to affect and reward, it is thought that the modulation of nicotine withdrawal symptoms may contribute to their effectiveness.

Objective: To assess the relative efficacy of varenicline and bupropion SR plus intensive counseling on smoking cessation and emotional functioning.

Design and Setting: Placebo-controlled randomized clinical trial at a university medical center.

Participants: In total, 294 community volunteers who wanted to quit smoking.

Interventions: Twelve weeks of varenicline, bupropion SR, or placebo plus intensive smoking cessation counseling (10 sessions, for a total of approximately 240 minutes of counseling).

Main Outcome Measures: Prolonged abstinence from smoking and weekly measures of depression, negative affect, and other symptoms of nicotine withdrawal.

Results: Significant differences were found in abstinence at the end of treatment and through the 3-month post quit follow-up visit, favoring both active medications compared with placebo. At the 6-month post quit follow-up visit, only the varenicline vs placebo comparison remained significant. Varenicline use was also associated with a generalized suppression of depression and reduced smoking reward compared with the other treatments, while both active medications improved concentration, reduced craving, and decreased negative affect and sadness compared with placebo, while having little effect (increase or decrease) on anxiety and anger. No differences were noted in self-reported rates of neuropsychiatric adverse events.

Conclusions and Relevance: In a community sample, varenicline exerts a robust and favorable effect on smoking cessation relative to placebo and may have a favorable (suppressive) effect on symptoms of depression and other affective measures, with no clear unfavorable effect on neuropsychiatric adverse events.

Ferketich AK, Diaz P, Browning KK, et al. Safety of Varenicline Among Smokers Enrolled in the Lung HIV Study. *Nicotine & Tobacco Research*. 2012;15(1):247–254.

Introduction: The prevalence of smoking is high among the human immunodefi ciency virus (HIV)-infected population, yet there are few studies of tobacco dependence treatment in this population. This paper reports the safety of varenicline versus nicotine replacement therapy (NRT) and describes preliminary results about the effectiveness of varenicline versus NRT in HIV-infected smokers.

Methods: Participants completed 12 weeks of telephone counseling and either varenicline or NRT. Varenicline was encouraged as the preferred intervention; NRT was used for those unable/unwilling to take varenicline. Adverse events (AEs), related to pharmacotherapy, were monitored. Biochemically confirmed abstinence at 3 months was examined. Inverse probability of treatment weighted logistic regression models was fit to compare participants on varenicline to those on NRT.

Results: Among participants on varenicline (*n* = 118), the most common AEs were nausea, sleep problems, and mood disturbances. One person reported suicidal ideation; there were no cardiovascular complications. There were no differences in the varenicline AE profile between participants on combination antiretroviral therapy (ART) and those not on ART. The percentages of confirmed abstainers were 11.8% in the NRT group and 25.6% in the varenicline group. The odds of being abstinent were 2.54 times as great in the varenicline group compared with the NRT group in the propensity weighted model (95% *CI* 1.43– 4.49).

Conclusions: In this preliminary study, the safety profile of varenicline among HIV-infected smokers resembles findings among smokers without HIV. In addition, varenicline may be more effective at promoting abstinence in this population. Future randomized clinical trials are warranted.