Tobacco smoking and new developments in public health and clinical interventions

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The public policy environment regarding tobacco use in the United States has experienced a dramatic change during the past year. Along with calls for regulatory review of cigarettes, important new scientific information has become available regarding the health effects of environmental tobacco smoke and the efficacy of nicotine replacement therapy, which is used to support smoking cessation efforts. Specifically, recent studies have suggested that environmental tobacco smoke exposure increases risk for coronary heart disease in nonsmoking adults in addition to causing lung cancer and other respiratory diseases. Children are exposed to environmental tobacco smoke at home and in public, resulting in increased risk of bronchitis, pneumonia, bronchial hyperresponsivity, and sudden infant death syndrome. In a climate of increasing concern about the direct and indirect effects of tobacco smoke, three independent meta-analyses concluded that nicotine replacement therapy increased smoking cessation efficacy two- to threefold. In addition, research is beginning to identify factors associated with successful and unsuccessful cessation attempts using nicotine replacement therapy, resulting in the possibility of individualized treatments and clinical interventions designed for maximum efficacy.

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Although population rates of smoking have declined gradually in the United States since the early 1960s, 26% of adults (representing 46 million Americans) continue to smoke [1]. Tobacco use remains the leading preventable cause of illness and death in the United States, with approximately 1000 new smokers (virtually all under the age of 18) identified every day [2]. With the benefit of hindsight, it may be the case that the period of 1993 to 1994 covered by this review was a bellwether one for tobacco control in the United States. Based on allegations that tobacco companies manipulate the amount of nicotine in cigarettes to promote addiction, the US Food and Drug Administration discussed publicly the possibility of regulating tobacco products as drugs. Two prominent tobacco addiction researchers made a sweeping public health proposal to gradually reduce the nicotine level in US cigarettes over the next 20 years to the point where cigarettes would no longer support addictive use [3•].

This period also saw an increase in scientific knowledge related to tobacco smoking. Many of these advances occurred in two key areas: new information regarding the effects of environmental tobacco smoke (ETS), also called *passive smoking* or *secondhand smoke*; and scientific evidence on the efficacy of tobacco cessation treatments. These advances are worth considering in some detail because, in conjunction with developments in the public policy realm, they create the possibility of a synergistic effect. As the general public becomes more aware of the public health risks created by ETS and that effective, proven treatments exist for tobacco addiction, there may be more grassroots support for tobacco control efforts.

New information on the health effects of environmental tobacco smoke

Over the past two decades, scientific information has accumulated indicating that exposure to ETS poses a significant health risk, even to those who do not smoke directly. Much of this scientific evidence was summarized in the 1992 report of the US Environmental Protection Agency (EPA) on ETS, entitled *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* [4]. The EPA classified ETS as a

Abbreviations
EPA—Environmental Protection Agency; ETS—environmental tobacco smoke.

class A (known human) carcinogen, responsible for as many as 3000 lung cancer deaths in nonsmokers every year [4]. Although there was some evidence that ETS exposure was linked to an increased risk of coronary heart disease, the EPA declined to identify it as a known risk factor for heart disease pending additional scientific study. He *et al.* [5••] reported the results of a large case-control study involving 185 never-smoking Chinese women exposed to ETS from their husbands (at home), at work, or both. Their odds ratio estimates were 2.12 for exposure to a husband's ETS and 2.45 for exposure at work. Moreover, there was a significant linear trend of increasing risk with increased exposure in the workplace, suggesting a dose-response relationship similar to that observed with direct smoking. This finding constitutes important evidence that ETS creates increased risks not only for lung cancer and other respiratory illnesses, but also for coronary heart disease.

The impact of ETS is most evident in children. The EPA report concluded that ETS contributed to 150,000 to 300,000 cases of lower respiratory infections in children under the age of 18 months, as well as increased the number and severity of childhood asthma attacks [4]. Regrettably, exposure of children to ETS remains very high. In a survey of over 4000 children in England and Wales, Cook *et al.* [6] found 53% of children between the ages of 5 and 7 years were exposed to cigarette smoke at home or in public settings. This report was confirmed with salivary cotinine that increased some 31-fold from mean levels of 0.29 ng/mL in children with no household exposure to 9.03 ng/mL for children whose parents both smoked more than 20 cigarettes per day.

Recent studies have also indicated additional health risks resulting from such exposure. Variability in peak expiratory flow rate is strongly correlated with nonspecific bronchial hyperresponsiveness. A study of 1237 7-year-old children observed that peak expiratory flow rate variability increased 13.7% in nonasthmatic children with mothers who smoked and 54.7% in nonatopic children with asthma [7]. In children during their first 1.5 years of life, there was a dose-dependent increase in the incidence of bronchitis or pneumonia from a relative risk of 1.3 in households where members smoked one to nine cigarettes per day to a relative risk of 2 in households where members smoked 20 to 39 cigarettes per day (referenced to children in nonsmoking households) [8•]. This study was notable because none of the mothers of the study subjects had ever smoked; therefore, the results were not contaminated by prenatal effects of maternal smoking.

A major national study of over 2200 infants in New Zealand provided important new evidence regarding the link between parental smoking and sudden infant death syndrome [9]. Mothers who smoked during pregnancy had infants with a relative risk of sudden infant death syndrome at 4.09 times greater than that of infants whose mothers did not smoke; this finding is in accord with previous studies. However, it cannot resolve the confound between prenatal effects of maternal smoking and postnatal exposure to ETS. The New Zealand group conducted interviews regarding the smoking of the father and other household members. Smoking by the father (odds ratio = 2.41) or other household members (odds ratio = 1.54) increased the risk of sudden infant death syndrome in addition to the risk presented by maternal smoking. It appears that smoking during pregnancy remains the predominant risk factor for sudden infant death syndrome, but this study suggests a significant additional risk due to postnatal ETS exposure.

Scientific support for smoking cessation treatments

Recent research findings have greatly expanded our understanding of the most effective clinical interventions to assist patients who are motivated to quit smoking. One consistent observation has been that clinicians can provide significant aid to their patients who smoke [10]. Given that 70% of smokers see a physician each year [11], these findings should further motivate clinicians to intervene in this chief avoidable cause of illness and death.

Some of the most promising findings concern nicotine replacement therapy. A series of reports from different investigators in different treatment settings, beginning in 1989, indicated that the transdermal nicotine patch was a safe and effective aid (compared with placebo treatment) to smoking cessation. Virtually all of these studies involved extensive clinical interventions conducted with highly motivated volunteers. Overall, these studies show that the nicotine patch doubles rates of successful smoking cessation [12–14].

Within the past year, more methodologically sophisticated studies have been published. Levin *et al.* [15] reported that in a study of 62 patients treated with nicotine patches, those given active patch treatment experienced less craving for cigarettes, less negative affects, less hypoarousal, less increase in appetite, and a decrease in depression. The ability of the patch to reduce selected withdrawal symptoms agrees with the findings of other studies that have examined the withdrawal syndrome in some detail. Of particular interest was Levin *et al.'s* [15] examination of patients who "slipped" (*ie*, smoked a cigarette during treatment). Patients wearing active patches rated "slip" cigarettes as less satisfying and tasting worse than those smoked by patients wearing placebo patches.

Other investigators examined the efficacy of nicotine patch treatment with a variety of adjuvant treatments. Fiore *et al.* [16•] reported the results of two different patch treatment studies, one utilizing weekly group smoking cessation counseling, the other using brief individual counseling. Whereas group counseling pro-

duced superior outcomes at the end of treatment (59% active vs 40% placebo, $P<0.05$) as compared with individual counseling (37% active vs 20% placebo, $P<0.05$), active patch users were significantly more likely to quit with either type of counseling. Hurt *et al.* [17•] explored the efficacy of the patch when coupled with brief physician advice and individual follow-up conducted by a nurse (the National Cancer Institute model for smoking cessation treatment). This treatment model also produced a robust cessation advantage for active patch users both at the end of treatment (46.7% active vs 20% placebo, $P<0.001$) and 1 year later (27.5% vs 14.2%, $P=0.011$).

Although the above studies provided closer analogues to actual clinical practice settings, one survey stands out as an example of nicotine patch use in the real world. Orleans *et al.* [18••] conducted a telephone follow-up with 1070 elderly patients who filled prescriptions for nicotine patches through a state-level prescription plan for the elderly. According to this survey, only 54% of patch users received initial advice from a physician or pharmacist, and fewer than 2% used any formal cessation program along with their patches. Despite this disappointingly low level of adjuvant care, 29% of the sample reported being abstinent 6 months after their quit date (due to the nature of the study, these self-reports were not confirmed biochemically). Clinical trials involving nicotine patch therapy have typically used treatment regimens that last from 6 to 16 weeks; Orleans *et al.* [18••] reported that 44% of real-world patch users used the patch continuously for less than 30 days. This finding suggests that manufacturer recommendations for long treatment periods coupled with gradual dosage reduction ("weaning") are unlikely to be followed.

A disturbing finding in the data collected by Orleans *et al.* [18••] was that 47% of patch users smoked a puff or more while wearing the patch. Those who smoked while wearing the patch were markedly less likely to quit successfully ($P<0.001$). This report supports other recent findings that smoking early in the course of patch treatment (within the first 2 weeks) appears to be a powerful predictor of long-term failure, with about 90% of those who slip during the first 2 weeks returning to fulltime smoking within 6 months [19]. This indicator suggests that clinicians should "front-load" their follow-up contacts in the 1st days or weeks after a quit date to maximize the success of patch treatment. Other predictors of success or failure in quitting tobacco use by the nicotine patch treatment appear less robust. Kenford *et al.* [19] reported that a wide variety of dependence measures (carbon monoxide level, number of cigarettes smoked, years of smoking, and so forth) did not predict outcome, nor did withdrawal severity or percentage of nicotine replacement during treatment. A large study conducted in Australia by Gourlay *et al.* [20] found that success was positively associated with being male, over the age of 40, being motivated to quit, being concerned about weight gain, and living with a spouse or partner. Smoking marijuana and living with other smokers were associated with negative outcomes. These studies are important steps towards identifying the factors that place patients at risk for relapse while using the patch, and ultimately for allowing individualization of treatment. Clearly more work remains to be done in this realm.

The number of studies conducted to date assessing the efficacy of nicotine replacement therapy (whether by gum, patch, nasal spray, or inhaler) have provided the opportunity to combine results across individual studies using the technique of meta-analysis (Table 1). Two recent meta-analyses evaluated multiple forms of nicotine replacement therapy. One study examined results from 40 clinical trials (28 trials of 2 mg nicotine gum, six trials of 4 mg nicotine gum, and six trials of the patch) [21•]; another examined 53 trials (42 gum, nine patch, one nasal spray, one inhaler) [22•]. Both studies concluded that nicotine replacement therapy in any form was significantly more effective than placebo therapy. Tang *et al.* [21•] confirmed in the findings of two previous nicotine gum meta-analyses that the gum is more effective when used in specialized smoking cessation settings than in general practice, but Silagy *et al.* [22•] concluded that nicotine replacement therapy was successful independent of the setting in which it was offered.

Table 1. Comparison of efficacy and tolerability of nicotine replacement therapies

Nicotine replacement product	Cessation efficacy	Side-effect profile	Abuse liability
Nicotine gum	+	+	++
Transdermal nicotine	++	++	+
Nicotine nasal spray	++?	+++?	+++?
Nicotine inhaler	++?	++?	?

+ = mild; ++ = moderate; +++ = major; ? = uncertain based on current literature.

A third meta-analysis focused only on nicotine patch trials (17 such studies met inclusion criteria as placebo-controlled, randomized, double-blind studies) [23••]. Although limited to a single type of nicotine replacement therapy, this meta-analysis concluded that patients using active nicotine patches were two to three times more likely to quit at the end of treatment and to remain so 6 months later. Of particular note is that the relative benefit of active patch treatment was independent of the intensity of adjuvant treatment, *eg*, active patch users were two to three times more likely to quit than were placebo patch users whether they received weekly group smoking cessation counseling or brief physician advice and follow-up. This difference between patch and gum efficacy in primary care settings may be due to the greater ease of use and compliance with the patch. Fiore *et al.* [23••] also concluded that there was no significant benefit to extending patch

treatment beyond 8 weeks or to weaning (gradual dose reduction) and that 16- and 24-hour patches appeared equally effective.

Future research directions

The publication of three independent meta-analyses, all agreeing that nicotine replacement therapy is an effective treatment for smoking cessation, is an important step forward in making the case that smoking can be treated as effectively as any other chronic disease. Significant work remains to be done, however. Weight gain following smoking cessation remains a significant concern for many people and may deter some from even making an attempt to quit. Overall, people who quit smoking gain 5 to 10 pounds of weight thereafter [24]. There is limited evidence that nicotine replacement via gum or patch can delay weight gain [25], but more research is needed on the mechanisms of postcessation weight gain and possible responses to it.

Another common problem during the acute phase of withdrawal is "negative affect," such as depression, anger, or anxiety. Persons experiencing significant negative affect are at a much greater risk of returning to smoking [26]. Preliminary research is being conducted examining the efficacy and safety of combining nicotine replacement therapy with antidepressant or antianxiety medication. Cognitive-behavioral therapies to help manage emotional vulnerability may also prove helpful in this regard. Finally, more research is needed to identify clinically relevant markers for individualizing treatment. Smoking cessation research should aim not only to determine efficacy rates for different treatments, but also to identify those persons most likely to benefit from a given treatment. This will allow clinicians to make rational, scientific decisions about optimizing treatment for their patients who smoke.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• Of outstanding interest

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