

# Smoking Cessation: Progress, Priorities, and Prospectus

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The authors review developments in understanding smoking cessation interventions over the past decade. Noteworthy is the unprecedented growth of research and knowledge that has left a deeper understanding of how best to use new and existing behavioral and pharmacologic tools and strategies to help smokers quit. The status of public-health-level interventions is evaluated, questions are raised concerning their efficacy, and suggestions are offered for further refinement of these intervention strategies. Development of cessation guidelines is reviewed, and the state of knowledge concerning behavioral and pharmacologic interventions is summarized. The authors also present agendas for behavioral and pharmacologic research related to smoking cessation and discuss individual difference factors among smokers that may prove to be important in designing new and refining existing treatments.

## Background

This is the third in a series of articles intended to provide an update on the current status of research on, and issues pertaining to, smoking and smoking cessation (Lichtenstein, 1982; Lichtenstein & Glasgow, 1992). We begin by reviewing information on population incidence and prevalence of smoking, followed by an examination of key issues and predictions raised by the prior reviews—most of which remain salient and unresolved. We then give our perspective on the myriad developments in smoking cessation clinical research over the past decade, focusing especially on systematic development of evidence-based guidelines for treatment, contrasting pharmacologic and behavioral approaches, and raising yet again more questions regarding the future of smoking cessation in the decade to come. By necessity, this review is exclusive; we follow the example of our predecessors in focusing mostly on cessation rather than prevention efforts—a topic that requires its own review—and we must, reluctantly, be selective even in reviewing recent developments because of the explosion of treatment-related research.

## Trends in Smoking Incidence and Prevalence

Tobacco use contributes to over 450,000 deaths annually and is the leading cause of preventable morbidity, mortality, and health expense in the United States (Centers for Disease Control and Prevention [CDC], 1994b, 1994c). Recent surveys reported increases in youth smoking and slowing in adult prevalence reduction (CDC, 1998a, 1998b). For example, in 1997, 35.8% of high school students reported lifetime prevalence of having smoked at least one cigarette every day for the past 30 days. Despite a steady yearly decrease in smoking prevalence, and an increase in the quit ratio (the ratio of former smokers to ever-smokers in the population) since 1965, for the first time ever in 1991 smoking prevalence

failed to decrease and the quit ratio failed to increase (CDC, 1992). In the year 2000, 23.2% of U.S. adults were current smokers (CDC Behavioral Risk Factor Surveillance System Web site: <http://apps.nccd.cdc.gov/brfss/>). More disturbing, perhaps, are the disparities in smoking prevalence along sociodemographic dimensions: that is, 17.0% versus 34.0% for Asian Pacific islanders compared with Alaskan American natives; 11.6% versus 35.4% for those with more than 16 years of education compared with those who attended but did not complete high school; 12.0% versus 29.0% for those older than 65 years compared with those 44 years of age or younger (CDC, 1999). (The latter statistic, however, may owe as much to premature-smoking-related mortality as to older individuals' ability to finally quit smoking.) Smoking prevalence is also significantly and positively associated with factors such as poverty and comorbid psychiatric disorders, most notably, depression, alcoholism, substance abuse, and schizophrenia (Dalack, Healy, & Meador-Woodruff, 1998; Glassman, 1993; Lasser et al., 2000). Thus, smoking prevalence is largely a function of increases in smoking initiation and failure to quit among established smokers.

The selection hypothesis of smoking prevalence argues that smokers able to quit successfully are those who are relatively unfettered by characteristics that make it difficult to quit, that is, they are less nicotine dependent, and they are less likely to suffer from psychiatric comorbidity (Fagerstrom et al., 1996; Hughes, 1993). Following this logic, continuing smokers will consist mostly of those who will be unable to quit, for example, because of problems with nicotine dependence, psychiatric comorbidity, and other factors associated with increased rates of smoking. As a result, smoking prevalence should begin to stabilize as fewer smokers overall are able to quit. If the selection hypothesis holds true, we will be faced increasingly with issues surrounding the development of more effective treatments that target the needs of the special, hard-core-smoking populations and with the challenge of disseminating existing and new treatments so that they reach, motivate, and are utilized by these smokers. At the same time, segments of the young adult population, such as college students, are taking up smoking at higher rates than previously (Rigotti, Lee, & Wechsler, 2000; Wechsler, Rigotti, Gledhill-Hoyt, & Lee, 1998), and it is unclear whether existing treatments will work for

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these younger smokers. So we are faced with at least the double challenge of motivating and treating what may be a recalcitrant group of older smokers and a group of younger smokers whose reasons for smoking remain largely unknown, as does their ultimate trajectory toward entrenched tobacco dependence.

### The Continuum of Care: Where Have We Been and Where Are We Going?

Perhaps the single most important issue highlighted by our predecessors in this series was the tension in shifting from the predominantly intensive clinical approach to smoking cessation, on the one hand, to the public-health-based, broad dissemination perspective, on the other, which they dubbed the “clinical-public health continuum” (Lichtenstein & Glasgow, 1992). The argument for a public-health-based model of treatment dissemination is reinforced, in part, by what we know about smokers’ motivation to quit and the means by which smokers try to quit. For example, in 1994 most smokers (70%) reported wanting to quit completely (CDC, 1996). The majority, however, are not ready to quit within the next 6 months, and motivation is lowest among low-socioeconomic-status (SES) groups (Abrams & Biener, 1992; Velicer et al., 1995). The vast majority of smokers (97%) quit on their own or with minimal assistance; very few utilize formal treatment services (Fiore, Novotny, & Pierce, 1990). Moreover, although intensive treatment programs are efficacious (i.e., they have demonstrated efficacy in tightly controlled research settings), their effectiveness (i.e., how they work and can be disseminated in real-world settings and populations) is likely to remain low. Barriers include inability to reach the broadest segment of the smoking population; desire of most smokers to quit on their own; low utilization; high dropout; high cost; and lack of third-party reimbursement for treatment expenses. In addition, these programs do not reach underserved smokers, who often cannot afford or do not seek expensive smoking cessation clinic programs (U.S. Department of Health and Human Services, 1992).

Thus, there remains an acute need to provide the motivated smokers with the means to quit and to reach, in addition, the less motivated smokers in ways that guarantee contact. The challenge from the public health perspective, therefore, is to disseminate widely accepted, low-cost, efficacious treatments to the greatest number of smokers. By contrast, expensive and more efficacious treatments (e.g., combined pharmacologic and behavioral interventions delivered by smoking cessation specialists) are by definition less able to be disseminated widely and are less likely to appeal to most smokers. As a result, a compelling argument was made that so-called alternative service delivery methods, such as physician or health care provider interventions, work site interventions, and community-wide approaches, should take center stage largely because of their promise of increased efficiency, which is defined as Population  $\times$  Reach  $\times$  Efficacy (Abrams et al., 1996). That is, even if the absolute efficacy of an intervention delivered is moderate or even small, its efficiency will be large if it reaches enough smokers.

To be fair, Lichtenstein and Glasgow (1992) did not suggest abandoning research on more intensive treatments. Rather, they questioned whether an asymptote had been reached in the search for effective ingredients in intensive clinical research designs and whether, in fact, most of the efficacy of intensive treatments could

be accounted for by increased contact as compared with the effects of specific treatment components. They also questioned the cost-effectiveness of intensive clinic-based treatments relative to those that could be more readily disseminated. However, they maintained that intensive treatments would find their niche in terms of offering hard-core or recalcitrant smokers (e.g., high-risk medical patients or heavy, dependent smokers who have been unable to quit) a (one hopes) cost-effective means of quitting.

Now, a decade later, we have the benefit of hindsight and considerable research to evaluate the ways in which the public health model has been embraced by the research and intervention delivery communities and the degree to which each of the alternative delivery service vehicles—health care providers, work sites, and communities—has performed.

### Work Sites

Work-site health promotion interventions, including those with a smoking cessation component, have demonstrated some efficacy (Abrams, Emmons, Linnan, & Biener, 1994; Jeffrey et al., 1993; Pelletier, 1993). Unfortunately, most work-site trials have been plagued with significant methodological problems, such as low participation rates, employee self-selection bias, few work sites, and unit of randomization and analysis issues (e.g., using the work site and not the individual as the unit). Other problems have included highly structured, expensive interventions limiting dissemination, relatively short duration interventions, and the difficulty of separating intervention effects from secular trends and other macrolevel contextual influences on smoking rates (e.g., local and state policy changes).

Two recently completed work-site intervention trials (Glasgow, Terborg, Hollis, Severson, & Boles, 1995; Sorensen et al., 1996) overcame most of the aforementioned methodological problems, were the most statistically powered studies of their kind, and reached the same general conclusion: There is no evidence for differential efficacy of an intervention versus a comparison condition. Both studies targeted multiple behaviors for change (e.g., diet, physical activity, smoking), which may have diffused the focus on smoking, and one study demonstrated significant intervention effects on other behaviors (Sorensen et al., 1996). To be sure, the results for smoking are disappointing and require explanation. Among the most plausible are (a) smoking is such a difficult behavior to change that it requires a level of intervention intensity that is difficult if not impossible to realize because of inherent constraints in many work-site environments, and (b) there is considerable variability in individual work site response to intervention that precludes observing an intervention main effect. The latter explanation is particularly compelling because high variability in response to the intervention was observed in both studies—some work sites responded well to the interventions, whereas others responded poorly. This suggests that increased study is required to tailor interventions to the context of particular work sites—being able to understand what structural, cultural, and other work-site-specific factors enhance or impede behavior change at the level of the individual smoker. In our opinion, the negative results for work-site studies should serve as a challenge, rather than as an indictment of the approach, because the problem of variability in intervention response can in theory be addressed

and because work sites retain tremendous potential for reaching a majority of smokers.

### *Community-Level Interventions*

Similar to work-site studies, despite some promising early results (Farquhar et al., 1990), large, methodologically sound studies have failed to provide convincing evidence that community approaches produce significant reductions in the population prevalence of smoking, at least in North America (cf. Puska et al., 1983). The Community Intervention Trial for Smoking Cessation (COMMIT) matched 11 pairs of communities, representing over 20,000 smokers, and randomly assigned one of each pair to a 4-year intervention or comparison condition (COMMIT Research Group, 1995a, 1995b). The intervention, carried out by community volunteers, local agencies, and staff, was implemented through four community task forces representing each of four channels: public education through media and community-wide events, health care providers, work sites and other organizations, and cessation resources. Process measures indicated that nearly all mandated activities were implemented in a timely fashion. Notably, the trial targeted heavy smokers. Prevalence data among the study population aged 25 to 64 years showed no intervention effect on heavy smoking prevalence (COMMIT Research Group, 1995a). Cohort data similarly showed no effect on heavy smokers, but there was a significant intervention effect (3%) for light to moderate smokers (COMMIT Research Group, 1995b). Arguably, extrapolating from the cohort results, the public health impact of the COMMIT intervention was an additional 3,000 light to moderate smokers quit in the 11 communities that participated in the study.

Other large-scale community-level intervention studies have yielded similarly disappointing results. The Minnesota Heart Health study, a 5-year, community-level, multicomponent, and delivery channel intervention, which targeted multiple risk factors including smoking, failed to show a significant intervention effect on smoking in their cohort sample, although cross-sectional analyses showed a modest effect for quitting among women (Lando et al., 1995). The Stanford Five City Project reported a small treatment effect for quitting but no effect on smoking prevalence (Fortmann, Taylor, Flora, & Jatulis, 1993). The Pawtucket Heart Health Program failed to demonstrate any intervention effect (Carlton, Lasater, Assaf, Feldman, & McKinlay, 1994). The successor to COMMIT, the National Cancer Institute's (NCI) American Stop Smoking Intervention Trial for Cancer Prevention (ASSIST) was not so much a controlled intervention trial as it was a dissemination of strategies with periodic surveillance used in COMMIT but implemented at the statewide level, with state health departments and other agencies heading up broad coalitions. There has been to date no clear evidence that ASSIST has had a significant population impact on smoking cessation per se. However, a 7% reduction in per capita cigarette consumption was attributable to the ASSIST program (Manley et al., 1997).

The cynical view of results of community-level intervention studies is that these efforts are disappointing at best and a total waste of effort and money at worst. We view the latter opinion as too harsh. For example, despite its limited effectiveness, the COMMIT intervention was still cost-effective, comparing favorably with a number of other preventive interventions (Shipley,

Hartwell, Austin, Clayton, & Stanley, 1995). It is possible that some of the component parts of the intervention were effective for subgroups of smokers. Moreover, we echo some of Cummings's (1999) conclusions regarding whether community interventions are a good investment. It is perhaps unrealistic to expect a community-level intervention to exert its effects when not even a decade has passed (cf. Puska et al., 1983). This is, in part, because this sort of intervention should be working on changing societal norms and policies regarding tobacco, and this requires sustained effort.

Community-level interventions should, to the extent possible, strive to implement intervention strategies that have been proven effective in efficacy trials or that have the benefit of inferred causality through other established epidemiologic and econometric evaluation methods (e.g., effects of pricing and policy changes on tobacco consumption). We strongly advocate that any community-level intervention be tied closely to a formal evaluation of its effectiveness in terms of smoking cessation, if not in the setting of a controlled trial, then at least in terms of surveillance to allow comparisons in cessation trends among communities that differ in terms of community-level intervention activities. To do otherwise, we believe, would be a waste of our precious resources. There is also a need for community-level interventions to move away from thinking about reaching entire populations. As we have seen, reach is an important factor in the public health equation for smoking cessation, but the intervention needs to reach those most in need: smokers who are heavy dependent, smokers with comorbid psychiatric conditions, and smokers who for whatever reason are unable to quit with minimal assistance. Finally, community-level interventions may be quite good at setting the stage for cessation efforts by increasing motivation to quit, boosting awareness of the benefits of quitting, and increasing awareness of treatment resources. However, we venture that these interventions have been hobbled by the inability to provide effective tools for smokers, especially heavy dependent smokers, to help them quit. For example, self-help materials, as they are currently configured, are minimally effective (Fiore et al., 1996, 2000). Nicotine replacement therapy (NRT), by contrast, has been proven efficacious and safe for virtually all smokers (Fiore et al., 1996, 2000). Community-level interventions may therefore need to work to increase access to proven efficacious treatments such as NRT (especially because patch and gum products are available over the counter; OTC) and to focus not only on motivating the smoker to seek out such treatment but also on working at the policy level to change health insurance reimbursement and payment practices so that underserved smokers can afford to use the most efficacious treatments. One strategy may be to mainstream NRT, once considered an expensive, intensive treatment, into community-level interventions to increase efficiency by addressing the efficacy part of the equation (Shiffman, Mason, & Henningfield, 1998).

### *Health Care Provider Interventions*

There are two compelling reasons to suppose that cessation interventions delivered by health care providers can and should be widely promulgated: Smokers come into contact with the health care system on a frequent basis, providing the opportunity for intervention, and interventions delivered by health care providers are efficacious. More than 70% of smokers have contact with a

physician each year (Davis, 1988), and health care providers have multiple occasions to provide personalized cessation interventions to patients who smoke. Smokers who receive even brief clinical interventions demonstrate significantly increased cessation rates compared with those who receive no advice, and there is a dose-dependent relationship between the intensity of person-to-person contact and successful cessation outcome (Fiore et al., 1996, 2000). Moreover, smokers often cite the importance of physicians' advice in influencing their decision to quit smoking (S. Burns, Cohen, Gritz, & Kottke, 1994).

Primary care clinicians, however, are not taking full advantage of opportunities to intervene with their patients who smoke. Only about half of current smokers report that their physicians have either asked them about smoking or advised them to quit (Goldstein et al., 1997). In one recent survey (Thorndike, Rigotti, Stafford, & Singer, 1998), cessation counseling rates by physicians were found to have increased from 16.0% of smokers in 1991 to 29.0% in 1993 and then to have decreased to 21.0% in 1995. Among a population-based sample of smokers who had seen a physician during the previous year, only 51.0% reported that they were talked to about their smoking, 45.5% were advised to quit, 14.9% were offered specific assistance, and 3.0% had a follow-up appointment arranged (Goldstein et al., 1997).

Although most physicians believe in the importance of addressing smoking with their patients (Wechsler, Levine, Idelson, & Coakley, 1996), incorporating counseling into routine practice remains a challenge. Barriers include time demands; provider uncertainty about how to provide counseling; skepticism about the efficacy of counseling; insufficient reimbursement; and lack of office resources, systems, and support (Orleans, Glynn, Manley, & Slade, 1993; Walsh & McPhee, 1992). These barriers influence physician readiness to adopt smoking cessation interventions into their routine office practice (Main, Cohen, & DiClemente, 1995).

Previous controlled trials have demonstrated the efficacy of intervention strategies designed to increase physicians' adoption of components of the National Cancer Institute's "4As" smoking cessation strategy: Ask about smoking at every visit, Advise all smokers to quit, Assist the patient to stop smoking, and Arrange follow-up to reinforce the cessation messages and to address relapse (Manley, Epps, Husten, Glynn, & Shopland, 1991). Efficacious strategies for increasing the frequency and intensity of clinician-delivered smoking cessation interventions include linking identification of smoking status with the use of a vital-sign stamp, using other reminders to prompt physicians to intervene, training physicians in counseling skills, and providing patients with access to nicotine replacement and educational materials in the medical office setting (Fiore et al., 1995; Kottke et al., 1992; McPhee & Detmer, 1993). One recent study demonstrated that a brief multicomponent intervention including NRT, when appropriate, tailored to smokers' level of motivation, and performed by general practitioners and office staff outperformed usual care (brief advice to quit; Pieterse, Seydel, DeVries, Mudde, & Kok, 2001).

However, most previous studies were efficacy trials that used the practices of physicians who chose to participate in smoking cessation studies or resident clinics rather than representative samples of community physicians. Moreover, many of the experimental interventions that were found to be effective (e.g., assessment of smokers, chart reminders, treatment algorithms, patient educa-

tional materials) were implemented in clinical settings by research staff rather than by the physicians or office staff. Recently, a large, multicomponent dissemination trial tested an intervention that included medical office staff training, office systems to support counseling, and physicians' continuing medical education. At the patient level of reporting, smokers in the physician intervention communities were more likely to report receiving material about smoking from their doctors than smokers in comparison communities, but differences in other smoker-reported physician activities, such as setting a quit date, were not detected (Ockene et al., 1997). Thus, effective strategies are needed to enhance the adoption of efficacious smoking cessation interventions within a population of primary care physicians and practices. Moreover, the impact of such an intervention at the level of the population of smokers must also be formally evaluated. Sufficient evidence also exists to suggest that interventions delivered by other health care providers (e.g., nurses, physician assistants, dentists, pharmacists) are efficacious and that there are additive effects with multiple providers (S. Burns et al., 1994; Severson, Andrews, Lichtenstein, Gordon, & Barckley, 1998). Moreover, there is good evidence now to suggest that interventions among smokers hospitalized as a result of smoking-related illnesses can be efficacious, although these interventions are not yet widely adopted or disseminated (France, Glasgow, & Marcus, 2001). Medicaid now offers prescription benefits for pharmacologic smoking cessation aids in several states (CDC, 2001). More research is needed on how best to exact and institutionalize structural changes in policies and practices to facilitate delivery of smoking cessation messages and resources in various health care settings (Lichtenstein, 1997).

### *Other Public Health Approaches*

Although space limitations preclude comprehensive discussion, we would be remiss not to mention important efforts in the arena of media, policy and legislation, health care benefit, and other societal-level interventions. Several states and communities have directed campaigns of multimedia counter-tobacco advertising, proscription of advertising to minors, legislation to ban smoking in public and other areas, increased tobacco taxes, and so forth. Noteworthy examples are efforts by states such as California, Massachusetts, Oregon, Arizona, and Florida, which have witnessed steeper declines in smoking prevalence than most other states, which can reasonably be attributed to these multipronged efforts (Kessler & Myers, 2001). Remarkably, these efforts have also been directly linked to declines in the incidence of cardiovascular diseases at the population level (Fichtenberg & Glantz, 2000). Medicaid can provide prescription benefits for pharmacologic smoking cessation aids, and since 1998, the three major health care plans in Minnesota have provided coverage for NRT and bupropion (Solberg et al., 2001). It remains to be seen whether these changes in prescription coverage will result in significantly increased cessation rates, but we have every reason to be optimistic. Consequently, we enjoin all those who identify with the behavioral medicine perspective to embrace the public health perspective in thinking about creative ways in which policy, legislative, and treatment efforts can be combined to maximize motivation and resources necessary for tobacco users to quit.

### *Current Status of Public Health Interventions*

Has the public health model with its emphasis on effectiveness research taken center stage? Not quite, but it certainly shares the limelight with efficacy research, in particular studies of pharmacologic interventions for smoking cessation, which have burgeoned in the past decade (see *What's New Since 1992?* section). Efficacy and effectiveness models of research must share the same stage and act in harmony, for the results of one set of studies fuel the other. Only when a sufficient evidence base exists for a given treatment approach, whether it is pharmacologic, behavioral or other, can it serve as a potential treatment tool for widespread dissemination. So what works to help smokers quit?

#### What's New Since 1992?

##### *Evidence, Meta-Analyses, and Guidelines*

In our opinion, among the most important developments in smoking cessation research and practice in the past decade are the evidence-based guidelines and reports documenting the efficacy of particular pharmacologic and nonpharmacologic interventions for smoking cessation and the rapid growth of pharmacologic intervention studies, particularly those involving NRT.

In 1996, the U.S. Agency for Health Care Policy and Research (AHCPR) issued their "Clinical Practice Guideline for Smoking Cessation" (Fiore et al., 1996). The British Health Education Authority sponsored a similar effort, entitled "Smoking Cessation Guidelines for Health Professionals" (Raw, McNeill, & West, 1998). Both guidelines are evidence-based and relied heavily on meta-analyses of published research studies to formulate conclusions and recommendations. The British Guidelines used meta-analyses performed by the AHCPR authors, as well as those performed as part of the Cochrane Library (1998), an online, regularly updated database of smoking cessation clinical trials. Both the United States and British guidelines focused on interventions provided by health professionals, in particular primary care physicians. The American Psychiatric Association also published smoking cessation guidelines that presented more of a focus on dealing with the problem of smoking among those for whom primary care treatment has failed, patients with psychiatric difficulties, and patients in smoke-free facilities (Hughes et al., 1996). The respective guidelines are quite similar in their conclusions regarding effective interventions for smoking cessation. Most recently, the AHCPR guideline was updated (Fiore et al., 2000; [www.surgeongeneral.gov/tobacco/](http://www.surgeongeneral.gov/tobacco/)) as part of a collaboration between the Agency for Health Research and Quality (formerly AHCPR); the NCI; the National Heart, Lung, and Blood Institute; the National Institute on Drug Abuse; the CDC; the Robert Wood Johnson Foundation; and the University of Wisconsin Center for Tobacco Research and Intervention. Here we focus briefly on the results presented in the updated Guideline and selectively review what we believe are particularly noteworthy findings and conclusions.

The reader is referred to the source (Fiore et al., 1996) for details concerning how the Guideline was constructed, criteria for inclusion of studies in the meta-analyses, and so forth. It is worth noting, however, that the original Guideline identified 3,000 research articles published between 1975 and 1994, and the update (Fiore et al., 2000) identified an additional 3,000 articles published

between 1994 and 1999, a testament to the rapid increase in clinical trials efficacy research emphasis upon smoking cessation. It is also noteworthy that more than one million copies of the 1996 Guideline and its affiliated products have been disseminated. However, the public health impact of this dissemination is difficult to evaluate, and implementation of the Guideline in various treatment settings, and evaluation of the efficacy of its use, remains a challenge (Sippel, Osborne, Bjornson, Goldberg, & Buist, 1999).

##### *Structural and Psychosocial Aspects of Treatment*

Most of the conclusions reached in the initial Guideline remained true in the update. In 1992 Lichtenstein and Glasgow speculated that "more is better, usually" (p. 521) asserting that personal contacts distributed over time, and not necessarily number of intervention components, are probably most important in determining successful quitting. As usual, our predecessors were mostly right. In meta-analyses, efficacy was strongly and positively associated with time spent in counseling, defined either as session length, total contact time, or number of treatment sessions. Analysis of format types (e.g., self-help, proactive telephone counseling, group counseling, and individual psychotherapy) also showed that more was better, with number of combined formats demonstrating a positive relationship with outcome. Of all format types, individual counseling was superior in terms of its effect (odds ratio [OR] = 1.7), although proactive telephone counseling and group counseling were also found to be efficacious (ORs = 1.2 and 1.3, respectively). The effect for self-help was inconsistent and weak compared with other formats, and it did not appear that combining different types of self-help approaches conferred any advantage in terms of quitting.

The meta-analyses also addressed the efficacy of particular types of psychosocial content. No evidence for efficacy could be detected for the following content categories: relaxation/breathing exercises, contingency contracting, weight and/or diet issues, cigarette fading, acupuncture, and negative affect. The categories of content areas that enjoyed statistically significant associations with cessation included (a) in-treatment social support; (b) extra-treatment social support (i.e., providing direction or support to increase support in the smoker's environment); (c) problem solving (providing practical information such as skills training, relapse prevention, and stress management); and (d) aversive smoking procedures such as rapid smoking, rapid puffing, and other smoke exposure.

The analyses of content should be viewed with caution because intervention studies rarely use a particular content in isolation; content tends to be correlated with other aspects of treatment (e.g., more sessions = more content), and studies often tailor content to the needs of the smokers being studied. Nevertheless, in future cessation studies, researchers should take some guidance in focusing on, including, and improving content that is supported by evidence. Future researchers should neither abandon research on other content areas that do not currently enjoy the benefit of evidence-based support, although our recommendation is to use with caution. These content categories or treatment components may benefit particular subgroups of smokers (e.g., negative affect treatments may benefit smokers predisposed toward depression when quitting smoking).

Despite the apparent strengths of meta-analysis, it is important to remain critical of general findings and recommendations. For example, whereas the Guideline (Fiore et al., 1996, 2000) suggests that social support and problem solving are important, active ingredients of effective behavioral treatments, the devil still lies in the details.

### *A Research Agenda for Behavioral Interventions*

In 1993, Shiffman threw down the gauntlet, claiming that behavioral smoking cessation is in a rut. This claim was based in part on the observation that innovations in behavioral techniques or approaches for cessation had dwindled in the late 1980s compared with the 1960s and 1970s. He also correctly observed that most of the techniques found to be efficacious had been combined in favor of multicomponent cessation programs and delivered by means of various modalities. Moreover, researchers have confirmed that multicomponent programs enjoy greater efficacy compared with single component programs (Fiore et al., 2000). To move us out of a rut, Shiffman further recommended, among other things, that more attention needs to be paid to how developments in theory or basic science are implemented in treatment, with a rededication to basic research on smoking behavior and nicotine dependence; that we need to pay attention to treatment process; and that more work needs to be done to explore the unrealized promise of patient-treatment matching.

With perhaps a few exceptions, it does not seem that there has been much innovation in developing new behavioral cessation treatments since Shiffman's (1993) review (but contrast this with the proliferation of modalities for delivery of treatments and patient-treatment matching strategies). Cognitive-behavioral mood management techniques have been developed and evaluated, focusing on managing depressed mood postcessation (Hall, Munoz, & Reus, 1994; Hall et al., 1996). It does not appear, though, that this added treatment component boosts efficacy beyond more traditional cognitive-behavioral multicomponent treatment packages (Fiore et al., 2000). However, there may be insufficient research on this topic to do it justice with meta-analysis. Moreover, it remains to be determined whether this approach is differentially effective for smokers who are at high risk for cessation-induced exacerbation of depressive symptoms. Another approach, motivational interviewing (MI) or motivational enhancement (Rollnick, Butler, & Stott, 1997), emphasizes motivating less-than-ready individuals to begin to make changes in thoughts and behaviors that will eventually propel them toward control of their addiction. The advantage of this approach is that it targets the low range of motivation, whereas typical treatments are better matched to more highly motivated individuals. Preliminary studies with smokers indicate some efficacy (Butler et al., 1999; Colby et al., 1998), but more studies are needed (and are currently underway) to fully evaluate MI's potential. Another quasibehavioral treatment is biomarker feedback, which is designed ostensibly to motivate or reinforce behavior change. Biomarkers include indices of smoke and nicotine intake/exposure, such as carbon monoxide or cotinine, and measures of tobacco-related tissue cell/tissue damage and toxicity, such as pulmonary function, precancerous lesions, and evidence of genetic damage. More systematic research is needed to evaluate the full potential of this sort of feedback in motivating smokers to make a quit attempt and to reinforce maintenance of

cessation, for example, if biomarkers show reversibility of risk or damage on cessation.

Despite the relative paucity of new behavioral treatments, it is our sense that there has been a return to basic science issues and to theory. The lag between translation of the results of basic science into therapeutic applications is long, so it may be some time before new behavioral treatments are developed. We are, however, optimistic. Two areas that we believe deserve increased and more-immediate research emphasis are intra- and extratreatment social support and problem-solving/relapse prevention, both of which are associated with favorable outcomes (Fiore et al., 2000). Researchers still do not understand exactly the process by which these treatment components work and, with few exceptions (Piasecki & Baker, 2001; West, Edwards, & Hajek, 1998), little has been done in the way of forging interventions to maximize the potential influence of social support. One should also look to recent developments in theoretical understanding of the process of relapse and its converse, the maintenance of cessation, to help guide development of more effective interventions in this regard (Ockene et al., 2000).

Finally, we urge readers to consult the individual articles that constitute the evidence for the Guideline meta-analyses ([www.surgeongeneral.gov/tobacco/](http://www.surgeongeneral.gov/tobacco/)) and come to their own interpretation of what constitutes the active (or inactive) ingredients of behavioral treatments. Indeed, this should be the starting point for research on enhancing existing treatments and even on developing new ones. Researchers must not fall into the trap of expecting the meta-analyses to be the last word on the subject.

### *Match Making, High Stepping, and Master Tailoring*

Other issues that deserve comment have to do not so much with behavioral treatment components or content as with how and to whom intervention elements are delivered. Treatment matching and stepped care models have been discussed but have received scant research attention (Abrams et al., 1996; Orleans, 1993). The major theoretical advantage of matching is that smokers can be assessed according to some relevant, predictive dimension prior to treatment, be assigned to receive the treatment that is appropriate and adequate for them, and can avoid thereby the cumulative burdens of trial and failure. Treatment matching should also improve cost-effectiveness. Preliminary evidence suggests that matching treatments to degree of nicotine dependence (e.g., dose of nicotine gum, nicotine nasal spray) and to level of motivation to quit (e.g., with tailored self-help materials or expert systems feedback) improves efficacy (Herrera et al., 1995; Velicer, Prochaska, Fava, Laforge, & Rossi, 1999).

Stepped care models of treatment usually include a matching component, but then step up the intensity of treatment at the point of failure. Some models step up treatment according to various algorithms that take into account the reasons for failure (Abrams et al., 1996; Hughes, 1994). Stepped care models for smoking cessation have not yet been systematically evaluated (cf. S. S. Smith et al., 2001). Their unrealized promise lies in recycling treatment failures (perhaps very quickly after an initial slip, e.g., S. S. Smith et al., 2001), maintaining motivation to quit, and recognizing that nicotine dependence is a chronic relapsing condition that may require sustained treatment to improve efficacy compared with short-term static treatments.

Promising developments that may help address problems in treatment matching and stepped care are tailored communications and computer and information technologies, such as the World Wide Web, telephone interactive voice recognition, and interactive video (Robinson, Patrick, Eng, & Gustafson, 1998). Tailoring smoking cessation communication and information has largely focused on print communications, but this is rapidly changing (Abrams, Mills, & Bulger, 1999). With the aid of computer technology, smoking cessation resources could be tailored quite specifically to the individual smokers, and tailoring could be dynamic and close to real time, with communications changing and adapting to the smokers' experience as they progress through the process of quitting (Kreuter, Strecher, & Glassman, 1999; Velicer & Prochaska, 1999). (See also Aveyard et al., 1999.) More research is needed to see how rapidly developing communication technologies can be best leveraged to reach especially the smokers who are least motivated to quit or who have been recalcitrant to previous treatments (Robinson et al., 1998). One should not ignore, however, developments in interpersonal delivery of interventions and information such as by means of telephone counseling (Lichtenstein, Glasgow, Lando, Ossip-Klein, & Boles, 1996; Zhu et al., 1996).

### *Pharmacologic Interventions*

The Guideline (Fiore et al., 2000) makes it clear that several forms of NRT are efficacious: nicotine gum, the transdermal nicotine patch, the nicotine inhaler, and nicotine nasal spray. Two non-nicotine pharmacologic treatments, bupropion hydrochloride, an atypical antidepressant with noradrenergic and dopaminergic activity, and clonidine, a centrally acting antihypertensive agent, have also demonstrated efficacy since the 1996 Guideline and are recommended treatment options (Fiore et al., 2000; Hurt et al., 1997). Bupropion has received Food and Drug Administration (FDA) approval for smoking cessation, whereas clonidine has not. Table 1 depicts the 6-month abstinence estimated ORs and 95% confidence intervals for the different treatments relative to placebo. Overlapping confidence intervals indicate that the treatments have statistically nondistinguishable effects. A recent head-to-head comparison of the nicotine patch, gum, inhaler, spray showed no differential efficacy (Hajek et al., 1999).

Despite some evidence that high-nicotine-dependence smokers may benefit more from nicotine gum (especially 4 mg gum) and nasal spray (Herrera et al., 1995; Sutherland et al., 1992), the majority of the evidence suggests that smokers in general benefit from all forms of demonstrated efficacious pharmacotherapies. Therefore, the choice of treatment should depend to a large degree on factors such as patient and provider preference, affordability, and side effects. For example, clonidine is considered a second-line pharmacologic agent partly because of increased likelihood of side effects and rebound blood pressure problems on discontinu-

ation of the drug. It is also clear that NRT works with little or no adjunctive behavioral treatment. This is not to say, however, that behavioral treatment is not important. Rather, it appears that the amount of behavioral treatment sets the base rate for quitting and that adding NRT doubles this quit rate (Hughes, 1995; Hughes, Goldstein, Hurt, & Shiffman, 1999).

The FDA granted approval for OTC sales of the gum in 1995 and the patch in 1996. This decision was based on extensive clinical and safety experience (Shiffman, Pinney, Gitchell, Burton, & Lara, 1997), trials demonstrating efficacy in OTC-like environments, and the desire to increase smokers' access to proven effective therapies and thereby increase the likelihood that motivated smokers would use NRT and quit (Hughes et al., 1999). Some studies have suggested that the public health benefit of OTC has been considerable (Shiffman et al., 1998). However, the efficacy of the gum and patch in this environment is less than that observed in controlled clinical trials and probably depends to a significant degree on factors such as underdosing, ceasing use prematurely, using inappropriately, and having an (un)availability of supplemental behavioral treatment. For example, use of a program consisting of telephone support and tailored cessation materials boosted quit rates significantly for those OTC patch and gum users who availed themselves of this resource compared with patch users who did not (Shiffman, Paty, Rohay, DiMarino, & Gitchell, 2000; Shiffman, Paty, Rohay, DiMarino, & Strecher, 2001).

### *A Research Agenda for Pharmacologic Treatments*

One obvious but largely neglected area of study is determining mechanisms of action. For example, NRT works to alleviate withdrawal distress, yet it is unclear how much of its efficacy can be attributed to relief of withdrawal symptoms (West, 1992). It is also unclear to what extent NRT products replace the primary reinforcing effects derived from tobacco use. Therapeutic effects may differ for different NRT products. Nicotine nasal spray, with its relatively rapid onset, may more closely mimic the effects of smoking in terms of central nervous system stimulation and other factors. Products such as the gum and the inhaler may capitalize on behavioral aspects such as replacement of behaviors related to smoking and self-control of administration. NRT may also exert its effects through other mechanisms including having instructional or expectancy factors; making cigarettes less reinforcing, possibly preventing a slip from becoming a relapse; or disrupting the pairing of nicotine intake and environmental cues for smoking (Hughes, 1993). Surprisingly little is known about mechanisms of efficacy for bupropion and other antidepressants such as nortriptyline. These compounds exert small effects on symptoms of withdrawal (Hall et al., 1998; Prochazka et al., 1998; Shiffman, Johnson, et al., 2000), and there is some evidence for mood modulation, but it is unclear whether these effects are responsible for cessation efficacy. The emphasis of pharmacologic randomized

Table 1  
*Odds Ratios (95% Confidence Intervals) for Efficacious Smoking Treatments Relative to Placebo*

Gum	Patch	Spray	Inhaler	Bupropion	Clonidine
1.5 (1.3–1.8)	1.9 (1.7–2.2)	2.7 (1.8–4.1)	2.5 (1.7–3.6)	2.1 (1.5–3.0)	2.1 (1.4–3.2)

clinical trial research is on demonstrating a main effect for the active versus the placebo drug. Unfortunately, this often begets a one-size-fits-all approach to use of the medication and belies considerable variability in treatment response. A significant main effect usually does not mean significant benefit for every smoker in the active drug condition; rather, there is likely to be a continuum of responders to nonresponders. Focusing on the extreme groups may prove to be an interesting strategy in determining what individual factors are responsible for treatment response. Some studies have attempted to understand which smokers respond differentially to pharmacologic intervention, notably the patch (Kenford et al., 1994; Swan, Jack, & Ward, 1997) and fluoxetine (Hitsman et al., 1999; Niaura et al., in press). The latter studies found that elevated pretreatment symptoms of depression predicted positive response to fluoxetine versus placebo. Understanding mechanisms of action not only is theoretically important but also should help guide development of new therapeutic compounds and may aid in tailoring of pharmacologic treatments to the particular needs of individual smokers.

Should pharmacologic treatments be seen as adjuncts to behavioral treatments or stand-alone therapies? At least for NRT, it appears that the two work additively (Hughes et al., 1999), although formal tests of this proposition are lacking, especially for combinations of behavioral treatments with the patch and behavioral treatments with non-NRT compounds. It is important, therefore, to know what kind of behavioral treatment components work best with pharmacologic agents and what format and delivery systems are best suited to each product and situation. Is there dose-related incremental efficacy when intensity of behavioral treatment (components and/or contact) is increased and overlaid, for example, on use of the patch? Stated more simply, how much more can behavioral treatment add to patch efficacy? Hughes (1995) also posed several hypotheses concerning the mechanisms by which behavioral and pharmacologic treatments might combine to increase treatment efficacy: (a) Behavioral treatments improve skills necessary to achieve and maintain abstinence, whereas pharmacologic treatment improves withdrawal; (b) pharmacologic treatment provides relief of withdrawal early on and provides the necessary bridge through the most difficult period, whereas behavioral treatment provides skills necessary to prevent relapse subsequently; (c) behavioral skills may be specifically helpful for a subset of smokers, whereas pharmacologic treatment helps another subset; and (d) one treatment may increase compliance with the other (Hughes, 1995). There have been no systematic investigations of these or other proposed mechanisms whereby behavioral and pharmacologic treatments may potentiate one another.

The issue of combining pharmacotherapies deserves additional attention. There is mixed evidence that combinations of NRT products boost efficacy compared with use of individual products (Blondal, Gudmundsson, Olafsdottir, Gustavsson, & Westin, 1999; Bohandana, Nilsson, & Martinet, 1999; Sutherland, 1999). However, combined use of the patch and gum appears to alleviate withdrawal symptoms more than either product alone (Fagerstrom, 1994), and there is no evidence for increased toxicity (Kornitzer, Boutsen, Dramaix, Thijs, & Gustavsson, 1995). The combination of bupropion and the patch was also found to be efficacious, at least in the short term, with no evidence of increased adverse events for the combination (Jorenby et al., 1999). So the question remains: For which smokers are combinations of particular prod-

ucts helpful, that is, those with breakthrough withdrawal symptoms, those with a need for additional behavioral replacement, those whose level of nicotine replacement is insufficient, those who need additional support during high risk for relapse situations, those who need different agents to address different withdrawal symptoms (e.g., depression vs. anxiety), or those for whom treatment of comorbidity (e.g., major depression) is also required?

Two other issues deserve comment: (a) Continued development of pharmacologic approaches to smoking cessation (what's in the product-development pipeline) and (b) the potential for long-term use of pharmacologic treatments to sustain cessation. New forms of NRT continue to be developed and evaluated. The nicotine lozenge and sublingual tablet are approved for use in Europe (Britton et al., 2000) and will probably be introduced to the U.S. consumer as prescription products in the near future. It is unclear whether these products confer a significant advantage over other NRT products. More exciting, perhaps, are treatments that target other potential mechanisms of action for cessation. Cigarette smoking inhibits monoamine oxidase (MAO A and B) in the brain (Berlin & Anthenelli, 2001; Fowler et al., 2000). This increases levels of dopamine and breaks down acetylcholine so smoking increases cholinergic and adrenergic transmission. One study found short-term efficacy for smoking cessation using moclobemide, a MAO A inhibitor (Berlin et al., 1995). What is intriguing about this research is that the effects of smoking on MAO inhibition in the brain are quite large and diffuse and do not appear to be attributable to the effects of nicotine per se but rather to some other aspects of smoking that exert psychoactive effects (Fowler et al., 1998). It remains to be seen what precise role MAO plays in the expression of tobacco dependence and whether MAO inhibitors will prove efficacious for smoking cessation.

The revised Guideline (Fiore et al., 2000) also drew attention to recent studies demonstrating the efficacy of nortriptyline for cessation (Hall et al., 1998; Prochazka et al., 1998). It is not clear how these medications could be used except perhaps as second-line agents, contingent on bupropion failure. There is no strong evidence to support the use of other antidepressants at this time, although as new and atypical antidepressants are developed it may be worth testing their efficacy for smoking cessation at least in small, "proof of concept" pilot studies. There has also been some promising work using combined agonist/antagonists (e.g., nicotine patch with mecamylamine) demonstrating good effects (Rose, Behm, & Westman, 1998), but it remains to be demonstrated how viable this approach may be for widespread use, given the possibility of significant side effects. Another avenue of exploration concerns developing antagonist or agonist/antagonist drugs that target specific subtypes of nicotinic receptors in the brain that are thought to be primarily responsible for mediating the reinforcing properties of nicotine (Picciotto, Caldarone, King, & Zachariou, 2000). Finally, work is being conducted on immunologically mediated approaches to reductions in self-administration of nicotine-containing products. One example is a nicotine vaccine that may "innoculate" the smoker, preventing nicotine from reaching regions in the brain that govern reinforcement and reward (Pentel et al., 2000). Whether any of these new approaches will prove fruitful remains to be seen. However, we predict research will continue in the pharmaceutical arena for some time to come, and it will be conducted quickly and efficiently by the pharmaceutical industry if there is sufficient promise of financial return on the research

investment. Toward this end, strategic private/government/industry partnerships should be forged and rapid disclosure of study results, both positive and negative, should be encouraged to move the field along at a rapid pace. Should the pipeline for new drug products dry up, however, we will need to focus more on how efficacious pharmacologic treatments can best be used and perhaps targeted to subgroups of smokers to maximize therapeutic efficacy.

One final issue deserves comment—whether it may be feasible and safe for smokers to use pharmacotherapy for long periods of time to sustain abstinence. NRT products are typically indicated for use for 8–12 weeks. Some smokers, though, will use NRT products for even up to several years (Hughes, 1998), and it appears that safety and abuse potential are within tolerable limits (Benowitz, 1998). There are, however, to our knowledge no randomized controlled trials of long-term use of NRT products. One recent industry-sponsored trial evaluated the efficacy of using bupropion versus placebo for 1 year among smokers who had successfully quit smoking during a 7-week open-label treatment phase with bupropion (Hays et al., 2001). Brief behavioral counseling was provided at each treatment visit throughout the open label and double-blind phases of the study. Participants were followed for an additional year after long-term treatment. Results supported the efficacy of treatment for all intervals except for the final follow-up. Long-term pharmacologic treatment may be worth pursuing, but several issues arise. Among these are the additional benefit derived from drug treatment beyond supportive behavioral counseling and whether ex-smokers need to be maintained continuously on a drug or whether they could use it as needed (e.g., to prevent a slip or prevent a slip from becoming a relapse). Cost-effectiveness issues also loom with long-term treatment. In light of cost, safety, and abuse-liability issues with certain drugs, perhaps the most important question is determining who really will benefit from long-term treatment.

#### Cost-Effectiveness, Dissemination, Adoption, and Implementation

There is now no doubt that smoking cessation treatment is both cost-effective and cost-beneficial (Cromwell, Bartosch, Fiore, Hasselblad, & Baker, 1997; Curry, Grothaus, McAfee, & Pabiniak, 1998; Warner, 1997). Indeed, smoking cessation interventions are arguably the most cost-effective of any preventive or other medical interventions (Tengs et al., 1995). Moreover, interventions are cost-effective across a range of intensity, for example, from clinician advice to pharmacotherapy to specialized clinics, as well as across populations such as pregnant women, hospitalized smokers, and smokers who have suffered a myocardial infarction (Parrott, Godfrey, Raw, West, & McNeill, 1998). So one potential limitation identified as a concern 10 years ago (Lichtenstein & Glasgow, 1992) turns out to be not a concern but a strength.

Why, then, if cessation interventions are cost-effective and cost-beneficial, are they not being more widely disseminated and adopted, especially by health care systems (McPhillips-Tangum, 1998; Warner, 1998)? There are myriad structural issues and barriers that are described elsewhere (Eisenberg, 1997; Jeddelloh, 1996). More important, perhaps, is that interventions still cost something, and this cost must be borne by the consumer or by third-party payers, such as health insurance companies, governments, and employers. Third-party payers want to see short-term

return on investment, and this has been hard to demonstrate with cessation interventions despite evidence that smokers tend to use health care services disproportionately (Pronk, Goodman, O'Connor, & Martinson, 1999). Rapid turnover within health care plans also makes it difficult to realize concrete financial gains as a result of smoking cessation, the benefits of which may not accrue for some years (Goldstein & Niaura, 1998). Some have also argued that, although short-term medical expenditures related to smoking cessation might decrease, long-term expenditures might increase, in part, because of increased longevity (Barendregt, Bonneux, & Van De Mass, 1997). How are we to respond to this dilemma? Paying for smoking cessation may be more salable if short-term return on investment can be demonstrated for subgroups of smokers. This appears to be the case, for example, with pregnant smokers (Adams & Young, 1999). In addition, it may be possible to show short-term benefits of cessation among subgroups of smokers who are high users of health care services, such as post-MI and stroke patients (Lightwood & Glantz, 1997). Another way to respond to the dilemma would be to ignore the economic arguments for the moment and simply insist that providing maximum access to resources at no or reduced cost to the smokers who want to quit is a societal priority because it is the right thing to do in terms of preserving and improving the public health. Will this argument auger well with those who decide how public and private monies are spent? Time and politics will tell.

We would be remiss if we did not at least mention the tobacco settlement in which over 200 billion dollars will be distributed by the tobacco industry to 46 state governments (4 other states settled separately for 40 billion dollars) over a period of 25 years (see [www.naag.org/tobaccopublic/library.cfm](http://www.naag.org/tobaccopublic/library.cfm) for the full Attorneys General report on the Master Settlement Agreement). Proper use of these funds represents tremendous potential to address enormous public health issues, such as prevention of tobacco use among youth and providing access to smoking cessation resources for current smokers. Surely, the settlement presents the opportunity to disseminate what we know are efficacious and cost-effective treatments, as codified in the Guideline, to motivated smokers. At this juncture, volumes have been written about the settlement, mostly as editorial comments in the scientific and popular press, and we will not review the range of opinions on how this money should be used (Lima & Siegel, 1999). We predict, though, that with the exception of a handful of long-sighted, well-organized states, most of it will be squandered on politically expedient concerns other than tobacco and that the overall impact of the settlement on prevalence of smoking in the United States will be minimal. Indeed, recent reports have suggested that a small fraction of funds is currently being spent on tobacco prevention, treatment, and research (Kessler & Myers, 2001).

#### Other Issues

##### *Harm Reduction*

Considerable interest has been generated recently by the consideration of alternatives to complete abstinence as desirable outcomes of tobacco-use intervention efforts. This approach has been referred to as harm reduction, and is predicated on data suggesting a strong dose-dependent relationship between exposure to tobacco toxins and subsequent morbidity and mortality (D. M. Burns,

1997). Moreover, some unknown proportion of smokers who may be unable or unwilling to quit may find the prospect of reducing exposure to reduce harm an acceptable alternative to total abstinence. To some unknown degree, normative influences may also be shifting attention away from the notion that smoking is deadly and that abstinence is the only safe alternative to smoking.

Research is only now being proposed and conducted on methods to reduce toxin exposure, so it is too early to render judgment on the empirical merits of this approach. (Readers should not confuse harm reduction with efforts by the tobacco industry in either the past or the future to develop a "safe cigarette." Harm reduction here refers to reducing exposure to tobacco toxins through behavioral and/or pharmacologic means.) One of the interesting consequences of adopting a harm reduction philosophy is that there is a shift in focus away from abstinence (although this is not necessarily abandoned as the most desirable outcome) to other outcomes such as reduction in smoke exposure and, most important, exposure to biologically relevant toxins related to mechanisms of disease (Stratton, Shetty, Wallace, & Bondurant, 2001). Moreover, reduction, theoretically, can be achieved in a variety of ways; that is, not only in sustained reductions in the amount of tobacco ingested but also in changed patterns of tobacco use, such as in achieving periods of temporary abstinence. An exemplar would be to encourage pregnant women to abstain at least during their pregnancies.

Shiffman et al. (1998) have outlined principles that should guide a harm reduction philosophy and approach to tobacco control. Among these principles are the assumptions that (a) the purpose of reducing exposure to tobacco toxins is to reduce the death and disease caused by tobacco; (b) the long-range goal should be to leave smokers both tobacco and nicotine free and should not reduce the likelihood of eventual cessation; (c) any method used to reduce exposure, especially pharmacologic agents such as NRT products, should pose no added safety risks; (d) exposure reduction therapies should not worsen an individual's level of nicotine dependence and should not lead to increased population prevalence of nicotine dependence or expansion of use beyond the smoking population; and (e) pharmacologic means, if used to reduce tobacco toxin exposure, should not appeal to adolescents. The degree to which pharmacologic interventions, and in particular NRT products, can result in acceptable, safe, and verifiable reductions in toxin exposure will be the target of considerable research and intervention efforts for some time to come.

### *Individual Differences and Special Populations*

Interest in individual characteristics of smokers that might predict treatment response has been abundant, but a few areas stand out as particularly deserving of attention: genetic influences, gender differences, psychiatric comorbidities, and adolescent smoking and prevention.

Numerous studies of twins have confirmed what appears to be moderate to large genetic influences on various aspects of smoking behavior (Kendler, 1998). In general, genetic influence tends to be stronger for persistent smoking, inability to quit smoking, and transition to regular smoking than it is for smoking initiation and early stages of smoking (Carmelli, Swan, Robinette, & Fabsitz, 1992; Heath & Martin, 1993). However, environmental effects are also potent, and studies to date have not been able to effectively

examine Gene  $\times$  Environment interactions. Lacking in particular are family studies of smoking and nicotine dependence phenotypes (Cheng, Swan, & Carmelli, 2000). Such studies are necessary to determine what are the heritable forms of smoking behaviors and aspects of nicotine dependence that may or may not portend response to different tobacco dependence treatments. At the same time, genetic association studies have pointed to specific candidate genes, such as the dopamine transporter gene polymorphism SLC6A3-9, that may be linked to smoking status, age of smoking initiation, and length of prior quit attempts (Lerman et al., 1999; Sabol et al., 1999). Other genes have been identified that regulate, in part, metabolism of nicotine (Pianezza, Sellers, & Tyndale, 1998) and may influence development of nicotine dependence. Increasingly, we shall see studies that examine whether such candidate genes moderate the effects of smoking cessation treatments, particularly pharmacologic treatments. However, studies such as these should be guided by theoretical and practical understanding of how genes and treatments operate at molecular biologic and other levels (Gelernter, 1997), so that we have, a priori, some idea of how genes and treatments ought to interact to decrease the possibility of Type I errors in searching for Gene  $\times$  Treatment interaction effects (Pomerleau & Kardia, 1999).

Possible gender differences in ability to quit smoking, with and without treatment, have come under increasing scrutiny (Wetter, Fiore et al., 1999). Several studies suggest that women as compared with men have more difficulty quitting smoking, despite evidencing less nicotine dependence (Wetter, Kenford et al., 1999). Moreover, women in particular may be less responsive to NRT. Some evidence exists to suggest that women smokers may be influenced more by non-nicotine-related stimuli related to smoking, which may explain in part decreased responsivity to NRT (for review see Perkins, 2001; Perkins, Donny, & Caggiula, 1999). However, very little is known regarding the array of factors, ranging from drug sensitivity to sociocultural influences, that may ultimately explain potential gender differences in smoking initiation, prevalence, risk for relapse, and response to treatment. Understanding gender differences in smoking cessation, including possibly smoking for weight control, responding to nicotine, and responding to treatments, may lead to improved interventions for smoking cessation for both women and men (Perkins et al., 2001; U.S. Department of Health and Human Services, 2001).

The past decade has seen numerous studies document strong relationships between smoking and psychiatric comorbidities, including especially mood disorders, alcohol and other substance abuse and dependence, attention-deficit and hyperactivity disorder, and schizophrenia. One recent population-based study estimated that 41% of persons suffering from current mental illness were smokers and that over 40% of the tobacco in the United States is consumed by persons with a comorbid psychiatric disorder (Lasser et al., 2000). Particularly relevant for the population of smokers are high lifetime prevalence rates of depression and alcohol/substance abuse (Glassman, 1993) compared with the nonsmoking general population. Moreover, psychiatric comorbidities, whether historical or current, appear to significantly impede efforts at smoking cessation (Hughes et al., 1996), and conversely, quitting smoking may significantly increase risk of relapse to major depressive disorder, at least among those with such a prior history (Glassman, Covey, Stetner, & Rivelli, 2001). At issue, therefore, is understanding reasons that comorbid psychiatric conditions increase the

likelihood of smoking and decrease the likelihood of quitting and using this understanding to adapt existing or develop new interventions targeted to the needs of these subgroups. For example, if history or current symptoms of depression portend treatment failure, will treatments that target increases in symptoms of depression precipitated by cessation be efficacious for this subgroup of smokers? More generally, if smokers with certain psychiatric disorders smoke to redress associated symptoms, can treatments, either pharmacologic or behavioral, be developed that serve a function similar to the effects of smoking, thereby decreasing dependence on tobacco and nicotine and increasing the likelihood of cessation? NRT products should theoretically show good efficacy in this regard, but there is as of yet little evidence to suggest they are differentially effective for smokers with and without psychiatric comorbid conditions.

The Guideline (Fiore et al., 2000) has also pointed to the importance of considering how treatments may be best developed and adapted for special populations, including, for example, racial and ethnic minorities, pregnant women, adolescents, those suffering from smoking-related illnesses and who may be hospitalized or receiving health care in a variety of treatment settings, smokers with psychiatric comorbidity/chemical dependency, and older smokers. We refer the reader to the Guideline for a more comprehensive discussion of these issues, but we wish to highlight recent developments with regard to adolescent prevention and treatment efforts.

A recent study presented the results of what is arguably the largest school-based prevention intervention of its kind (Peterson, Kealey, Mann, Marek, & Sarason, 2000). The Hutchinson Smoking Prevention Project (HSPP) determined the long-term impact of a theory-based, social influences model of intervention beginning at Grade 3 and progressing through Grade 12. The intervention was implemented in 20 schools, with 20 control schools matched on prevalence of tobacco use, school district size, and location. The intervention was grounded soundly in behavioral theory and contained all of the essential ingredients for school-based tobacco prevention as recommended by a national expert panel convened by the NCI (Glynn, 1989), as well as implementing all of the elements for school-based tobacco prevention efforts as recommended by the CDC (CDC, 1994a). This study is a model in terms of study design, intervention implementation with sustained fidelity, follow-up rates that are unprecedented, assessment of long-term outcomes, statistical power that is more than adequate, and data analysis with sophisticated methods. No significant intervention effects were observed.

The results are disappointingly negative but arguably quite real. We do not believe that an exercise in trying to determine how the study was flawed would be productive, but the results suggest that, perhaps, researchers should abandon the social influences model of prevention, at least as it is currently conceived and implemented (Clayton, Scutchfield, & Wyatt, 2000). It is also worth noting that some successes in school-based prevention have been reported (e.g., Botvin, Baker, Dusenbury, Botvin, & Diaz, 1995). These latter studies focused on a broader life-skills perspective and targeted multiple problem behaviors, so there may be some lessons to be learned from this perspective. It is also important to note that some states that have implemented the CDC school-based guidelines for tobacco prevention have witnessed declines in smoking prevalence (Bauer, Johnson, Hopkins, & Brooks, 2000; Rohde et

al., 2001). Prevention efforts that have also incorporated a family based intervention component also show promise (Spath, Redmond, & Shin, 2001). However sobering the results of the HSPP may appear, they nonetheless compel investigators to pursue with even greater vigor research into what will actually constitute effective prevention strategies.

Although prevention efforts are being challenged, so are smoking cessation treatments for the adolescent smoker. Reviews suggest that 3–6-month outcomes of behaviorally based cessation programs achieve abstinence rates of about 13% (Sussman, Lichtenman, Ritt, & Pallonen, 1998). This coupled with evidence that adolescent regular smokers are similar to adult smokers in terms of reasons for smoking, difficulty quitting, and other criteria for tobacco dependence (Hurt et al., 2000) has led to efforts to treat these smokers with NRT. Yet, despite evidence of safety, tolerability, and decreased withdrawal symptoms among adolescents treated with the nicotine patch, efficacy has not been demonstrated (Hurt et al., 2000; T. A. Smith et al., 1996). However disappointing, it must be recognized that treatment of the adolescent smoker is still in its infancy. Numerous issues remain to be addressed, including variability in motivation, trust, and the therapeutic relationship with authority figures; the need to actively participate in decisions regarding treatment, confidentiality of treatment; and the need for additional behavioral supportive treatments, to name a few. We expect that, however daunting, research will continue to proliferate in this area because of the health-related importance of cessation early on in the life course.

### Concluding Comments

This is an exciting and challenging time for smoking cessation research and clinical practice. The attention now focused on tobacco-related research is unprecedented. We have witnessed the formation of the Society for Research on Nicotine and Tobacco, the first scientific organization whose sole focus is on tobacco-related research. Major funding initiatives devoted to tobacco research have been sponsored by the NCI, the National Institute on Drug Abuse, and philanthropic organizations such as the Robert Wood Johnson Foundation. In 1999, these organizations funded several Transdisciplinary Tobacco Use Research Centers (TTURCs). The TTURCs represent an effort to bridge the gap among disciplines, from molecular genetic to epidemiologic to clinical applications to policy implications of the scientific findings, to better understand the etiology of tobacco use and nicotine dependence and to translate this knowledge into practical interventions. The transdisciplinary focus is particularly important, as it is a means for disciplinary experts to learn each others' scientific language, methods, and paradigms from which ideally will spring entirely novel ways to think about tobacco use, dependence, and treatment. Whoever reviews the field in 10 years will be able to evaluate whether the TTURCs were a success in terms of significantly advancing our knowledge of tobacco dependence and its management. In our opinion, however, it is only through sincere yet difficult efforts to cross traditional disciplinary scientific boundaries that the research community will be able to forge innovations in interventions that will truly meet the needs of all smokers and will have a significant impact on the public health.

Finally, we should not ignore the global burden of disease, of which tobacco use remains a significant and growing cause (Mur-

ray & Lopez, 1996). Although we in developed countries such as the United States have witnessed an abundance of scientifically based efforts to reduce tobacco use with considerable success, in the global context we are a minority. Prevalence of smoking and tobacco use in many developed and developing countries is high and continues to rise (see <http://tobacco.who.int/> for World Health Organization statistics on prevalence of tobacco use worldwide). We must look beyond our own borders to disseminate our knowledge of what works to help combat the global tobacco-use epidemic.

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