

Critical Review

Nicotine for the Fetus, the Infant and the Adolescent?

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Abstract

The recent expansion of Nicotine Replacement Therapy to pregnant women and children ignores the fact that nicotine impairs, disrupts, duplicates and/or interacts with essential physiological functions and is involved in tobacco-related carcinogenesis. The main concerns in the present context are its fetotoxicity and neuroteratogenicity that can cause cognitive, affective and behavioral disorders in children born to mothers exposed to nicotine during pregnancy, and the detrimental effects of nicotine on the growing organism. Hence, the use of nicotine, whose efficacy in treating nicotine addiction is controversial even in adults, must be strictly avoided in pregnancy, breastfeeding, childhood and adolescence.

Keywords

- *adolescence*
- *carcinogenesis*
- *fetotoxicity*
- *Nicotine Replacement Therapy*
- *pregnancy*
- *teratogenicity*

Introduction

WITH THE prospect of causing one billion deaths in the 21st century, cigarette smoking has entrapped the planet in a pandemic of tobacco-related morbidity and mortality of unprecedented proportion (Ginzel, 2001). Since addiction to nicotine is at its core, one should expect that efforts be focused on helping smokers to overcome their addiction to nicotine. Instead, nicotine, as in 'Nicotine Replacement Therapy' (NRT), is becoming a more and more heavily promoted tool for smoking cessation.

In support of NRT, it is claimed that the main cause of the health damage inflicted by smoking is the cigarette smoke with its contingent of over 4000 substances, many of which are toxic or carcinogenic, but not the nicotine to which the smoker is addicted. Therefore, it is argued, if the addiction to cigarette smoking is too powerful to respond to treatment, providing nicotine via NRT or even smokeless tobacco in place of cigarettes is the correct course of action. This argument is then further strengthened by portraying nicotine as largely innocent, on par with caffeine, thereby ignoring the abundant evidence that nicotine itself can imperil health due to a host of adverse effects independent of its addictiveness.

But even if the toxicity of nicotine were accepted as a given, would medicinal nicotine from NRT not be preferable to nicotine contaminated with the bulk of poisons in cigarette smoke? Although this question may suggest an affirmative answer, it actually hides the need for uncompromised quitting as the only truly lasting solution. There are at least two points to consider. For one, the satisfying experience of a deep inhalation of cigarette smoke correlates with a sudden, steep spike of the blood nicotine level. The generally much gentler and more protracted rise following ingestion of NRT or smokeless tobacco can neutralize the unpleasantness of withdrawal symptoms during quitting attempts but it fails to eliminate the urge to smoke, prompting a relapse to smoking. The unsuccessful quitter then smokes either in alternation or even concurrently with NRT. Despite the inevitable increase in nicotine exposure that this practice entails, it was officially endorsed by the 'the new rules' (see later). Second, for both the addict and the counselor, the true labor of quitting is comfortably postponed or suspended by resorting to a simple pill or patch. By making 'quitting' look so effortless, the health concerns and attitudes toward smoking will have lost their urgency.

When the concept of treating nicotine addiction with nicotine first emerged in the early 1980s, pharmaceutical companies seized upon the opportunity to develop and market several nicotine preparations for this purpose. Available today are nicotine chewing gum, transdermal patch, lozenges, nasal spray and inhaler, which enjoy increasing popularity among cessation specialists and smokers who are trying to quit. However, a critical commentary questions the overall utility and success rate of NRT as an aid to smoking cessation (Polito, 2006). Also, according to a new meta-analysis, the long-term benefit of NRT is modest, while existing treatment guidelines, based on only 6–12 months of follow-up, overestimate the lifetime benefit and cost-efficacy of NRT (Etter & Stapleton, 2006).

Despite the lack of evidence for long-term effectiveness, NRT use continues to grow. In the United Kingdom the Committee on Safety of Medicines (CSM) and the Medicines and Healthcare Regulatory Authority (MHRA) have issued new rules, extending the use of nicotine in smoking cessation to the most vulnerable recipients, the unborn child, the neonate and children as young as 12 (Action on Smoking and Health, 2005). Yet, in the only two trials conducted in pregnancy, NRT patches had no greater effect on smoking cessation than placebo (Coleman et al., 2004). Neither did NRT prove effective in a study of 120 adolescent smokers (Moolchan et al., 2005).

Whether or not successful in achieving quitting, the recommendation to use NRT in pregnancy and childhood raises the most serious concerns because of potential long-term consequences of nicotine action for this target group. In addressing these concerns, we first review the current state of the science on nicotine's pharmacological profile with its diverse impact on body functions, in particular its implication in carcinogenesis, and then zero in on those effects of nicotine that specifically impinge upon the developing and growing organism, the primary objective of this article.

A brief synopsis of nicotine action

More than 100 years ago nicotine was first used as a tool in physiological research. When nicotine was found to duplicate several effects of acetylcholine (ACh), one of the principal neurotransmitters in the central and peripheral nervous systems, this type of 'cholinergic' transmission was designated 'nicotinic'.

The transmission occurs across a synapse between a presynaptic nerve ending from which ACh is released and the adjacent postsynaptic neuronal cell body or effector cell that carries specialized receptors normally stimulated by ACh but also responsive to nicotine. Nicotinic cholinergic transmission via nicotinic cholinergic receptors (nAChRs) is a vital process indispensable for the normal functioning of the living organism but vulnerable to impairment by nicotine. This is one target for nicotine in the mature nervous system. Yet in the developing nervous system, very early in gestation, nAChRs are expressed prior to the formation of the neurons, which later establish synaptic contact with the nAChRs. By modifying the function of these receptors, nicotine can interfere with the normal developmental role of ACh (Falk, Nordberg, Seiger, Kjaeldgaard, & Hellstrom-Lindahl, 2005). These effects occur in the range of amounts of nicotine derived from smoking or equivalent sources.

Nicotine also exerts multiple effects on the afferent portion of the nervous system. In lowest effective doses it stimulates vagal sensory nerve endings in the lungs, producing reflexly a generalized relaxation of the skeletal musculature and an activation of the electroencephalogram (EEG) correlated with mental alertness. This intriguing combination, experienced and valued by the smoker, is likely to contribute to nicotine's addictive property (Ginzel, 1987).

Recently an entirely new dimension was added to the wide spectrum of nicotine action. Neuronal nicotinic acetylcholine receptors, nAChRs, expressed on many different nonneuronal cell types throughout the body, including lymphocytes, macrophages, dendritic cells, adipocytes, keratinocytes, endothelial cells and epithelial cells of the intestine and lung, appear to be implicated in inflammatory conditions and diseases as diverse as ulcerative colitis, chronic pulmonary obstructive disease, Parkinson's and Alzheimer's disease (Gahring & Rogers, 2006).

Among the classical effects of nicotine are those on heart and blood vessels mediated via nAChRs in the peripheral autonomic nervous system. Nicotine affects adult heart rate and rhythm and accelerates fetal heart rate. More recently, a key role of the inner lining of blood vessels, the endothelium, in maintaining adequate blood flow to organs was discovered. In the human brachial artery, the endothelium-dependent dilatation was found to be impaired by nicotine from cigarette smoke as well as from NRT nasal spray (Neunteufl et al., 2002). After a mere 30-minute exposure to environmental tobacco smoke (ETS), a substantial reduction in the coronary flow velocity

reserve, indistinguishable from that seen in habitual smokers, was observed in healthy young nonsmokers (Otsuka et al., 2001). The underlying mechanism was found to be the inhibition by nicotine of the self-regulatory coronary vasodilatation in response to nitric oxide released by endothelial cells. Since this effect of nicotine reaches its maximum already in the small amounts present in ETS, the difference between passive and active smoking as to their effects on blood vessels is greatly narrowed. Heart disease from smoking only one to four cigarettes per day is probably due to this mechanism (Bjartveit & Tverdal, 2005). By increasing platelet aggregation and low density cholesterol (LDL) while lowering high density cholesterol (HDL), nicotine favors clot formation that may lead to heart attacks and strokes. Nicotine, especially in the presence of a high cholesterol diet, stimulates the growth of vascular smooth muscle cells and promotes plaque formation and atherosclerosis (Jeremy, Mikhailidis, & Pittilo, 1995). The American Heart Association (2006) has questioned the suitability of NRT for patients with heart disease and for pregnant smokers.

Nicotine has a whole spectrum of other effects at different stages of fetal and adult development, which should not be ignored by those administering or receiving NRT. Some of these are: an increase in airway resistance; a decrease in fetal respiratory movements; a decrease in alpha1-antitrypsin associated with an increase in elastase favoring the development of emphysema; gastrointestinal vasoconstriction combined with a reduction in prostacyclin leading to stomach ulcers; a depression of the immune response; and multiple effects on hormones, especially a lowering of estrogen due to an increase in its metabolism leading to an earlier onset of menopause, osteoporosis and cardiac problems (US Department of Health and Human Services, 1988).

Nicotine and carcinogenesis

One of the reasons for protecting the developing and growing organism from exposure to nicotine is the prominent role nicotine plays in both 'initiation' and 'promotion', the two cardinal stages in carcinogenesis. Nicotine can be transformed to one of the most potent lung carcinogens, the tobacco-specific nitrosamine, NNK. As an initiator, NNK is a prime candidate among the many carcinogens in cigarette smoke responsible for starting the process toward cancer in active and passive smokers (Hecht, 2004; Hecht, Hochalter, Villalta, & Murphy, 2000). NNK

and its metabolites are found in the first urine of infants born to smoking mothers, supporting the hypothesis that in utero exposure to tobacco carcinogens could be carcinogenic later in life (Lackmann et al., 1999). Transplacental carcinogenesis associated with smoking during pregnancy may involve, in addition to nicotine and NNK, other carcinogens from cigarette smoke. Reduced detoxification capabilities and increased susceptibility to DNA damage render the fetus especially vulnerable to carcinogenic risk (Whyatt et al., 2001). NNK and metabolites have also been recovered from elementary school children and adults exposed to ETS (Hecht et al., 2001), attesting to the fact that even the relatively small amounts of nicotine in ETS can be transformed to NNK in the recipient. Added to this are the minute concentrations of NNK in ETS that had been formed earlier in stored and burning tobacco. Nicotine ingested from NRT can also undergo transformation to NNK (Hatsukami et al., 2004). Fetal pulmonary neuroendocrine cells as well as lung cancer cells express nAChRs that bind NNK and nicotine which, in turn, stimulate the growth of these cells (Minna, 2003). The fact that human lung cancer cells of all histological types carry nAChRs suggests that nicotine itself may also play a direct role in the pathogenesis of lung cancer (Minna, 1993).

Tumor growth occurs when the critical balance between cell proliferation and programmed cell death (apoptosis) in normal healthy tissues is disturbed. At blood concentrations achieved by smoking, ETS exposure, or NRT, nicotine activates via nAChRs the cellular signalling pathway Akt, a protein kinase, which stimulates cell proliferation and inhibits apoptosis (Tsurutami et al., 2005). Activated Akt has been identified in all lung cancer samples taken from smokers. By this mechanism nicotine promotes unregulated growth and tumor formation, an effect that is not limited to the lungs but can also occur in cancers of other organs. Nicotine in NRT can be expected to act in a similar way (Heusch & Maneckjee, 1998).

Nicotine from cigarettes or NRT might also confer a proliferative advantage to already existing tumors. At concentrations even lower than those in smokers' blood, nicotine stimulates proliferation of endothelial cells and the formation of new blood vessels (angiogenesis), a basic requirement for tumor growth and metastasis (Villablanca, 1998). Furthermore, through activation of protein kinase C, nicotine accelerates migration and invasion of human lung cancer cells (Xu & Deng, 2006). All

these actions define nicotine as an effective tumor promoter. As smoking-related promotion is now being recognized as the primary etiologic mechanism in carcinogenesis dominating over smoking-related initiation (Hazelton, Clements, & Moolgavkar, 2005), nicotine, implicated in both processes, ought to be a major aim for intervention instead of a tool advocated for use in smoking cessation.

New research using human tissues raised the question whether nicotine is 'potentially a multi-functional carcinogen' (Campain, 2004), since it produces concomitant genotoxic and antiapoptotic effects, first steps in the neoplastic process. In human gingival fibroblasts nicotine induced rapid DNA damage at in vitro concentrations equivalent to those found to occur in the plasma of tobacco users (Argentin & Cicchetti, 2004). Genotoxicity observed in human tonsillar tissue and lymphocytes as well as in upper aerodigestive tract epithelia also suggests a direct tumor-initiating effect of nicotine (Kleinsasser et al., 2005; Sassen et al., 2005).

Smoking is now recognized as the second most significant cause of cervical cancer after human papilloma virus (International Agency for Research on Cancer, 2003). Nicotine which accumulates in cervical mucus after active and passive smoking and smokeless tobacco use (McCann et al., 1992), and which is also highly concentrated in the cervical mucus of women who use nicotine patches (*Cancer Weekly*, 1995), was found not only to promote rapid tumor growth and its lympho-angiogenic spread but also to inhibit an anti-proliferative factor (Lane, Gray, Mathur, & Mathur, 2005).

Although the preceding experimental data focus largely on adult cancer incidence implicating nicotine as a causative factor, similar scenarios can be expected to play out over time following fetal or childhood exposure to nicotine. Transplacental carcinogenesis associated with smoking during pregnancy may also involve, in addition to nicotine, other carcinogens found in cigarette smoke.

Nicotine in pregnancy and childhood

Nicotine also acts as a neuroteratogen. There is now abundant evidence that normal fetal development can be disrupted more specifically by nicotine than by any other component of cigarette smoke. Nicotine, which impacts the brain during critical stages of its intrauterine development in experimental animals, is

in the offspring of smoking mothers also the most likely cause of the deficits in learning and memory, and the emotional and behavioral problems seen in childhood and later in life (Levin & Slotkin, 1998; Slikker, Xu, Levin, & Slotkin, 2005; Slotkin, 1998). In this context, a higher incidence of attention deficit hyperactivity disorder (ADHD), lower adult intelligence and mental retardation have been reported (Drews, Murphy, Yeargin-Allsopp, & Decoufle, 1996). Higher order sensory function depends in part on the activation of nAChRs in the sensory cortex by its natural transmitter acetylcholine. When nicotine, even if only transiently, usurps these receptors in the developing sensory cortex during a critical period, it can permanently alter sensory-cognitive function (Metherate, 2004). Just published new findings provide experimental evidence that nicotine exposure in pregnancy is responsible for auditory-cognitive deficits in the offspring. Children with cognitive hearing deficits have difficulty in understanding speech and verbally presented information in noisy settings, and may be unable to tell the difference between similar sounds (Liang et al., 2006). Prenatal nicotine also primes the adolescent brain for depression (Law et al., 2003), and for nicotine addiction in future years (Abreu-Villaa, Seidler, Tate, Cousins, & Slotkin, 2004; Kandel & Davies, 1994; O'Callaghan et al., 2006).

Significantly lowered levels of catecholamines found in umbilical cord blood in response to hypoxemia during parturition may explain the increased perinatal morbidity and mortality associated with smoking during pregnancy (Oncken et al., 2002). A blunted catecholamine response to hypoxic stress with a greater risk of death to offspring was also observed in rats receiving nicotine throughout gestation. Prenatal nicotine exposure can also have a permanent impact on lung development and function with potential long-term health consequences (Fauroux, 2003). Nicotine crosses the placenta and activates nicotinic receptors located at a wide range of lung cells. In rat experiments, in doses equivalent to those ingested by smoking mothers, nicotine causes what appears to be a faster aging of the lungs in the offspring, characterized by enlarged alveoli, fewer alveoli, a smaller surface area for gas exchange and microscopic emphysema (Maritz & Windvogel, 2003). NRT use during pregnancy and breast-feeding when the neonate lungs are still developing should be avoided (Alm, Lagercrantz, & Wennergren, 2006). Prenatal nicotine exposure can permanently alter lung development and airway function (Sandberg, Poole,

Hamdan, Arbogast, & Sundell, 2004). Prenatal and postnatal nicotine exposure have been causally implicated in Sudden Infant Death Syndrome (SIDS) (Cohen et al., 2002; Huang, Wang, Dergacheva, & Mendelowitz, 2005; McMartin et al., 2002; Milerad, Vege, Opdal, & Rognum, 1998; US Department of Health and Human Services, 2006). NRT use during the first 12 weeks of pregnancy increased the risk of congenital malformations (Morales-Surez-Varela, Bille, Christensen, & Olsen, 2006).

A well-known consequence of smoking during pregnancy is the incidence of low birth weight (LBW) babies, but even in the absence of LBW, nicotine that reaches some 15 percent higher levels on the fetal side of the placenta than on the maternal side, affects fetal brain development and newborn neurobehavior (Lambers & Clark, 1996). Nicotine concentrates in fetal blood, amniotic fluid and breastmilk. Breast-feeding by smoking or ETS exposed mothers continues the delivery of nicotine to the baby (Dahlstrom, Ebersjo, & Lundell, 2004). Postnatal exposure to cigarette smoke also appears to act through nicotine: in a study of 4399 children aged six to 17 years, even the lowest exposure, as monitored by the levels of cotinine, the main metabolite of nicotine, in blood, urine, saliva and hair, was found to significantly impair, in a dose-related manner, the children's reading, math and reasoning scores (Yolton, Dietrich, Auinger, Lanphear, & Hornung, 2005).

Nicotine in adolescence

According to recent human and animal research, adolescents are more susceptible to developing nicotine dependence than adults, because a single drug exposure can lead to lasting neuronal changes associated with learning and memory (Fagen, Mansfelder, Keath, & McGehee, 2003). The earlier the exposure to nicotine, the greater is the impact on the neuronal circuitry of the still developing brain causing irreversible effects on hippocampal structure, function, learning and memory (Slotkin, 2002). This experimental finding was borne out in a study of 5863 students, where a single experience with cigarettes reported at age 11 was found to significantly increase the risk of becoming a smoker as an adolescent even after three intervening years of non-smoking. This dormant vulnerability, termed 'sleeper effect' (Fidler, Wardle, Brodersen, Jarvis, & West, 2006), must be made widely known to help prevent preteens from early experimentation with cigarettes or other tobacco

products. Early exposure to nicotine can also make children more vulnerable later to stress or depression, prompting them to try some form of nicotine again.

Adolescent smokers have only recently started to receive NRT. Some of them reported simultaneous use of NRT and cigarettes. Nonsmoking teens have also tried NRT and some have even indulged in regular use (Klesges, Johnson, Simes, Zbikowski, & Robinson, 2003). The easy availability of NRT poses a special risk for the curious and adventurous young. Like smoking, NRT has the potential of priming the brain for nicotine addiction and leading to illegal drug use.

A review of teen smoking cessation approaches reveals their complexity and the lack of an effective solution (Mermelstein, 2003). What appears to be missing from the majority of interactions with young people is a totally honest confrontation and a truthful dissection of the tobacco problem in its entirety (Ginzel, 2002).

The new rules

Against this background, it is with much concern that we confront the recently proposed rules issued by the Committee on Safety of Medicines (CSM) and by the Medicines and Healthcare Regulatory Authority (MHRA) for the use of NRT in the UK (Action on Smoking and Health, 2005), likely to set a precedent for other countries to follow. According to these new rules, all forms of NRT can be used by pregnant smokers; different forms of NRT can be used alternatively or concurrently; NRT can be used while still smoking (!) and can be prescribed for up to nine months if needed; and all forms of NRT can be used by young smokers aged 12 to 17 years as well as by patients with cardiovascular disease if so advised.

These new rules differ fundamentally from past recommendations. Molyneux (2004) states that the effectiveness of NRT in adolescents and children who smoke has not been established, and he also urges smokers not to smoke while using NRT. NRT, especially by transdermal patch, delivers more nicotine to the fetus than smoking does. Nicotine concentrations in fetal rat brain are 2.5 times higher than the mother's blood nicotine level when on continuous nicotine feed; a similar ratio can be expected in pregnant women using the patch (Sarasin et al., 2003). Smokers who use NRT may have nicotine concentrations up to three times higher than the approved dose (Chan, Jeremy, Stansby, & Shukla, 2004). The US Surgeon General's Report

of 2001 on Women and Smoking states: 'Because of uncertainties over the safety of nicotine replacement during pregnancy, FDA has assigned a Pregnancy Category C warning to nicotine gum ("Risk cannot be ruled out") and a Pregnancy D warning to transdermal nicotine ("Positive evidence of risk")' (US Department of Health and Human Services, 2001, p. 557). Since many of tobacco smoke's harmful effects on the unborn baby can be attributed to nicotine, NRT or smokeless tobacco products are not a safe alternative to smoking during pregnancy (Cohen et al., 2005). No data are available on long-term effects of NRT use on fetal outcomes (Oncken, Bert, Ockene, Zapka, & Stoddard, 2000). The uncertainty of benefit and the risk of NRT use in pregnancy and by teens are echoed throughout the literature dealing with this topic. The risk of oral NRT use also received new emphasis by the recent finding that nicotine causes concomitant genotoxic and antiapoptotic effects in human gingival fibroblasts, potentially the first step in the neoplastic process (Argentin & Cicchetti, 2004).

It is obvious that the smoker whose body is busy dealing with the nicotine contingent in inhaled smoke ought not to be burdened with additional amounts of nicotine delivered from NRT but should be resolutely supported to overcome the addiction to nicotine altogether. This cannot be achieved by recommending or prescribing nicotine through NRT. The ultimate goal must be total cessation of smoking and nicotine intake in any form. NRT simply substitutes one form of nicotine for another but is neither safe nor as effective as other cessation aids (Hutter, Moshhammer, & Neuberger, 2006; Marks, 2005, 2006; Moshhammer & Neuberger, 2006). Originally, the tobacco industry opposed the makers of NRT, but now both industrial enterprises seem to be finding common ground as tobacco and NRT have begun reinforcing each other and keeping the addiction to nicotine alive.

Concluding comments

Prescribing or simply recommending an over-the-counter purchase of one form or another of NRT is unquestionably quicker and less engaging for the health professional than any in depth one-to-one counsel that tries to inspire mind and heart of the mother-to-be so as to make her cherish and protect the new life she has been entrusted with; it is also

easier than a straight talk with a teen or preteen about a future eclipsed by addiction, disease and premature death, exploring the real reasons that made them light up in the first place (Ginzel, 2002). It is easy not only for the counselors to prescribe NRT, it is also easy for the clients to receive it: they may conveniently assume that this is all that needs to be done, and the urge to smoke may go away in due course. While there is compelling experimental and clinical evidence that nicotine harms the developing fetus in several ways, evidence is lacking that NRT aids smoking cessation in pregnancy. There are pregnant women today who would have quit but are wearing nicotine patches, persuaded by the safety assurances about NRT use. Moreover, new evidence reveals that offering a remedy for a risky behavior inadvertently promotes it by suggesting that the risk is manageable (Bolton, Cohen, & Bloom, 2006).

If the new UK rules, which extend and multiply a regimen ill-conceived from the start were followed and also adopted by other countries, they would perpetuate nicotine addiction rather than diminish it. And so would a recently proposed policy of extended, or even indefinitely continuing (!), use of the so-called 'clean nicotine' of NRT (Gray et al., 2005). This could actually set us on a path eventually leading to the end of tobacco control as we know it. Tobacco control must be nicotine control. Without nicotine control, nicotine addiction and nicotine's multifarious and insidious impact on the user would persist and spread at the peril of the unborn, the next generation and public health in general.

Some 4000 years ago the code of Hammurabi decreed the penalty of death for anyone who would harm a child. In an editorial in the *New York Times* in March 1985, William G. Cahan of the Memorial Sloan Kettering Cancer Center identified smoking as the most prevalent form of child abuse. Will nicotine now join this deplorable distinction?

Abbreviations

ACh, acetylcholine; ADHD, attention deficit hyperactivity disorder; CSM, Committee on Safety of Medicines; ETS, environmental tobacco smoke; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare Regulatory Authority; nAChRs, nicotinic cholinergic receptors; NNK, tobacco specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NRT, nicotine replacement therapy; SIDS, sudden infant death syndrome.

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