ORIGINAL ARTICLE

Placebo-Controlled Trial of Cytisine for Smoking Cessation

Robert West, Ph.D., Witold Zatonski, M.D., Magdalena Cedzynska, M.A., Dorota Lewandowska, Ph.D., M.D., Joanna Pazik, Ph.D., M.D., Paul Aveyard, Ph.D., M.D., and John Stapleton, M.Sc.

ABSTRACT

BACKGROUND

Cytisine, a partial agonist that binds with high affinity to the $\alpha_4\beta_2$ nicotinic acetylcholine receptor, is a low-cost treatment that may be effective in aiding smoking cessation. This study assessed the efficacy and safety of cytisine as compared with placebo.

METHODS

We conducted a single-center, randomized, double-blind, placebo-controlled trial. Participants were randomly assigned to receive cytisine or matching placebo for 25 days; participants in both groups received a minimal amount of counseling during the study. The primary outcome measure was sustained, biochemically verified smoking abstinence for 12 months after the end of treatment. Of 1542 adult smokers screened, 740 were enrolled and 370 were randomly assigned to each study group.

RESULTS

The rate of sustained 12-month abstinence was 8.4% (31 participants) in the cytisine group as compared with 2.4% (9 participants) in the placebo group (difference, 6.0 percentage points; 95% confidence interval [CI], 2.7 to 9.2; P=0.001). The 7-day point prevalence for abstinence at the 12-month follow-up was 13.2% in the cytisine group versus 7.3% in the placebo group (P=0.01). Gastrointestinal adverse events were reported more frequently in the cytisine group (difference, 5.7 percentage points; 95% CI, 1.2 to 10.2).

CONCLUSIONS

In this single-center study, cytisine was more effective than placebo for smoking cessation. The lower price of cytisine as compared with that of other pharmacotherapies for smoking cessation may make it an affordable treatment to advance smoking cessation globally. (Funded by the National Prevention Research Initiative and others; Current Controlled Trials number, ISRCTN37568749.)

From the Cancer Research UK Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, London (R.W., J.S.); the Cancer Center and Institute of Oncology, Cancer Epidemiology and Prevention Department, Warsaw, Poland (W.Z., M.C., D.L., J.P.); and the UK Centre for Tobacco Control Studies, Primary Care Clinical Sciences, University of Birmingham, Birmingham, United Kingdom (P.A.). Address reprint requests to Dr. West at the Department of Epidemiology and Public Health, University College London, 2-16 Torrington Pl., London WC1E 6BT, United Kingdom, or at robert.west@ucl.ac.uk, or to Dr. Zatonski at the Cancer Center and Institute of Oncology, Cancer Epidemiology and Prevention Department, 5 Roentgen St., 02-781 Warsaw, Poland.

N Engl J Med 2011;365:1193-200.

Tobacco smoking contributes to some 5 million premature deaths each year worldwide.[1] It is highly addictive, with more than 95% of unaided attempts at cessation failing to last 6 months.[2] Every year that a smoker delays quitting beyond the mid-30s, the person loses 3 months of life expectancy.[3] The World Health Organization's Framework Convention on Tobacco Control identifies evidence-based approaches to promote smoking cessation, which include mass-media campaigns, tax increases on tobacco, and help for smokers wanting to stop.[4] Success in quitting is increased by behavioral support and a range of pharmacotherapies.[5-8] Some pharmacotherapies have been shown to be cost-effective life-preserving treatments.[5,9]

However, of the more than 1 billion smokers in the world, two thirds live in countries in which the average household income is less than $200 per week and in which treatment of this kind is not paid for by insurance plans or national health care systems. In these countries, smoking-cessation medications are much more expensive than smoking. In China, for example, a typical course of smoking-cessation pharmacotherapy costs the equivalent of $230 for an 8-week course of nicotine-replacement therapy, $123 for an 8-week course of bupropion, or $327 for a 12-week course of varenicline, whereas 20 cigarettes typically cost around 73 cents and can cost as little as 15 cents (Xiao D, Beijing Institute of Respiratory Medicine: personal communication). In India, nicotine-replacement therapy costs approximately $150 for a course, bupropion $100, and varenicline $200; 20 cigarettes typically cost $1.10, but bidis (indigenous cigarettes) cost as little as 5 cents per packet (Sarkar B, Public Health Foundation of India: personal communication).

The compound cytisine could address the problem of cost. It is extracted from the seeds of *Cytisus laborinum* L. (Golden Rain acacia)[10] and has been available in former socialist economy (FSE) countries for more than 40 years as an aid to smoking cessation under the brand name Tabex (Sopharma AD).[11,12] It was first marketed in Bulgaria in 1964[13] and then became widely available in FSE countries, including Poland.[11] When a number of FSE countries joined the European Union, Tabex was withdrawn from some of them. However, it continued to be marketed in Poland, a country with a strong antismoking climate and active involvement of health professionals, where it is available for the equivalent of $15 for a course of treatment,[11] and in Russia, where it is available over the counter for the equivalent of $6 for a course.

Cytisine has an unusual history of development, and the preclinical studies of optimal dosing that would normally precede a trial of this kind were not conducted. Previous studies have strongly suggested that cytisine may be effective in helping smokers to stop,[6,11,12,14,15] but to date, there have been no large, placebo-controlled, randomized trials that would meet modern regulatory standards.[11,12]

Cytisine is a partial agonist that binds with high affinity to the $\alpha_4\beta_2$ subtype of the nicotinic acetylcholine receptor.[11,12] This receptor subtype has been implicated in the development and maintenance of nicotine dependence[16] and was the primary target for the drug varenicline, which has proved effective in aiding smoking cessation.[8] Studies in nonhuman species have shown that cytisine does not cross the blood–brain barrier well, and it has been argued that, at the dose used for smoking cessation, cytisine would be expected to have limited efficacy.[17] But it is not clear whether the data from nonhuman species can be generalized to humans, and the findings noted above indicate the need for a full-scale efficacy trial that conforms to modern standards.

We conducted a study to assess cytisine's efficacy and safety in a context that could be replicated globally, with a relatively short treatment course (25 days) and minimal contact with health professionals. Although this treatment regimen may limit overall abstinence rates, the relative efficacy as compared with placebo should still be manifest.

METHODS

STUDY OVERSIGHT

We conducted and monitored the study according to Good Clinical Practice guidelines (the legal standard required for clinical trials in the European Union) at the smoking-cessation clinic of the Maria Sklodowska-Curie Memorial Cancer Center, in Warsaw, Poland. It was sponsored by University College London, London, and authorized by the Polish Health Ministry. Funded by the United Kingdom's National Prevention Research Initiative, it was approved by the ethics committees at both the University College London and Maria Sklodowska-Curie Memorial Cancer Center. All participants provided written informed consent. The study protocol and statistical analysis plan are available with

the full text of this article at NEJM.org. All the authors vouch for the accuracy and completeness of this report as well as the fidelity of the report to the study protocol.

STUDY DESIGN

This study was a single-center, double-blind, parallel-group trial with participants randomly assigned to either the active drug or placebo in an equal ratio. Behavioral support and the number of follow-up sessions were kept to a minimum to simulate, as much as possible, what might happen in a routine clinical situation.

The schedule of sessions was as follows: eligibility assessment performed by telephone, baseline clinic visit (during which randomization and drug dispensing occurred), telephone calls from a member of the clinic staff on the target quit day and 1 week later (with an optional clinic visit), a clinic visit 4 weeks after the target quit date, then telephone follow-up calls followed by a clinic visit for participants claiming abstinence 6 and 12 months after the end of treatment (Fig. 1). Smoking-cessation advice, which was delivered primarily at the baseline clinic visit, covered how to take the medication, what side effects might occur, and how to minimize and cope with cravings and withdrawal symptoms. Subsequent telephone sessions included a review of problems encountered. The timetable of clinic visits and telephone calls was intended to provide the optimal balance between appropriate pharmacovigilance and minimization of additional support, which would be too costly to implement globally.

STUDY SAMPLE

Participants were adults who smoked 10 or more cigarettes per day and who were willing to attempt to stop smoking permanently, were not pregnant or breast-feeding or planning to become pregnant, were willing to attend all study sessions, were able to read and write Polish and provide informed consent, and could be contacted by telephone. Exclusion criteria were a diagnosis of a current psychiatric disorder or a medical condition that was contraindicated according to the cytisine label (with "arterial hypertension" and "advanced arteriosclerosis" taken to mean uncontrolled hypertension and a previous diagnosis of severe atherosclerosis, respectively). Smokers were not excluded if they had serious smoking-related diseases.

Participants agreed that they would not use any smoking-cessation medications other than the assigned study drugs and that they would make their best effort not to use any tobacco products. A relapse was defined as self-reported smoking of five or more cigarettes during the specified follow-up period (6 or 12 months).

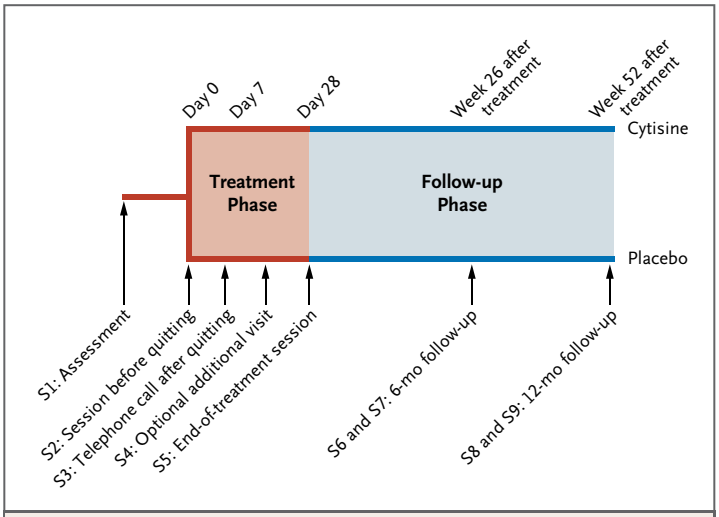

Figure 1. Timing of Study Procedures.
Session numbers are indicated by S1 through S9. Sessions 3, 6, and 8 were telephone sessions. The others were clinic visits.

STUDY MEDICATIONS

The regimen for the study medications consisted of six 1.5-mg tablets per day (one tablet every 2 hours) for 3 days (days 1 through 3), five tablets per day for 9 days (days 4 through 12), four tablets per day for 4 days (days 13 through 16), three tablets per day for 4 days (days 17 through 20), and two tablets per day for the final 5 days (days 21 through 25). The target quit date was scheduled for the fifth day. This regimen has been licensed for cytisine in several countries that entered the European Union in 2004, and it was used in an observational study in which participants treated with cytisine had sufficiently high quit rates to suggest efficacy.[11,15] Cytisine and matching placebo were provided free of charge by the manufacturer, Sopharma AD. Other than also providing the randomization schedule, the manufacturer had no input to the study or its reporting.

STUDY PROCEDURES

Randomization was performed by a statistician at Sopharma, who generated a list of study-group assignments for 740 participants with nQuery Advisor software. The assignments were made in variable block sizes of either 20 (10 assignments to

the cytisine group and 10 to the placebo group) or 10 (5 assignments to each group) to minimize bias over time and to ensure equal groups of 370 participants each. Trial staff and participants were unaware of the group assignments and the randomization scheme.

The case-report form for the trial was based on the clinic's existing protocols, supplemented by additional measures as necessary. The form was written in English, translated into Polish, and then back-translated into English to check for accuracy. At the first visit, data collected included age, sex, employment status and type of job, marital status, score for nicotine dependence (with the use of the Fagerström Test for Nicotine Dependence [FTND], on which scores range from 0 to 10, with higher scores indicating greater dependence),[18] number of cigarettes smoked daily, duration of smoking, and status with respect to previous quit attempts.

At the 6-month and 12-month follow-up points, attempts were made to contact all participants by telephone (with repeated attempts, if necessary). For participants who reported abstinence, arrangements were made for a clinic visit to confirm abstinence by measuring the carbon monoxide concentration in exhaled breath. Participants received payment to cover expenses for attending follow-up sessions.

At every contact, participants were asked whether they had had any adverse events or symptoms since the last contact and, if they said "yes," were asked to describe them. The verbatim descriptions were summarized by the investigators in the report forms and database and were coded according to standard terms in the *Medical Dictionary for Regulatory Activities* (MedDRA).[19] The incidence of events was analyzed according to the MedDRA System Organ Class categorization and preferred terms. At the start and end of treatment, blood pressure was measured, and depression was assessed with the use of the Beck Depression Inventory (on which scores range from 0 to 63, with higher scores indicating more severe depression).[20]

OUTCOME MEASURES

The primary outcome was 12 months of abstinence after the end of treatment, with abstinence defined according to the Russell Standard criteria.[21] The original protocol specified abstinence for 6 months as the primary outcome and abstinence for 12 months as a secondary outcome. This was changed before unblinding and data analysis, in response to the European Medicines Agency guidelines, which recommend 12 months as the preferred follow-up point. To be classified as abstinent, participants had to report that they had smoked fewer than five cigarettes in each of the previous 6 months at the 6-month and 12-month follow-up visits and that they had not smoked any cigarettes in the week before the follow-up visit, and they had to have a carbon monoxide concentration in exhaled breath of less than 10 ppm at the 12-month follow-up visit. A carbon monoxide concentration of less than 10 ppm was also required for participants who visited the clinic at 6 months. In addition, participants who visited the clinic 4 weeks after the quit day had to report that they had not smoked in the previous 2 weeks, with abstinence verified by a carbon monoxide concentration of less than 10 ppm.

Secondary outcomes were sustained abstinence for the first 6 months and point prevalence at 12-months, defined as abstinence for the week before the 12-month follow-up visit, with verification by a carbon monoxide concentration of less than 10 ppm. The criteria for abstinence at 6 months were the same as those for abstinence at 12 months, but with verification by carbon monoxide measurement at the 6-month end point.[21]

STATISTICAL ANALYSIS

With the use of previous trial data as a guide, we estimated that we would need to enroll 740 participants (370 in each group) to detect a between-group difference of 6 percentage points (6% vs. 12%) for the primary outcome, with 80% power and at an alpha level of 0.05.

The analyses of outcomes were based on the intention-to-treat principle, with treatment considered to have failed in participants who were lost to follow-up.[21] The absolute percentage-point difference between participants who met the criteria for abstinence in the two groups was tested with the use of Fisher's exact test. The relative rate of abstinence (the percentage of patients in the cytisine group who met the abstinence criteria divided by the percentage in the placebo group) was also calculated. The 95% confidence interval was calculated for all measures. The relative rates and percentage-point differences were calculated for adverse events reported by 10 or more participants. Logistic regression was used to examine efficacy, with adjustment for baseline characteristics.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

In the recruited sample, the baseline average number of cigarettes smoked daily, carbon monoxide concentration in exhaled breath, and FTND score for nicotine dependence were all high[22] (Table 1). Approximately half the participants worked in manual occupations. More than 80% had tried to stop smoking previously.

Figure 2 shows the numbers of patients who were enrolled, and the numbers who were excluded.[23] In most cases, the reason for exclusion was that the patient did not want to chance being randomly assigned to placebo when he or she could obtain a low-cost prescription for cytisine. The first participant was enrolled on December 10, 2007, and the last follow-up contact was on September 2, 2010. The follow-up rate for the primary outcome was 77.3% (572 participants), and there was no evidence of a significant difference in the follow-up rate between study groups. Of the 168 participants (22.7%) who did not complete the assessments necessary for the analysis of the primary outcome, 121 (72.0%) were known to have smoked from the follow-up assessments that they did complete. There was also no evidence of a significant difference between study groups in this rate. Only for the remaining 47 participants (6.4% of all participants) was it necessary to assume continued smoking or a relapse.

Table 1. Characteristics of the Study Participants.*

Characteristic	Cytisine (N=370)	Placebo (N=370)
Male sex — no. (%)	183 (49.5)	161 (43.5)
Age — yr	47.8±12.6	48.5±12.6
Married — no. (%)†	190 (51.4)	207 (56.1)
Employment involving manual labor — no. (%)‡	196 (54.3)	178 (50.0)
Tried to stop smoking previously — no. (%)	307 (83.0)	301 (81.4)
No. of cigarettes smoked daily	23.0±8.7	22.5±9.6
Carbon monoxide in exhaled breath — ppm	19.2±8.7	18.2±9.0
Duration of smoking — yr	28.1±11.6	28.6±11.7
FTND score§	6.3±2.1	6.1±2.2
Beck Depression Inventory score¶	10.5±7.5	10.7±7.9

* Plus–minus values are means ±SD. There were no significant differences (P<0.05) between the groups on any measure.
† Data on marital status were missing for one participant in the placebo group.
‡ Data on occupation were missing for 9 participants in the cytisine group and 14 participants in the placebo group.
§ Scores on the Fagerström Test for Nicotine Dependence (FTND) range from 0 to 10, with higher scores indicating greater dependence. The mean score for all Polish smokers is 3.6.[22] One participant had a missing score for FTND item 1; the overall score for this participant was calculated by scaling up the scores on the remaining 5 items. An additional 142 participants were known to have scored either 0 or 1 on FTND item 1, but which score was not known; these participants were given a score of 0.5 on item 1.
¶ Scores on the Beck Depression Inventory range from 0 to 63, with higher scores indicating more severe depression.

OUTCOMES

Table 2 shows a benefit of cytisine on smoking cessation, as measured on the basis of the primary outcome (Russell Standard criteria for abstinence at 12 months) (P<0.001 by Fisher's exact test). The net improvement in the abstinence rate with cytisine was 6 percentage points. The relative rate of abstinence in the cytisine group as compared with that in the placebo group was 3.4. Adjustment for all baseline characteristics shown in Table 1 had a negligible effect. There was also evidence of an effect on the secondary measures, Russell Standard criteria for abstinence at 6 months (P<0.001) and point prevalence at 12 months (P=0.01).

ADVERSE EVENTS

There were 7 serious adverse events (4 in the cytisine group and 3 in the placebo group): 5 deaths (2 in the cytisine group, due to lung cancer and cardiac arrest, and 3 in the placebo group, due to lung cancer, hemorrhagic stroke, and chronic obstructive pulmonary disease) and 2 hospitalizations (both in the cytisine group, for stroke and tracheal cancer). Most events took place after the treatment phase of the trial and involved participants with long-standing illnesses. There were 203 additional, nonserious events (120 in the cytisine group and 83 in the placebo group), involving 135 participants (76 in the cytisine group and 59 in the placebo group). Aggregated gastrointestinal disorders, largely comprising stomachache, dry mouth, dyspepsia, and nausea, were reported more frequently in participants receiving cytisine than in those receiving placebo (Table 3). Fifty-four nonserious adverse events were rated as moderate and 1 as severe in the cytisine group, as compared with 32 rated as moderate and 3 as severe in the placebo group. These involved 34 participants (9.2%) in the cytisine group and 26 participants (7.0%) in the placebo group. The difference was not significant (relative rate, 1.3; 95% confidence interval [CI], 0.8 to 2.1).

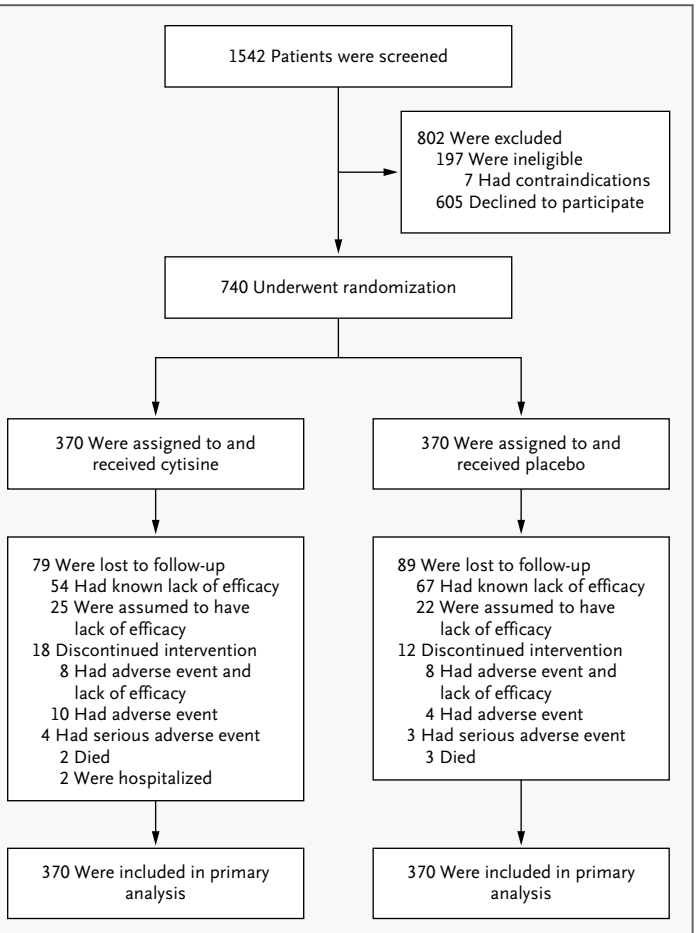

Figure 2. Numbers of Patients Who Were Enrolled in the Study and Included in the Primary Analysis.

The patients lost to follow-up included some patients who discontinued the intervention or who had a serious adverse event.

The rate of drug discontinuation or dose reduction was also similar in the two groups (6.2% [23 of 370 participants] in the cytisine group vs. 4.6% [17 of 370] in the placebo group; relative rate, 1.3; 95% CI, 0.7 to 2.5). Among the 445 participants for whom the score on the Beck Depression Inventory at the end of treatment was available, the mean (±SD) scores were similar in the two groups: 7.3±7.7 in the cytisine group and 8.0±7.9 in the placebo group (P=0.40).

In addition to the symptom reports, increases in self-monitored blood pressure were reported by 13 participants (9 in the cytisine group and 4 in the placebo group; relative rate with cytisine as compared with placebo, 2.2; 95% CI, 0.7 to 7.2). (Some participants with controlled hypertension were monitoring their blood pressure or being regularly assessed by their primary care doctor.) In 10 participants (7 in the cytisine group and 3 in the placebo group), the reported increase occurred during the treatment phase of the study (relative rate, 2.3; 95% CI, 0.6 to 9.0). Of these participants, 6 in the cytisine group attended the clinic visit soon after treatment ceased. All blood-pressure readings were lower than pretreatment measurements. An analysis of the change from baseline blood pressure among all participants who attended the clinic visit 4 weeks after the end of treatment showed no evidence that the change was affected by cessation of smoking (mean change from baseline pressure: systolic, −0.2 mm Hg [95% CI, −3.0 to 3.2]; diastolic, 0.7 mm Hg [95% CI, −1.4 to 2.8]), by whether cytisine or placebo had been taken (mean between-group difference in the change from baseline pressure: systolic, −0.8 mm Hg [95% CI, −3.9 to 2.2]; diastolic, −1.1 mm Hg [95% CI, −3.0 to 0.8]), or by an interaction between these two factors (F=0.5 with 1 and 428 df; P=0.47).

DISCUSSION

This trial provides evidence of the efficacy of cytisine as an aid in smoking cessation. Cytisine resulted in more gastrointestinal adverse events than did placebo; rates of discontinuation or dose reduction were similar with cytisine and placebo.

The relative difference in smoking cessation between cytisine and placebo (relative rate, 3.4) was higher than previous studies have shown for varenicline (2.3) and nicotine-replacement therapy (1.6).[6,7] However, the absolute difference in the rate of abstinence between participants receiving cytisine and those receiving placebo in this trial (6 percentage points) was lower than that shown for varenicline and similar to that shown for nicotine-replacement therapy. Combining cytisine with more intensive behavioral support may result in higher absolute quit rates.[24] Also, the treatment period was only 4 weeks, as compared with 8 weeks for nicotine-replacement therapy and 12 weeks for varenicline, and it is possible that efficacy could be improved by a longer regimen.

Varenicline acts both to reduce cravings and to make cigarettes less satisfying if a lapse occurs, thereby reducing the risk of a full-blown relapse.[25] The same may be true for cytisine.

Table 2. Effect of Cytisine on Smoking Cessation.*

Outcome	Cytisine (N=370)	Placebo (N=370)	Percentage-Point Difference (95% CI)	Relative Rate (95% CI)†
	percent (number)			
Primary outcome: abstinence for 12 mo	8.4 (31)	2.4 (9)	6.0 (2.7–9.2)‡	3.4 (1.7–7.1)
Abstinence for 6 mo	10.0 (37)	3.5 (13)	6.5 (2.9–10.1)‡	2.9 (1.5–5.3)
Point prevalence at 12 mo	13.2 (49)	7.3 (27)	5.9 (1.6–10.3)§	1.8 (1.2–2.8)

* The primary outcome was abstinence for 12 months after treatment ended, according to Russell Standard criteria. The secondary outcomes were abstinence for 6 months according to Russell Standard criteria and the point prevalence at 12 months defined as abstinence in the week before the 12-month follow-up visit. The Russell Standard criteria involve classification of loss to follow-up as treatment failure, biochemical verification of smoking abstinence at the final follow-up point, and self-report of continuous abstinence (fewer than 5 cigarettes smoked in each of the 6-month follow-up periods). There were no significant associations between baseline measures and the primary outcome.
† The relative rate is the percentage in the cytisine group divided by the percentage in the placebo group.
‡ P<0.001.
§ P=0.01.

Table 3. Adverse Events Reported by 10 or More Study Participants.*

Event	Cytisine (N=370)	Placebo (N=370)	Percentage-Point Difference (95% CI)†	Relative Rate (95% CI)‡
	percent (number)			
Any gastrointestinal event	13.8 (51)	8.1 (30)	5.7 (1.2 to 10.2)§	1.7 (1.1 to 2.6)
Upper abdominal pain	3.8 (14)	3.0 (11)	0.8 (–1.8 to 3.4)	1.3 (0.6 to 2.8)
Nausea	3.8 (14)	2.7 (10)	1.1 (–1.5 to 3.6)	1.4 (0.6 to 3.1)
Dyspepsia	2.4 (9)	1.1 (4)	1.4 (–0.5 to 3.2)	2.2 (0.7 to 7.2)
Dry mouth	2.2 (8)	0.5 (2)	1.6 (0 to 3.3)	4.0 (0.9 to 18.7)
Any psychiatric event	4.6 (17)	3.2 (12)	1.4 (–1.4 to 4.2)	1.4 (0.7 to 2.9)
Dizziness	2.2 (8)	1.1 (4)	1.1 (–0.7 to 2.9)	2.0 (0.6 to 6.6)
Somnolence	1.6 (6)	1.1 (4)	0.5 (–1.1 to 2.2)	1.5 (0.4 to 5.3)
Any nervous system event	2.7 (10)	2.4 (9)	0.3 (–2.0 to 2.6)	1.1 (0.5 to 2.7)
Headache	1.9 (7)	2.2 (8)	–0.3 (–2.3 to 1.8)	0.9 (0.3 to 2.4)
Skin and subcutaneous tissue	1.6 (6)	1.4 (5)	0.3 (–1.5 to 2.0)	1.2 (0.4 to 3.9)

* The incidence of events was analyzed according to the *Medical Dictionary for Regulatory Activities* System Organ Class (SOC) categorization and preferred terms. Participants who reported more than one event in a system category were counted only once for the category. SOC categories for other events (those reported by fewer than 10 participants) were as follows: general (five events with cytisine and five with placebo), cardiac (four with cytisine and two with placebo), musculoskeletal and connective tissue (three with cytisine and three with placebo), infections (one with placebo), immune system (one with placebo), and metabolism and nutrition (one with placebo).
† Differences were calculated according to values before rounding.
‡ The relative rate is the percentage in the cytisine group divided by the percentage in the placebo group.
§ P=0.02. There were no other significant differences.

This study was not large enough for an assessment of uncommon adverse events with cytisine use. The latest Periodic Safety Update Report provided to the European authorities, based on more than 7 million exposed persons, did not identify any safety signals. There have been reports of neuropsychiatric adverse events, including suicidal ideation, with varenicline, which is a similar class of drug. Although the incidence is not higher than would be expected by chance,[26,27] it seems appropriate to continue to undertake surveillance for such rare events among persons taking cytisine.

In conclusion, cytisine was effective for smoking cessation in this single-center trial. The lower cost of cytisine as compared with that of other pharmacotherapies for smoking cessation may make it an attractive treatment option for smokers in low-income and middle-income countries.[28]

Supported by a grant from the United Kingdom National Prevention Research Initiative (to Dr. West), which included contributions from the British Heart Foundation, Cancer Research UK, Chief Scientist Office of the Scottish Government Health Directorates, Department of Health, Diabetes UK, Economic and Social Research Council, Research and Development Office of Health and Social Care in Northern Ireland, Medical Research Council, and Welsh Assembly; and by grants from Cancer Research UK (to Dr. West and Mr. Stapleton) and the National Institute for Health Research (to Dr. Aveyard).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the members of the Trial Steering Committee (Michael Ussher, Lindsay Stead, Elspeth Lee, Robert Hewings, Martin Edwards, and Dorota Olszak); the members of the Data Monitoring and Ethics Committee (Peter Hajek, Ann McNeill, and Lesley Owen); the doctors (Ewelina Bobek-Pstrucha, Joanna Jonska, Elzbieta Karpinska, Marzena Piasecka, Joanna Surowinska, Ewelina Sliwka, Olga Tronina, and Ewa Wazna), nurses (Teresa Kankiewicz, Mirosława Kleszcz, Katarzyna Marczyk, Elzbieta Milkowska, Malgorzata Pokorska, Dorota Sadowska, and Magdalena Starosciak), psychologists and therapists (Anna Blogosz, Anna Debska, Justyna Koziorowska, Marta Porebiak, Irena Przepiorka, and Agnieszka Smolinska), and secretarial staff (Halina Gaj, Joanna Szwechowicz, and Ewa Tarnowska) who assisted with the conduct of the trial; Ognyan Donev of Sopharma for performing the randomization and providing study medication; and Prof. Piotr Tutka for his help and advice before and during the study.

REFERENCES

1. WHO report on the global tobacco epidemic: the MPOWER report. Geneva: World Health Organization, 2008.
2. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction 2004;99:29-38.
3. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519.
4. Framework convention on tobacco control. Geneva: World Health Organization, 2003.
5. Treating tobacco use and dependence: 2008 update. Rockville, MD: Public Health Service, 2008.
6. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2010;12:CD006103.
7. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2008;1:CD000146.
8. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007;1:CD000031.
9. National Institute for Clinical Excellence technology appraisal guidance. No. 38. Nicotine replacement therapy (NRT) and bupropion for smoking cessation. London: National Institute for Clinical Excellence, 2002.
10. Tutka P. Nicotinic receptor partial agonists as novel compounds for the treatment of smoking cessation. Expert Opin Investig Drugs 2008;17:1473-85.
11. Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from molecule to therapeutic efficacy. Pharmacol Rep 2006;58:777-98.
12. Etter JF, Lukas RJ, Benowitz NL, West R, Dresler CM. Cytisine for smoking cessation: a research agenda. Drug Alcohol Depend 2008;92:3-8.
13. Stoyanov S, Yanachkova M. Treatment of nicotinism with the Bulgarian drug, Tabex. Chimpharm Sofia 1965;2:13.
14. Vinnikov D, Brimkulov N, Burjubaeva A. A double-blind randomised placebo-controlled trial of cytisine for smoking cessation in medium-dependent workers. J Smoking Cessation 2008;3:57-62.
15. Zatonski W, Cedzynska M, Tutka P, West R. An uncontrolled trial of cytisine (Tabex) for smoking cessation. Tob Control 2006;15:481-4.
16. Gotti C, Guiducci S, Tedesco V, et al. Nicotinic acetylcholine receptors in the mesolimbic pathway: primary role of ventral tegmental area alpha6beta2* receptors in mediating systemic nicotine effects on dopamine release, locomotion, and reinforcement. J Neurosci 2010;30:5311-25.
17. Rollema H, Shrikhande A, Ward KM, et al. Pre-clinical properties of the alpha4beta2 nicotinic acetylcholine receptor partial agonists varenicline, cytisine and dianicline translate to clinical efficacy for nicotine dependence. Br J Pharmacol 2010;160:334-45.
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119-27.
19. Medical Dictionary for Regulatory Activities (MedDRA) Maintenance and Support Services Organization (MSSO) home page. (http://www.meddramsso.com.)
20. Beck AT, Beamesderfer A. Assessment of depression: the Depression Inventory. Mod Probl Pharmacopsychiatry 1974;7:151-69.
21. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005;100:299-303.
22. Fagerström K, Furberg H. A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence across countries. Addiction 2008;103:841-5.
23. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91.
24. Mottillo S, Filion KB, Belisle P, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. Eur Heart J 2009;30:718-30.
25. West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. Psychopharmacology (Berl) 2008;197:371-7.
26. Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. Drug Saf 2010;33:289-301.
27. Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. BMJ 2009;339:b3805.
28. Shafey O, Eriksen M, Ross H, Mackay J. The tobacco atlas. 3rd ed. Atlanta: American Cancer Society, 2009.