The Impact of Repeated Cycles of Pharmacotherapy on Smoking Cessation: A Longitudinal Cohort Study

Smoking cessation pharmacotherapy can double quit rates. However, smokers often fail after a single quit attempt, and quitting smoking often involves multiple quit attempts over the course of months or years. Few studies have tested the impact of providing repeated courses of pharmacotherapy to help smokers recover from relapses and engage in new cessation attempts. As part of a study of chronic disease management for smoking cessation, we followed a cohort of smokers that was offered up to 4 courses of pharmacotherapy over 2 years. We examined their continued interest in using pharmacotherapy and the effect of that treatment.

Methods. Setting and Participants. We recruited smokers, regardless of their interest in quitting, from 50 rural primary care clinics throughout the state of Kansas. Smokers were excluded if they were younger than 18 years, smoked fewer than 10 cigarettes per day, smoked fewer than 25 cigarettes in the past 30 days, did not speak English, did not have a working telephone, and did not consider one of the participating physicians to be their primary care physician. Smokers were also excluded if they were pregnant or planning to become pregnant within the next 2 years, were planning to move out of the study area, had dementia or severe mental illness, or lived with a smoker already enrolled in the study. For the present analysis, we also excluded smokers who died or were incarcerated during the 2-year follow-up period. We also excluded participants who took varenicline tartrate, a drug not offered as part of the study, resulting in a final cohort of 726 smokers. This study was approved by the ethics committee of the University of Kansas Medical Center, Kansas City.

Intervention. At 6-month intervals (months 0, 6, 12, and 18), participants were asked if they wanted to receive a 6-week course of 21-mg/d nicotine patch or a 7-week course of bupropion hydrochloride sustained release, 150 mg twice daily. Participants requested pharmacotherapy by either returning a stamped postcard or calling research staff at a toll-free telephone number. All participants were followed up for 2 years. Smokers were randomly assigned to receive 1 of 3 different levels of chronic disease management to support smoking cessation. Rates of use of pharmacotherapy were similar across the treatment arms, and the primary outcomes of this study have been reported previously. In addition to pharmacotherapy management, the 2 disease management groups received telephone counseling. Counselors used motivational interviewing techniques following a semistructured protocol to promote a smoking cessation attempt or encourage relapse prevention for abstinent smokers.

Measurements and Follow-up. The baseline questionnaire included an assessment of demographic characteristics and nicotine dependence. Smoking cessation was defined as self-reported 7-day point prevalence abstinence from cigarettes and was assessed at the end of each 6-month cycle via a brief telephone survey. Follow-up calls were completed for 91%, 87%, 83%, and 85% of participants following cycles 1, 2, 3, and 4, respectively.

Statistical Analyses. To reduce self-selection bias and isolate the effects of repeated courses of medication on cessation, we created a generalized linear mixed model using the SAS GLIMMIX procedure (SAS Institute Inc, Cary, North Carolina), which allowed us to assess the effects of participant characteristics on whether they requested pharmacotherapy over multiple periods. Variables significant at the .05 level were incorporated into a second generalized linear mixed model that examined the effect of pharmacotherapy on smoking cessation over multiple periods.

In our longitudinal analyses, subjects were censored at the end of any treatment cycle in which they failed to request medication: this permitted us to compare the 6-month quit rates among participants who had used or not used pharmacotherapy during that cycle. Because we wanted to examine the impact of repeated cycles of pharmacotherapy on smokers who had failed to quit during a prior medication-assisted attempt, we also censored subjects who had stopped smoking at the end of the previous treatment cycle. The flow of continuing smokers across 4 consecutive cycles of pharmacotherapy-assisted quit attempts and those censored is described in the Figure. SAS version 9.1 software was used for all statistical analyses (SAS Institute Inc).

Results. The Figure describes medication use across the 4 consecutive cycles of pharmacotherapy-assisted quit attempts. Of the 726 participants, 464 (63.9%) took medication in the first cycle of treatment. Among continuing smokers, 202 of 383 (52.7%), 81 of 177 (45.8%), and 44 of 68 (64.7%) opted for second, third, and fourth consecutive cycles of pharmacotherapy, respectively. In the generalized linear mixed model, a positive relationship existed between the probability of requesting medication and baseline stage of change, baseline motivation, and previous nicotine replacement therapy.

Cessation rates were consistently higher for pharmacotherapy users compared with nonusers. Smokers who...
opted to use pharmacotherapy had 6-month quit rates of 17.4% (n=464), 12.4% (n=202), 16.0% (n=81), and 15.9% (n=44) after the first, second, third, and fourth consecutive rounds of pharmacotherapy, respectively (Figure). The odds ratios (95% confidence intervals) for quitting among pharmacotherapy users vs nonusers were 2.56 (1.53-4.28), 1.83 (0.90-3.69), 1.85 (0.75-4.58), and 2.08 (0.40-10.92) after the first, second, third, and fourth cycles of treatment, respectively.

In a generalized linear mixed model that controlled for baseline characteristics related to pharmacotherapy use, pharmacotherapy use was found to be significantly associated with the probability of quitting (odds ratio, 1.99; \( P = .002 \)). The probability of quitting was not related to the number of previous pharmacotherapy-assisted quit attempts (odds ratio, 1.004; \( P = .81 \)).

Comment. The study has several limitations. Smokers who chose to use pharmacotherapy were self-selected. However, we did adjust for baseline factors related to pharmacotherapy use, pharmacotherapy use was found to be significantly associated with the probability of quitting (odds ratio, 1.99; \( P = .002 \)). The probability of quitting was not related to the number of previous pharmacotherapy-assisted quit attempts (odds ratio, 1.004; \( P = .81 \)).

Nevertheless, this study showed that 1 in 2 smokers was willing to make a second pharmacotherapy quit attempt within 6 months of a treatment failure. Willingness to reengage in treatment did not diminish over time. Pharmacotherapy appeared to remain effective even in the presence of multiple prior treatment failures. These results support a model of care in which smokers in whom treatment initially fails are quickly reengaged in a new, pharmacotherapy-assisted quit attempt. Insurance programs that currently limit the number of courses of treatment that smokers receive should reexamine those policies.

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Low-Carbohydrate Diet and Blood Lipid Levels: How Good and How Fast?

We read with interest the article by Jenkins et al describing the lipid-lowering advantages of a low-carbohydrate diet high in vegetables proteins over a high-carbohydrate diet. Their findings are reassuring (low-carbohydrate diet does not increase cardiovascular risk) and in line with observational data indicating that restriction of refined carbohydrates in the diet, substituted with vegetable sources of fat and protein, may moderately reduce the risk of coronary heart disease in women.

There is at least one important message from the study by Jenkins et al challenging the current view about the effect of diet on low-density lipoprotein cholesterol (LDL-C) levels: diet generally produces only modest LDL-C level reduction in the range of 7% to 12%, which may lead readers to underestimate the true effect of diet on lipid levels. According to this estimate, the LDL-C level reduction induced by the low-carbohydrate diet would have been 21 mg/dL (to convert to millimoles per liter, multiply by 0.0259) at best (12% of baseline), whereas it was 36 mg/dL (21% of baseline), which is what one is accustomed to see with low-dose statin use, on the average. Interestingly enough, the maximal effect on LDL-C levels was obtained in 2 weeks.

Too small (for numbers of participants), too short (for length of follow-up), and too extreme (for the percentage of carbohydrate) are, however, the adjectives that need to be challenged to have these encouraging results translated into clinical practice. The reader needs to be convinced that this kind of diet may be applicable to selected patients who have to purchase and prepare their own meals and that the robust changes in a tested diet can be maintained for periods longer than the few weeks studied in the trial. Longer trials examining actual cardiovascular events are needed to convince the skeptical physician, accustomed to the drug-intensive style of medicine, of the benefit of yet another unique and difficult-to-achieve dietary regimen.

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We thank Giugliano and colleagues for their kind words on the possible value of our study. We agree absolutely that the study was small, of short duration, and extreme in terms of carbohydrate restriction. As Giugliano and colleagues rightly noted, the aim of the study was proof of principle that high-fat and high-protein diets of plant origin may have advantages over animal product–based diets in terms of LDL-C level reduction, with benefits also for the total–high-density lipoprotein cholesterol ratio and blood pressure reduction.

Such diets have proved beneficial for heart disease in cohort studies. Moderate–to high–vegetable protein diets have been proposed recently by Giugliano and colleagues as part of the dietary treatment of the metabolic syndrome. Lower–glycemic load diets have been associated with greater weight loss in subjects with postprandial hyperinsulinemia and in reducing cardiovascular disease in those who were overweight in the Nurses Health Study. These dietary approaches will all tend to limit the proportion of rapidly di-