Tobacco Harms, Nicotine Pharmacology, and Pharmacologic Tobacco Cessation Interventions for Women

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Firsthand and secondhand tobacco use is linked to a multitude of harmful illnesses, adverse perinatal outcomes, and death. Cessation attempts among women may be hampered by their unique biologic response to nicotine. Current research has revealed epigenetic changes from intrauterine nicotine exposure that have intergenerational consequences. Multiple studies have demonstrated the efficacy of various pharmacologic tobacco cessation interventions in conjunction with behavioral counseling. Based on this evidence, the US Preventative Services Task Force (USPSTF) 2015 guideline recommends pharmacologic therapy for all nonpregnant persons who smoke in addition to behavioral counseling. The effectiveness of pharmacologic treatments among pregnant women is less clear, with far fewer studies evaluating potential benefits and harms. While exposure to pharmacologic therapies raises concerns for fetal safety, these potential risks must be weighed against those of continued tobacco use, which guarantees fetal exposure to nicotine. First-line tobacco cessation medications include nicotine replacement therapy (NRT), bupropion, and varenicline. Second-line medications include nortriptyline and clonidine. Pharmacokinetics, effectiveness, regimens, and safety profiles for nonpregnant, pregnant, and lactating women are reviewed. Alternative tobacco cessation options and potential new pharmacologic tobacco cessation agents are discussed. Initiating brief interventions, using the 5A's and 5R's model is described.

Keywords: breastfeeding, bupropion, clonidine, electronic nicotine delivery systems, nicotine, nicotine replacement therapy (NRT), nortriptyline, pregnancy, smoking, smoking cessation, tobacco cessation, varenicline

INTRODUCTION

According to the World Health Organization there are currently one billion persons who smoke in the world, with 6 million deaths yearly due to tobacco use.[1] In the United States, 21.3% of adults used tobacco products regularly, and a total of 25.5% of adults reported at least some use in 2013 through 2014.[2] Use of tobacco products is the most common cause of premature death, responsible for 20 million early deaths in the United States during the past 50 years.[3] While the majority of these deaths occurred in persons who smoked, approximately 15% occurred in non–tobacco users who were exposed to secondhand smoke.[3]

Tobacco addiction involves a complex interplay between genetics, epigenetics, environment, and psychological state. Cigarettes can contain up to 4000 chemicals and, when burned, up to 7000 chemical compounds.[3] These include nicotine, hydrocarbons, carbon monoxide, fungicides, pesticides, and hundreds of additives. Tobacco can contain heavy metals, including lead and mercury, that are released when burned.[4] Sixty-nine of these chemicals are carcinogenic, and hundreds more are toxic.[3]

Despite the myriad of associated health care risks associated with smoking, 13.6% of US women smoke.[2] Women may feel tobacco cessation would be too difficult to attempt, may not believe smoking is that harmful, or may have tried to quit in the past and been unsuccessful. Some women fear the medications used for tobacco cessation. During pregnancy, women may continue to smoke because they believe it reduces their anxiety and depression, despite having feelings of guilt or shame about exposing their fetus to nicotine.[5,6] Some women do not quit because they smoked through a previous pregnancy without apparent harm to the fetus or due to concerns that the stress of quitting will negatively affect the pregnancy.[5]

Although it is common knowledge among clinicians that tobacco use has major health consequences, clinicians may struggle to assist women with tobacco cessation. Clinicians may also have concerns about tobacco cessation medications or may be unfamiliar with safety and risk profiles.[7] Understanding the complex issues surrounding tobacco cessation and women, available pharmacologic support, and use of brief interventions will improve the clinician's ability to encourage and support women during quit attempts.[7] Although a detailed review of the harms associated with tobacco use is beyond the scope of this article, interested readers are referred to *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*, published in 2014.[3]

PHARMACOLOGY OF NICOTINE ADDICTION

Nicotine is the primary addictive substance in tobacco. Nicotine is absorbed through skin, mucous membranes in the mouth and nose, and pulmonary alveoli. Nicotine diffuses rapidly into the bloodstream when tobacco is smoked, reaching a maximum blood concentration within 5 minutes. When administered transdermally, the peak blood concentration

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Quick Points

- Women use and metabolize tobacco differently than men, which affects their ability to quit.
- Epigenetic research demonstrates multigenerational harm associated with tobacco use during pregnancy.
- Used alone or in combination, tobacco cessation medications significantly improve long-term abstinence rates.
- Behavioral interventions are the first-line approach for pregnant women.
- The safety and effectiveness of tobacco cessation medications has limited evidence for use during pregnancy.
- Nicotine replacement therapy is considered an option during lactation. Bupropion and varenicline safety during lactation are unknown.
- Clinicians should use brief intervention strategies, including the 5A's and 5R's, at each office encounter.

occurs after several hours.[4] When smoked, nicotine reaches the brain in less than 20 seconds, where it binds to neuronal nicotinic acetylcholine receptors.[4] These receptors function primarily to regulate release of multiple neurotransmitters including dopamine and serotonin, as well as norepinephrine, acetylcholine, glutamate, and endorphins.[4,8] The addictive effect of nicotine is thought to be primarily through the increased release of dopamine in the midbrain, which is part of the neuronal reward system.[4,8] Nicotinic acetylcholine receptor sites are widespread outside of the central nervous system as well and can be found in the peripheral nervous system, respiratory tract, endothelial cells, and immune system.[9]

The rapid neuronal response to nicotine positively reinforces smoking behavior. Other aspects of addiction include the environmental context, the expectation of increased well-being, and the association of smoking with pleasurable activities. Continued smoking is also supported by negative reinforcement: reduction of negative states such as pain, poor concentration, or withdrawal symptoms.[4]

Nicotine is metabolized to cotinine primarily in the liver, by the cytochrome 450 enzyme system, specifically *CYP2A6*.[8] Recent research demonstrates 173 genetic variants in the *CYP450* system.[10] These genetic variations affect how rapidly an individual metabolizes nicotine. The rate of metabolism affects the frequency and amount of nicotine used and the individual's susceptibility to tobacco-related disease.[8,10–13] For example, central nervous system effects of nicotine are more prolonged in those who metabolize nicotine slowly, increasing their likelihood of becoming addicted, but also increasing success with tobacco cessation. Persons who metabolize nicotine more rapidly will increase their frequency of smoking in response to dropping nicotine levels and are more responsive to nicotine replacement therapy (NRT) than those who metabolize nicotine less rapidly.[8,10,13] Recent studies have demonstrated genome-wide variations as well. African American, Asian, and American Indian individuals are generally slower metabolizers of nicotine.[8,11] These pharmacogenetic and pharmacogenomic factors have implications when choosing what pharmacologic assistance to offer for nicotine cessation.

Nicotine blood concentration drops within a few hours after smoking a cigarette, triggering behavioral, cognitive, and physical symptoms known as withdrawal.[14] Symptoms may include irritability, anger, anxiety, restlessness, dysphoria, difficulty concentrating, and sleep fragmentation, all of which usually peak in the first week and resolve over 2 to 4 weeks, although some individuals have symptoms for 6 months or more.[14] Physical symptoms, including hunger and weight gain, are widely reported but inconsistent.[14]

The Effects of Tobacco in Women

Women use, absorb, and metabolize tobacco differently than men. Women tend to metabolize nicotine more rapidly than men, due to more cytochrome *CYP2A6* activity, which appears to be associated with estrogen levels.[8] Women may be more likely than men to suffer health harms from smoking, including more rapidly declining pulmonary function at the same level of nicotine exposure and more frequent development of chronic obstructive pulmonary disease.[15] Compared to men, women are more likely to have more psychological dependence on smoking.[15,16]

Women are more likely than men to smoke in order to avoid negative states or to help them cope with negative emotions, especially depression and anxiety.[15–17] Women also have more difficulty quitting overall, with more withdrawal symptoms, more negative affect, and lower cessation rates.[15] Avoidance of these negative symptoms is frequently used as a rationale for continued smoking and/or failed tobacco cessation attempts.[16]

Dietz et al discovered that pregnant women, African American, and Hispanic populations have higher rates of nondisclosure than nonpregnant women who smoke and members of other ethnic groups.[18] A pregnant woman's resistance to self-disclosure is often associated with feelings of guilt and shame associated with strong social stigma.[6] In addition, approximately 25% to 35% of pregnant women who quit smoking relapse during their pregnancy.[19]

Effect of Nicotine Use During Pregnancy

Nicotine readily crosses the placenta, where it binds to fetal neuronal acetylcholine receptors.[20] Nicotine also appears to harm the placenta itself, altering both placental development and function.[21] Sbrana et al found multiple markers associated with increased oxidative stress and abnormal metabolism in the placenta of women who smoked.[22] Abnormal placental

function, including restriction of oxygen and nutrient transfer across the placenta, are the putative etiologies underlying the known associations between smoking and preterm birth (PTB) and low birth weight (LBW).[21,22]

Animal and human studies have revealed several harmful effects of nicotine, including reduction in uterine artery blood flow; variable changes in fetal oxygenation and acid-base balance; fetal neurotoxicity leading to delayed or impaired brain development; delayed lung maturation causing diminished lung size, volume, and function; and increased risk of sudden infant death syndrome.[7,20,23] Many of these effects on the fetus are due to abnormal DNA methylation, leading to aberrant protein binding that interrupts the transcription of DNA, changing gene expression.[20] Mitochondrial DNA (mDNA) is also damaged by maternal smoke exposure, leading to excess mDNA copies made to cope with the state of decreased energy availability. These excess and abnormal mDNA copies are found in the cord blood of newborns with poor outcomes following prenatal exposure to nicotine.[20] In addition, since mDNA is maternally inherited, there is concern for damage to future generations of children, even if they are not directly exposed to nicotine.[20]

The epigenetic changes caused by abnormal activation of nicotinic acetylcholine receptors during early brain development may be the mechanism for the increased incidence of attention deficit hyperactivity disorder, depressive disorders, reduced cognitive and academic ability, and other neurobehavioral problems in children of mothers who smoke.[20,24] In contrast to adults, prenatal exposure to nicotine desensitizes neurotransmitter actions in the fetus. The resulting symptoms of depression, inattention, and hyperactivity in adolescents and adults appear to be partially corrected by nicotine use, suggesting a biologic basis for future smoking addiction.[20]

FIRST-LINE PHARMACOLOGIC AGENTS FOR TOBACCO CESSATION

Nicotine Replacement Therapy

The US Preventive Services Task Force (USPSTF) 2015 guideline recommends tobacco cessation counseling and pharmacologic treatment for all persons who smoke tobacco.[25] NRT provides nicotine without the other harmful substances found in tobacco smoke. US Food and Drug Administration (FDA)-approved NRT includes over-the-counter gum, lozenges, or patches, and 2 prescription options: a nasal spray or an inhaler.[7] This variety of delivery options and the ability to titrate use allows persons attempting tobacco cessation to feel in control over cravings and nicotine withdrawal symptoms. Multiple studies have shown that NRT is an effective aid in achieving tobacco abstinence, generally doubling successful long-term cessation rates when compared to placebo (Table 1).[25–27]

The various formulations of NRT are considered almost equally effective, with inhaler, nasal spray, or lozenge being marginally superior to nicotine gum.[27] Combination NRT typically includes an NRT patch with an intermittent formulation like gum, lozenge, nasal spray, or inhaler. The patch supplies a steady level of nicotine, while an intermittent delivery method provides peak serum levels within 10 to 20 minutes, allowing the woman to adjust to withdrawal symptoms.[27] Combination NRT yielded higher quit rates when compared to single-method NRT and bupropion (Wellbutrin SR, Zyban) and has shown equivalent efficacy to varenicline (Chantix).[27] The safety of various NRT formulations and regimens have been well established, but relative contraindications include cardiac arrhythmias, angina, and recent myocardial infarction.[7] Table 2 summarizes the uses of tobacco cessation medications.

Bupropion

The antidepressant, bupropion, has demonstrated efficacy in tobacco cessation, with long-term tobacco abstinence rates similar to those found among users of NRT (Table 1).[7,26,28] Bupropion increases available dopamine while acting as a nicotinic acetylcholinergic receptor partial agonist that blocks the effect of nicotine.[28,35] Consequently, the urge to smoke and nicotine withdrawal symptoms are reduced.[28] Additionally, women who smoke may be drawn to bupropion because of its ability to decrease weight gain associated with tobacco cessation. Unfortunately, once bupropion is stopped, weight gain is similar to having never used the medication.[7]

Since bupropion takes a week to achieve a steady state, women are advised to select a quit date within the first 2 weeks of starting bupropion therapy. Recent research has shown that a dosage of 150 mg per day is as effective as the traditional dosage of 300 mg per day.[26,28] The recommended length of treatment is 7 to 12 weeks, but longer treatment lengths may be considered. Cessation is less likely to occur among those who are still smoking despite 7 weeks of continuous therapy.[28]

The most common side effects of bupropion use include dry mouth, insomnia, and nausea.[26,28] Titrating the dosage during the first week of use appears to decrease the frequency of common side effects.[35] Although there have been concerns that bupropion is related to an increased risk of seizures, research among smoking populations has found that seizures are rare and affect approximately 1 of 1000 to 1 of 1500 individuals (Table 2).[27,28]

Varenicline

As a selective nicotinic receptor partial agonist, varenicline offsets nicotine withdrawal symptoms through the release of dopamine while reducing smoking reward by blocking nicotinic dopaminergic activation.[29] Several studies have confirmed the efficacy of varenicline taken in a dosage of 1 mg twice per day to successfully increase long-term tobacco cessation by 2- and 3-fold compared to nonpharmacologic quit attempts.[27,29] When compared to single forms of NRT or bupropion, successful quit rates are higher with use of varenicline.[27,29] In contrast, equal effectiveness occurred when varenicline and combination NRT long-term quit rates were compared (Table 1).[27,29]

Flexible quit dates, as well as flexible dosing regimens from 0.5 mg to 2 mg per day over a 12-week period, are well tolerated and effective.[29] The standard dosage of 1 mg taken twice per day has been found to have a modest increase in cessation rates compared to 1 mg per day dosing (relative risk [RR],1.25; 95% confidence interval [CI], 1.0-1.55).[27,29] When compared to placebo, low-dose regimens have been found to

Table 1. Results of Studies Evaluating Pharmacologic Tobacco Cessation Interventions Among the General Population

Author, Year of Publication Study Design	Sample and Description	Results
Cahill et al[27] 2013 Cochrane systematic review	267 trials N = 101,804 Meta-analysis of RCTs of pharmacologic treatments for tobacco cessation	NRT was more effective than placebo (OR, 1.84; 95% CI, 1.71-1.99; 119 trials, n = 51,265). Combination NRT was more effective than single NRT (RR, 1.34; 95% CI, 1.18-1.51; 9 trials, n = 4664). Bupropion was more effective than placebo (OR, 1.82; 95% CI, 1.60-2.06; 36 trials, n = 11,440). Bupropion and NRT were equally effective (OR, 0.99; 95% CI, 0.86-1.13; 9 trials, n = 1763). Bupropion with NRT was not more effective than NRT alone (RR, 1.23; 95% CI, 0.67-2.26; 6 trials, n = 1106). Varenicline was more effective than placebo (OR, 2.88; 95% CI, 2.40-3.47; 15 trials, n = 7474). Varenicline low dose was more effective than placebo (RR, 2.09; 95% CI, 1.56-2.78; 4 trials, n = 1272). Varenicline was more effective than single forms of NRT (OR, 1.57; 95% CI, 1.29-1.9; indirect comparison). Varenicline and combination NRT were equally effective (OR, 1.06; 95% CI, 0.75-1.48; indirect comparison). Varenicline was more effective than bupropion (OR, 1.56; 95% CI, 1.26-1.93; 3 trials, n = 1622). Nortriptyline with NRT was not more effective than NRT alone (RR, 1.29; 95% CI, 0.97-1.72; 4 trials, n = 1219). Clonidine was more effective than placebo (RR, 1.63; 95% CI, 1.22-2.18; 6 trials, n = 776). Cytisine was more effective than placebo (RR, 3.98; 95% CI, 2.01-7.87; 2 trials; n = 937).
Hughes et al[28] 2014 Cochrane systematic review	73 trials N = 29,856 Meta-analysis of RCTs of antidepressants for tobacco cessation	Bupropion was more effective than placebo (RR, 1.62; 95% CI, 1.49-1.76; 44 trials, n = 13,728). Bupropion and NRT were equally effective (RR, 0.96; 95% CI, 0.85-1.09; 8 trials, n = 4096). Bupropion with NRT was not more effective than NRT alone (RR, 1.19; 95% CI, 0.94-1.51; 12 trials, n = 3487). Nortriptyline was more effective than placebo (RR, 2.03; 95% CI, 1.48-2.78; 6 trials, n = 975). Nortriptyline with NRT was not more effective than NRT alone (RR, 1.21; 95% CI, 0.94-1.55; 4 trials, n = 1644). Bupropion and nortriptyline were equally effective (RR, 1.30; 95% CI, 0.85-1.09; 3 trials, n = 417).

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Table 1. Results of Studies Evaluating Pharmacologic Tobacco Cessation Interventions Among the General Population

Author, Year of Publication Study Design	Sample and Description	Results
Cahill et al[29] 2016 Cochrane systematic review	39 trials N = 25,290 Meta-analysis of RCTs of nicotine receptor partial agonists for tobacco cessation	Varenicline 1 mg twice/day was more effective than placebo (RR, 2.24; 95% CI, 2.06-2.43; 27 trials, n = 12,625). Varenicline 1 mg/day or variable doses (mean 1.35 mg/day) were more effective than placebo (RR, 2.08; 95% CI, 1.56-2.78; 4 trials, n = 1266). Varenicline was more effective than NRT (RR, 1.25; 95% CI, 1.14-1.37; 8 trials, n = 6262). Varenicline was more effective than bupropion (RR, 1.39; 95% CI, 1.25-1.54; 5 trials, n = 5877).
Anthenelli et al[26] 2016 RCT	N = 8144 Comparison of varenicline, bupropion, and nicotine patch to placebo	Nicotine patch was more effective than placebo (OR, 1.81; 95% CI, 1.49-2.19; n = 2048). Bupropion was more effective than placebo (OR, 1.89; 95% CI, 1.56-2.29; n = 2034) and equivalent to the patch (OR, 1.04; 95% CI, 0.88-1.24). Varenicline was more effective than placebo (OR, 2.74; 95% CI, 2.28–3.30; n = 2037), bupropion (OR, 1.45; 95% CI, 1.24–1.70), and NRT patch (OR, 1.52; 95% CI, 1.29-1.78).
Koegelenberg et al[30] 2014 RCT	N = 435 Varenicline versus varenicline combined with NRT	Varenicline combined with NRT patch was more effective than varenicline alone (OR, 2.13; 95% CI, 1.32-3.43).

Abbreviations: CI, confidence interval; NRT, nicotine replacement therapy; OR, odds risk; RCT, randomized control trial; RR, relative risk.

Table 2. Tobacco Cessation Pharmacotherapy: Dosage, Patient Education, Safety, Common Side Effects, and Efficacy

Medication	Dosage	Patient Instructions	Safety	Common Side effects	Efficacy
NRT[a]	See individual formulations	See individual formulations	Despite reports of possible increase in chest pains and heart palpitations, NRT does not appear to increase cardiac disease. Relative contraindications: cardiac arrhythmias, angina, recent myocardial infarction. Warn to keep out of reach of children or pet. Potential to lower intrauterine and breast milk nicotine levels. Nicotine linked to SIDS, and decreased lung development.	Most side effects are minor with minimal SAE. Smoking or NRT can decrease milk supply. See individual formulations	NRT can double the chances of long-term cessation in the general population. Combination NRT increases effectiveness. Inconclusive study results for efficacy during pregnancy.
Nicotine gum[a] (Nicorette)	2-4 mg gum, as needed; up to 24, 2 mg pieces/day or 20, 4 mg pieces/day ≤ 12 weeks. If first cigarette < 30 minutes after rising or smokes > 10 cigarettes/day, use 4 mg dose.	OTC; Nothing by mouth 15 min prior and during use. Chew gum slowly until a tingling or nicotine peppery taste occurs, then park gum between cheek and gums. Begin to chew again as tingling fades, repeating the process until tingle gone (30 minutes). May repeat once within the hour.	Category C[c,d]	Mouth soreness, hiccups, dyspepsia, and jaw ache; these are usually mild and transient.	

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Medication	Dosage	Patient Instructions	Safety	Common Side effects	Efficacy
Nicotine lozenges[a] (Nicorette lozenge)	2-4 mg lozenge, as needed up to 20 lozenges/day ≤ 12 wks. Use 4 mg dose if < 30 minutes to first cigarette after rising or smokes > 10 cigarettes/day.	OTC; nothing by mouth 15 minutes prior and during use. Slowly dissolve; may park between cheek and gums; don't chew and minimize swallowing while dissolving.	Category C[c,d]	Mouth soreness, hiccups, and dyspepsia; these are usually mild and transient.	
Nicotine inhaler[a] (Nicotrol)	10 mg cartridge as needed up to 16/day ≤ 12 weeks	Stop smoking before use. Patients may self-titrate to the level of nicotine they require. Most successful patients in the clinical trials used 6-16 cartridges/day. Best effect was achieved by frequent continuous puffing (20 minutes).	Category C[c,d]	Local irritation in mouth and throat	
Nicotine nasal spray[a] (Nicotrol NS)	Each actuation of 0.5 mg/spray. Use 1 spray/nostril with urge to smoke as needed up to 40 mg/day (80 sprays) ≤ 12 weeks.	Stop smoking with initiation; administer with head tilted slightly back, avoiding sniffing, swallowing, or inhaling while administering.	Category C[c,d]	Chest tightness, nasal irritation, dyspepsia, tingling in limbs, constipation, stomatitis.	

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Medication	Dosage	Patient Instructions	Safety	Common Side effects	Efficacy
Nicotine patch[a] (Nicoderm)	21 mg, 14 mg, or 7 mg patch 16-24 h/day. If > 10 cigarettes/day or if < 30 min to first cigarette after rising begin with 21 mg patch for 6 weeks, then 14 mg patch for 2 weeks, then 7 mg patch for 2 weeks. If < 10 cigarettes/day begin with 14 mg patch for 6 weeks, then 7 mg patch for 2 weeks.	OTC; Stop smoking with initiation. Apply to a clean, dry, hairless location on the upper chest, upper arm, or hip. Rotate application sites; remove before bed to decrease insomnia and strange dreams.	Category D[c,d]	Skin irritation, insomnia	
Bupropion SR[a] (Zyban; Wellbutrin SR)	150 mg/day for 3 days, then increase to 150 mg twice per day for 7-12 wks.	Begin 1-2 weeks before quit date.	Seizure risk 1:1000-1:1500; Exclude use if history of seizures or eating disorders; Category C[c,d]; Breastfed infant exposure 0.2% of weight adjusted maternal dose with limited data available for potential side effects.	Dry mouth, insomnia, nausea	Equivalent to NRT doubling long-term cessation rates in the general population. Insufficient and inconclusive study results for efficacy during pregnancy.

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Table 2. Tobacco Cessation Pharmacotherapy: Dosage, Patient Education, Safety, Common Side Effects, and Efficacy

Medication	Dosage	Patient Instructions	Safety	Common Side effects	Efficacy
Varenicline[a] (Chantix)	Start 0.5 mg/day for 3 days, then increase to 0.5 mg twice per day for 4 days, then increase to 1 mg twice per day for 12 weeks. Low-dose regimen: Start 0.5 mg/day for 3 days, then increase to 0.5 mg twice per day for 12 weeks.May continue 6 mon for maintenance.	Begin 1-2 weeks before quit date. Nausea resolves with time. Taking last dose at suppertime may reduce insomnia.	FDA warns use may be associated with cardiovascular events. Current evidence indicates small possible risk of neuropsychiatric events among those with psychiatric disorders. Cardiovascular events may be slightly increased among those already at risk for these illnesses. Benefit appears to outweigh risk. Category C[c,d]; no data evaluating safety for pregnancy or lactation.	Nausea, insomnia, abnormal dreams, headache	Considered the most effective tobacco cessation aid. Increases long-term cessation by 2-3 times compared to placebo. Quit rates similar to combination NRT. No data evaluating efficacy during pregnancy or lactation.
Clonidine[b] (Catapres, Kapvay)	Initial dose: 0.1 mg twice daily, may increase weekly by 0.1 mg if needed; transdermal patch 0.10-0.20 mg/day in a weekly patch.	Initiate up to 3 days before or on quit date. Apply transdermal patch weekly to a clean, dry, hairless location between neck and waist. Side effects strongly related to dosage. Avoid driving or other hazardous activities if sedating. Do not discontinue therapy abruptly.	Category C[c,d]; not shown to be effective in pregnant women; Recommendation to use other agents due to relatively high serum levels and potential side effects in breastfed infants.	Dry mouth, drowsiness, dizziness, sedation, constipation, postural hypotension. Abrupt discontinued use can cause nervousness, agitation, headache, tremor.	Increases quit rates compared to placebo; less effective than other forms of pharmacologic cessation aids. No data evaluating efficacy during pregnancy or lactation.

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Table 2. Tobacco Cessation Pharmacotherapy: Dosage, Patient Education, Safety, Common Side Effects, and Efficacy

Medication	Dosage	Patient Instructions	Safety	Common Side effects	Efficacy
Nortriptyline[b] (Palemor, Aventyl HCL)	Initiate 25 mg/day increasing gradually to 75-100 mg/day for 12 weeks; may consider extending up to 6 months; consider titrating serum levels according to APA Guidelines for depression.	Choose quit date 10-28 days after initiated. If side effects impair physical abilities avoid driving.	Contraindicated if history of MI or have arrhythmias or severe liver disease. Category D[c,d]; not shown to be effective in pregnant women; breastfed infants serum levels range 0%-24% of maternal plasma levels. No adverse effects have been reported with maternal dosages of 25 to 175 mg/day.	Dry mouth, blurred vision, urinary retention, lightheaded, and shaky hands	Doubles quit rates compared to placebo. Efficacy similar to NRT and bupropion.

Abbreviations: APA, American Psychiatric Association; FDA, US Federal Drug Administration; MI, myocardial infarction; OTC, over-the-counter; SAE, serious adverse events; SIDS, sudden infant death syndrome.
[a] First-line FDA-approved tobacco cessation medications.
[b] Second-line non-FDA-approved tobacco cessation medications.
[c] FDA Pregnancy risk letter categories that may continue to be used in package inserts until June 29, 2018: Category C = Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women, but potential benefits may outweigh potential risks; Category D = There is positive evidence of fetal risks based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may be acceptable for use in pregnant women despite potential risks.[31]
[d] A new FDA pregnancy and lactation labeling final rule went into effect June 30, 2015. The new rule replaces pregnancy letter categories with narrative sections and subsections for pregnancy, lactation, and females and males of reproductive potential. Prescription drugs approved after June 2001 package inserts will gradually be replaced with the new labeling. Drugs approved prior to June 30, 2001, are not subject to the new rule but must remove pregnancy letter categories by June 29, 2018. Labeling for over-the-counter drugs will not change.[31]
Sources: Fiore et al[7]; Cahill et al.[27] Nicotine: Lexicomp.[32] Clonidine: LactMed Data Bank.[33] Nortriptyline: LactMed Data Bank.[34]; Bupropion hydrochloride: Lexicomp.[35] Varenicline: Lexicomp.[36] Bupropion: LactMed Data Bank.[37]

effectively increase cessation rates with fewer side effects (RR, 2.08; 95% CI, 1.56-2.78).[27,29] An extension of treatment for an additional 12 weeks is warranted to improve likelihood of long-term cessation among those who can successfully quit at least one week prior to the end of the first 12 weeks.[29]

The most common side effect among varenicline users is mild to moderate nausea that tends to resolve with time.[29] Additional varenicline side effects, in decreasing frequency, include insomnia, abnormal dreams, and headaches (Table 2).[29] In 2008, a black box warning was added to varenicline and bupropion labeling in response to early postmarketing concerns of potential associations with neuropsychiatric adverse events. Extensive research involving large observational cohort studies and meta-analysis of randomized controlled trials (RCTs) have not been able to confirm these concerns.[26] A recent large RCT evaluating NRT, bupropion, and varenicline with the occurrence of neuropsychiatric adverse events in populations with and without a history of psychiatric disorders found there was no association of moderate-to-severe neuropsychiatric events among persons without psychiatric disorders.[26] Although the findings were less clear for those persons with preexisting psychiatric disorders, the authors concluded that any increased risk in this group would be small.[26] In response to these findings, the FDA is removing the black box warning of potential associations with neuropsychiatric adverse events from varenicline and bupropion labeling.[31] Finally, varenicline may be associated with a slight increased risk in cardiovascular events among persons already at risk for cardiovascular disease.[29] It is anticipated that a recently completed study evaluating cardiac events following use of varenicline will provide clarification.[29]

Combination Pharmacology

NRT may be combined with varenicline or bupropion. An RCT comparing varenicline with a nicotine patch to varenicline plus placebo patch found varenicline in combination with a nicotine patch to have significantly higher abstinence rates than varenicline alone.[30] Although varenicline plus nicotine patch users experienced more side effects, only skin reactions reached statistical significance, while the varenicline-only group had more abnormal dreams and headaches.[30] In 6 studies, bupropion plus NRT was equally effective as NRT alone (Table 1).[27]

Other Pharmacologic Agents for Tobacco Cessation

When first-line medications are contraindicated or do not achieve tobacco cessation, there are 2 second-line non-FDA-approved pharmacologic agents that may be considered.[7,27] Clonidine (Catapres, Kapvay), an antihypertensive drug, has been shown to aid in withdrawal symptoms and improve quit rates (Table 1).[27] Close supervision is required as dose-related side effects of sedation and postural hypotension may occur (Table 2).[27] Nortriptyline (Pamelor, Aventyl HCL), a tricyclic antidepressant, may assist in minimizing the depressive symptoms associated with tobacco cessation.[34] Several RCTs have demonstrated that nortriptyline tobacco cessation is effective and has minimal side effects (Table 1).[27]

TOBACCO CESSATION PHARMACOTHERAPY DURING PREGNANCY

Pregnancy is considered an ideal time for smoking cessation. As many as 45% of women who smoke quit before their first prenatal visit, a quit rate significantly higher than found in the general population.[38,39] However, the increasing levels of estrogen during pregnancy further activates the *CYP450* system, causing more rapid metabolism of nicotine, thus making it harder to quit.[15] In addition, pregnant women who metabolize nicotine more rapidly are less likely to be successful in quit attempts.[40] Women who continue to smoke during pregnancy also may differ demographically from those who spontaneously quit, in having less social support and lower educational and socioeconomic levels.[38,41] In addition, some studies have shown an association between higher levels of depression and stress in women who continue to smoke compared to those who stop smoking during pregnancy.[38,41,42] A woman's perception that smoking reduces increased stress associated with pregnancy may influence the decision to continue smoking.[42]

Cessation of tobacco use in pregnancy is associated with improved pregnancy outcomes, with clinical trials revealing an 18% drop in LBW and PTB and an average increase of 39 grams in birth weight.[38,41] A large prospective cohort study revealed no association with LBW if tobacco cessation was achieved by the 18th gestational week.[43] Although tobacco cessation holds the greatest potential for reducing risks, reduction in number of cigarettes smoked to fewer than 9 per day may modify the risk of LBW and PTB.[43]

In 2015, the USPSTF reaffirmed their 2009 recommendation to use behavioral interventions to assist pregnant women with tobacco cessation.[25] Behavioral interventions are effective for 15% of the women who do not spontaneously quit smoking during pregnancy.[25] For the 85% who find behavioral interventions ineffective, additional intervention strategies can be considered. Research on the safety and effectiveness of FDA-approved tobacco cessation pharmacologic interventions in pregnancy is limited and results are conflicting, requiring the woman and clinician to weigh their associated potential benefits and risks.

Nicotine Replacement Therapy

NRT is the most studied pharmacologic intervention for pregnant women. Compared to smoking, diminished levels of nicotine and cotinine are seen during pregnancy among women using nicotine gum and nasal spray.[44,45] Similarly, use of the nicotine patch results in lower cotinine levels with comparable or reduced levels of nicotine.[45,46] The impact of NRT on maternal blood pressure, pulse, fetal heart rate, and uterine and umbilical artery resistance index is similar to continued smoking.[45,46] In addition, NRT use decreases exposure to the other toxic chemicals found in cigarettes and is meant to be a short-term intervention leading to total tobacco cessation.

Even though all forms of NRT are documented to significantly increase long-term cessation rates in the general population, studies evaluating the effectiveness and outcomes of NRT in pregnancy have had inconsistent findings.[6,25,39] While an earlier meta-analysis found significant

Table 3. Results of Systematic Reviews Evaluating Pharmacologic Tobacco Cessation Interventions Among the Pregnant Population

Author, Year of Publication Study Design	Sample and Description	Results
Coleman et al[39] 2015 Cochrane systematic review	9 trials N = 2210 Meta-analysis of RCTs of NRT for tobacco cessation during pregnancy with subgroup analysis of placebo and nonplacebo controlled trials.	NRT with behavioral support increased smoking cessation compared to behavioral counseling and placebo or behavioral counseling alone (RR, 1.43; 95% CI, 1.03-1.93; 8 trials, n = 2199). Subgroup analysis of 5 placebo controlled trials indicated NRT with behavioral support did not significantly increase smoking cessation (RR, 1.28; 95% CI, 0.99-1.66; 5 trials, n = 1926). Subgroup analysis of 3 nonplacebo controlled trials indicated NRT with behavioral support increased smoking cessation (RR, 8.51; 95% CI, 2.05-35.28; 3 trials, n = 273).
Myung et al[47] 2012 Meta-analysis	7 trials N = 1386 Meta-analysis of RCTs of pharmacologic treatments for tobacco cessation during pregnancy with subgroup analysis of placebo and nonplacebo controlled trials.	Pharmacotherapy (various forms for NRT, patch, gum, lozenges, and bupropion) increased smoking cessation (RR, 1.80; 95% CI, 1.32-2.44; 7 trials, N = 1386). Nicotine patch was more effective than placebo or no medication (RR, 1.60; 95% CI, 1.05-2.43; 4 trials, n = 967). Bupropion was more effective than no medication (RR, 3.33; 95% CI, 1.06-10.49; 1 trial, n = 44). Subgroup analysis of 3 placebo controlled trials indicated pharmacotherapy did not significantly increase smoking cessation (RR, 1.25; 95% CI, 0.86-1.82; 3 trials, n = 474). Subgroup analysis of 4 nonplacebo controlled trials indicated pharmacotherapy increased smoking cessation (RR, 3.17; 95% CI, 1.83-5.50; 4 trials, n = 912).

Abbreviations: NRT, nicotine replacement therapy; RCT, randomized controlled trial; RR, relative risk; CI, confidence interval.

improvement in cessation rates using NRT versus placebo or counseling, these results were not supported by a 2015 Cochrane review.[39,47] Although rates of tobacco cessation were increased by roughly 40% among the participants using NRT, when nonplacebo RCTs were omitted from analysis, NRT and placebo were found to be equally effective (Table 3).[39]

In 2015, the USPSTF review of systematic reviews concluded that the evidence evaluating the effects of NRT during pregnancy is insufficient to weigh the balance of benefits and harms of use.[25] Finally, a 2016 longitudinal cohort study found a 79% absolute cessation rate among women using a nicotine patch for a median duration of 54 days (36-72 days). After discontinuing the patch, 68% of these women did not smoke again during or after pregnancy.[48] The nicotine patch was associated with a lower risk of PTB (adjusted odds ratio [OR], 0.21; 95% CI, 0.13-0.34) and small-for-gestational-age (SGA) infants (adjusted OR 0.61; 95% CI, 0.41-0.91). The authors noted that the duration of nicotine patch use (5-10 weeks) was longer compared with other studies (2-4 weeks).[48]

Although the evidence is limited, NRT has not been directly linked to adverse perinatal outcomes.[25,39,47] Higher abstinence rates and lower cotinine levels among NRT intervention groups may have contributed to several studies finding fewer adverse outcomes of LBW and PTB and higher birth weights.[25,47] In addition, one large trial evaluating 2-year-old children found a higher survival rate with no impairment (ie, disability or behavior and development problems) among the women using NRT compared to women using placebo (73% vs 65%).[49]

Information regarding the effectiveness of different NRT formulations is limited, with most trials using a patch as the method of nicotine replacement. The low rate of adherence among women randomized into NRT study groups contributes to the difficulty of fully evaluating the effectiveness and safety of NRT in pregnancy.[50] In addition, the change in nicotine pharmacokinetics in pregnancy may decrease the effectiveness of standard NRT dosages, contribute to cessation difficulty, and indicate a need for initially using a higher NRT dosage.[51] The association of higher cessation rates among women using NRT for a longer duration of time supports the importance of using an adequate dosage and treatment length.[48]

NRT initiation instructions for pregnant women are similar to those who are not pregnant. Once an adequate dosage

is established, use should be maintained for 4 to 6 weeks prior to beginning a gradual taper (Table 2). An advantage to using an intermittent formulation is the lower total daily dosage of nicotine compared to the continuous dosage from a nicotine patch.[52] When patches are used, the recommendation is to limit the time worn to 16 hours per day, as clinical data indicate 16 or 24 hours are equally effective.[51]

Bupropion

While bupropion avoids fetal exposure to nicotine, there are limited data on effects to the fetus. Current research indicates that pregnant women metabolize bupropion similarly to nonpregnant women, with bupropion and its active metabolites found in umbilical venous plasma at concentrations lower than maternal plasma concentrations.[53,54] Although overall data from available research on bupropion have not demonstrated any major teratogenic effects, a National Birth Defects Prevention study noted an association of a small absolute risk of left outflow tract heart defects (N = 10; adjusted OR, 2.6; 95% CI, 1.2-5.7).[55–58] Further investigation observed a slightly elevated risk of ventricular septal defect with first-trimester bupropion use (OR, 1.6; 95% CI, 1.0-2.8) but was unable to confirm a left-sided heart defect risk.[59]

In addition to decreasing nicotine withdrawal symptoms, bupropion targets common concerns of weight gain and depression.[35] Limited research has been done on the effectiveness of bupropion for pregnancy tobacco cessation. The lone available prospective RCT comparing bupropion to placebo was able to recruit only 11 women to the study.[39] The results of a prospective matched controlled observational study of 44 pregnant women suggested an increased quit rate among those using bupropion (10 of 22; 45% quit) compared to those in the control group (3 of 22; 14% quit) (Table 3).[56] In a longitudinal cohort study, Berard et al observed a cessation rate of 81% among those women who initiated bupropion in the first trimester. The women took bupropion for an average of 87 days.[48] After discontinuing the medication, 60% remained smoke free during the remainder of pregnancy and postpartum. A lower risk for PTB was found among the bupropion users (OR, 0.12; 95% CI, 0.03-0.50).[48] Bupropion prescribing recommendations for pregnant women remain the same as those for tobacco cessation in the general population. Although information is limited, there does not appear to be any additional adverse effects in the maternal population.[39]

Varenicline

Varenicline has limited available data regarding its effectiveness and safety in pregnancy. Preclinical animal studies using doses greater than 36 times normal human doses have not shown any congenital anomalies.[60] Although it is not known if varenicline crosses the human placenta, its pharmacokinetics suggest that the drug is capable of passing to the fetus.[36] A recently completed (May 2016) prospective population-based cohort study is expected to provide additional information on effectiveness and safety during pregnancy.[61]

TOBACCO CESSATION PHARMACOTHERAPY DURING POSTPARTUM AND BREASTFEEDING

While the majority of women who spontaneously stop smoking during pregnancy maintain cessation throughout pregnancy, postpartum relapse rates tend to increase rapidly over time with only one-third remaining abstinent after one year.[38,39,50] There is little research to help guide tobacco cessation interventions, including pharmacotherapy, during the postpartum period. While breastfeeding is not contraindicated for women who smoke, continued smoking while breastfeeding exposes infants to nicotine through inhalation and orally, as nicotine readily passes into breast milk with concentrations as high as 2 to 3 times those found in maternal plasma.[22] The American Academy of Pediatrics considers the use of NRT with breastfeeding as an option if the dosage of nicotine is less than what would occur with smoking, recommending intermittent formulations.[62] Although nicotine and cotinine breast milk concentrations are similar between women who actively smoke and those using 21-mg-per-day patches, they are significantly lower with 14-mg-per-day and 7-mg-per-day patches.[63]

Bupropion and its metabolites are excreted into breast milk, with an average infant exposure of 2% of the weight-adjusted maternal dose (range 1.4%-10.6%).[37] The only reported infant adverse event was a seizure in a 6-month-old with an afebrile respiratory illness. Lack of maternal and infant serum or breast milk levels in this case makes it difficult to connect the seizure to bupropion exposure.[37] Nonetheless, FDA labeling discourages use of bupropion while breastfeeding.

Currently, there are no available reports describing the use of varenicline during lactation. It has been postulated from pharmacokinetic varenicline properties that the drug would be excreted into breast milk.[36] Effects on the infant remain unknown and contribute to labeling discouraging use during lactation.

ALTERNATIVE TOBACCO CESSATION AIDS

Electronic nicotine delivery systems (ENDS), also called e-cigarettes, are a non-FDA-approved method of nicotine acquisition via vapor inhalation. Although relatively new, ENDS use is expanding across all segments of the population. This is especially apparent among adolescents where use increased from 1.3% in 2011 to 16% in 2015, creating concerns for future transition to smoking.[31] In response to this potential health threat, the FDA has extended its oversight to e-cigarettes in an effort to restrict their sale to minors.[31]

While ENDS are another tobacco product, use as a potential cessation agent that has the advantage of fulfilling the sensorial and behavioral aspects of smoking is being explored. A 2016 Cochrane review comparing e-cigarettes to placebo found use of an e-cigarette increased the likelihood of abstinence at 6 months (relative risk [RR], 2.29; 95% CI, 1.05-4.96; 2 RCT; 662 participants).[64] Comparison to nicotine patches did not find a significant difference in cessation rates (RR, 1.26; 95% CI, 0.68-2.34; 1 trial; 584 participants).[64] The quality of evidence for these studies was graded as low and very low.[64]

Although the main components of ENDS are nicotine and propylene glycol, general statements concerning their

Table 4. Clinician Resources for Improving Tobacco Cessation Intervention Knowledge and Skills

Resource	Website Address
Smoking Cessation for Pregnancy and Beyond: A Virtual Clinic	https://www.smokingcessationandpregnancy.org/
Treating Tobacco Use and Dependence, a Quick Reference Guide for Clinicians	http://www.healthquality.va.gov/tuc/phs_2008_quickguide.pdf
AAFP Tobacco and Nicotine Cessation Toolkit	http://www.aafp.org/patient-care/public-health/tobacco-nicotine/toolkit.html?cmpid = _van_915
CDC resource for Health Care Professionals	http://www.cdc.gov/tobacco/campaign/tips/partners/health/hcp/
Quitline FAQs for Health Care Providers	http://www.cdc.gov/tobacco/campaign/tips/partners/health/hcp-quitline-faq.html
FAQs for Health Care Providers	http://www.cdc.gov/tobacco/campaign/tips/partners/health/hcp-faq.html
Printable pocket-sized tobacco intervention card	http://www.cdc.gov/tobacco/campaign/tips/partners/health/materials/twyd-5a-2a-tobacco-intervention-pocket-card.pdf
The Community Guide	https://www.thecommunityguide.org/topic/tobacco
AAP - Clinicians & Clinical Practice	http://www2.aap.org/richmondcenter/Clinicians_ClinicalPractice.html
ACOG Self-instructional Guide and Toolkit	http://www.acog.org/~/media/Departments/Tobacco%20Alcohol%20and%20Substance%20Abuse/SCDP.pdf?dmc = 1&ts = 20130123T1641376641
The Foundation for Health Smart Consumers	http://www.smartcarepro.com/

Abbreviations: AAFP, American Academy of Family Physicians; AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians & Gynecologists; CDC, Centers for Disease Control and Prevention; FAQs, frequently asked questions.

safety cannot be made because of the wide variation of devices and fluids available.[64] When used for smoking cessation, the most common side effects of dry mouth and throat irritation resolved over time.[64] No serious adverse events were reported among the studies included in the Cochrane review.[64] However, significant burns from exploding devices as well as nicotine poisonings among children have occurred.[65]

Two novel pharmacotherapies that may become available in the near future include nicotine vaccines and cytisine (Tabex). Ongoing research is working toward the development of a vaccine that blocks nicotine's activation of the brain's pleasure receptors.[27] A 2013 Cochrane review of 4 trials evaluating 2 different vaccines did not find an improvement in cessation rates.[27] Cytisine, a nicotine receptor partial agonist, has been used successfully in Central and Eastern Europe for tobacco cessation. Cytisine shows promise, with 2 trials demonstrating significant improvement in tobacco cessation rates (Table 1).[27,29] Common side effects included nausea, restlessness, insomnia, irritability, and headache.[27,29]

Research evaluating complementary and alternative therapies for tobacco cessation has been inconclusive with contradictory findings for astragalus, black pepper, eucalyptus oil, guided imagery, meditation, melatonin, prayer, psychotherapy, and relaxation therapy.[66] Cochrane reviews evaluating acupuncture, hypnotherapy, and exercise interventions were unable to establish efficacy for tobacco cessation.[67–69] The authors warn that caution should be used when interpreting these findings due to limitations involving methodological flaws and lack of evidence.

Several studies have explored variations of behavioral counseling. Stead and Lancaster reported group therapy to be more effective than do-it-yourself or minimalist interventions but were unable to conclude if group therapy was superior or more economical than intensive counseling.[70] A Cochrane review expressed confidence in the efficacy of text messaging and phone support as strategies for increasing smoking cessation rates, especially among individuals with less education.[71] The authors noted that the majority of included studies used text messaging as the communication medium in high-income countries with strong tobacco control policies.[71]

CLINICAL IMPLICATIONS

Despite strong evidence that tobacco cessation interventions are effective, their widespread implementation in clinical settings remains the exception. Many clinicians cite their lack of cessation training and personal intervention skills as obstacles.[7] Improving clinician knowledge deficits through tobacco cessation training is a critical strategy for improving these skills.[7] Table 4 lists clinician training resources. Additional clinician barriers include time constraints, fear of jeopardizing patient relationships, lack of confidence in the intervention, lack of financial resources, and the presence of comorbid conditions in the patient.[7] Successful intervention strategies need to be applied at every office visit, taking into consideration that women's smoking behaviors are influenced by biologic factors, family, social network, and social environment.

Table 5. The 5A's and 5R's Brief Tobacco Cessation Intervention

5As	
Ask	Ask patients about tobacco use and status at every visit.
Advise	Advise patients who smoke of the importance of quitting smoking.
Assess	Assess whether patients who smoke are ready and willing to stop smoking at this time.
Assist	Assist patients who smoke and express readiness to quit by offering counseling and/or tobacco cessation medications.
Arrange	Arrange for follow-up face to face or by phone at least one week after quit date.
5Rs	
Relevance	Relevance assists patients who smoke in identifying why quitting smoking is personally relevant, being as specific as possible.
Risks	Risk identification allows patients who smoke to identify and verbalize the negative aspects of smoking.
Rewards	Rewards assessment helps patients who smoke to identify the benefits of quitting smoking.
Roadblocks	Roadblocks are barriers identified by patients who smoke that may prohibit or impede their ability and willingness to stop smoking.
Repetition	Repetition by health care providers asking about willingness to stop smoking and encouraging patients who smoke that it may take several attempts before success is achieved.

Source: Fiore et al.[7]

The first step toward improving tobacco cessation is to incorporate a brief smoking cessation counseling intervention utilizing the 5A's and 5R's (Table 5).[7] This counseling method provides clinicians a logical protocol to address smoking cessation. When conducting tobacco cessation counseling, clinicians should incorporate elements from motivational interviewing, which focuses on open communication and reflective listening, creating a positive environment that is nonjudgmental and promotes an exchange of ideas that empowers the woman to make a change.[72] Inviting the woman for a return visit devoted to the issue of smoking will encourage further engagement in tobacco cessation interventions.

When a woman desires to stop smoking, it is important to offer all options. The addition of pharmacotherapies to behavioral counseling significantly increases tobacco cessation rates.[7,25,27] Consideration of the timing and number of cigarettes smoked each day influence the medication and dosage recommended. In addition, age, ethnicity, and use of other medications that may affect the *CYP2A6* system should be considered.[8,10,13] Discuss the advantages and disadvantages of various medications, history of previous relapses, and preferences. While the use of first-line medications as single agents increases cessation rates, the combination of NRTs or varenicline with NRT have been found to improve success rates even further.[27,29] Variations in quit dates, dosages, and duration of pharmacotherapy may improve adherence rates.[27] Second-line medications may be considered when first-line medications are contraindicated or fail to achieve tobacco cessation.[7]

Pregnant women are generally very motivated to quit, with high quit rates in the first trimester, but those who continue to smoke may have more difficulty due to a variety of factors including faster nicotine metabolism.[15,39] Behavioral cessation interventions are first-line treatment in pregnant women who smoke, since the safety and effectiveness of pharmacotherapies during pregnancy are largely unknown.[25] When women are unresponsive to behavioral therapy the risks of medication use should be balanced with the known and very significant risks to the fetus associated with continued maternal tobacco use. High rates of pregnancy and postpartum relapse indicate the importance of continued counseling.[38,39,49] Except for NRT, the lack of information on tobacco cessation pharmacotherapies during lactation limits clinicians' ability to confidently recommend their use. Women can be advised that the use of NRT is associated with lower serum nicotine levels and avoidance of other tobacco chemicals.[62]

CONCLUSION

Recent research is helping clinicians understand the reasons for the highly addictive and harmful effects of tobacco, not only for the woman using tobacco but for everyone in her environment. Social networks play a significant role in continued tobacco use and smoking cessation, and clinicians must be able to provide sensitive and culturally appropriate counseling and advice. All medications have potential contraindications, side effects, and drug interactions that must be considered and discussed with the woman. Pregnancy, postpartum, and lactation require thoughtful assessment of the benefits and risks of pharmacotherapies. While complementary and alternative therapies have demonstrated no more effectiveness than placebo, it is worthwhile to offer safe options that may aid coping with withdrawal symptoms. No matter what method is chosen, close follow-up and support improves long-term cessation.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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