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Oregon Health Authority

Abbreviated Class Review: Tobacco Cessation Medications

Month/Year of Review: April 2012

FDA Approved Medications		Non-approved Alternatives
Nicotine transdermal patch	Bupropion sustained -release	Clonidine
Nicotine lozenge	Varenicline (Chantix®)	Nortriptyline
Nicotine gum		
Nicotine inhaler (Nicotrol®)		
Nicotine nasal spray (Nicotrol®)		

See Appendix 2 for dosing, duration and administration information.

Reason for Review:
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, and cardiovascular disease. This review will evaluate current comparative effectiveness evidence to assist in establishing recommendations for the therapeutic agents indicated for smoking cessation.

Issues:
1. What is the comparative efficacy of smoking cessation products in promoting long-term tobacco abstinence?
2. Is there any evidence that there is a meaningful difference in agents in safety that would favor one agent over another?
3. Is there any evidence that there is a difference in efficacy or safety in special populations?

Methods:
Search Strategy
An Ovid MEDLINE search was conducted using the following search terms:

Varenicline; bupropion; nicotine replacement therapy; nicotine patch; nicotine gum; nicotine lozenge; nicotine nasal spray; nicotine inhaler; smoking cessation; tobacco abstinence
The search was limited to controlled trials conducted with humans in English language publications from 2010 to present.

Results:
The MEDLINE search retrieved 181 full citations. After a full evaluation of citations and abstracts, 8 head-to-head using FDA approved agents were identified for further review. Three articles were included here: one article about varenicline on cardiovascular risk and two articles on varenicline dosing are discussed in section IV FDA Alerts. The majority of the RCTs identified were excluded for wrong study type (observational, case study), for the wrong endpoint (smoking reduction, decreased disease occurrence), for the wrong duration (trials less than 6 weeks), for very specific subpopulations (chronic binge drinkers, Japanese men over 40) or for duplication (already included in another article or review).

The search of the Cochrane, CADTH, AHRQ, and NICE websites did identify new systematic reviews and/or guidelines. These are included in section II Systematic Review and section III Guidelines.
The search of the DERP, and VA/DoD websites did not identify any relevant new systematic reviews.

Conclusions:
The collective conclusions of the Canadian Agency for Drugs and Technologies in Health[1], U.S. Department of Health and Human Services[2], and the Cochrane Collaboration systematic reviews[3-8], as well as the guidelines of the UK's National Institute for Clinical Excellence[9] and the US Preventive Task Force[10] share many similar recommendations. There is strong evidence that all of the FDA approved smoking cessation products are efficacious compared with placebo in terms of abstinence rates. There is strong evidence that bupropion and nicotine replacement therapy (NRT) formulations are equally effective for tobacco abstinence rates. There is moderate to strong evidence that varenicline has the higher rate of abstinence success when compared with bupropion or NRT. There is strong evidence that combining the nicotine patch with another NRT therapy improves abstinence rates over NRT monotherapy. There is strong evidence that clonidine is efficacious compared with placebo for tobacco cessation. There is moderate to strong evidence that nortriptyline is effective compared with placebo for tobacco cessation. There is strong evidence that combining behavioral therapy with tobacco cessation medications increase the rate of long-term (greater than 6 months) abstinence. There is inconclusive evidence that combining bupropion with NRT is more effective than monotherapy. There is insufficient evidence to recommend any medication for special populations including pregnant or lactating women, adolescents or the mentally ill.

Varenicline has some safety issues not seen with bupropion or NRT products.[11-12] From systematic reviews, there is strong evidence that varenicline is safe to use over a 12 week period, although limitations may be appropriate in patients with a neuropsychiatric or cardiovascular history. A small increase in risk of serious cardiovascular events may exist for patients with cardiovascular disease taking varenicline; however the evidence is insufficient to form a conclusion. There is a black box warning for potential serious neuropsychiatric events (depression and suicidal tendencies) especially in those patients with a history of mental illness (bupropion also carries this warning). A recent study however, found no difference in the

rates of neuropsychiatric hospitalizations between NRT and varenicline patients.+13 Post-marketing trials on psychiatric safety of varenicline are ongoing.

Recommendations:

1. 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.
2. Due to no differences in safety or efficacy between the NRT products, evaluate comparative costs for further decisions.
3. Make bupropion sustained release (generic Zyban) a preferred drug.
4. Make varenicline a preferred agent on the PDL with a quantity limit for twelve weeks of treatment within 6 months.
5. 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 (Appendix 1).

I. BACKGROUND/CURRENT LANDSCAPE/SUMMARY

Cigarettes are responsible for more than 443,000 deaths annually. One in every five deaths last year was smoking related, and according to the US Department of Health and Human Services, more than 50% of long-term cigarette smokers are killed from smoking-related diseases. Smoking cigarettes can negatively affect every physiological system in a smoker's body. Unfortunately, smoking doesn't only affect the person smoking. Thousands of non-smoking Americans die from heart and lung disease associated with second-hand smoke. Children exposed to second-hand smoke are at higher risk for sudden infant death syndrome (SIDS), respiratory diseases, long term ear infections and other health issues. More than 193 billion dollars in health care costs and lost productivity is spent annually on chronic diseases caused by tobacco use.[14-15]

Although cigarette smoking rates have dropped by more than half since the 1960s, approximately 20% of American adults and teenagers are current smokers.[15] Among those, about 70% express an interest in quitting. In 2010, about half of all adult smokers made an attempt to stop smoking, but only 6.2% reported remaining smoke-free after one year. Among those who attempted to quit and those successfully quit in the last two years, 31.7% used either counseling or medications and 4.3% used both.[14]

The consequences of tobacco addiction are a large problem in the Medicaid population. The prevalence of smokers in the Medicaid population is nearly twice that of the general population. In Oregon, three times as many adult Medicaid patients smoke compared with the general population.[16] Rates of tobacco cessation in the Medicaid population remain especially low. Patients with private health plans are 41% more likely to have quit smoking than Medicaid patients.[14] The estimated annual cost to the state is $290 million dollars.[16] A recent cost-benefit analysis looked at what

savings smoking cessation programs might bring state Medicaid programs. The analysis estimated the short-term return on investment of the savings attached to reduced cardiovascular hospital admissions and found for every dollar spent in the smoking cessation program (medications, counseling, etc.) $3.12 was saved from reduced admissions. A potential annual savings of $388 per patient.[17]

Seven medications are FDA approved for treatment of tobacco dependence. Five are nicotine replacement therapy (NRT) available in various formulations. As the name implies, NRT contain a measured amount of nicotine and are designed to help a smoker gradually wean themselves off nicotine while abstaining from cigarette smoking. Depending on the formulation, these agents can help with the withdrawal symptoms (the patch, gum and lozenge) and help with more immediate nicotine cravings (inhaler, nasal spray, gum, and lozenge). All five are meant for short-term use (12-24 weeks or less). The nasal spray and inhaler agents are available by prescription only. Safety concerns include use in cardiovascular patients, pregnancy and breast-feeding women, and minors.[18]

There are two agents approved that are non-nicotine products. Bupropion is an anti-depressant medication that has affects on dopamine receptors in the central nervous system (CNS). It is thought to affect the pleasure-seeking center in the brain, although its mechanism of action in smoking cessation is unknown. It has been used in combination with some of the NRT products. Bupropion can increase the seizure threshold and shouldn't be used in patients prone to seizures. It also has not been approved for pregnancy/breastfeeding or minors. Varenicline (Chantix®) is a partial nicotinic agonist approved to treat smoking dependence. It acts at the same receptors nicotine occupies but without the receptor stimulation nicotine provides. Patients therefore experience less craving and withdrawal symptoms. Varenicline is the newest medication for tobacco dependence and has less safety data than the alternative agents. Choosing among medications requires consideration of the benefits and risks, with attention to each patient's medical and psychiatric status. In 2009, the FDA issued a boxed warning for both varenicline and bupropion concerning neuropsychiatric symptoms, depressed mood, and suicidal thoughts and behavior.[19] Also, a recent drug-safety communication noted that it may be associated with a small increase in the risk of cardiovascular events. Varenicline should not be used with NRT agents.[18]

Many medications have been prescribed for tobacco dependence as off-label agents. These non-FDA approved medications have a wide range in the amount of evidence supporting their use. Two medications, clonidine (an anti-hypertensive) and nortriptyline (an antidepressant) have the most data supporting their use. However, evidence is limited for their use and both should be considered as second-line agents after the FDA-approved medications discussed above. Other medications including the SSRIs (i.e. fluoxetine) and naltrexone have little to no data supporting their use in tobacco dependence and are not recommended for use.[18]

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II. Systematic Reviews:

Canadian Agency for Drugs and Technologies in Health (CADTH)[1]*:*

The Canadian Agency for Drugs and Technologies in Health (CADTH) provided a technology report in September 2010 (updated October 2011) to assess the clinical effectiveness and cost effectiveness of medications for smoking cessation. The review evaluated the comparative clinical effectiveness of varenicline, bupropion and NRT agents, the effectiveness of combining various agents, the effectiveness of adding behavioral support therapy to drug therapy, and the effectiveness of treating special populations (including adolescents, those who are pregnant and those with psychiatric disorders).

More than 3500 citations were originally identified and 143 included in the meta-analysis. Articles were included for clinical evaluation if they met the following criteria: the article was a randomized control trial with a follow up of at least six months; the population was smokers that mirrored the general population (both genders, all ages, multiple ethnicities) unless a specific population was studied (adolescents); the intervention studied was bupropion, varenicline, NRT or behavioral support therapy with an active or placebo comparator; and the outcome was biochemically identified smoking abstinence.

After screening for criteria, 143 articles were included for analysis. Quality ratings were assigned to each article after review using a combination of the Jadad and Hailey scales. Ratings ranged from high to poor quality, although the majority of articles (53% were given the highest rating.

All seven medications were more effective than placebo at helping patients remain tobacco free after six months and one year. Comparing bupropion with NRT treatment showed no difference in abstinence rates one year after quitting (OR 1.03, 95% CI 0.84-1.27). Among individual nicotine replacement products, no difference was found between abstinence rates after one year. Patients on varenicline had the highest odds of being tobacco free one year after quitting versus placebo (OR 2.7, 95% CI 2.25- 3.24), bupropion (OR 1.43, 95% CI 1.11-1.84) , and NRT (OR 1.47, 95% CI 1.2-1.82). Most combinations of medications showed no improvement over monotherapy in abstinence rates. The exception was two combinations of NRT formulations: using the nicotine patch with the nicotine gum or nasal spray was more effective than the patch alone (at six months, patch + gum: OR 2.1, 95% CI 1.18- 3.71; patch + spray: OR 2.4, 95% CI 1.27-4.5).

All medications were associated with higher numbers of adverse events compared with placebo and the nicotine spray seemed to be associated with more adverse events than nicotine patch (OR 3.83, 95% CrI 1.07 to 13.76) or nicotine inhaler (OR 5.12, 95% CrI 1.28 to 20.48). The nicotine patch, bupropion, and varenicline showed a higher proportion of withdrawals due to adverse events compared with placebo with pooled OR's of 1.41 (95% CI 1.02 to 1.94), 1.74 (95% CI 1.31 to 2.31), and 1.52 (95% CI 1.09 to 2.12) respectively. More studies are needed to see what therapy, if any works best in special populations including pregnancy and the mentally ill; one study showed the use of the nicotine patch in adolescents improved tobacco

abstinence rate compared with placebo for up to six months (OR 4.93, 95% CI 0.95- 25.57). There was no analysis for smoking cessation agents in patients with cardiovascular disease. The evidence of head-to-head comparisons between medications is limited.

Conclusions:

1. There is high quality evidence NRT, bupropion and varenicline are all efficacious compared with placebo in treating tobacco dependence and promoting long-term cessation.
2. There is high quality evidence that there is no difference in efficacy in varenicline, bupropion and NRT in tobacco abstinence rates.
3. There is high quality evidence that there is no difference between NRT formulations in smoking abstinence rates.
4. There is high quality evidence that all seven tobacco cessation products have higher relapse rates than placebo.
5. There is high to good quality evidence that combining the nicotine patch with the nicotine gum or nasal spray was more efficacious than the patch alone.
6. There is good to fair quality evidence that adding the nicotine patch or gum to behavioral therapy was more effective than behavioral therapy alone.
7. In special populations, there is high to fair quality, limited evidence that there is no difference in smoking abstinence rates between NRT, NRT + behavioral therapy, or behavioral therapy alone vs. placebo in pregnant woman
8. In special populations, there is good to fair quality, limited evidence that the nicotine patch is more effective than placebo in adolescents.
9. In special populations, there is good to poor quality evidence that none of the current medications available are more effective than placebo in patients with mental illness.

US Department of Health and Human Services[2]:

A meta-analysis by the US Department of Health and Human Services assessed randomized trials to create a public health service-sponsored clinical practice guideline in May 2008. This clinical practice guideline and systematic review was sponsored by a group effort of Federal Government agencies and nonprofit organizations including the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control (CDC), the National Heart, Lung and Blood Institute (NHLBI), and the National Cancer Institute (NCI). The review focuses on eleven topics including the effectiveness of combining counseling and medication relative to either counseling and medication alone, effectiveness of varenicline, effectiveness of medication combinations, effectiveness of long-term use, and effectiveness in special populations (including adolescents, those who are pregnant and those with psychiatric disorders).

Articles were included if they were a randomized, placebo/comparison controlled trial of a tobacco use treatment intervention with follow-up results at least 5 months after the quit date; was published between January 1975 and June 2007 in English in a peer-reviewed journal; and addressed one of

the 11 topics chosen for review. Recommendations based on the articles were given a strength of evidence (A, B, or C) rating based on the quality and quantity of data.

Seven FDA indicated medications were evaluated in the systematic review. Other medications used off-label for tobacco dependence were also included. 83 trials were included in a meta-analysis comparing the effectiveness of smoking cessation medications with respect to the rate of abstinence 6 months after treatment. This review identified all seven medications effective in increasing the odds of achieving abstinence compared to placebo. A meta-analysis was performed to allow for comparisons of medications between other active medications. Varenicline 2mg/day (number of trials, N=5) demonstrated the greatest odds of remaining tobacco free six months after quitting (OR 3.1 , 95% CI 2.5-3.8) and was associated with an estimated abstinence rate of 33%. Combination NRT was also associated with a higher estimated abstinence rate of 37% (most pharmacotherapies showed an estimated rate of 19% to 26%). Subjects on all forms of NRT, except for the lozenge formulation, were more likely to be tobacco free compared to placebo. The nicotine nasal spray and the high dose (>25mg) nicotine patch shared the second highest odds after varenicline (both: OR 2.3, 95% CI 1.7-3.0). Bupropion SR (N=26) use was also associated with greater odds of being tobacco free compared with placebo at six months (OR 2.0, 95% CI 1.8-2.2). Clonidine (N=3) and nortriptyline (N=5) are used off-label to treat tobacco dependence; patients in both treatment arms were more likely to still be tobacco free at six months than their placebo counterparts. Combination therapy that included the nicotine patch was shown to be very effective. The patch when combined with the nicotine inhaler (OR 2.2, 95%CI 1.3-3.6), bupropion SR (OR 2.5, 95%CI 1.9-3.4), nortriptyline (OR 2.3, 95%CI 1.3-4.2), or the nicotine gum/inhaler (OR 3.6, 95%CI 2.5-5.2) showed improved effectiveness at 6 months compared with placebo.

Conclusions:

1. There is evidence that first-line medications varenicline, bupropion, nicotine patch, gum, inhaler and nasal spray appear to be effective smoking cessation treatments. (Strength of evidence A)
2. There is evidence that the nicotine lozenge is an effective smoking cessation treatment. (Strength of evidence B)
3. There is evidence that second-line smoking cessation medications, clonidine and nortriptyline, appear to be effective smoking cessation treatments when used under a physician's supervision. (Strength of evidence A)
4. There is evidence that using a combination of the nicotine patch and other NRT or bupropion appear to be effective smoking cessation treatments. (Strength of evidence A)
5. There is evidence that the combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. (Strength of evidence A)
6. There is insufficient evidence supporting the use of smoking cessation medications in the following special populations: pregnant women, adolescents, smoke-less tobacco users, and light smokers who smoke less than 10 cigarettes per day.

The Cochrane Collaboration[3-8]*:*

In 2008, a systematic review evaluated if nicotine replacement therapy is more effective than placebo at achieving abstinence from smoking. Thirteen other objectives were analyzed including if one NRT formulation is more effective than the others, if combination NRT is more effective than monotherapy, or if NRT is more effective than other smoking cessation treatment.
Articles were included if they were an RCT where a NRT was compared with placebo, an active comparator, or no treatment at all. The primary outcome was abstinence from smoking with a follow up of at least six months. A meta-analysis was performed on the 111 articles selected for review. All forms of NRT were shown to be more effective than placebo in maintaining tobacco abstinence (RR 1.58, 95% CI 1.5-1.66) at six months. Of the five forms of nicotine products, patients on the nasal spray (number of trials, N=4) and the lozenge (N=6) had the greatest probability of remaining smoke-free (RR 2.02, 95% CI 1.49-3.73; RR 2.0, 95% CI 1.63-2.45 respectively). The inhaler (N=4; RR 1.9, 95% CI 1.36-2.67), the patch (N=41; RR 1.66, 95% CI 1.53-1.81), and the gum (N=53; RR 1.43, 95% CI 1.33-1.53) were also found more efficacious than placebo. Only three trials directly compared NRT therapies; none of the three found any significant difference between formulations. Two trials looked at NRT versus bupropion but neither found a significant difference in sustained quit rates. Seven trials compared combination therapy (patch + another NRT agent) with NRT monotherapy. Patients using combination therapy had higher rates of abstinence at six months than patients using one NRT (RR 1.35, 95% CI 1.11 to 1.63).

A 2009 review looked at whether anti-depressant use helps in quitting tobacco. Twelve antidepressants were assessed in this systematic review for effectiveness in tobacco cessation. FDA-approved atypical antidepressant bupropion; SSRIs fluoxetine, sertraline and paroxetine; MAO inhibitors mocolobemide, and selegiline; tricyclics nortriptyline, doxepin and imipramine; venlafaxine; tryptophan; and St. John's Wort were all included. Other inclusion criteria were RCT with a placebo or active comparator and at least six months follow up.
A meta-analysis was conducted with the data gathered from the 66 articles which met criteria. The majority of articles evaluated bupropion (number of articles, N=49) or nortriptyline (N=9). Both were found to be efficacious in helping patients remain tobacco free at six months (bupropion RR 1.69, 95%CI 1.53-1.85; nortriptyline RR 2.03 95%CI 1.48-2.78). Adding bupropion or nortriptyline to NRT was not more effective than either anti-depressant alone, and in direct comparator trials both were as effective as NRT as monotherapy. Three trials compared bupropion to varenicline. Patients in the bupropion arms had lower quit rates at six months than those in the varenicline groups (RR 0.66, 95% CI 0.53-0.82). No treatment effects were seen with venlafaxine, the SSRIs or the MAO inhibitors. No long-term data was found for St. John's Wort, tryptophan, doxepin and imipramine.

In 2011 a systematic review examined varenicline and its effectiveness as a smoking cessation agent. Articles were included if they were a RCT which compared varenicline to placebo, bupropion or NRT. All trials were required to have a follow-up period of at least six months. Fourteen trials were identified for inclusion; the majority had a placebo control (number of trials, N=11), three trials compared varenicline to bupropion and two open-label trials had a NRT comparator. The varenicline patients in all comparator trials had higher rates of tobacco abstinence: vs. placebo at six months (RR 2.31, 95% CI 2.01-2.66), vs. bupropion at one year (RR 1.52, 95% CI 1.22-1.88), and vs. NRT at six months (RR 1.13, 95% CI 0.94-1.35; not significant).

Clonidine, an alpha-2 receptor agonist, is often used off-label for smoking cessation. A 2008 updated systematic review analyzed the effectiveness of clonidine for this. Six trials were included for meta-analysis; three used transdermal clonidine and three used the oral form. All trials were RCT, placebo controlled with at least six months follow-up. Patients using clonidine had higher rates of quitting at six months than those receiving placebo (RR 1.63, 95% CI 1.22-2.18).

Patients with mental illness have higher rates of tobacco dependence than the general population. They are also more difficult to treat because of their mental illness. A 2010 systematic review evaluated smoking cessation trials in schizophrenic populations. Articles were included if they were a RCT with a schizophrenic or schizoaffective adult smoker population. Any tobacco intervention was acceptable for inclusion, although a placebo or active control was required. Unlike many tobacco cessation reviews, reduction in smoking was an outcome along with abstinence. A total of 21 articles were included for analysis; 11 trials used smoking cessation as an outcome. Of those, seven compared bupropion with placebo and found bupropion use was associated with higher quit rates at the end of treatment (RR 2.84, 95% CI 1.66-4.99) and at six months follow-up (number of trials, N=5), (RR 2.78, 95% CI 1.02-7.58). No significant differences were seen in schizophrenic symptoms (positive or negative) between the placebo and bupropion groups. Three trials compared NRT plus behavioral therapy versus routine care or placebo. No significant difference in cessation or smoking reduction was seen. Results were similar in two cross-over nicotine patch studies: no difference was seen between the patch and placebo groups. Other pharmacological interventions examined: topiramate, clozapine, atomoxetine, and galantamine were found to be either inconclusive or ineffective.

Pregnant smokers are an often targeted population for smoking cessations interventions. Smoking during pregnancy can cause demonstrated harm to the fetus and mother. Use of pharmacological tobacco abstinence agents is controversial during pregnancy, leaving behavioral therapy as the treatment of choice. A 2009 systematic review examined smoking cessation interventions during pregnancy and their success rates. Articles were included if they were a RCT with pregnant adult smokers and had a primary outcome of smoking cessation. In the 65 articles included for analysis, patients who were targeted with a smoking cessation intervention were less likely to continue smoking in the third trimester than those with no intervention (RR 0.94, 95% CI 0.92-0.96). Five of the trials employed NRT as the intervention. Using NRT did not appear to have any more efficacy than other non-pharmacologic interventions, but did cause greater safety concerns. One NRT trial was discontinued early due to large statistically significant difference between the NRT and placebo groups in adverse events, including fetal death.

Conclusions:

1. There is high quality evidence that the nicotine inhaler, nasal spray and patch are effective medications for smoking cessation.
2. There is good quality evidence that the nicotine gum and lozenge are effective medications for smoking cessation.
3. There is good quality evidence to conclude that combination NRT that includes the nicotine patch is more effective than monotherapy.
4. There is insufficient evidence to conclude if bupropion is more effective than NRT.
5. There is good quality evidence that bupropion is an effective medication for smoking cessation.
6. There is good quality evidence that nortriptyline is an effective medication for smoking cessation.

7. There is limited good-to-fair quality evidence that SSRIs fluoxetine, paroxetine, and sertraline are not effective medications for smoking cessation.
8. There is good quality evidence that varenicline is an effective medication for smoking cessation.
9. There is limited good quality evidence that varenicline is a more effective medication for smoking cessation than bupropion.
10. There is limited fair-to-poor quality evidence that varenicline is a more effective medication for smoking cessation than NRT.
11. There is limited good-to-fair quality evidence that clonidine is an effective medication for smoking cessation.
12. There is fair quality evidence that bupropion is an effective medication for smoking cessation in schizophrenic and schizoaffective populations.
13. There is insufficient evidence to conclude if NRT is an effective smoking cessation therapy in schizophrenic and schizoaffective populations.
14. There is fair-to-poor quality evidence that smoking cessation interventions in pregnant women decrease smoking rates.
15. There is insufficient evidence to conclude if NRT is a safe or effective smoking cessation therapy in pregnant populations.

Remaining Issues:

- Further studies are needed to assess the relative effectiveness and safety of the seven FDA-approved medications for long-term treatment, in general and for specific subpopulations (women; adolescents; older smokers; smokeless tobacco users; individuals with psychiatric disorders, including substance use disorders; post-myocardial infarction patients).
- Further studies are needed to evaluate the use of combined tobacco dependence medications in general and for specific subpopulations (e.g. highly dependent smokers).
- Further studies are needed to assess the effectiveness of pre-quit NRT use in increasing abstinence rates.
- Further studies are needed to address the comparative efficacy of OTC treatments versus prescription treatment
- Further study is needed to determine if smoking for a longer duration after starting varenicline is more effective at improving long-term abstinence than the original varenicline packaging recommendation of one week.

III. Guidelines

1. Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities.[9]

Developer:
National Institute for Health and Clinical Excellence

Published:
2008

Recommendations:

i. There is high quality evidence that brief interventions by healthcare professionals to advise and discuss smoking are effective in helping smoking cessation.
ii. There is high quality evidence that individual or group behavioral counseling is effective in aiding tobacco cessation.
iii. There is high quality evidence that medications available for tobacco dependence (bupropion, varenicline, and nicotine replacement therapy) are effective in assisting smoking cessation.
iv. The guideline recommends using professional judgment when prescribing tobacco cessation medication in special populations including pregnant or breastfeeding mothers and adolescents.

Critique:

The NICE smoking cessation guideline is aimed at a large target audience and is expansive in scope.
Search criteria are given in broad descriptions, but with direction to appendices with more detailed information. Internal and external peer reviews were conducted to validate the guideline. A hierarchy of Evidence Rating system was used to assess the quality and strength of the evidence
This guideline is funded by the Government of the United Kingdom.

2. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement[10]

Developer:
U.S. Preventive Services Task Force

Published:
Update 2009

Recommendations:

i. There is high quality evidence that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products
ii. There is high quality evidence that clinicians ask all pregnant women about tobacco use and provide augmented, pregnancy tailored counseling for those who smoke.

iii. There is evidence that combination of medication and counseling therapy is more effective at increasing cessation rates of either alone.

Critique:
The Task Force is an independent expert panel funded by the US Government. The target audiences for this guideline are healthcare providers in the primary care setting. Expert opinion consensus is given great weight in the guideline, particularly for subjects such as screening which are difficult to quantify using RCTs. Evidence is ranked on the strength and source of data as "high, moderate and low certainty of net benefit" and then graded through the panels consensus on the degree of magnitude of that benefit: grade A is thought to provide substantial benefit while grade D provides no benefit.

IV. FDA Safety Alerts

In 2011, the FDA reviewed new safety information for varenicline concerning cardiovascular and neuropsychiatric adverse events.[11-12] Varenicline (Chantix ®) may be associated with an increased risk of cardiovascular adverse events. The new data on cardiovascular safety came from a recent RCT evaluating the safety and efficacy of varenicline. The trial was twelve weeks of treatment with varenicline or placebo and then 40 weeks of follow-up in a population of stable cardiovascular disease patients. The continuous abstinence rate from week 9 to week 52 showed the varenicline arm was significantly more likely to remain tobacco free (OR 3.14, 95% CI 1.93- 5.11; *P*= 0.0001). However, a small number of participants experienced a serious cardiovascular adverse event, more often to the varenicline group than the control: nonfatal MI 2.0% vs. 0.9%, need for coronary revascularization 2.3% vs. 0.9%, new diagnosis of PVD 1.4% vs. 0.9%. The trial was not powered to quantify the statistical differences seen.[13]

The FDA instructed Pfizer to add the new cardiac safety information to the "Warnings and Precautions" in Chantix labeling and prescribing information. Given the risk of serious cardiovascular events occurring in this population (patients with cardiovascular disease who continue to smoke), the FDA advises weighing the risks and benefits for individual patients before treating CVD patients with varenicline. They have instructed Pfizer to conduct a large meta-analysis of RCT and will issue another update when reviewed.[12]

The FDA did not require Pfizer to alter labeling for the risk of neuropsychiatric adverse events. Two large VA and Department of Defense sponsored observational studies were recently reviewed by the FDA. Both studies compared varenicline and nicotine replacement therapy (NRT); adverse safety outcomes included hospitalizations due to neuropsychiatric events. Neither study found a difference in rates of neuropsychiatric hospitalizations between varenicline and NRT; because of this, the FDA did not advise any change to the labeling of Chantix. The FDA noted some concerns with the two studies. They were not powered to detect very rare adverse events and adverse events were tracked only when they resulted in hospitalizations. Pfizer is currently conducting a large clinical trial focused on neuropsychiatric safety. Results are anticipated in 2017.[13]

A recent clinical trial was the impetus for a change in the dosing recommendations for varenicline by Pfizer. Previously varenicline has been dosed so to allow the patient to smoke concurrently with the first week of taking varenicline and instruct patients to quit on the eighth day of varenicline use. The new alternative instructions allow patients to quit anytime between day 8 and day 35 after varenicline is started. [20]

The trial was a double-blind RCT where 659 patients were randomized in a 3:1 ratio to varenicline or placebo. Subjects received treatment for 12 weeks and were followed for an additional 24 weeks. They were instructed to quit smoking sometime between day 8 and day 35; endpoints were abstinence at weeks 9 to 12 and weeks 9 to 24. Patients in the varenicline group were more likely than the placebo subjects to be tobacco abstinent through weeks 9 to 12 (53.1% vs. 19.3%; OR 5.9, 95% CI 3.7-9.4) and weeks 9 to 24 (34.7% vs. 12.7%; OR 4.4, 95% CI 2.6-7.5). Adverse events were minor and were similar among both arms. The trial was of good to fair quality.[21]

On the basis of the success of the flexible-date trial, a small UK study set out to see if continued tobacco use for an additional three weeks after starting varenicline improved outcomes. Unlike the previous trial, this study had set quit dates. Patients were randomized to receive varenicline (n=52) or placebo (n=48) for the initial three weeks of treatment, during this time they continued smoking. After week three, all subjects were receiving varenicline and at the end week four all subject were to stop smoking. Patients who smoked during the initial four weeks of varenicline had an increased sustained abstinence rate at 12 weeks (47.2% vs. 20.8%, p=0.005) than the placebo subjects.[22] Although small, this trial was of good to fair quality. More study is needed, however, to establish if this dosing regimen or flexible dosing improves the effectiveness of varenicline.

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Appendix 1:Proposed PA Criteria

Tobacco Abstinence

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 #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 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:** Approve treatment for up to 6 months.

Appendix 2 Medication Information

NAME	STRENGTH	FORM	ROUTE	FREQUENCY
Nicotine[23] Transdermal Patch	21 mg 14 mg 7 mg	Patch	Transdermal	Over 10 cigs/day: use one 21 mg patch/day for 4-6 wk, then use one 14 mg patch/day for 2 wk, then use one 7 mg patch/day for 2 wk 10 or less cigs/day: use one 14 mg patch/day for 6 wk, then use one 7 mg patch/day for 2 wk
Nicotine[23] inhaler (Nicotrol®)	10 mg	Inhaler	Inhalation	Inhale with continuous puffing over 20 min; initial, 6 to 16 cartridges/day for up to 12 weeks, then gradually discontinue over 6 to 12 weeks; MAX 16 cartridges/day
Nicotine nasal spray[23] (Nicotrol®)	100 mg	Nasal spray	Intranasal	1 spray in each nostril initially 1 to 2 times per hour, at least 8 times/day up to MAX of 5 doses/h, 40 doses/24 h; gradually discontinue; MAX duration, 3 months
Nicotine lozenge[24]	4 mg 2 mg	Lozenge	Buccal	Patients who smoke first cigarette >30 minutes after waking: One 2-mg lozenge every 1–2 hours during weeks 1–6; then one 2-mg lozenge every 2–4 hours during weeks 7–9; and once 2-mg lozenge every 4–8 hours during weeks 10–12. Patients who smoke first cigarette ≤30 minutes after waking: One 4-mg lozenge every 1–2 hours during weeks 1–6; then one 4-mg lozenge every 2–4 hours during weeks 7–9; and one 4-mg lozenge every 4–8 hours during weeks 10–12
Nicotine gum[24]	4 mg 2 mg	Gum	Buccal	Patients who smoke <25 cigarettes daily: Chew a 2-mg piece of gum every 2 hours during weeks 1–6; chew a 2-mg piece every 2–4 hours during weeks 7–9; and chew a 2-mg piece every 4–8 hours during weeks 10–12 of therapy. Alternatively, chew a 2-mg piece of gum whenever the urge to smoke occurs; do not exceed 2 pieces (4 mg) per hour Patients who smoke ≥25 cigarettes daily: Chew a 4-mg piece of gum every 2 hours during weeks 1–6; chew a 4-mg piece every 2–4 hours during weeks 7–9; and chew a 4-mg piece every 4–8 hours during weeks 10–12 of therapy Alternatively, chew a 4-mg piece whenever the urge to smoke occurs; do not exceed 2 pieces (8 mg) per hour
Bupropion[25] Sustained-release	150 mg	Tablet	Oral	150 mg orally in the morning for 3 days, then increase to 150 mg 2 times a day (MAX dose 300 mg/day) for 7-12 weeks; treatment should begin 1 week before the patient stops smoking
Varenicline[26]	1 mg 0.5 mg	Tablet	Oral	Initial, 0.5 mg orally once daily for days 1 through 3, then 0.5 mg twice daily for days 4 through 7, then 1 mg twice daily; duration of treatment is 12 weeks; an additional 12 weeks in patients who have successfully stopped smoking may increase the likelihood of long-term abstinence
Clonidine[27]	0.3 mg 0.2 mg 0.1 mg	Tablet Patch	Oral Transdermal	Oral: Initial: 0.1 mg twice daily; titreate by 0.1 mg/day every 7 days if needed; dosage range used in clinical trials: 0.15-0.75 mg/day; duration of therapy ranged from 3-10 weeks in clinical trials Transdermal: Initial: 0.1 mg/24 hour patch applied once every 7 days and increase by 0.1 mg at 1-week intervals if necessary; dosage range used in clinical trials: 0.1-0.2 mg/24 hour patch applied once every 7 days; duration of therapy ranged from 3-10 weeks in clinical trials
Nortriptyline[28]	75 mg 50 mg 25 mg	Capsule	Oral	25 mg daily, and then gradually increase to a target dosage of 75–100 mg daily Initiate nortriptyline therapy 10–28 days before date set for cessation of smoking Nortriptyline was continued for approximately 12 weeks in clinical studies