

New developments in approaches to smoking cessation

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Tobacco use is the leading cause of unnecessary illness and death in the United States consuming billions of dollars in scarce health care resources. In the period under review, several new treatments for tobacco addiction were introduced. New nicotine delivery systems, a nasal spray and an inhaler, reduced craving and withdrawal compared with placebo and improved medium- to long-term cessation rates. Nicotine patches and gum became available without a prescription in the United States, offering the potential for increased use and synergy between public health efforts and commercial advertising. Important new safety data were obtained on the use of nicotine replacement therapies in potentially high risk groups, such as adolescents, pregnant women, and persons with serious cardiovascular disease, indicating that these therapies pose little or no additional risk.

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Abbreviation

AHCPR US Agency for Health Care Policy and Research

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Tobacco use remains the leading preventable cause of unnecessary illness and premature death in the United States, accounting for about 430,000 deaths every year and direct health care expenditures in excess of \$50 billion (US \$) per annum [1]. Due to increasing rates of tobacco use in the rest of the world (particularly in developing nations), the global implications of tobacco use are even more dire [2]. The balance of scientific evidence points to nicotine as the agent in tobacco that promotes continued use in the face of such significant personal health risks; *ie*, nicotine is the addictive agent in tobacco. This presents something of a paradox, because nicotine does not appear to play a direct causal role in much of tobacco-related morbidity and mortality [3]. In fact, nicotine, delivered in forms other than tobacco, appears to be a safe and effective treatment for tobacco addiction.

In April of 1996, the US Agency for Health Care Policy and Research (AHCPR) released its *Clinical Practice Guideline on Smoking Cessation* [1]. This document contained empirically derived recommendations for primary care clinicians, smoking cessation specialists, and health care administrators generated from an exhaustive review of the past 20 years of smoking cessation research and more than 50 meta-analyses. In particular, the *Guideline* recommended universal assessment of smoking status during health care visits, providing at least a minimal smoking cessation intervention to every patient who smokes, and an expanded use of pharmacotherapies to assist smoking cessation.

Clinical tobacco intervention

About 70% of persons who smoke make one or more clinic visits in a typical year [4]. Numerous studies have documented that smoking status is not routinely assessed in many clinics, and even fewer clinicians provide a minimal smoking cessation message during clinic visits. Kottke *et al.* [5] surveyed almost 8000 patients from 44 clinics in the Minneapolis-St. Paul area and found that provision of preventive care services, including smoking cessation, was less than national goals. The most commonly identified barriers to clinical tobacco intervention involve doubts about efficacy and required time on the part of clinicians. Rollnick *et al.* [6] reported favorable results with a group of general practitioners who were trained in a semistructured intervention that placed more emphasis on eliciting goals and solutions from patients than is typical in traditional, provider-oriented interventions. Total intervention time remained a concern, however. Other attempts to decrease the time demand on the clinician by augmenting cessation programs with

videotapes [7] or telephone support [8] had no impact on relapse rates, although the latter did increase the rate at which relapsed smokers set a new quit date. The negative result for long-term telephone support is perhaps not surprising, given the modest results observed with more intensive, face-to-face relapse prevention programs [9]. The majority of smoking relapses occur in a very brief period following the quit date [10], suggesting that interventions need to be "front-loaded" for maximum benefit.

The intervention model endorsed in the AHCPR *Guideline* [1] called for a system-based approach with universal assessment of smoking status, provision of brief counseling at each visit, and follow-up for persons willing to initiate a cessation attempt. Systematic approaches are both reasonable and effective in primary care settings [11] and appear to benefit from a synergy produced by involving multiple health care professionals (physicians, nurses, pharmacists, health educators, etc.) in smoking cessation efforts [1]. Combining the talents of diverse health care clinicians to produce high cessation rates has a parallel in combining different treatment modalities. Smoking cessation provides a very robust example of the benefits of combining behavior therapy with pharmacotherapy. Because the two treatment modalities operate via different mechanisms, they have the potential to produce additive effects [12], an outcome confirmed by the AHCPR meta-analyses [1].

Pharmacotherapy

On the basis of an extensive clinical literature using nicotine replacement therapies such as nicotine gum and the nicotine patch, the AHCPR *Guideline* [1] recommended that all smokers motivated to make a quit attempt be offered pharmacotherapy, except in the case of specific medical contraindications. The nicotine patch was suggested as the primary pharmacotherapy, due to superior treatment response and ease of use (vis-à-vis nicotine gum) [1]. In 1996, nicotine gum and two brands of nicotine patch became available in nonprescription form in the United States, although other countries had granted nonprescription status earlier. Public health advocates anticipated an increase in the use of these products, because it was no longer necessary to make a clinic visit to obtain a prescription, although the increase in availability was likely to be offset by lower success rates [13•]. Nonprescription status also heralded an increase in direct-to-consumer advertising by the manufacturers, offering the possibility of synergy between product advertisements and existing public health programs [14•].

Since the *Guideline* was released, several additional smoking cessation pharmacotherapies have become available in the United States. Nicotine nasal spray provides rapid peak absorption levels of nicotine that are more similar to those produced by smoking than nicotine gum or patch. Blondal *et al.* [15] reported that nicotine nasal

spray was superior to placebo for up to 6 months following the quit date; although absolute cessation rates in the nicotine group were higher as much as 2 years later, the differences were not statistically significant.

Another method of delivering nicotine without tobacco is the nicotine inhaler. This device resembles a cigarette holder on which the user puffs, drawing vapor containing nicotine into the mouth and upper throat, where it is absorbed through the buccal mucosa (no combustion is involved). In addition to providing nicotine for relief of craving to smoke [16,17], the inhaler offers a possible additional benefit of mimicking many of the behavioral components of smoking and allowing gradual reduction of nicotine dose. A large clinical trial conducted by Schneider *et al.* [18] showed that nicotine inhalers produced superior abstinence (relative to placebo) at up to 3 months following the quit date, but there were no significant differences at 6 or 12 months. Hjalmarson *et al.* [19] found a significant advantage for the nicotine inhaler at 12 months (28% continuously abstinent vs 18% for placebo users). The difference in results between these two trials may reflect population differences, especially in the use of the inhalers. There also appears to be significant variability in plasma levels of nicotine, due both to the form of nicotine delivery and to individual differences in nicotine metabolism [20]. An additional concern regarding both nicotine nasal spray and inhalers is their potential abuse liability. A well-designed laboratory study involving assessment of physiologic and psychologic effects of measured doses of cigarette smoke, nicotine nasal spray, and nicotine inhaler revealed that both the nasal spray and inhaler had lower "liking" scores among regular smokers and that the side effects of the two were likely to militate against abusive use [21].

Finally, due to the powerful role of negative mood states in withdrawal from cigarettes [22•,23], researchers are interested in the potential therapeutic utility of psychoactive agents other than nicotine. Bupropion, an antidepressant, has demonstrated its efficacy in a large clinical trial [24]. Another approach involved the use of an anxiolytic, buspirone. In a placebo-controlled, double-blind study, buspirone had no significant impact on withdrawal symptoms or cessation rates, even when participants were split on the basis of precessation anxiety scores [25•]. Given the a priori hypothesis that buspirone would be most effective among those with greater anxiety, this negative result is particularly noteworthy.

Special populations

Most of the behavioral treatments and pharmacotherapies described here can be applied to the general population of persons who smoke tobacco. There are also populations of special interest, whether due to high risk for relapse, safety concerns, or simply because they are seldom studied. The latter category includes adolescent smokers.

Despite the efforts of primary prevention programs in the United States, about 3000 persons under 18 years of age begin smoking each day [26]. Many of these persons are daily smokers, and are subject to the same withdrawal symptoms that adult smokers experience when they refrain from smoking. Smith *et al.* [27•] reported the results of an open-label treatment program that provided 8 weeks of nicotine patch therapy to 22 smokers aged 13 to 17 years. Although only one participant (4.5%) was able to maintain abstinence for 6 months, significant relief from withdrawal symptoms was observed during patch therapy, and the patches were well tolerated. Clearly, there is much room for improvement in the treatment of underage smokers.

Equally unique in the smoking cessation literature were findings reported by Wright *et al.* [28]. Six pregnant women (between 28 and 37 weeks' gestation) who had been unable to stop smoking during their pregnancies were monitored in an inpatient setting while wearing a nicotine patch for 8 hours. Significantly, no adverse effects were observed in either the women or their fetuses during use of the patch. Nicotine replacement therapies typically deliver only a fraction of the nicotine seen with ad lib smoking, and they do so with none of the carbon monoxide, tar, and carcinogens that are present in cigarette smoking, so they appear to be of *prima facie* lower risk during pregnancy. The empirical findings of this study, although they do not pertain to long-term use, provide important support for the safety of nicotine patch therapy, at least in the latter stages of pregnancy.

A third group of particular interest is persons with significant cardiovascular disease. Smoking is a preventable contributing factor, but despite clear, personal evidence of the health risk, many such patients are unable to quit without additional assistance. Because nicotine in any form is a cardiac stimulant and promotes release of catecholamines, many physicians have been reluctant to use nicotine replacement therapies in patients with cardiovascular disease. As noted, cigarette smoke contains elements not found in nicotine replacement therapies, and it appears that cigarette smoke in particular increases blood coagulability, an acute risk factor [29]. A large study of the use of transdermal nicotine in patients with cardiovascular disease, conducted at 10 Veterans Affairs medical centers, provided strong evidence that a 10-week course of nicotine patches did not increase the risk of serious cardiovascular events, compared with placebo [30••]. Long-term cessation rates in this study were modest, suggesting that more intensive treatment may have been desirable.

Modest weight gain following smoking cessation is so ubiquitous that those who fear it hardly constitute a "special population"; however, there appear to be individuals for whom the fear of weight gain is so strong that it

forestalls making a smoking cessation attempt [31•]. In others, weight gain may prompt a relapse to smoking, particularly among women who are chronic dieters [32•]. This is a persistent clinical problem in smoking cessation. Although nicotine replacement therapies, or pharmacotherapies such as caffeine and ephedrine, may delay weight gain, any protective effect is lost when the medication is discontinued [33]. Perkins *et al.* [31•] have argued that it may be more realistic to address irrational fears of weight gain (because the health risks of the typical postcessation weight gain are minimal compared with the risks of continued smoking) than to search for a "magic bullet" that will prevent weight gain. More research is needed in this area, both to elucidate the mechanisms involved in postcessation weight gain and to refine clinical strategies to address the phenomenon.

Conclusions

Smoking continues to be a serious public health problem, claiming a terrible toll of needless suffering, expense, and premature death. Effective treatments do exist, but clinicians are often unaware of who is at need and how best to deliver services. Systemic changes in health care delivery that provide for universal assessment of smoking status, and at least a minimal intervention at each clinic visit, show great promise. New pharmacotherapies for smoking cessation, such as nicotine nasal spray, nicotine inhalers, and bupropion, are safe and effective. Established treatments, such as nicotine gum and patches, are now available in nonprescription form, increasing their functional availability for those who have little or no contact with traditional health care services. New research findings also suggest that nicotine replacement therapies pose less risk in pregnant women, in persons with significant cardiovascular disease, and in adolescent smokers than was thought previously. More work remains to be done in improving cessation rates, matching patients to optimal treatments, and addressing problems such as postcessation weight gain, but significant progress is being made in confronting the tobacco epidemic.

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