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Effect of Varying Levels of Disease Management on Smoking Cessation

A Randomized Trial

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Background: Cigarette smoking is a chronic, relapsing illness that is inadequately addressed in primary care practice.

Objective: To compare cessation rates among smokers who receive pharmacotherapy alone or combined with either moderate- or high-intensity disease management that includes counseling and provider feedback.

Design: Randomized clinical trial from June 2004 to December 2007.

Setting: 50 rural primary care practices.

Participants: 750 persons who smoke more than 10 cigarettes per day.

Intervention: Pharmacotherapy alone (n = 250), pharmacotherapy supplemented with up to 2 counseling calls (moderate-intensity disease management) (n = 249), or pharmacotherapy supplemented with up to 6 counseling calls (high-intensity disease management) (n = 251). Interventions were offered every 6 months for 2 years. All participants were offered free pharmacotherapy. Moderate-intensity and high-intensity disease management recipients had postcounseling progress reports faxed to their physicians.

Measurements: Self-reported, point-prevalence smoking abstinence at 24 months (primary outcome) and overall (0 to 24 months) analyses of smoking abstinence, utilization of pharmacotherapy, and discussions about smoking with physicians (secondary outcomes). Research assistants who were blinded to treatment assignment conducted outcome assessments.

Results: Pharmacotherapy utilization was similar across treatment groups, with 473 of 741 (63.8%), 302 of 739 (40.9%), 175 of 732 (23.9%), and 179 of 726 (24.7%) participants requesting pharmacotherapy during the first, second, third, and fourth 6-month treatment cycles, respectively. Of participants who saw a physician during any given treatment cycle, 37.5% to 59.5% reported that they had discussed smoking cessation with their physician; this did not differ across the treatment groups. Abstinence rates increased throughout the study, and overall (0 to 24 months) analyses demonstrated higher abstinence among the high-intensity disease management group than the moderate-intensity disease management group (odds ratio [OR], 1.43 [95% CI, 1.00 to 2.03]) and among the combined disease management groups than the pharmacotherapy-alone group (OR, 1.47 [CI, 1.08 to 2.00]). Self-reported abstinence at 24 months was 68 of 244 (27.9%) and 56 of 238 (23.5%) participants in the high- and moderate-intensity disease management groups, respectively (OR, 1.33 [CI, 0.88 to 2.02]), and 56 of 244 (23.0%) participants in the pharmacotherapy-alone group (OR, 1.12 [CI, 0.78 to 1.61] for combined disease management vs. pharmacotherapy alone).

Limitation: The effect of pharmacotherapy management cannot be separated from the provision of free pharmacotherapy, and cessation was validated in only 58% of self-reported quitters.

Conclusion: Smokers are willing to make repeated pharmacotherapy-assisted quit attempts, leading to progressively greater smoking abstinence. Although point-prevalence abstinence did not differ at 24 months, analyses that incorporated assessments across the full 24 months of treatment suggest that higher-intensity disease management is associated with increased abstinence.

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Cigarette smoking is a chronic illness characterized by repeated cycles of quit attempts and relapse. Most models for addressing smoking cessation are based on single, short-term interventions lasting only a few weeks or months (1). Although most smokers will not quit after a single intervention, few studies have addressed the chronic nature of nicotine dependence by providing systematic, repetitive treatment opportunities (1). Providing treatment only to smokers who are already prepared to quit further limits the reach of current smoking cessation interventions (2). New models of chronic disease care might provide an alternative approach for expanding the reach and effectiveness of smoking cessation efforts (3).

Physicians are in direct contact with approximately 70% of smokers each year (4, 5). Their potential role in promoting smoking cessation has been well delineated and

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Context

Smoking cessation is difficult and may require repeated or intensive interventions.

Contribution

In this multicenter trial, 750 primary care patients who smoked at least 10 cigarettes per day were randomly assigned to pharmacotherapy (nicotine patch or bupropion), pharmacotherapy supplemented with up to 2 calls from trained counselors, or pharmacotherapy supplemented with up to 6 counseling calls. Utilization of the interventions, which were offered every 6 months for 2 years, declined over time. Smoking abstinence rates at 2 years were 23%, 24%, and 28% in the 3 groups.

Caution

Pharmacotherapy was free. Smoking abstinence was self-reported.

—The Editors

incorporated into current clinical practice guidelines (1). With the development of new, more effective prescription pharmacotherapy for smoking cessation, the role of primary care practices in promoting smoking cessation is now more important than ever. Unfortunately, only half of the smokers who see their physicians are asked about their smoking (6), and even fewer receive advice from their health care provider to quit or receive pharmacotherapy or follow-up (4, 7). Smoking cessation counseling competes with other pressing clinical tasks, and beyond brief advice, many physicians feel they are too busy to routinely and repeatedly counsel participants who smoke (8–10).

To assist primary care physicians in the treatment of rural smokers, we developed KanQuit, a smoking cessation program based on the chronic care model (4), which integrates principles of disease management into the treatment of smokers seen in rural primary care. Our objective was to enroll smokers, regardless of their willingness to quit, into a disease registry and compare cessation rates among smokers who received pharmacotherapy alone or combined with either moderate-intensity or high-intensity disease management that includes counseling and provider feedback.

METHODS

Design Overview

We did a randomized, single-blind trial of varying levels of disease management for smoking cessation. We recruited participants who smoked more than 10 cigarettes per day from rural primary care clinics across Kansas and randomly assigned them to receive pharmacotherapy alone, pharmacotherapy supplemented by 1 to 2 counseling calls every 6 months (moderate-intensity disease management), or pharmacotherapy supplemented by up to 6 counseling calls every 6 months (high-intensity disease management). For recipients of moderate-intensity and high-intensity disease management, we faxed periodic progress reports to their physician. We offered all participants free pharmacotherapy (either bupropion or transdermal nicotine patch) every 6 months. We enrolled participants from June 2004 to October 2005 and followed them for 24 months, completing follow-up in December 2007. All participants provided written informed consent. The University of Kansas Medical Center's Human Subjects Committee approved the study.

Setting and Participants

We conducted our study in 50 rural primary care practices in the Kansas Physicians Engaged in Prevention Research network (11). As part of a rural primary care research experience, trained medical students systematically screened participants, identified smokers, and recruited them for this study, regardless of their interest in quitting (12). We considered smokers eligible if they had a primary care physician who participated in this study; were older than 18 years; smoked more than 10 cigarettes per day for at least 1 year and for at least 25 of the past 30 days; spoke English; and had a telephone. We excluded smokers if they were pregnant or planned to become pregnant, planned to move out of the study area, had signs of dementia or mental illness that would preclude participation, or lived with a smoker already enrolled in the study. Of the 1827 smokers we screened, 61% met criteria for study entry (**Figure 1**). Of these, we enrolled 67%.

Randomization and Interventions

Participant Randomization

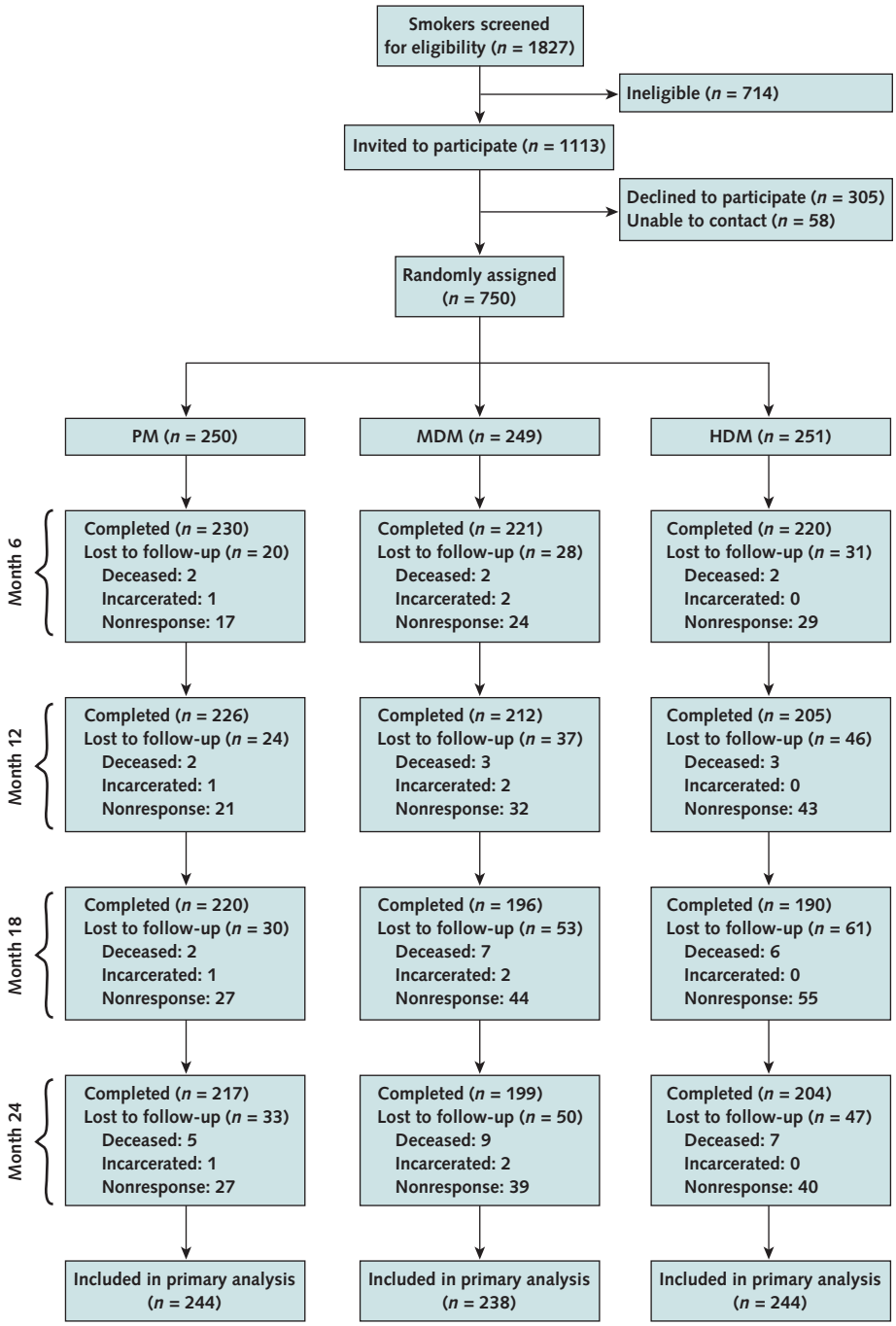
Randomization occurred at the participant level. A computer-generated random-number table was used to generate allocation cards in blocks of 24, with allocation equally distributed across treatment groups. To conceal allocation, we placed these cards in sequentially numbered, opaque, sealed envelopes. After research assistants verified participant eligibility and completed the baseline assessment, the project director opened the next sequential sealed envelope and determined the participant's treatment allocation.

One of 9 counselors trained in smoking cessation and motivational interviewing (12) conducted all interventions from a single central site. We assigned participants to counselors without regard to practice site.

Pharmacotherapy

At baseline, all smokers received a health education mailing that consisted of a welcome letter, information about the use of bupropion and the nicotine patch for smoking cessation, and copies of "You Can Quit Smoking: Consumer Guide" (13) and "When Smokers Quit—The Health Benefits Over Time" (14). At baseline and at 6, 12, and 18 months, participants received a mailed offer for free pharmacotherapy that consisted of either a 6-week course of a nicotine patch (21 mg/d) or a 7-week course of

Figure 1. **Study flow diagram.**



HDM = high-intensity disease management; MDM = moderate-intensity disease management; PM = pharmacotherapy management.

sustained-release bupropion (150 mg twice daily). Participants interested in using either medication could return a postage-paid postcard or call a toll-free number. We screened all participants who requested pharmacotherapy for potential contraindications (15). Participants with absolute contraindications for a given drug were ineligible to receive that drug but were offered the option of receiving the other drug. Participants with contraindications to both drugs were not eligible to receive medication from the study but could participate in all other aspects of the intervention. For participants who requested bupropion and those with relative contraindications to the nicotine patch, research staff faxed a prescription request to their primary care physicians.

This prescription request delineated any relative contraindications or potential drug interactions. For these participants, their physicians made the final assessment of the appropriateness of the bupropion or the patch. For participants without contraindications to the nicotine patch or on receipt of a faxed, signed prescription, the bupropion or patches were mailed to the participant along with instructions for use.

Disease Management

In addition to pharmacotherapy, the moderate-intensity and high-intensity disease management groups received educational support, telephone counseling, and periodic progress reports with counseling suggestions faxed to their physician. Every 6 months, they received a KanQuit newsletter that addressed tips on quitting smoking, talking with their physician about smoking, and using pharmacotherapy for cessation. The newsletters were personalized to include study updates, counselor photographs, physician feature stories, and testimonials of participants who had quit smoking.

We offered participants assigned to moderate-intensity disease management up to 2 telephone-based counseling sessions every 6 months (1 session to promote a quit attempt and 1 additional follow-up session for those who made a quit attempt). We offered participants assigned to high-intensity disease management up to 6 counseling calls every 6 months to either promote quitting or prevent relapse. We scheduled calls at the participant's convenience, and they varied according to the participant's quit plan but followed a rough schedule of calls at 1, 3, 6, 9, and 16 weeks after the onset of each 6-month treatment cycle. Counselors used motivational interviewing techniques and followed a semistructured protocol to promote a cessation attempt or, for abstinent smokers, to encourage relapse prevention. During counseling calls, case managers reminded participants about the availability of pharmacotherapy and, for interested participants, provided immediate support for acquiring either the nicotine patch or bupropion, as described previously.

We faxed personalized progress reports with suggestions for interventions to the participant's physician after the first counseling call (both moderate-intensity and high-intensity disease management participants) and after the last counseling call (high-intensity disease management participants only) during each 6-month cycle. We faxed additional progress reports to the participant's physician whenever the moderate-intensity or high-intensity disease management participant set a quit date.

Outcomes, Measurements, and Follow-up

Research assistants who were blinded to treatment group assignment conducted assessments by telephone at baseline and at 6, 12, 18, and 24 months.

Primary Outcome

The primary outcome measure was self-reported 7-day abstinence at 24 months, defined as not having smoked a cigarette during the previous 7 days. Although self-reported abstinence has been considered sufficient for population-based smoking cessation studies (16), to test for a reporting bias between treatment groups, we validated self-

Table 1. **Baseline Characteristics of Study Participants**

Characteristic	Total Participants (n = 750)	PM Group (n = 250)	MDM Group (n = 249)	HDM Group (n = 251)
Mean age (SD), *y*	47.2 (13.1)	47.1 (13.4)	48.2 (12.4)	46.4 (13.5)
Women, *n (%)*	439 (58.5)	144 (57.6)	144 (57.8)	151 (60.2)
Education less than high school, *n (%)*	385 (51.3)	128 (51.2)	129 (51.8)	128 (51.0)
Mean cigarettes smoked per day (SD), *n*	23.7 (10.4)	24.3 (11.0)	23.8 (10.3)	22.9 (10.0)
Mean Fagerström score (SD)*	5.2 (2.2)	5.2 (2.2)	5.2 (2.2)	5.0 (2.1)
Previous use of bupropion, *n (%)*	245 (32.7)	83 (33.2)	74 (29.7)	88 (35.1)
Previous use of nicotine replacement, *n (%)*	397 (52.9)	128 (51.2)	128 (51.4)	141 (56.2)
Other smokers in household, *n (%)*	345 (46.0)	119 (47.6)	116 (46.6)	110 (43.8)
Mean motivation to quit (SD)†	8.7 (2.1)	8.7 (2.0)	8.6 (2.2)	8.6 (2.0)
Mean confidence to quit (SD)†	6.1 (2.7)	5.9 (2.7)	6.1 (2.8)	6.3 (2.6)
Stage of change, *n (%)*				
Precontemplation	65 (8.7)	22 (8.8)	20 (8.0)	23 (9.2)
Contemplation	457 (60.9)	158 (63.2)	153 (61.5)	146 (58.2)
Preparation	228 (30.4)	70 (28.0)	76 (30.5)	82 (32.7)
Medical condition, *n (%)*				
Hypertension	258 (34.4)	95 (38.0)	78 (31.3)	85 (33.9)
Hyperlipidemia	269 (35.9)	91 (36.4)	86 (34.5)	92 (36.7)
Diabetes	101 (13.5)	43 (17.2)	30 (12.1)	28 (11.2)
Chronic lung disease	202 (26.9)	65 (26.0)	73 (29.3)	64 (25.5)
Heart disease	73 (9.7)	24 (9.6)	29 (11.7)	20 (8.0)
History of depression	304 (40.5)	107 (42.8)	96 (38.6)	101 (40.2)

HDM = high-intensity disease management; MDM = moderate-intensity disease management; PM = pharmacotherapy management.
* The Fagerström test score for nicotine dependence ranges from 0 to 10. Scores ≥6 indicate greater levels of nicotine dependence.
† Motivation and confidence to quit smoking scores range from 0 to 10.

Table 2. **Utilization of Pharmacotherapy (Nicotine Patch or Bupropion), by Treatment Period**

Month	Participants, *n/n (%)**			Odds Ratio (95% CI)†	
	PM	MDM	HDM	HDM vs. MDM	HDM or MDM vs. PM
0–6	142/247 (57.5)	160/245 (65.3)	171/249 (68.7)	1.19 (0.81–1.76)	1.53 (1.10–2.13)
6–12	114/247 (46.2)	93/244 (38.1)	95/248 (38.3)	1.01 (0.69–1.48)	0.71 (0.51–0.99)
12–18	65/247 (26.3)	49/240 (20.4)	61/245 (24.9)	1.28 (0.83–1.96)	0.82 (0.57–1.17)
18–24	55/244 (22.5)	65/238 (27.3)	59/244 (24.2)	0.84 (0.55–1.28)	1.18 (0.82–1.70)

HDM = high-intensity disease management; MDM = moderate-intensity disease management; PM = pharmacotherapy management.
* The denominator changes over time because some participants died or were incarcerated.
† Marginal odds ratios estimated from the generalized linear mixed model, which indicated the presence of a treatment-by-time interaction ($P < 0.01$).

reported abstinence at months 12 and 24 (salivary cotinine level <15 ng/mL in a mailed saliva sample) (17). Because of the high resistance of participants to providing salivary samples at month 12, we also conducted validation by proxy report from a significant other at month 24 for quitters who did not return a salivary sample (18).

Secondary Outcomes

Secondary outcomes included self-reported 7-day abstinence at 6, 12, and 18 months. We assessed utilization of pharmacotherapy on the basis of whether the participant requested bupropion or the transdermal nicotine patch during any given 6-month treatment cycle. At the conclusion of each 6-month cycle, we also asked participants whether they had seen their physician in the previous 6 months and, if so, whether they had discussed smoking cessation.

Other Measures

At baseline, we assessed age, sex, education level, and major comorbid conditions. Smoking history included number of cigarettes smoked per day, previous bupropion use, previous nicotine replacement use, and stage of readiness to stop smoking (19). We assessed nicotine dependence by using the Fagerström test for nicotine dependence (20). We assessed importance and confidence in quitting separately by using an 11-point Likert scale ranging from no importance or confidence (0 points) to extreme importance or confidence (10 points).

Monitoring Procedures

Kansas University Medical Center's institutional review board approved the data safety and monitoring plan. Although we did not explicitly ask participants about adverse effects, counselors recorded spontaneous reports of adverse events during intervention calls and research assistants did so during semiannual assessments. Adverse reports were reported to the Kansas University Medical Center Human Subjects Committee. Data quality monitoring efforts included dual data entry, examination of frequency distributions and range checks, and identification and verification of missing values.

Statistical Analysis

Power calculations indicated that 250 participants per group would have 80% power to compare high-intensity disease management with moderate-intensity disease management and 95% power to compare combined high-intensity disease management and moderate-intensity disease management with pharmacotherapy alone, on the basis of 10%, 15%, and 25% self-reported quit rates for pharmacotherapy alone, moderate-intensity disease management, and high-intensity disease management, respectively.

We conducted all data analyses (except where specified) by using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). We generated descriptive statistics for baseline measures to assess imbalance across treatment groups. We used generalized linear mixed models for the primary end point (self-reported abstinence at 24 months) and for overall (0 to 24 months) self-reported abstinence, pharmacotherapy use, and participant–physician discussions about smoking (21). The 2 primary tests of the KanQuit study were comparisons of self-reported cessation rates between high-intensity disease management and moderate-intensity disease management and between high- and moderate-intensity disease management combined and pharmacotherapy alone. In addition, we considered 2 sensitivity analyses that imputed missing data as "smokers" and imputed missing data as "quit." Generalized linear mixed models included terms for main effects of treatment group, time, and their interaction. We fit the models by using the PROC NLMIXED procedure. For the sensitivity analyses, we did not impute data for participants known to have died or been incarcerated. We averaged our generalized linear mixed model estimates over the participant random effects to arrive at marginal estimates of the effects of intervention (21, 22). We compared validated abstinence at 12 and 24 months by using unconditional logistic regression models.

Although we administered the intervention from a central location, we assessed for clustering of treatment effects with the participating primary care practices. We used a generalized linear mixed model to test for this clustering by using a logistic regression model with a random intercept term to allow for facility effects (21). On the basis

Table 3. **Changes in Smoking Status of Participants Over Time**

Status at Beginning of Cycle	Total Participants, *n*	Status at Completion of Cycle: PM Group				Total Participants, *n*	Status at Completion of Cycle: MDM Group			
		Smoke, *n (%)*	Quit, *n (%)*	Nonresponse, *n (%)*	Dead or Incarcerated, *n (%)*		Smoke, *n (%)*	Quit, *n (%)*	Nonresponse, *n (%)*	Dead or Incarcerated, *n (%)*
		Month 6					Month 6			
Baseline										
Smoke	250	204 (81.6)	26 (10.4)	17 (6.8)	3 (1.2)	249	185 (74.3)	36 (14.5)	24 (9.6)	4 (1.6)
		Month 12					Month 12			
Month 6										
Smoke	204	172 (84.3)	21 (10.3)	11 (5.4)	–	185	154 (83.2)	16 (8.7)	14 (7.6)	1 (0.5)
Quit	26	9 (34.6)	16 (61.5)	1 (3.9)	–	36	2 (5.6)	33 (91.7)	1 (2.8)	–
Nonresponse	17	7 (41.2)	1 (5.9)	9 (52.9)	–	24	7 (29.2)	–	17 (70.8)	–
		Month 18					Month 18			
Month 12										
Smoke	188	163 (86.7)	15 (8.0)	10 (5.3)	–	163	132 (81.0)	10 (6.1)	17 (10.4)	4 (2.5)
Quit	38	16 (42.1)	18 (47.4)	4 (10.5)	–	49	15 (30.6)	30 (61.2)	4 (8.2)	–
Nonresponse	21	6 (28.6)	2 (9.5)	13 (61.9)	–	32	9 (28.1)	–	23 (71.9)	–
		Month 24					Month 24			
Month 18										
Smoke	185	151 (81.6)	26 (14.1)	7 (3.8)	1 (0.5)	156	120 (76.9)	21 (13.5)	13 (8.3)	2 (1.3)
Quit	35	4 (11.4)	28 (80.0)	1 (2.9)	2 (5.7)	40	8 (20.0)	32 (80.0)	–	–
Nonresponse	27	6 (22.2)	2 (7.4)	19 (70.4)	–	44	15 (6.8)	3 (6.8)	26 (59.1)	–

HDM = high-intensity disease management; MDM = moderate-intensity disease management; PM = pharmacotherapy management.

of the 24-month outcome, we found no evidence of a clustering effect (23).

We computed costs from a provider perspective (that is, including only direct, variable costs associated with executing each intervention). Principal intervention costs were associated with counseling and pharmacotherapy. Counselor time and time associated with pharmacotherapy management were recorded through a computerized tracking log and valued at local hourly wages plus fringe benefits. Pharmacotherapy was valued at prevailing online prices plus mailing costs. Telephone and fax charges were valued at long-distance rates. Costs were valued in 2005 U.S. dollars to reflect when the intervention began.

Role of the Funding Source

This study was funded by the National Cancer Institute. GlaxoSmithKline provided the study medication. Neither source had any role in the design, conduct, or analysis of this study or the decision to submit the manuscript for publication.

RESULTS

Randomization resulted in groups with similar baseline characteristics (**Table 1**). In addition to smoking, 427 (57%) participants had at least 1 other major risk factor for cardiovascular disease. Participants reported seeing their physician a median of 3.5 times in the 12 months before the study. Participants smoked on average 24 cigarettes per day; 30.4% were at the preparation stage of quitting, 60.9% at the contemplation stage, and 8.7% at the precontemplation stage.

Before the 24-month follow-up, 24 participants died or were incarcerated. Of the 750 participants, loss to follow-up due to nonresponse varied by treatment group (**Figure 1**), with 22.0% of the pharmacotherapy group, 31.3% of the moderate-intensity disease management group, and 31.1% of the high-intensity disease management group lost to follow-up during 1 or more of the assessment periods ($P = 0.03$).

Utilization of Counseling

During the course of the 24-month intervention, high-intensity disease management participants completed an average of 8.2 counseling calls (range, 0 to 24), and moderate-intensity disease management participants completed an average of 3.6 calls (range, 0 to 7). Engagement in counseling declined during the course of the intervention; 90.9%, 67.9%, 57.3%, and 54.3% of high-intensity disease management participants and 90.0%, 68.2%, 60.3%, and 59.2% of moderate-intensity disease management participants participated in at least 1 counseling session during the first, second, third, and fourth treatment cycles, respectively (**Appendix Table 1**, available at www.annals.org). The average number of calls completed was 3.2, 1.8, 1.6, and 1.7 for high-intensity disease management recipients and 1.3, 0.9, 0.7, and 0.7 for moderate-

Table 3—Continued

Total Participants, n	Status at Completion of Cycle: HDM Group			
	Smoke, *n (%)*	Quit, *n (%)*	Nonresponse, *n (%)*	Dead or Incarcerated, *n (%)*
	Month 6			
251	179 (71.3)	41 (16.3)	29 (11.6)	12 (0.8)
	Month 12			
179	130 (72.6)	27 (15.1)	21 (11.7)	1 (0.6)
41	9 (22.0)	31 (75.6)	1 (2.4)	–
29	6 (20.7)	2 (6.9)	21 (72.4)	–
	Month 18			
145	107 (73.8)	22 (15.2)	14 (9.7)	2 (1.4)
60	14 (23.3)	37 (61.7)	8 (13.3)	1 (1.7)
43	10 (23.3)	–	33 (76.7)	–
	Month 24			
131	109 (83.2)	17 (13.0)	5 (3.8)	–
59	13 (22.0)	44 (74.6)	1 (1.7)	1 (1.7)
55	14 (25.5)	7 (12.7)	7 (61.8)	–

intensity disease management recipients during the first, second, third, and fourth treatment cycles, respectively.

Utilization of Pharmacotherapy

We identified a treatment-by-time interaction in utilization of pharmacotherapy ($P < 0.01$). Thus, comparisons between treatment groups in use of pharmacotherapy were derived at each survey period (**Table 2**). Pharmacotherapy uptake differed in the pooled disease management groups compared with the pharmacotherapy-alone group, with an increase in uptake during the first 6 months (odds ratio [OR], 1.53 [95% CI, 1.10 to 2.13]) but lower uptake in the disease management groups during the following 6 months (OR, 0.71 [CI, 0.51 to 0.99]). Requests for pharmacotherapy declined after the first 6 months. Among all participants, 63.8%, 40.9%, 23.9%, and 24.7% requested pharmacotherapy during the first, second, third, and fourth treatment cycles, respectively. By the end of the study, 23%, 33%, 23%, 12%, and 9% of participants had requested a total of 0, 1, 2, 3, or 4 cycles of pharmacotherapy, respectively. Overall, 41.1% of pharmacotherapy cycles used bupropion and 58.9% used the nicotine patch, with no difference in choice of pharmacotherapy among the treatment groups.

Support From Health Care Providers

In the 3 treatment groups, 635 (84.7%) participants reported 1 or more office visits with their physician, with a median of 5 visits, during the 2-year study. Of participants who saw a physician during any given treatment cycle, 37.5% to 59.5% reported that they discussed smoking cessation with their physician (**Appendix Table 2**, available at www.annals.org). This proportion did not vary between the high-intensity and moderate-intensity disease management groups (OR, 1.03 [CI, 0.75 to 1.41]) or for the pooled disease management groups versus the pharmacotherapy-alone group (OR, 0.92 [CI, 0.70 to 1.19]) (**Appendix Table 2**, available at www.annals.org).

Smoking Cessation

Throughout the study, smokers moved through different transitional states of smoking status (**Table 3**). In our primary 24-month analysis, after missing values were imputed as equal to smoking, the 7-day point-prevalence of self-reported abstinence was 27.9% and 23.5% in the high-intensity and moderate-intensity disease management groups, respectively (OR, 1.33 [CI, 0.88 to 2.02]) (**Table 4**). The cessation rate in these disease management groups combined was similar to the 23.0% self-reported cessation rate in the pharmacotherapy management group (OR, 1.12 [CI, 0.78 to 1.61]). Sensitivity analysis showed these effects to be similar across other methods of handling missing data, except when nonresponse was imputed as having quit smoking.

Secondary overall analyses (0 to 24 months), however, showed that self-reported abstinence rates were higher in the high-intensity than in the moderate-intensity disease management group during the study (OR, 1.43 [CI, 1.00 to 2.03] [no imputation]) and higher in the combined disease management groups than in the pharmacotherapy-alone group (OR, 1.47 [CI, 1.08 to 2.00] [no imputation]) (**Table 4** and **Figure 2**). Findings in the sensitivity analysis were similar, except when we classified all missing values as still smoking.

The rate of validation of self-reported abstinence was similar in the 3 treatment groups at both 12 and 24 months, indicating that there was no apparent bias in self-reported abstinence associated with more intensive treatment. Cotinine-confirmed abstinence rates at 12 months were 11.3% and 9.8% in the high-intensity and moderate-intensity disease management groups, respectively (OR, 1.24 [CI, 0.69 to 2.22]) (**Table 4**). The cotinine-confirmed abstinence rate in the pooled disease management groups was higher than the 5.3% abstinence rate in the pharmacotherapy-alone group (OR, 2.33 [CI, 1.24 to 4.38]). Confirmed abstinence rates at 24 months, using either cotinine validation or proxy, were similar among the 3 treatment groups (**Table 4**).

Cost Analysis

Pharmacotherapy costs did not significantly differ across the 3 treatment groups ($209 per participant for pharmacotherapy alone and moderate-intensity disease management and $225 for high-intensity disease management; $P = 0.64$). During the study, time devoted to pharmacotherapy and disease management was 0.5, 3.8, and 7.7 hours per participant in the pharmacotherapy-alone,

Table 4. **Self-Reported and Validated Abstinence***

Time Point	Self-Reported 7-Day Point Prevalence, *n/n (%)*		
	PM	MDM	HDM
Month 6	26/247 (10.5)	36/245 (14.7)	41/249 (16.5)
Month 12	38/247 (15.4)	49/244 (20.1)	60/248 (24.2)
Month 18	35/247 (14.2)	40/240 (16.7)	59/245 (24.1)
Month 24	56/244 (23.0)	56/238 (23.5)	68/244 (27.9)
	Validated 7-Day Point Prevalence, *n/n (%)*		
Month 12†	13/247 (5.3)	24/244 (9.8)	28/248 (11.3)
Month 24‡	33/244 (13.5)	35/238 (14.7)	36/244 (14.8)

	HDM vs. MDM		(HDM and MDM) vs. PM	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Statistical comparisons				
Month 24 (no imputation) (n = 708)§	1.31 (0.85–2.02)	0.22	1.19 (0.82–1.73)	0.35
Month 24 (missing = smoker) (n = 741)	1.33 (0.88–2.02)	0.18	1.12 (0.78–1.61)	0.54
Month 24 (missing = quit) (n = 741)§	1.23 (0.84–1.66)	0.30	1.42 (1.01–1.99)	0.04
Month 12 (validated) (n = 643)	1.24 (0.69–2.22)	0.47	2.33 (1.24–4.38)	0.01
Month 24 (validated) (n = 620)	1.00 (0.60–1.68)	0.99	1.19 (0.76–1.87)	0.44
Overall (baseline to 24 months [no imputation]) (n = 708)§	1.43 (1.00–2.03)	0.05	1.47 (1.08–2.00)	0.02

HDM = high-intensity disease management; MDM = moderate-intensity disease management; OR = odds ratio; PM = pharmacotherapy management.
* All missing values were classified as smoking.
† Validated by salivary cotinine measurement (<15 ng/mL).
‡ Validated by salivary cotinine measurement(<15 ng/mL) or a significant other.
§ Generalized linear mixed model for self-reported abstinence did not provide evidence for a treatment-by-time interaction ($P > 0.19$ in each case). Saliva samples were not provided by 33.3%, 34.7%, and 31.6% of the self-reported quitters at 12 months and by 39.7%, 33.9%, and 30.3% at 24 months in the HDM, MDM, and PM groups, respectively.

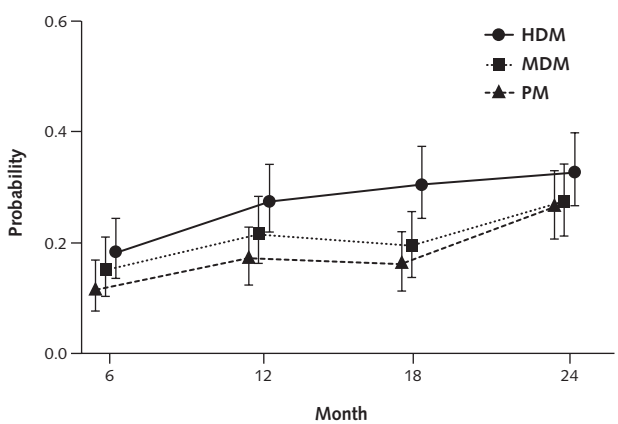
moderate-intensity, and high-intensity disease management groups, respectively. These differences in counselor time led to significant differences among the 3 groups in mean total intervention costs per participant ($231 [SD, $222] for pharmacotherapy alone, $348 [SD, $236] for moderate-intensity disease management, and $460 [SD, $289] for high-intensity disease management; $P < 0.001$).

DISCUSSION

This study demonstrates the feasibility of treating smoking as a chronic disease by following a group of smokers and offering them repeated interventions to support quit attempts and treat relapses. In KanQuit, a large proportion of rural smokers were willing to participate in a 24-month smoking cessation program. For these smokers, offers of free pharmacotherapy, accompanied by a modest effort to coordinate prescriptions through primary care physicians, resulted in high levels of pharmacotherapy utilization and repeated pharmacotherapy-assisted quit attempts in all 3 treatment groups. Although abstinence at 24 months did not differ among the treatment groups, overall (0 to 24 months) data analyses suggest that more intensive disease management was associated with higher rates of smoking abstinence throughout the study.

In KanQuit, more intensive counseling was not consistently associated with higher utilization of pharmacotherapy, and faxes to physicians that provided participant-specific counseling and treatment suggestions were not associated with more frequent discussions between physicians and participants about smoking cessation. Thus, the effect of more intensive disease management on smoking cessation during the first 18 months of this intervention seems to be a direct result of the counseling itself and is not mediated through greater utilization of pharmacotherapy or more frequent discussions between physicians and participants.

Figure 2. **Population-averaged estimates of the probability of quitting smoking among the 3 study groups.**



Error bars represent 95% CIs for the population estimates. HDM = high-intensity disease management; MDM = moderate-intensity disease management; PM = pharmacotherapy management.

One of the most critical elements of a successful clinical intervention is the ability to reach the population at risk (2). Although many interventions for smoking cessation have resulted in high abstinence rates, participation in these programs is often as low as 1% to 10% (24). Even if programs result in high smoking cessation rates (for example, 30%), these programs may ultimately affect less than 3% of the total population of smokers. Although free pharmacotherapy can substantially increase the number of smokers willing to make a quit attempt (25), passive offers of free pharmacotherapy, such as those offered by state quitlines, still only reach about 3% of eligible smokers (26, 27). In KanQuit, the creation of a "disease registry" allowed enrollment of smokers into a smoking cessation intervention, regardless of their immediate interest in quitting. The high rates of participation in this study suggest that this approach could reach up to two thirds of the smokers encountered in primary care practices. The proactive engagement of these smokers in KanQuit, even at the modest levels provided to the pharmacotherapy management group, was associated with utilization of pharmacotherapy by more than three fourths of the smokers in the registry.

A MEDLINE search of studies published in English through October 2008 reveals that only a few studies have followed smokers beyond 6 to 12 months and attempted to reengage relapsed smokers in treatment. Although small early studies of relapsing smokers were discouraging (28, 29), larger studies have demonstrated that active treatment of relapsed smokers with transdermal nicotine patch (30), nicotine lozenge (31), or bupropion (32) is associated with higher cessation rates. Our study extends these previous findings by showing progressively higher rates of abstinence among smokers who have reengaged in treatment up to 4 times during 2 years.

Studies by Joseph and colleagues (33) and Fu and coworkers (34) have shown that most smokers for whom a quit attempt fails are interested in trying again. In a Veterans Affairs study by Partin and colleagues (35) in which smokers who had relapsed received telephone calls and their physicians received computerized reminders, 32% took advantage of smoking cessation pharmacotherapy. Our study suggests that even more smokers can be engaged in pharmacologic treatment of smoking cessation if proactive offers of treatment are repeated over time.

The strengths of our study include the randomized design, population-based recruitment, prolonged intervention and follow-up, and high rates of participant follow-up. The study is limited by the substantial variability in smoking cessation rates over time. The discrepancy between our overall (0 to 24 month) findings and 24-month point-prevalence of abstinence seems to be related to a large increase in abstinence reported by the pharmacotherapy management group from 18 to 24 months. This sudden and unexplained increase in smoking cessation was not associated with increased use of pharmacotherapy or discussion of smoking cessation between participants and physicians. It might represent a delayed effect of the pharmacotherapy management intervention or be related to forces external to the study itself, such as the release of varenicline in 2006 or new smoking restrictions in rural hospitals and rural communities. Nevertheless, how these external forces would have uniquely affected the pharmacotherapy group is hard to understand.

Additional limitations of the study are the lack of blinding of participants and the inability to isolate the effect of pharmacotherapy management from offers of free pharmacotherapy. We conducted all assessments by telephone or mail, and we relied on mailed saliva samples for biochemical verification. Although we validated self-reported smoking cessation in only 58% of participants at 24 months, the rate of validation was similar in all 3 treatment groups, suggesting that no bias in self-reported abstinence associated with treatment assignment occurred. Our study relied on transdermal nicotine patch and bupropion; use of newer, more effective agents might be associated with different results (36, 37). Finally, provision of free pharmacotherapy as part of this study limits the generalizability of these findings into current practice, in which financial support for pharmacotherapy is highly variable.

This study demonstrates that a disease management approach can reach a high proportion of smokers seen in primary care practice. Even smokers who are initially unwilling to quit are likely to engage in treatment during 2 years of follow-up. In the presence of free pharmacotherapy and pharmacotherapy management, most smokers will make 1 or more pharmacotherapy-assisted quit attempts. Although more intensive disease management was not associated with differences in smoking abstinence at 24 months, the overall (0 to 24 months) analyses illustrated an association between the intensity of the intervention and smoking cessation rates. To address this discrepancy, additional long-term studies on disease management for smoking cessation are needed.

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Appendix Table 1. Number of Counseling Calls Completed

Variable	Total Participants, *n**	Completed Counseling Calls by Participants During a Cycle, *n (%)*						
		0	1	2	3	4	5	6
Cycle 1†								
MDM	249	25 (10.0)	133 (53.4)	91 (36.5)	–	–	–	–
HDM	251	23 (9.1)	34 (13.5)	42 (16.7)	37 (14.7)	44 (17.5)	40 (15.9)	31 (12.3)
Cycle 2‡								
MDM	245	78 (31.8)	123 (50.2)	44 (17.9)	–	–	–	–
HDM	249	80 (32.1)	54 (21.6)	27 (10.8)	41 (16.4)	21 (8.4)	20 (8.0)	6 (2.4)
Cycle 3§								
MDM	244	97 (39.7)	120 (49.1)	27 (11.1)	–	–	–	–
HDM	248	106 (42.7)	38 (15.3)	27 (10.8)	35 (14.1)	29 (11.6)	6 (2.4)	7 (2.8)
Cycle 4‖								
MDM	240	98 (40.8)	112 (46.6)	30 (12.5)	–	–	–	–
HDM	245	112 (45.7)	29 (11.8)	27 (11.0)	22 (8.9)	20 (8.1)	21 (8.5)	14 (5.7)

HDM = high-intensity disease management; MDM = moderate-intensity disease management.
* The number of participants eligible for calls during each cycle changes over time because some participants died or were incarcerated.
† Cycle 1 is baseline to 6 months.
‡ Cycle 2 is 6 to 12 months.
§ Cycle 3 is 12 to 18 months.
‖ Cycle 4 is 18 to 24 months.

Appendix Table 2. Frequency of Patient–Physician Smoking-Related Discussions Among Participants Seen by a Physician, by Treatment Cycle*

Months	Had Discussions or Were Seen by Physician, *n/n (%)*		
	PM	MDM	HDM
0–6	97/171 (56.7)	84/164 (51.2)	94/158 (59.5)
6–12	75/155 (48.4)	70/148 (47.3)	63/137 (46.0)
12–18	67/156 (43.0)	55/124 (44.4)	54/130 (41.5)
18–24	61/141 (43.3)	51/136 (37.5)	47/125 (37.6)

PM = pharmacotherapy management; HDM = high-intensity disease management; MDM = moderate-intensity disease management.
* The generalized linear mixed model for having a patient–physician smoking-related discussion did not provide evidence for a treatment-by-time interaction ($P = 0.87$). Estimated marginal odds ratios from the generalized linear mixed model were 1.03 (95% CI, 0.75 to 1.41) for high-intensity disease management versus moderate-intensity disease management and 0.92 (CI, 0.70 to 1.19) for high-intensity disease management and moderate-intensity disease management versus pharmacotherapy.