Nicotine & Tobacco Research, Volume 11, Number 11 (November 2009) *1265–1273*

Review

What do we know about the role of pharmacotherapy for smoking cessation before or during pregnancy?

Cheryl A. Oncken & H. R. Kranzler

Abstract

Significance: Given the substantial health risks of smoking during pregnancy, and the potential of pharmacotherapy to enhance quit rates, a need exists to examine the utility of pharmacotherapy for smoking cessation during pregnancy.

Literature Review: We briefly review the first-line medications that are recommended for smoking cessation in nonpregnant adults. Additionally, we review the toxicity of tobacco smoke and the potential risks of pharmacotherapy as evidenced by animal studies. We review in more detail studies conducted in pregnant women, including (a) observational studies, (b) short-term safety and longer term uncontrolled studies, and (c) randomized controlled clinical trials (both effectiveness and efficacy studies).

Discussion: Because the safety and efficacy of pharmacotherapy for smoking cessation during pregnancy have not been established, no definitive recommendations can be made on the topic. Effectiveness trials have shown that nicotine replacement therapy (NRT) enhances smoking cessation during pregnancy, but efficacy trials have not shown an advantage for NRT compared with placebo treatment. Small sample size or poor medication compliance (with either the dose or the duration of treatment) may contribute to lack of efficacy in placebo-controlled NRT trials. However, these trials showed that NRT did not adversely affect birth outcomes and increased birth weight. Based on these findings and the fact that all medications have some risk, psychosocial interventions should be the first treatment option for pregnant smokers. Additional research is needed to determine fully the risks and benefits of the various pharmacotherapies for smoking cessation during pregnancy.

Introduction

Cigarette smoking during pregnancy is one of the most important modifiable causes of poor pregnancy outcomes in developed countries. Maternal smoking increases the risk of spontaneous abortion, placental complications (abruption and previa), preterm premature rupture of membranes, preterm delivery (<37 weeks), low birth weight (<2,500 g), fetal and neonatal death, and sudden infant death syndrome (SIDS) (U.S. Department of Health and Human Services [USDHHS], 2001). Prenatal tobacco exposure may also increase the risk of long-term behavioral and cognitive abnormalities in children (Fried & Watkinson, 2001; Fried, Watkinson, & Gray, 2003). The public health implications of maternal smoking are substantial. In the United States, maternal smoking is responsible for 30% of low birth weight babies, 10% of premature deliveries, and 5% of all infant deaths (Salihu, Aliyu, Pierre-Louis, & Alexander, 2003).

Because of the serious health risks, efforts are needed to aid women of reproductive age quit smoking. Smoking cessation prior to pregnancy would prevent in utero fetal tobacco exposure. Although quitting smoking early in pregnancy yields the most health benefits, quitting smoking at any time during pregnancy is beneficial. Quitting smoking by 16 weeks (MacArthur & Knox, 1988) or even as late as the last trimester results in a near normal–birth weight infant (Ahlsten, Cnattingius, & Lindmark, 1993). Cognitive functioning in children may also improve with cessation during pregnancy (Sexton, Fox, & Hebel, 1990).

In this article, we review the potential role of pharmacotherapy in smoking cessation treatment both before and during pregnancy. We briefly review first-line pharmacotherapies that are recommended for nonpregnant smokers and potential emerging treatments for smoking cessation (i.e., the nicotine vaccine; Fagerstrom & Balfour, 2006; Fiore et al., 2008). We also review toxicity of tobacco and the effects of nicotine in animals based on comprehensive review articles (Dempsey & Benowitz, 2001; Pauly & Slotkin, 2008). We used the *Physicians' Desk Reference* (PDR) for pregnancy category ratings of bupropion sustained release (SR) and varenicline and for information on the teratogenicity of these compounds in animals. We review more thoroughly studies that provide safety, efficacy, and/or effectiveness data on first-line pharmacotherapies when used during pregnancy. Specifically, we review short-term

Cheryl A. Oncken, M.D., M.P.H, *Departments of Medicine and Obstetrics and Gynecology, University of Connecticut School of Medicine, Farmington, CT*

H. R. Kranzler, M.D., *Departments of Psychiatry and Genetics and Developmental Biology, University of Connecticut School of Medicine, Farmington, CT*

Corresponding Author:
Cheryl A. Oncken, M.D., M.P.H, *Department of Medicine, MC 3940, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030-3940, USA. Telephone: 860-679-3425; Fax: 860-679-1250; E-mail: oncken@nso2.uchc.edu*

doi: 10.1093/ntr/ntp136
Advance Access published on August 28, 2009
Received December 18, 2008; accepted June 26, 2009

safety and longer-term efficacy in humans, as measured in both uncontrolled studies and randomized controlled clinical trials.

The following key terms were entered into PubMed to identify relevant studies of medications for smoking cessation during pregnancy: (a) nicotine and pregnancy, (b) nicotine and randomized and pregnancy, (c) nicotine patch and pregnancy, (d) transdermal and pregnancy, (e) nicotine gum and pregnancy, (f) bupropion and pregnancy, and (g) varenicline and pregnancy. We also examined review articles of pharmacotherapy for smoking cessation in pregnancy to identify randomized controlled studies not located by the aforementioned search strategy (Coleman, 2008; Oncken & Kranzler, 2003).

Pharmacotherapy for smoking cessation in nonpregnant adults

Medications are recommended as first-line treatment for smoking cessation in nonpregnant adults (Fiore et al., 2008). Seven first-line therapies have been shown to be safe and effective: five nicotine replacement therapies (NRTs; 2 and 4 mg nicotine gum, 2 and 4 mg nicotine lozenge, nicotine inhalation system [i.e., nicotine inhaler], nicotine nasal spray, and transdermal nicotine [nicotine patch]) and two nonnicotine medications (bupropion SR and varenicline). Since all these treatments have been shown to enhance quit rates, and there are no definitive treatment-matching studies, there is no preferred pharmacotherapy for smoking treatment. The choice of a particular medication is best guided by patient preference, previous response to various treatments, adverse effects that may arise, and potential medical precautions for an individual patient. A review of first-line treatments is as follows:

Nicotine replacement therapies

NRTs are agonist treatments designed to replace the nicotine usually obtained by smoking. They reduce craving for cigarettes, tobacco withdrawal symptoms (irritability, anxiety, difficulty concentrating, restlessness, increased appetite, depressed mood) and may replace some of the reinforcing effects of smoking (sustaining mood and attention states, management of stressful situations; Henningfield, Fant, Buchhalter, & Stitzer, 2005).

Because there are advantages and disadvantages to each NRT, the choice may depend on the characteristics and preferences of an individual smoker. In one clinical trial, where participants were randomized to different NRT formulations (gum, inhaler, nasal spray, and patch), the treatments were similar in relief of withdrawal symptoms, perceived helpfulness, and abstinence rates (Hajek et al., 1999).

Bupropion SR

Bupropion SR is a nonnicotine medication effective for smoking cessation. Bupropion SR inhibits the neuronal reuptake of dopamine and norepinephrine (Hurt et al., 1997) and also may be a weak antagonist of the nicotinic receptor (Fryer & Lukas, 1999). Although bupropion SR is also prescribed as an antidepressant, its main effect for smoking cessation is through relief of nicotine withdrawal symptoms (Hurt et al.).

Varenicline

Varenicline is the first nicotinic receptor partial agonist developed as a pharmacological treatment for smoking cessation. Varenicline is selective for the $\alpha_4\beta_2$ nicotinic receptor. This receptor plays a key role in tobacco addiction by mediating the reinforcing effects of smoking (Coe et al., 2005). The agonist properties of varenicline reduce cravings and nicotine withdrawal symptoms. The antagonistic properties of varenicline block the reinforcing effects of smoking (Gonzales et al., 2006).

Table 1 reviews the estimated efficacy, adverse effects, and precautions and potential contraindications in nonpregnant

Table 1. Estimated efficacy[a] and precautions with first-line pharmacotherapies in nonpregnant smokers[b]

Treatment	Estimated abstinence rates (95% *CI*)	Estimated *OR* (95% *CI*)	Adverse effects	Precautions/ contraindications**
Placebo	13.8	1.0		
Nicotine gum (6–14 weeks)	19.0 (16.5–21.9)	1.5 (1.2–1.7)	Jaw soreness, mouth sores, gum bleeding, nausea, vomiting, or hiccups	Temporomandibular joint disorder; poor dentition
Nicotine inhaler	24.8 (19.1–31.6)	2.1 (1.5–2.9)	Cough, mouth and throat irritation	Asthma
Nicotine nasal spray	26.7 (21.5–32.7)	2.3 (1.7–3.0)	Sneezing, runny and watery eyes	Sinus or nasal problems
Nicotine patch (6–14 weeks)	23.4 (21.3–25.8)	1.9 (1.7–2.2)	Local irritation at patch site, heartburn, headache, dizziness, and sleep disturbance	Severe skin problems
Bupropion SR	24.2 (22.2–26.4)	2.0 (1.8–2.2)	Insomnia, dry mouth, headache, nausea, anxiety, rare risk of seizure	History of seizures; alcoholism; eating disorders. Avoid in persons taking MAOIs
Varenicline (1 mg twice daily)	33.2 (28.9–37.8)	3.1 (2.5–3.8)	Nausea, vivid dreams, insomnia, and headache; rare reports of severe neuropsychiatric adverse effects	Reduced kidney function; monitor for psychiatric adverse effects

Note. OR = odds ratio; SR = sustained release; MAOIs = monoamine oxidase inhibitors.

[a]Estimated abstinence rates based on a meta-analysis of 6-month quit rates (Fiore et al., 2008).

[b]All nicotine replacement therapies should be used with caution in persons with arrhythmias, heart disease, and diabetes.

smokers. No one pharmacotherapy is the preferred treatment for smoking cessation, as they are all effective for this indication. However, the recent meta-analysis used for this table showed that nicotine gum is the least effective and varenicline the most effective of these treatments. The utility of a treatment in an individual patient also depends on the safety, tolerability, and perceived helpfulness of the agent. Although potentially, these medications might also be efficacious in pregnant smokers, research is needed to test this hypothesis empirically and to evaluate the safety of these medications in this special population of smokers.

Nicotine vaccines

Nicotine vaccines have been developed for the treatment of tobacco dependence (Hatsukami et al., 2005). The goal of a nicotine vaccine is to stimulate antibodies to nicotine so that nicotine is bound in the plasma and does not reach the brain. Although nicotine is not immunogenic, nicotine stimulates an immune response when linked to an appropriate carrier protein (e.g., cholera B toxin, pseudomonas exotoxin A; Fagerstrom & Balfour, 2006). A gradual reduction in brain nicotine exposure could aid in smoking cessation. Although it would seem likely that smokers would compensate for reduced brain nicotine levels, this has not been observed in clinical trials (Nides, 2008).

The nicotine vaccine is a novel investigational treatment for smoking cessation. Its safety and efficacy need to be determined in nonpregnant smokers. The vaccine concept is also appealing for the treatment of pregnant smokers because it has the potential to minimize fetal nicotine exposure.

Rationale for examining pharmacotherapy for smoking treatment during pregnancy

Data in nonpregnant smokers suggest that pharmacotherapy may increase quit rates in pregnant smokers. Consequently, a need exists to study the potential efficacy of pharmacotherapies in pregnancy. One meta-analysis suggests that quit rates during pregnancy average 13% with augmented psychosocial behavioral treatments compared with 7% for usual care (Fiore et al., 2008). Another meta-analysis estimates that psychosocial interventions help an additional 6 of 100 pregnant smokers achieve cigarette abstinence (Lumley, Oliver, Chamberlain, & Oakley, 2004). These low quit rates may reflect that many pregnant women quit smoking prior to entering prenatal care; the women who continue to smoke in the second trimester and are included in clinical trials may be more resistant to treatment (Fingerhut, Kleinman, & Kendrick, 1990). Moreover, other reviews suggest that the chance of quitting smoking during pregnancy is inversely related to the level of maternal smoking. Behavioral counseling results in approximately a 20% quit rate in women who smoke fewer than 10 cigarettes/day, a 15% quit rate in women who smoke 10–19 cigarettes/day, and a 5% quit rate in women who smoke more than 20 cigarettes/day (Windsor, Oncken, Henningfield, Hartmann, & Edwards, 2000). Since quit rates are lowest in heavier smokers, and these women are at highest risk for adverse pregnancy outcomes (USDHHS, 2001), there is a particular need to study pharmacotherapy for smoking cessation in heavier smokers.

Studying the risk/benefit profile of pharmacotherapies is especially important since they are used as treatments for smoking cessation in prenatal care. Surveys suggest that 10%–30% of practitioners prescribe or recommend pharmacotherapy for pregnant smokers (Herbert, Coleman, & Britton, 2005; Hickner, Cousineau, & Messimer, 1990; Oncken, Pbert, Ockene, Zapka, & Stoddard, 2000; Price, Jordan, & Dake, 2006). Thirty percent of pregnant women report discussing smoking cessation pharmacotherapy (NRT or bupropion SR) with their health care provider, and 10% report using at least one pharmacotherapy for smoking cessation (Rigotti, Park, Chang, & Regan, 2008).

In the absence of definitive studies, the decision whether to use a particular medication requires an estimation of the risks of continued smoking, the risks of administering pharmacotherapy, and the likelihood that a pharmacotherapy would aid in smoking cessation for an individual patient. History of adverse pregnancy outcomes and previous treatment response to pharmacotherapy for smoking cessation are also important treatment considerations. To put in perspective the potential risks of smoking and the potential risks and benefits of pharmacotherapies, the following sections review these topics in detail.

Overview of potential toxicity of components of tobacco smoke

Cigarette smoke is a complex mixture of more than 4,000 chemicals and 100 mutagens and carcinogens. Carbon monoxide, nicotine, and lead are documented fetal neurotoxins (Dempsey & Benowitz, 2001). The following are the main constituents that have been implicated in fetal toxicity:

Carbon monoxide

Carbon monoxide is the most abundant substance obtained from cigarette smoking, with an estimated dose of 10–23 mg of carbon monoxide per cigarette (Dempsey & Benowitz, 2001). Carbon monoxide binds avidly to hemoglobin (where oxygen typically binds), yielding carboxyhemoglobin in place of oxyhemoglobin and reducing the oxygen available for normal fetal growth and development. Maternal carboxyhemoglobin concentrations of 10% would result in a decrease in available oxygen supply to the fetus akin to a 60% reduction in blood flow (Benowitz, 1991). In animal studies, cellular hypoxia has been associated with alterations in neurotransmitter systems, alterations in cognition and behavior, and poor fetal growth. One of the potential benefits of pharmacotherapy in pregnancy would be to lessen the potential deleterious effects of carbon monoxide (Benowitz et al., 2000; Dempsey & Benowitz).

Nicotine

Nicotine crosses the human placenta and fetal concentrations are correlated with maternal levels. Nicotine is structurally similar to acetylcholine, a neurotransmitter important for brain and nervous system development. It has been hypothesized that nicotine prematurely signals adrenal cells to stop dividing and to begin differentiation, resulting in a loss of adrenal gland function. In one study, the offspring of rats given 6 $mg \cdot kg^{-1} \cdot day^{-1}$ of nicotine throughout gestation exhibited a blunted catecholamine response to a hypoxic challenge postnatally and had an increased rate of death compared with controls (Slotkin, Lappi, McCook,

Lorber, & Seidler, 1995). This study provides a mechanistic link between prenatal nicotine exposure and SIDS.

Animal studies also suggest that prenatal nicotine exposure may contribute to anxiety, hyperactivity, and cognitive impairment in the offspring (Pauly & Slotkin, 2008). Neurotoxicity of nicotine is augmented with intermittent hypoxia (Zechel et al., 2005). Sheep studies suggest that nicotine is a vasoconstrictor and may be related to decreased uteroplacental blood flow observed with smoking (Xiao, Huang, Yang, & Zhang, 2007). Hemodynamic effects of acute nicotine could increase heart rate and blood pressure and could theoretically contribute to placental abruption.

Oxidizing chemicals

Oxidant gases in cigarette smoke can lead to inflammation and thrombosis. They also reduce the availability of nitric oxide, which plays a key role in placental vasoconstriction and prevention of premature labor (Fiore et al., 2008).

Carcinogens

Tobacco smoke contains more than 69 carcinogens. Placental transfer of at least one tobacco-specific carcinogen has been documented (Milunsky, Carmella, Ye, & Hecht, 2000). Prenatal exposure to carcinogens could influence long-term cancer risk, although the data are conflicting. Moreover, carcinogen exposure could reduce infant birth weight by increasing DNA damage and oxidative stress. In one study, *CYP1A1* and *GSTT1*, maternal metabolic genes important in the metabolism of carcinogens, interact with maternal smoking to affect infant birth weight (Wang et al., 2002).

Hydrogen cyanide, cadmium, lead, and other toxic components have been implicated in fetal toxicity, particularly in the areas of fetal growth and fetal neural development. A detailed review of the fetal toxicity of tobacco is beyond the scope of this review, but can be found elsewhere (Dempsey & Benowitz, 2001).

Potential toxicity of pharmacotherapies (animal studies)

Nicotine replacement therapy

The toxicity of nicotine in animals is also relevant to NRT. Prescription NRTs are Food and Drug Administration rated as a category D in pregnancy (positive evidence of human fetal risk, but the benefits of use may be acceptable despite the risk), and nicotine gum is rated as a category C. (Either studies in animals have revealed adverse effects on the fetus [teratogenic or embryocidal or other] and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus; Micromedex Health Care Series, 2009.) Consequently, it is important that human studies using NRT administer equivalent or lower doses of nicotine than usually observed with smoking. One concern about NRT administration is that formulations such as the patch potentially deliver a higher overall fetal dose than an intermittent formulation (Dempsey & Benowitz, 2001; Slotkin, 2008). This concern would be most relevant in lighter smokers (<10 cigarettes/day). The risk/benefit profile may be favorable if smoking cessation is achieved and/or fetal exposure to nicotine and other toxic chemicals is reduced.

Bupropion

Bupropion is listed as a category C drug in pregnancy (risk cannot be ruled out; PDR, 2008). Animal studies (bupropion 15–45 times human exposure) showed no conclusive evidence of impaired fertility or fetal harm. However, two rabbit studies demonstrated a slight increase in nonspecific fetal abnormalities (PDR). Animal studies suggest that prenatal bupropion exposure is associated with an increase in anxiety, an increased reward responding to cocaine, and increased stress responsiveness in the offspring (Pauly & Slotkin, 2008). The clinical significance of these findings is not known.

Varenicline

Varenicline is a Category C in pregnancy. Varenicline is not teratogenic in rats and rabbits at doses 36–50 times that of human exposure. In rabbits, administration of varenicline 30 $mg \cdot kg^{-1} \cdot day^{-1}$ (50× human exposure) reduces birth weight. The offspring of rats treated with varenicline 15 $mg \cdot kg^{-1} \cdot day^{-1}$ had a decrease in fertility and a heightened auditory startle (PDR, 2008). The significance of these findings is not known.

As previously noted, varenicline is highly selective for the alpha 4 beta 2 nAchR. Theoretically, varenicline would not interact with alpha 7 nAchR, the predominant nicotinic receptor expressed in the fetal brain that controls apoptosis and specific developmental regulatory effects. Furthermore, varenicline may not cause upregulation of nicotinic receptors because it is a partial and not a full agonist (Pauly & Slotkin, 2008). Animal studies are needed to evaluate the potential neurotoxicity of prenatal varenicline exposure in comparison with nicotine exposure and placebo.

Human studies of medications for smoking cessation treatment in pregnant women

In this section, we review the following studies: (a) noninterventional studies in which pregnant women taking medications were assessed for pregnancy outcomes, (b) short-term safety/efficacy studies that examined surrogate measures of safety (overall nicotine exposure after a single dose or under steady state conditions) and that estimate efficacy, (c) effectiveness studies, (d) randomized placebo-controlled trials.

Noninterventional (observational) studies

Nicotine replacement therapy

Teratogenicity. One retrospective study using Danish National Birth Cohort data examined the prevalence of congenital malformation among pregnant women who used NRT (patch, gum, or inhaler) during the first trimester (n = 250) compared with women who reported smoking (n = 16,812) and with nonsmokers (n = 55,915; Morales-Suarez-Varela, Bille, Christensen, & Olsen, 2006). Congenital malformations among

NRT users were higher compared with nonsmokers (relative prevalence rate ratio of 1.61 [1.01–2.58]). Because the number of subjects with congenital malformations in the NRT group was small, and the significance was marginal, these results should be interpreted with caution. Methodological concerns exist about possible undetected cases of spontaneous abortions among smokers (Fiore et al., 2008).

Adverse pregnancy outcomes (stillbirth). The Danish National Birth Cohort study assessed 87,032 pregnancies to determine the risk of stillbirth (fetal death after 20 weeks gestation) among NRT users, smokers, and smokers who concurrently used NRT compared with nonsmoking women (Strandberg-Larsen, Tingaard, Nybo Anderson, Olsen, & Groneaek, 2008). A total of 495 pregnancies (5.7 per 1,000 births) resulted in stillbirth. Smoking during pregnancy was associated with an increased risk of stillbirth, hazard ratio = 1.46 (95% *CI* = 1.17–1.82). Neither NRT use nor NRT use and concomitant smoking were associated with an increased risk of stillbirth.

Bupropion SR

Teratogenicity. The GlaxoSmithKline bupropion registry showed an increased risk of cardiovascular malformations among women who took bupropion in the first trimester. Consequently, two studies have been conducted to better address this issue (Chun-Fai-Chan et al., 2005; Cole et al., 2007).

There were no major malformations observed in the offspring of 136 women taking bupropion who were followed prospectively during the first trimester of pregnancy (Chun-Fai-Chan et al., 2005). Analysis of the United Health Care Database examined the rate of malformations in women exposed to bupropion during the first trimester of pregnancy ($n = 1{,}213$), other antidepressants during the first trimester ($n = 4{,}743$), and bupropion after the first trimester ($n = 1{,}049$) (Cole et al., 2007). The incidence of cardiac malformations in the group exposed to bupropion during the first trimester was 10.7/1,000 infants, comparable to the rate among other antidepressant users in the first trimester (10.8/1,000 infants), and among bupropion users after the first trimester (9.5/1,000 infants). This study shows that bupropion use in the first trimester does not increase the risk of cardiac congenital malformations compared with control groups.

Adverse pregnancy outcomes (spontaneous abortion). A prospective study followed 136 women who were taking bupropion in the first trimester (Chun-Fai-Chan et al., 2005). The comparison groups were women who were taking no medications (Non Teratogen control: [NTC]; $n = 133$) and women in the first trimester who were taking an antidepressant other than bupropion ($n = 89$). Comparison groups were matched for maternal and gestational age, alcohol consumption, and smoking.

In the bupropion group, there were 105 live births, 20 spontaneous abortions (SAs), 10 therapeutic abortions, 1 stillbirth, and 1 neonatal death. The SAs rate in the bupropion group were higher than the NTC control group (14.7% vs. 4.5%; $p = .009$) but not when compared with the antidepressant control group (14.7% vs. 12.3%; p = ns). The SA rate among women taking bupropion for depression was comparable to the rate among women being treated for tobacco use ([14/91] 15.4% vs. 6/37 [16.2%]). This small observational study suggests that bupropion use in the first trimester may increase the risk of spontaneous abortion comparable to that from treatment with other antidepressants. Additional studies are needed to examine this issue more definitively.

Smoking cessation. In a prospective controlled observational study, pregnant smokers receiving bupropion had a higher quit rate than controls who did not receive any medications (10/22 [45%] vs. 3/22 [14%]; $p = 0.047$; Chan, Einarson, & Koren, 2005).

Varenicline. We found no case reports or observational studies examining varenicline use during pregnancy.

Short-term safety studies and longer-term uncontrolled studies

Short-term safety studies can estimate acute and overall maternal nicotine exposure provided by NRT compared with usual smoking. The clearance of nicotine and cotinine (major metabolite of nicotine and reliable measure of overall nicotine exposure) is increased during pregnancy; the half-life of cotinine is approximately 8.8 hr (Dempsey, Jacob, & Benowitz, 2002). Consequently, cotinine concentrations can be expected to reach steady state after 3–4 days of NRT use.

Nicotine gum (single and multiple dose studies)

Studies have examined maternal nicotine concentrations after a single dose of 2, 4, or 8 mg nicotine gum. Collectively, these studies show that chewing 2 mg nicotine gum increases plasma nicotine by 2.9 ng/ml, 4 mg increases nicotine concentrations by 4.4–9.2 ng/ml, and 8 mg gum increases nicotine concentrations by 14.9 ng/ml (i.e., chewing 2 pieces of 4 mg gum simultaneously; Gennser, Marsal, & Brantmark, 1975; Lindblad & Marsal, 1987; Manning & Feyerabend, 1976). The increase in nicotine levels observed with the 8 mg dose is similar to concentrations observed with smoking one or two cigarettes (Gennser et al., 1975; Oncken et al., 1996). Together, these data suggest that smoking a single cigarette produces higher nicotine concentrations than those observed after chewing a piece of 2 mg gum. The nicotine concentrations typically observed with cigarette smoking are better approximated by chewing 4 or 8 mg gum.

In a multiple dose study of pregnant smokers (who smoked at least 10 cigarettes/day), women randomized to smoking cessation with 2 mg nicotine gum significantly decreased their nicotine and cotinine concentrations after 5 days of gum use compared with baseline smoking levels (Oncken et al., 1996). Moreover, alterations in fetal and maternal hemodynamics were also generally less with gum use compared with smoking.

Nicotine patch (single and multiple dose studies)

Pharmacokinetic studies of the patch have recruited pregnant women who smoke at least 15 cigarettes/day (Ogburn et al., 1999; Oncken et al., 1997). In a single dose study, 8 hr use of 21 mg nicotine patch produced nicotine concentrations similar to smoking approximately 1 cigarette/hour (Oncken et al., 1997). An inpatient study monitored pregnant women ($N = 21$) after smoking cessation using the 22 mg patch/24 hr for 4 days. Nicotine concentrations with the patch were similar to those obtained with ad lib smoking (Ogburn et al.). Safety measures (fetal heart rate and reactivity monitoring, measures of umbilical artery vascular resistance, and biophysical profiles) showed no evidence of fetal compromise during patch use (Ogburn

et al.). Women who participated in this study were offered transdermal nicotine for an additional 8 weeks. At the end of pregnancy, 38% of women were abstinent from smoking. The authors reported that although there were three pregnancies with serious adverse outcomes, none of these were attributable to patch use (Schroeder et al., 2002).

We found no published pharmacokinetic studies of the use during pregnancy of other nicotine replacement products (nicotine nasal spray, inhaler), bupropion SR, or varenicline.

Effectiveness and efficacy studies

We categorized studies as effectiveness (randomized, but not placebo controlled) or efficacy (randomized double-blind placebo controlled) studies. We chose to differentiate between these two types of studies because placebo-controlled studies are the gold standard to assess safety and efficacy of medications and are the most scientifically rigorous (Silverman, 2009). Randomized studies that are not placebo controlled may be confounded by (a) patient bias, (b) treatment team bias, and (c) evaluation bias (Pocock, 1991).

We reviewed the following outcomes: (a) quit rates, because smoking is known to be harmful during pregnancy, and quitting smoking has been shown to improve infant outcomes; (b) measures of tobacco and nicotine exposure, because many of the adverse reproductive outcomes are dose related to maternal smoking (USDHHS, 2001) and because tobacco reduction has also been correlated with increased birth weight (Li, Windsor, Perkins, Goldenberg, & Lowe, 1993); (c) pregnancy outcomes (SA rates, stillbirth, preterm delivery, and placental abruption rates) and birth outcomes (birth defects, gestational age, birth weight, neonatal and infant deaths) given that one goal of pharmacotherapy should be to improve infant and child health (Dempsey & Benowitz, 2001). Most of the studies were not of sufficient length to assess neonatal and childhood (cognitive and behavioral) outcomes. The outcomes reported also varied across studies. Consequently, we review the most commonly reported outcomes (quit rates, birth weight) and, where applicable, note effects on tobacco exposure measures or adverse pregnancy outcomes.

Three randomized controlled trials (Table 2) evaluated the *effectiveness* of NRT for smoking cessation (Hegaard, Kjaergaard, Moller, Wachmann, & Ottesen, 2003; Hotham, Gilbert, & Atkinson, 2006; Pollak et al., 2007). In both studies with a sufficient sample size, the NRT group had statistically higher quit rates compared with the control group (Hegaard et al.; Pollak et al.). In one study (Hegaard et al.), NRT was part of a multimodel intervention (intensive counseling and NRT administered only to heavier smokers), which was compared with a control group that received only behavioral counseling by a midwife. The intervention group had a higher biochemically verified quit rate compared with the control group, 7% versus 2% ($p < .003$). Since NRT was part of a multicomponent intervention, dismantling studies are needed to determine the effectiveness of NRT per se. In the study by Pollak et al., pregnant women who smoked at least five cigarettes/day were randomized to a cognitive behavioral treatment (CBT) group versus an NRT/CBT group. All women received six counseling sessions and women in the NRT/CBT group were given a choice of NRT (gum, patch, or lozenge). NRT dosage was reduced for light smokers. The quit rate in the NRT group was approximately double that in the control group. However, this study was stopped due to a safety concern: The NRT/CBT group had twice the serious adverse event (SAE) rate of the control group. The most frequent SAE in this study was preterm delivery (i.e., delivery at <37 weeks gestation). It is noteworthy that 32% of NRT subjects versus 12% of control subjects had a history of preterm delivery ($p < .05$) and after adjusting for this covariate, the difference in SAE rate between groups was no longer statistically significant.

Three NRT *efficacy* studies have been conducted in pregnancy (Kapur, Hackman, Selby, Klein, & Koren, 2001; Oncken et al., 2008; Wisborg, Henriksen, Jespersen, & Secher, 2000). In

Table 2. Randomized controlled studies of NRT in pregnancy

First author	Study type	*N*	Validated quit rates (Treatment vs. Control)	Birth outcomes	Comments
Pollack	Effectiveness: choice of gum, patch, or lozenge	181	18% vs. 7%[a]	Double the rate of SAEs in NRT group	2:1 randomization; SAEs mainly PTD; baseline imbalance of history of preterm delivery
Hotham	Effectiveness: patch	40	15% vs. 0%	NR	Noncompliance with patch
Hegaard[a]	Effectiveness: Choice of gum, patch, or both	647	7% vs. 2%	BW similar in the two groups	NRT as part of a multimodal intervention for heavier smokers only ($N = 75$)
Kapur	Efficacy: patch	30	24% vs. 0%	NR	Trial stopped due to distress in placebo subject
Wisborg	Efficacy: patch	250	28% vs. 25%	Greater BW in NRT group	186 g difference in BW; noncompliance with treatment
Oncken	Efficacy: 2 mg nicotine gum	194	18% vs. 15%	Greater BW and GA in NRT group	Modest effect on reduction; low gum use: Treatment group had lower LBW and PTD rates

Note. BW = birth weight; GA = gestational age; LBW = low birth weight; NR = not reported; NRT = nicotine replacement therapy; SAE = serious adverse event; PTD = preterm delivery.

[a]Adjusted end of pregnancy quit rates for attendance at counseling sessions.

one study, all women were given counseling by nurse midwife and nicotine patch (15 mg/16 hr) for 6 weeks or a matching placebo (Wisborg et al.). At the end of pregnancy, both quit rates (28% vs. 25%, respectively) and the mean number of cigarettes smoked per day (7.2 cigarettes vs. 7 cigarettes, respectively) were similar for the two groups. The mean birth weight was 186 g (95% *CI* = 35, 336) higher in the nicotine versus placebo group. There was a nonsignificant trend for the nicotine group to have a lower incidence of low birth weight babies than the placebo group. The authors hypothesized that a potential mechanism by which nicotine could increase birth weight was inhibition of thromboxane production (which causes vasoconstriction and platelet aggregation in the placental blood supply).

In another randomized placebo-controlled trial, pregnant smokers were randomized to behavioral treatment and 2 mg nicotine gum or a matching placebo (Oncken et al., 2008). Medication treatment was 6 weeks, with a 6-week taper. Gum dosage was based on number of cigarettes smoked per day. Quit rates at the end of pregnancy were nonsignificantly higher in the nicotine versus placebo group (18% vs. 14.9%). There was also a modestly greater reduction in cigarettes smoked per day and in cotinine concentrations in the nicotine group compared with the placebo group. Treatment retention was also greater in the nicotine versus the placebo group. Mean (*SD*) birth weight and gestational age were significantly higher in the nicotine gum versus placebo gum groups (3,287[569] g vs. 2,950 [657]g; $p < .001$; 38.9 wk [1.7] vs. 38.0 wk [3.3]; $p = .014$). The incidences of low birth weight and preterm infants were lower in the nicotine versus the placebo group (2% vs. 18%, $p < .001$, and 7% vs. 18%, $p < .02$, respectively).

In summary, randomized controlled intervention (effectiveness) studies have shown that NRT increases quit rates in pregnant smokers, but one trial raised concerns about safety (which was partially explained by confounding factors). In contrast, randomized placebo-controlled studies have not shown NRT to be efficacious in enhancing quit rates but have shown that NRT compared with placebo increases birth weight and may improve birth outcomes (i.e., decreasing the incidence of low birth weight and preterm delivery). An increase in birth weight in two placebo-controlled studies is clinically significant and requires additional research regarding potential mechanisms. In terms of strength of the evidence, placebo-controlled trials should be given more weight in determining safety and efficacy; however, ultimately it is the effectiveness of a pharmacotherapy in a clinical setting that determines whether it will be a useful adjunctive treatment for smoking cessation.

Demonstrations of the effectiveness but not the efficacy of medications for smoking cessation during pregnancy may be due to (a) the small number of clinical trials in pregnancy, (b) poor treatment compliance in efficacy studies with either the dose (Oncken et al., 2008) or the duration of treatment (Wisborg et al., 2000), (c) the wide range of inclusion/exclusion criteria and behavioral treatments between trials, (d) recruitment of participants from clinic settings compared with advertising, which may lend itself better to demonstrations of effectiveness rather than efficacy. The possibility also exists that pharmacotherapy is not effective for smoking cessation during pregnancy; although this would seem unlikely given the strength of data on efficacy of each pharmacotherapy in nonpregnant smokers.

Conclusions

The use of pharmacotherapy can enhance quit rates in nonpregnant individuals; any of the first-line treatments are acceptable choices. In women planning to become pregnant, quitting smoking prior to pregnancy would yield the greatest health benefits for the newborn. The optimal choice of treatment depends on the patient's preference, her response to previous treatments, and any medical precautions/contraindications that may exist for an individual patient.

Because all medications are assumed to have some risk, psychosocial interventions should be the first treatment option for smoking cessation during pregnancy. Because efficacy and safety have not been established for any of the first-line treatments, no definitive recommendations can be made regarding the use of pharmacotherapy for smoking cessation during pregnancy. Additional research is needed to determine more carefully the risks and benefits of the various pharmacotherapies for smoking cessation during pregnancy.

Funding

This report was supported in part by National Institutes of Health (NIH) grants DA15167, CA089053, RR06192, and AA13736 and the Robert Wood Johnson Foundation. CAO has received grant funding for smoking cessation studies from Pfizer pharmaceuticals and from Nabi Biopharmaceuticals.

Declaration of Interests

CAO has received nicotine and placebo nicotine replacement products at no cost from GlaxoSmithKline and Pharmacia & Upjohn Consumer Healthcare to conduct NIH studies of smoking cessation during pregnancy. She has received consulting fees for advisory board meetings from Pfizer Inc.

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