Nicotine Replacement Therapy During Pregnancy

Neal L. Benowitz, MD

CIGARETTE smoking is a major preventable cause of fetal death and injury, yet many women continue to smoke cigarettes throughout pregnancy. The most effective pharmacologic adjunct to smoking cessation therapy is nicotine replacement, including nicotine chewing gum or transdermal nicotine. However, the use of nicotine replacement therapy is contraindicated during pregnancy. The analysis presented herein suggests that the benefits of nicotine replacement therapy to aid smoking cessation in pregnant women who cannot stop smoking without such therapy substantially outweigh the risks of continued smoking or the risks of nicotine replacement per se.

PREVALENCE OF CIGARETTE SMOKING DURING PREGNANCY

Although the prevalence of smoking has declined in recent years and many women quit smoking when they become pregnant, 20% to 25% of pregnant American women continue to smoke throughout pregnancy; many of these women are heavy smokers. The National Health Interview survey of women pregnant in 1985 or with a birth in the previous 5 years found that 32% of white women smoked before pregnancy.[1] Although 39% of these smokers quit during their pregnancy, about 20% of the population of pregnant women continued to smoke.

Other recent surveys report smoking rates during pregnancy of 21% in 1985 and 1986 in 25 states and the District of Columbia,[2] 27.5% in 1986 in Missouri,[3] 19.9% in 1985 in Idaho, 26.1% in 1988 and 1989 in New York,[4] and 23% in 1989 in Ohio.[5] Among pregnant teenagers in Washington State, 32% and 37% smoked during pregnancy in 1984 and 1988, respectively.[6] Of note is that heavier smokers are much less likely to quit spontaneously during pregnancy than are lighter smokers, presumably reflecting a high level of dependence. Thus, although the average number of cigarettes smoked per day declines during pregnancy,[7] the prevalence of heavy smoking, defined as one pack (20 cigarettes) or more per day, during pregnancy remains substantial: 13.1%, 12.1%, and 11.6% in the Missouri, Idaho, and New York State studies, respectively.[3,4]

RISKS OF CIGARETTE SMOKING DURING PREGNANCY

Cigarette smoking during pregnancy substantially increases the risk of spontaneous abortion, prematurity, low birth weight, and perinatal mortality. Smokers have an increased risk of spontaneously aborting a chromosomally normal fetus, with an odds ratio of 1.2 to 1.8 compared with nonsmokers.[8-10] The incidence of low birth weight (<2500 g) increases with increasing cigarette consumption, and 21% to 39% of low-birth-weight births have been attributed to maternal cigarette smoking.[8] It is estimated that maternal smoking results in 4600 infant deaths in the United States each year.[8] These deaths are related to a higher than usual incidence of premature delivery related to abruptio placentae, placenta previa, and premature rupture of the membranes in smoking mothers, as well as intrauterine growth retardation. Furthermore, babies born to smoking mothers have a four times greater risk of a low Apgar score if the mother smokes two packs per day compared with babies of nonsmoking mothers (with correction for gestational age).[11]

Smoking does not appear to increase the risk of teratogenicity. Some studies show adverse effects of maternal cigarette smoking on child development.[12,13] However, these studies are somewhat difficult to interpret because of confounding with socioeconomic class, education of the parent, and passive smoking.

The major effect of cigarette smoking on birth weight has been termed the *fetal tobacco syndrome*, defined in terms of the following four points[14]:

1. The mother smoked five or more cigarettes per day throughout the pregnancy.
2. The mother had no evidence of hypertension during pregnancy.
3. The newborn had symmetrical growth retardation at term (greater than 37 weeks' gestation), defined as a birth weight of less than 2500 g and a ponderal index (weight in grams/length in centimeters cubed) exceeding 2.32.
4. No other cause of intrauterine growth retardation is obvious.

It is clear that cigarette smoking represents a major (if not *the* major) known risk to the fetus, and pregnant women should be strongly encouraged and assisted in stopping smoking. Prospective

From the Departments of Medicine, Psychiatry, and Pharmacy, University of California, San Francisco, and the Division of Clinical Pharmacology and Experimental Therapeutics, San Francisco General Hospital Medical Center.

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Reprint requests to the Division of Clinical Pharmacology and Experimental Therapeutics, San Francisco General Hospital Medical Center, 1011 Potrero Ave, Bldg 30, 5th Floor, San Francisco, CA 94110 (Dr Benowitz).

studies of smoking cessation therapy during pregnancy indicate that smoking cessation does result in improved birth weight.[7,15,16]

BENEFIT OF NICOTINE REPLACEMENT THERAPIES

Nicotine replacement therapies can enhance cessation rates in smokers who have been unable to stop smoking on their own. Tobacco smoking is maintained in most smokers by addiction to nicotine.[17] Tobacco dependence can be treated successfully. Behavioral therapies are successful for some smokers. Pregnant women who smoke are often highly motivated to quit and may be more responsive than are other patients to advice that they stop smoking. Prenatal smoking cessation programs have resulted in quitting rates of 9% to 43%.[7,15,16] But many smokers, particularly heavy smokers who are more dependent on nicotine, are still unable to quit.

Because of the pharmacologic nature of the addiction process, pharmacotherapy of tobacco dependence makes sense. At this time, the only pharmacologic therapy shown to be effective in smoking cessation is nicotine replacement therapy. Nicotine replacement therapy, using nicotine polacrilex chewing gum or transdermal nicotine delivery systems, can reduce tobacco withdrawal symptoms and enhance the efficacy of behavioral therapy. A meta-analysis of nicotine chewing gum therapy indicated an overall smoking cessation rate (in men and nonpregnant women) at 6 months of 27% for nicotine chewing gum compared with 18% for placebo chewing gum.[18] The trials were performed in smoking cessation clinics that were able to provide expert behavioral counseling. Another trial has shown a dose-response relationship for nicotine therapy and smoking cessation outcome.[19] In this trial, treatment with 4-mg nicotine chewing gum was found to be more effective than 2-mg nicotine chewing gum in highly dependent smokers. This rate of effectiveness was comparable with that obtained with 2-mg nicotine chewing gum in smokers with a medium or low level of dependence. Thus, nicotine replacement appears to be of particular value in more-dependent smokers. Similar data for smoking cessation rates have been observed with the use of transdermal nicotine delivery systems.[20,21]

Of note is a recent survey of Michigan family physicians indicating that 51% were dissatisfied with the effectiveness of available smoking cessation methods.[22] Twelve percent prescribed nicotine chewing gum to pregnant women who smoked, even though the label says its use is contraindicated in pregnancy.

POTENTIAL RISKS OF NICOTINE IN PREGNANCY

Nicotine could contribute to tobacco-related reproductive disorders; however, the nature and magnitude of its adverse effects are as yet unknown. While evidence for a causal link between cigarette smoking and reproductive disorders is well established, the pathophysiology is not. Smokers are exposed to several thousand chemicals in tobacco smoke, including nicotine and carbon monoxide. Nicotine and carbon monoxide are suspected to contribute to reproductive disturbances. An assessment of the potential contribution of nicotine is important for making decisions about risks vs benefits of nicotine substitution therapy during pregnancy.

A likely cause of growth retardation in fetuses of smoking mothers is induction of fetal hypoxia and/or ischemia, which could be produced by both carbon monoxide and nicotine. The developing fetus is normally in a state of relatively low oxygen tension. Oxygen delivery to the fetus is enhanced by adaptations that include the presence of fetal hemoglobin, which has a greater affinity for oxygen than does adult hemoglobin; higher hematocrit; higher fetal cardiac output; and high red blood cell 2,3-diphosphoglycerate level, which facilitates the release of oxygen from hemoglobin to tissues. Carbon monoxide impairs oxygen availability by binding avidly to fetal hemoglobin, thereby reducing the availability of oxygen to the fetus.[23] A maternal 10% blood carboxyhemoglobin level, which can be observed in a two-pack-per-day cigarette smoker, can be associated with a 10% to 15% higher carboxyhemoglobin level in the fetus than in the mother. This has been equated to a 60% reduction in fetal blood flow.[24,25]

Nicotine may contribute to fetal ischemia by its effects on the placental circulation. Nicotine infusion in pregnant sheep increases uterine vascular resistance and reduces uterine blood flow, effects that appear to be mediated by catecholamine release.[26] Smoking acutely and chronically reduces placental blood flow in pregnant women, presumably due to nicotine.[27,28] Both cigarette smoking and nicotine chewing gum increase fetal heart rate during the second trimester in humans, consistent with sympathetic neuroactivation.[29] During the third trimester in humans, cigarette smoking or nicotine gum chewing decreases fetal heart rate and reduces fetal breathing movements, both of which may be signs of fetal hypoxia.[29,30] Elevated levels of catecholamines in amniotic fluid in pregnant women who smoke during their third trimester indicate sympathetic activation in the fetus, consistent with fetal hypoxia and/or direct effects of nicotine.[30] Nicotine can also inhibit production of prostacyclin, a potent local vasodilator and inhibitor of platelet aggregation, in arteries. Reduced prostacyclin-like activity has been noted in umbilical arteries of cigarette-smoking mothers.[31] The above findings suggest that nicotine contributes to the adverse effects of cigarette smoking on reproduction, probably by acting on the uteroplacental circulation.

Fetal hypoxemia has also been considered to be a contributory cause of behavioral abnormalities, such as hyperactivity, short attention span, and lower scores on spelling and reading tests, which occur at a higher frequency in children whose mothers have smoked throughout pregnancy than in those born to nonsmoking mothers. In addition, chronic prenatal exposure to nicotine via maternal infusions in rats results in neurobehavioral disturbances in the offspring.[33] Other neonatal rat studies suggest that fetal exposure to nicotine may result in abnormal neurochemical development of the brain. Rats exposed to nicotine during gestation show delayed neural maturation and persistent defects in central catecholaminergic and cholinergic neuronal activity.[34,35] It is speculated that nicotinic cholinergic receptors normally function to modulate neuronal maturation in the fetus and that excessive neonatal exposure to nicotine impairs that development.

RELATIVE RISKS OF CIGARETTE SMOKING AND NICOTINE REPLACEMENT DURING PREGNANCY

Cigarette smoking delivers not only nicotine and carbon monoxide but also many other toxic chemicals to smokers. Smoking in general delivers more nicotine at a more rapid rate, resulting in more intense cardiovascular and central stimulation, than does nicotine from nicotine chewing gum or transdermal nicotine delivery systems. Therefore, nicotine replacement therapies are likely to present substantially lower risk than cigarette smoking, particularly heavy smoking, during pregnancy.

Delivery of Nicotine

Cigarette smokers systemically absorb about 1 mg of nicotine and 10 to 15 mg of carbon monoxide per cigarette.[17] Thus, a pack-per-day smoker consumes on average 20 mg of nicotine and 200 to 300 mg of carbon monoxide. Concentrations of nicotine and carboxyhemoglo-

bin in the blood tend to build up throughout the day with regular cigarette smoking, plateauing at levels of 20 to 35 ng of nicotine per milliliter and 5% to 10% carboxyhemoglobin. Significant concentrations of nicotine and carboxyhemoglobin persist overnight, even while the smoker sleeps, and smokers typically awaken with plasma nicotine concentrations of about 5 ng/mL and carboxyhemoglobin concentrations of 3% to 5%.

The average systemic absorption of nicotine from one piece of 2-mg nicotine polacrilex chewing gum is 1 mg.[36] No carbon monoxide or other toxins are absorbed. With the use of 12 pieces of nicotine chewing gum per day (which is more than most smokers use), about 12 mg of nicotine are absorbed, resulting in blood nicotine levels with chewing gum averaging one third to one half those observed in cigarette smokers (although in some people concentrations of nicotine may be similar when smoking and chewing the gum).

Transdermal nicotine delivery systems typically deliver about 15 to 20 mg of nicotine per day.[37] Peak plasma concentrations of nicotine typically range from 10 to 15 ng/mL and tend to fall somewhat overnight (owing to declining rates of nicotine release from the patch). Thus, the daily dose of nicotine and peak blood levels of nicotine from nicotine chewing gum or transdermal delivery systems are lower than those of one-pack-per-day cigarette smokers. Transdermal delivery systems do result in persistent exposure to nicotine that at some times of day, particularly overnight, may exceed those found in cigarette smokers.

Pharmacodynamic Considerations

Nicotine from cigarette smoke is absorbed rapidly through the lungs and into the circulation and results in transient high arterial blood concentrations that are delivered to the brain and other organs. The effects of nicotine are greater when doses are administered rapidly compared with when the same dose is given more slowly.[17] The rapid high-dose delivery of nicotine to the brain is thought to be responsible for much of the psychological stimulation and reward associated with cigarette smoking.

Nicotine from polacrilex chewing gum or transdermal delivery systems is absorbed slowly and does not produce the mental stimulation or euphoria reported after cigarette smoking. The blunted response is due both to lower concentrations reaching the brain and other target organs and to the development of acute tolerance, which is well known to occur to many effects of nicotine.

Despite the development of substantial tolerance to effects of nicotine, tolerance, at least to some effects, is not complete. For example, heart rate acceleration and catecholamine release have been shown to persist overnight in habitual cigarette smokers.[38,39] Persistent sympathetic neural activation is of importance because this could be a mechanism of adverse effects on the fetus. Presumably, the same pattern of sympathetic neural activation occurs in users of nicotine polacrilex chewing gum or transdermal nicotine delivery systems.

Cardiovascular Effects in Humans

The major cardiovascular effects of nicotine result from sympathetic neural activation.[17] In healthy people, cigarette smoking increases systolic blood pressure about 10 mm Hg and diastolic blood pressure 5 mm Hg, increases heart rate 10 to 20 beats per minute, and increases cardiac output, owing to both increased heart rate and cardiac contractility. Peripheral vascular changes include cutaneous vasoconstriction, systemic venoconstriction, and increased muscular blood flow. As discussed previously, placental blood flow may decrease, presumably due to contraction of the already maximally dilated uterine blood vessels.

As comparative data on effects on the uteroplacental circulation in humans are not available, it is reasonable to compare the systemic cardiovascular effects of smoking and nicotine replacement therapies to consider relative risks. The cardiovascular effects of single administrations of nicotine chewing gum (two 2-mg pieces) are similar in nature but a smaller magnitude to those of smoking a single cigarette.[40] Studies of the cardiovascular effect of nicotine gum chewed throughout the day have shown a similar increase in blood pressure but a smaller increase in heart rate compared with ad libitum cigarette smoking.[41]

Circadian cardiovascular effects of transdermal nicotine delivery systems have not yet been reported in the medical literature. In unpublished studies from my laboratory, the effects of transdermal nicotine on blood pressure and heart rate were less than those of cigarette smoking.

Of potential relevance to predicting effects of transdermal nicotine are studies of the effects of 14-hour intravenous infusions of nicotine, with or without concomitant cigarette smoking.[42] Circadian cardiovascular effects, including 24-hour urinary catecholamine excretion, were similar during intravenous nicotine and cigarette smoking conditions. Of note, the combined effects of intravenous nicotine and cigarette smoking (which results in average plasma nicotine concentrations 175% of those with either alone) were similar to the effects of either smoking or intravenous nicotine alone. This indicates a flat dose-response curve and suggests that if a person were to use nicotine replacement products and smoke as well, the cardiovascular effects will not be enhanced.

SUMMARY AND CONCLUSIONS

Epidemiologic evidence indicates a causal and dose-related relationship between cigarette smoking and adverse reproductive outcomes. Smoking cessation during pregnancy reduces the risk of reproductive problems and can be the opportunity for a permanent change in life-style to reduce the risk of later smoking-related chronic diseases. Because cigarette smoking results in exposure to many chemicals, it is impossible to ascertain the contribution of nicotine per se from epidemiologic data. Studies of the pharmacologic and toxicologic effects of nicotine in animals and experimental studies of the effects of cigarette smoking and nicotine in humans suggest that nicotine may contribute to adverse reproductive outcomes. Mechanisms of particular concern include reduction of uteroplacental blood flow and direct effects on the developing fetal brain.

Nicotine replacement therapy is clearly beneficial as an adjunct to smoking cessation therapy, particularly in more highly dependent smokers. It is the more dependent (ie, heavier) smoker who is at more risk for adverse reproductive outcome and who is less likely to stop smoking when becoming pregnant. Nicotine replacement therapy is likely to present less risk to the fetus than cigarette smoking. Cigarette smoking exposes the mother and the fetus to high levels of carbon monoxide and similar or higher concentrations of nicotine compared with those from nicotine replacement therapies. In addition, the more rapid delivery of nicotine from cigarette smoke produces higher concentrations of nicotine in the brain and other organs and more intense physiological effects. There is some concern that 24-hour-per-day sustained concentrations of nicotine, such as result from transdermal delivery systems, might have different effects than the rising and falling levels of nicotine seen in cigarette smokers. However, significant levels of nicotine are present overnight even in smokers when they do not smoke overnight, and available cardiovascular studies comparing cigarette smoking and nicotine replacement therapies show, if anything, smaller circadian cardiovascular effects with nicotine replacement com-

pared with cigarette smoking.

Thus, I conclude that the benefits of nicotine replacement therapy to aid smoking cessation in pregnant women who cannot stop smoking without such therapy substantially outweigh the risk of continued smoking or nicotine replacement therapy per se, at least in heavy smokers. I recommend formal clinical testing of nicotine replacement therapy in pregnant women who smoke, particularly in those who smoke 20 or more cigarettes per day and who have failed behavioral therapies. Such testing is medically indicated and ethically acceptable based on current concepts of benefits vs risks of nicotine replacement therapy.

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References

1. Fingerhut LA, Kleinman JC, Kendrick JS. Smoking before, during, and after pregnancy. *Am J Public Health*. 1990;80:541-544.
2. Williamson DF, Serdula MK, Kendrick JS, Binkin NJ. Comparing the prevalence of smoking in pregnant and nonpregnant women, 1985 to 1986. *JAMA*. 1989;261:70-74.
3. Stockbauer JW, Land GH. Changes in characteristics of women who smoke during pregnancy: Missouri, 1978-86. *Public Health Rep*. 1991;106:52-58.
4. Centers for Disease Control. Cigarette smoking among reproductive-aged women—Idaho and New York. *MMWR*. 1990;39:659-662.
5. Centers for Disease Control. Effects of maternal cigarette smoking on birth weight and preterm birth—Ohio, 1989. *MMWR*. 1990;39:662-665.
6. Davis RL, Tollestrup K, Milham S Jr. Trends in teenage smoking during pregnancy: Washington State, 1984 through 1986. *AJDC*. 1990;144:1297-1301.
7. Sexton M, Hebel JR. A clinical trial of change in maternal smoking and its effect on birth weight. *JAMA*. 1984;251:911-915.
8. Surgeon General. *The Health Consequences of Smoking for Women: A Report of the Surgeon General, 1983*. Washington, DC: US Government Printing Office; 1983:191-249. US Dept of Health and Human Services publication 410-869/1284.
9. Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. *Fertil Steril*. 1986;46:545-566.
10. Centers for Disease Control. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General, 1990*. Rockville, Md: Public Health Service, Office on Smoking and Health; 1990. US Dept of Health and Human Services publication No. CDC 90-8416.
11. Garn SM, Johnston M, Ridella SA, Petzold AS. Effect of maternal cigarette smoking on Apgar scores. *AJDC*. 1981;135:503-506.
12. Naeye RL, Peters EC. Mental development of children whose mothers smoked during pregnancy. *Obstet Gynecol*. 1984;64:601-607.
13. Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *J Dev Behav Pediatr*. 1990;11:49-58.
14. Niebyl P, Marks JS, McLaren NM, Remington PL. The fetal tobacco syndrome. *JAMA*. 1985;253:2998-2999.
15. MacArthur C, Newton JR, Knox EG. Effect of antismoking health education on fetal size: a randomized clinical trial. *Br J Obstet Gynaecol*. 1987;94:293-300.
16. Ershoff DH, Quinn VP, Mullen PD, Lairson DR. Pregnancy and medical cost outcomes of a self-help prenatal smoking cessation program in a HMO. *Public Health Rep*. 1990;105:340-347.
17. Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. *N Engl J Med*. 1988;319:1318-1330.
18. Lam W, Sze PC, Sacks HS, Chalmers TC. Meta-analysis of randomised controlled trials of nicotine chewing-gum. *Lancet*. 1987;2:27-30.
19. Tonnesen P, Fryd V, Hansen M, et al. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. *N Engl J Med*. 1988;318:15-18.
20. Hurt RD, Lauger GG, Offord KP, Kottke TE, Dale LC. Nicotine-replacement therapy with use of a transdermal nicotine patch: a randomized double-blind placebo-controlled trial. *Mayo Clin Proc*. 1990;65:1529-1537.
21. Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med*. 1991;325:311-315.
22. Hickner J, Cousineau A, Messmer S. Smoking cessation during pregnancy: strategies used by Michigan family physicians. *J Am Board Fam Pract*. 1990;3:39-42.
23. Longo LD. Carbon monoxide: effects on oxygenation of the fetus in utero. *Science*. 1976;194:523-525.
24. Longo LD. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. *Am J Obstet Gynecol*. 1977;129:69-103.
25. Bureau MA, Monette J, Shapcott D, et al. Carboxyhemoglobin concentration in fetal cord blood and in blood of mothers who smoked during labor. *Pediatrics*. 1982;69:371-373.
26. Resnik R, Brink GW, Wilkes M. Catecholamine-mediated reduction in uterine blood flow after nicotine infusion in the pregnant ewe. *J Clin Invest*. 1979;63:1133-1136.
27. Lehtovirta P, Forss M. The acute effect of smoking on intervillous blood flow of the placenta. *Br J Obstet Gynaecol*. 1978;85:729-731.
28. Philipp K, Pateisky N, Endler M. Effects of smoking on uteroplacental blood flow. *Gynecol Obstet Invest*. 1984;17:179-182.
29. Lehtovirta P, Forss M, Rauramo I, Kariniemi V. Acute effects of nicotine on fetal heart rate variability. *Br J Obstet Gynaecol*. 1983;90:710-715.
30. Manning FA, Feyerabend C. Cigarette smoking and fetal breathing movements. *Br J Obstet Gynaecol*. 1976;83:262-270.
31. Divers WA Jr, Wilkes MM, Babaknia A, Yen SSC. Maternal smoking and elevation of catecholamines and metabolites in the amniotic fluid. *Am J Obstet Gynecol*. 1981;141:625-626.
32. Ahlsten G, Ewald U, Tuvemo T. Prostacyclin-like activity in umbilical arteries is dose-dependently reduced by maternal smoking and related to nicotine levels. *Biol Neonate*. 1990;58:271-278.
33. Peters DAV, Taub H, Tang S. Postnatal effects of maternal nicotine exposure. *Neurobehav Toxicol*. 1979;1:221-225.
34. Navarro HA, Seidler FJ, Whitmore WL, Slotkin TA. Prenatal exposure to nicotine via maternal infusions: effects on development of catecholamine systems. *J Pharmacol Exp Ther*. 1988;244:940-944.
35. Navarro HA, Seidler FJ, Eylers JP, et al. Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems: evidence of cholinergic trophic influences in developing brain. *J Pharmacol Exp Ther*. 1989;251:894-900.
36. Benowitz NL, Jacob P III, Savanapridi C. Determinants of nicotine intake while chewing nicotine polacrilex gum. *Clin Pharmacol Ther*. 1987;41:467-473.
37. Benowitz NL, Chan K, Denaro CP, Jacob P III. Stable isotope methodology for studying transdermal drug absorption: the nicotine patch. *Clin Pharmacol Ther*. 1991;50:286-293.
38. Benowitz NL, Kuyt F, Jacob P III. Influence of nicotine on cardiovascular and hormonal effects of cigarette smoking. *Clin Pharmacol Ther*. 1984;36:74-81.
39. Benowitz NL. Increased 24-hour energy expenditure in cigarette smokers. *N Engl J Med*. 1986;315:1639-1640.
40. Benowitz NL, Porchet H, Sheiner L, Jacob P III. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther*. 1988;44:23-28.
41. Benowitz NL. Toxicity of nicotine: implications with regard to nicotine replacement therapy. In: Pomerleau OF, Pomerleau CS, eds. *Nicotine Replacement: A Critical Evaluation*. New York, NY: Alan R Liss Inc; 1988:187-217.
42. Benowitz NL, Jacob P III. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. *J Pharmacol Exp Ther*. 1990;254:1000-1005.