Searching for More Effective Smoking Cessation Treatment

The study by Rose and Behm in this issue (1) is a remarkable first attempt to improve smoking cessation by selecting treatment for individual patients based on an initial test period. Smoking cessation treatments specify a quit date, usually 2 weeks after the initiation of treatment. Rose and Behm used this 2-week period to identify those patients who would likely respond to nicotine replacement therapy, the simplest and safest treatment. The test was to identify those patients who decreased their smoking by 50% during open-label treatment with a nicotine transdermal patch. Most patients received one 21-mg patch daily, but heavier smokers received two patches. The one-third of patients who decreased their cigarette consumption by 50% or more then continued on the patch for 12 weeks. Half these patients remained abstinent at 12 weeks, and 22% remained abstinent at 6 months. The favorable prognosis for patients who immediately decreased smoking with nicotine patch treatment replicates earlier findings from Rose and colleagues (2).

The unique feature of this study is the double-blind comparison of three interventions for patients who did not decrease their smoking by 50% during the prequit phase. One-third were continued on nicotine patch, one-third received the nicotine patch plus bupropion, and one-third were switched to varenicline. Bupropion was titrated to 150 mg twice daily and varenicline to 1 mg twice daily. The treatment period lasted 12 weeks, and approximately 100 patients were in each group. At 12 weeks, the abstinence rate for treatment with nicotine patch alone was less than 7% for patients who had not decreased their smoking before the quit date, compared with 50% for those patients who had decreased smoking before the quit date. Patients who had bupropion added to the nicotine patch achieved a response rate of 19%, and patients who were switched to varenicline achieved a response rate of 12%, the latter effect not significantly different from the nicotine patch condition. At 6 months, among the patients who had not responded during the prequit phase, 7% of those on nicotine patch alone, 17% of those who received bupropion in addition, and 16% of those on varenicline were abstinent. Thus, the addition of bupropion to the nicotine patch for patients who did not respond quickly to patch alone significantly increased the response rate. Varenicline had longer-term effects that were also significantly better than the patch alone for nonresponding patients.

In a second phase of the study, a second intervention was made to try to "rescue" patients who relapsed during the first postquit week despite a favorable prequit response. This intervention was not as successful, unfortunately. However, the small number of participants in each group, approximately 30, may have contributed to the inconclusive findings.

Clinical lessons from the study include the finding that patients' self-report of cigarette consumption closely correlated with the results of carbon monoxide monitoring and that percent decrease in smoking predicted the clinical course better than absolute levels of cigarette consumption. The study design is complicated

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because of the multiple interventions, but it effectively used the 600 patients enrolled to answer questions as clinicians would address them: Does the simplest, safest treatment, nicotine patch, work for a given patient? If not, what additions (bupropion) or changes (varenicline) are likely to help? The answer is that nicotine patch alone works for half the patients, and the addition of bupropion will rescue about 20% of the remaining half. Over 6 months, only about 15%−20% of patients stop smoking with any of the three treatments. The nicotine patch challenge is a useful way to direct more effective treatment to those patients who show early on that they need it.

Although many patients in this study were helped, most had returned to smoking at 6 months, which points out the recalcitrance of this addiction to remediation. Public policy to discourage or prohibit smoking has been helpful, but the mass marketing of cigarettes and their continued adoption by young smokers, who are those most vulnerable to longer-term addiction, is problematic (3). Patients with psychiatric disorders other than obsessive-compulsive disorder, ADHD, and anxiety disorders were excluded, despite the fact that psychotic, depressed, and alcohol-abusing patients have much higher smoking rates and cigarette consumption than any other group (4). Rose and Behm speculate on whether the overall rate of response at 6 months suggests that longer-term treatments with multiple agents might be more effective for all patients, but studies have not yet addressed this question. More effective treatment is needed for the many patients who relapse in the course of the first 3 months of treatment.

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In the search for new treatments, it is also worthwhile to consider what brain mechanisms might underlie the difference in response between patients. Nicotine, like most drugs of abuse, hijacks neuronal receptors in the brain. A family of nearly a dozen nicotinic acetylcholine receptors, which normally respond to acetylcholine, are the mechanism used by nicotine to maintain addiction. Genetic variation in the expression and function of these nicotinic receptors is known to be a significant determinant of the liability to nicotine addiction and the response to nicotine replacement therapy (4, 5). It is possible that the Rose and Behm test, simple enough to be applied in any clinical treatment setting, identifies some of this genetic variation. If that is the case, then this clinical insight might also help identify which genetic variants are the most treatment resistant and might be the targets of additional treatment development.

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