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Cytisine versus Nicotine for Smoking Cessation

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ABSTRACT

BACKGROUND

Placebo-controlled trials indicate that cytisine, a partial agonist that binds the nicotinic acetylcholine receptor and is used for smoking cessation, almost doubles the chances of quitting at 6 months. We investigated whether cytisine was at least as effective as nicotine-replacement therapy in helping smokers to quit.

METHODS

We conducted a pragmatic, open-label, noninferiority trial in New Zealand in which 1310 adult daily smokers who were motivated to quit and called the national quitline were randomly assigned in a 1:1 ratio to receive cytisine for 25 days or nicotine-replacement therapy for 8 weeks. Cytisine was provided by mail, free of charge, and nicotine-replacement therapy was provided through vouchers for low-cost patches along with gum or lozenges. Low-intensity, telephone-delivered behavioral support was provided to both groups through the quitline. The primary outcome was self-reported continuous abstinence at 1 month.

RESULTS

At 1 month, continuous abstinence from smoking was reported for 40% of participants receiving cytisine (264 of 655) and 31% of participants receiving nicotine-replacement therapy (203 of 655), for a difference of 9.3 percentage points (95% confidence interval, 4.2 to 14.5). The effectiveness of cytisine for continuous abstinence was superior to that of nicotine-replacement therapy at 1 week, 2 months, and 6 months. In a prespecified subgroup analysis of the primary outcome, cytisine was superior to nicotine-replacement therapy among women and noninferior among men. Self-reported adverse events over 6 months occurred more frequently in the cytisine group (288 events among 204 participants) than in the group receiving nicotine-replacement therapy (174 events among 134 participants); adverse events were primarily nausea and vomiting and sleep disorders.

CONCLUSIONS

When combined with brief behavioral support, cytisine was found to be superior to nicotine-replacement therapy in helping smokers quit smoking, but it was associated with a higher frequency of self-reported adverse events. (Funded by the Health Research Council of New Zealand; Australian New Zealand Clinical Trials Registry number, ACTRN12610000590066.)

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A Quick Take animation is available at NEJM.org

Cytisine is a plant-based alkaloid found in members of the Leguminosae family.[1,2] Like varenicline, cytisine is a partial agonist of nicotinic acetylcholine receptors (nAChRs), with an affinity for the $\alpha 4\beta 2$ receptor subtype,[3] and a half-life of 4.8 hours.[4] Cytisine is a generic agent currently manufactured by Sopharma as Tabex and by Aflofarm Pharma as Desmoxan. It has been available both with and without prescription for smoking cessation since the 1960s, largely in Eastern Europe.[5] Four systematic reviews report cytisine to be superior to placebo for short-term and long-term abstinence.[6-9] When taken at the recommended dosage (1.5 to 9 mg per day for 25 days), cytisine is associated with no significant increase in adverse events as compared with placebo (20.5% vs. 19.6%), although gastrointestinal symptoms are more common (11.9% vs. 7.2%).[7]

Cytisine remains relatively unknown outside Eastern Europe despite calls for licensing worldwide[10-12] because of its proven benefits, low cost as compared with other cessation medications (cytisine, $20 to $30 for 25 days; nicotine-replacement therapy, $112 to $685 for 8 to 10 weeks; varenicline, $474 to $501 for 12 weeks),[11] and low cost per quality-adjusted-life-year.[13] Given that no trials have compared cytisine with nicotine-replacement therapy, we designed a noninferiority trial to investigate whether cytisine was at least as effective as nicotine-replacement therapy. We hypothesized that 25 days of cytisine plus low-intensity behavioral support would be at least as effective as 8 weeks of nicotine-replacement therapy plus low-intensity behavioral support for smoking cessation.

Methods

Study Oversight

The trial was conducted and monitored in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and is reported with fidelity to the protocol and statistical analysis plan included in the protocol,[14] available with the full text of this article at NEJM.org. The Health Research Council of New Zealand funded the trial, including the reimbursement of Quitline, which was engaged to recruit participants. Cytisine was supplied at no cost by the manufacturer, Sopharma. The research council, Sopharma, and the Extab Corporation had no role in the design of the trial, the collection, analysis, or interpretation of the data, or the writing of the report for publication. The protocol was approved by the New Zealand Multi-Region Ethics Committee and the Standing Committee on Therapeutic Trials. All participants provided oral informed consent. All authors were involved in the design and conduct of the trial and the writing of the manuscript. The first and second authors oversaw the conduct of the study, the seventh author performed all statistical analyses, and the first author supervised the writing of the manuscript.

Participants

This parallel-group, randomized, controlled, noninferiority trial was conducted in New Zealand.[14] The first randomization was conducted on March 29, 2011, and the last follow-up took place on February 4, 2013. Smokers were recruited through the New Zealand national quitline. To be included in the study, participants had to be at least 18 years of age, daily smokers, and motivated to quit. Potential participants were excluded if they were pregnant or breast-feeding, were taking smoking-cessation medication, were enrolled in another cessation program or study, had self-reported pheochromocytoma, had a systolic blood pressure above 150 mm Hg, a diastolic blood pressure above 100 mm Hg, or both, had schizophrenia, or had had a self-reported cardiovascular event in the 2 weeks before study enrollment.

Randomization

Eligible participants who had called the quitline were randomly allocated, by computer, to nicotine-replacement therapy or cytisine in a 1:1 ratio. Randomization was stratified with the use of minimization according to sex, ethnicity (Maori, Pacific Islander, or non-Maori and non–Pacific Islander), and cigarette dependence, which was determined by means of the Fagerström Test of Cigarette Dependence, in which smokers were assigned to one of two groups: those with scores of 5 or lower, indicating lower dependence, and those with scores greater than 5, indicating greater dependence.[15,16] Participants and researchers collecting outcome data were aware of treatment allocation.

PROCEDURES

All participants were offered low-intensity telephone behavioral support (an average of three calls of 10 to 15 minutes each from Quitline advisors over a period of 8 weeks). Participants assigned to nicotine-replacement therapy received vouchers from Quitline that were redeemable from community pharmacies for nicotine patches (in doses of 7 mg, 14 mg, or 21 mg) and for gum (2 mg or 4 mg) or lozenges (1 mg or 2 mg) or both gum and lozenges at a cost of NZ$3 for an 8-week supply of each item (the equivalent of €2, or approximately $2.50 in U.S. dollars). The type and strength of nicotine-replacement therapy were determined by Quitline advisors in accordance with national smoking-cessation guidelines[17] and participant preference. The cytisine group received a 25-day course of tablets by courier and were asked to reduce their smoking at their own pace during the first 4 days of treatment such that they were not smoking at all by the 5th day (i.e., their "quit date"). Participants followed the manufacturer's recommended dosing regimen: days 1 through 3, one tablet every 2 hours through the waking day (up to six tablets per day); days 4 through 12, one tablet every 2.5 hours (up to five tablets per day); days 13 through 16, one tablet every 3 hours (up to four tablets per day); days 17 through 20, one tablet every 4 to 5 hours (three tablets per day); and days 21 through 25, one tablet every 6 hours (two tablets per day). Participants in the cytisine group also received the vouchers for nicotine-replacement therapy sent to participants in the nicotine-replacement therapy group. They were asked to take the cytisine tablets for 25 days. If they had not stopped smoking by that time, or if they required ongoing support to refrain from smoking after that time, they were to redeem the vouchers for nicotine-replacement therapy.

At baseline, data were collected on demographics, smoking history, concomitant medication, motivation to quit smoking (with a score of 1 indicating very low motivation and a score of 5 indicating very high motivation), symptoms of withdrawal and the urge to smoke (both assessed with the Mood and Physical Symptoms Scale, with symptoms rated on a scale of 1 to 5, with 1 indicating none and 5 the most severe, and the urge to smoke scored on a scale of 0 to 10, with higher scores indicating greater strength of the urge to smoke and a greater duration of these urges),[18] alcohol use (assessed with the Alcohol Use Disorders Identification Test [AUDIT-C], rated on a scale of 0 to 12, with higher scores indicating a greater risk of alcohol dependence),[19] and satisfaction with smoking (assessed with the modified Cigarette Evaluation Questionnaire, which included 12 subscales; in each subscale, a score of 1 indicated not at all satisfied and a score of 7 indicated extremely satisfied).[20]

The primary outcome was continuous abstinence from smoking (self-reported abstinence since quit day, with an allowance for smoking a total of five cigarettes or less,[21] including during the previous 7 days) 1 month after quit day. Secondary outcomes assessed at 1 week and at 1, 2 and 6 months after quit day were self-reported treatment compliance (total number of cytisine tablets taken or the type, strength, and amount of nicotine-replacement therapy used); alcohol use[19]; motivation to quit; symptoms of tobacco withdrawal; and the strength of urges to smoke and the duration of these urges[18]; 7-day point prevalence for abstinence (no cigarettes, not a single puff, in the previous 7 days)[21]; continuous abstinence; smoking satisfaction[20]; concomitant medication; and, if still smoking, date returned to daily smoking and the number of cigarettes smoked per day. Self-reported adverse events were recorded at each follow-up call, coded in accordance with the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, Australian Modification, and classified by a medical practitioner as nonserious or serious (defined as death, life-threatening, hospitalization, or otherwise medically important) and according to severity (mild — awareness of event but easily tolerated; moderate — discomfort extensive enough to cause some interference with usual activity; or severe — inability to carry out usual activity). All adverse events were reviewed by an independent data safety and monitoring committee. At 1 week and 1 month we also asked participants in the cytisine group whether they would recommend cytisine as a cessation aid.

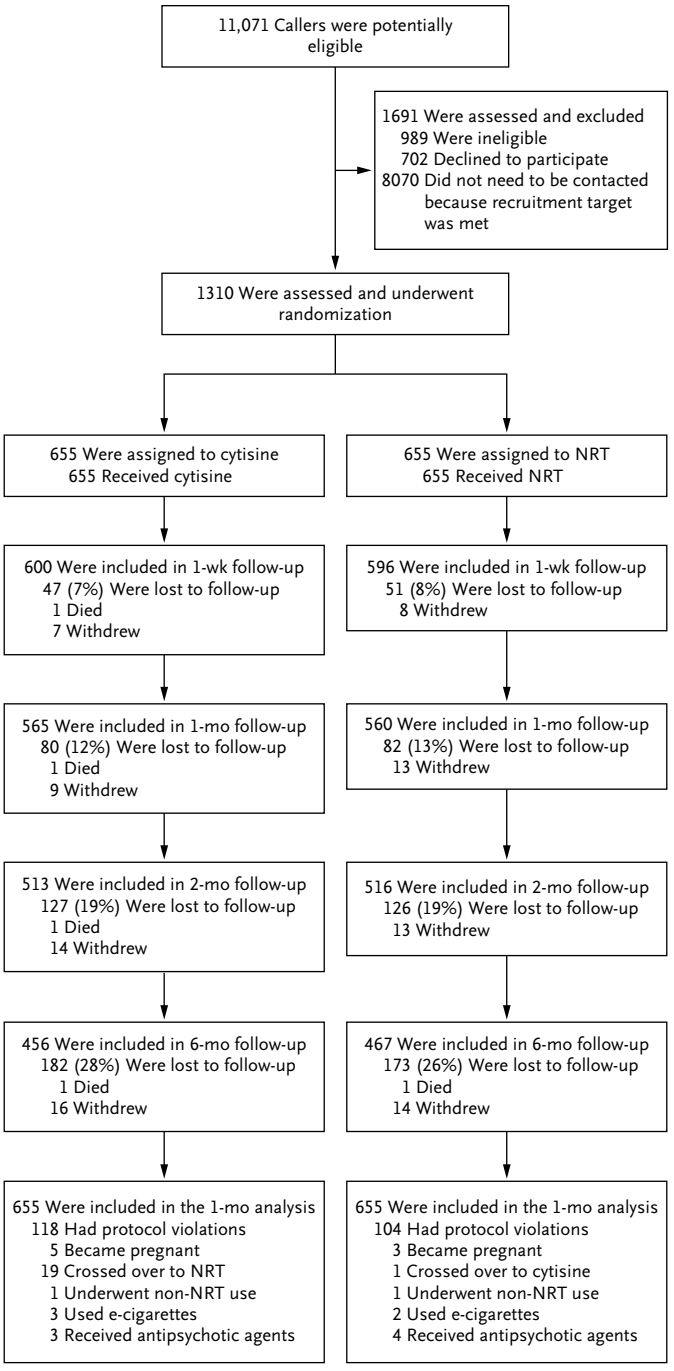

Figure 1. Recruitment and Retention of Participants throughout the Trial.
At initial assessment, the main reasons for ineligibility were current use of other smoking-cessation products or services (71%), schizophrenia (9%), uncontrolled blood pressure (9%), and pregnancy or breast-feeding (8%). For the 1-month analysis, protocol violations (as defined in the study) included loss to follow-up, death, and study withdrawal. NRT denotes nicotine-replacement therapy.

STATISTICAL ANALYSIS

For our sample of 1310 people (655 per group), we assumed a loss of 20% to follow-up and a power of 90% at the one-sided significance level of 0.025 (the equivalent of a two-sided significance level of 0.05) to detect a 5% difference in 1-month quit rates between groups. The 1-month quit rate in the cytisine group was assumed to be 55%, midway between the estimate of 60% for varenicline[8] and 50% for nicotine-replacement therapy.[22] A noninferiority margin of difference between the group proportions was set at 5%.

Analyses were performed with SAS Software, version 9.3 (SAS Institute), and were guided by a prespecified plan. Noninferiority for the primary outcome was evaluated by observing whether the lower bound of the two-sided 95% confidence intervals for the risk difference in quit rates between the groups was above the noninferiority limit of −5. The primary analyses were carried out on an intention-to-treat basis (participants for whom outcomes were missing were assumed to be smoking). In the case that noninferiority was evident, assessment as to whether cytisine had effectiveness superior to that of nicotine-replacement therapy was carried out according to the same approach but was compared with a zero difference. Per-protocol analyses excluded participants who had missing data at 1 month or who had major protocol violations (e.g., death, pregnancy, withdrawal from the study, loss to follow-up, or noncompliance). Compliance in the cytisine group was defined as having taken 80% or more of the required number of tablets within 1 month after the quit date (i.e., 80 tablets or more). Compliance in the nicotine-replacement therapy group was defined as having used nicotine-replacement therapy at both 1 week and 1 month after the quit date. Participants with missing data were assumed to be noncompliant with the study regimen. Complete case analysis was also undertaken, and quit rates, relative risk, risk difference, and the number needed to treat were calculated. Treatment groups were compared with the use of chi-square tests and unadjusted and adjusted logistic regression modeling (adjusting for minimization factors and education).

In prespecified subgroup analyses, the consistency of effects was assessed with tests for heterogeneity for the primary outcome according to

ethnicity (Maori vs. non-Maori), age (<40 years of age vs. ≥40 years of age), sex, and level of education (<12 years of schooling or no qualification vs. ≥12 years of schooling), type of cigarettes smoked (factory-made only, roll-your-own only, or factory-made and roll-your-own), and baseline AUDIT-C score (high vs. low). Post hoc subgroup analyses for the primary outcome were undertaken according to baseline level of cigarette dependence and use of nicotine-replacement therapy in the preceding 12 months. The change from baseline in symptoms of tobacco withdrawal (for abstainers), AUDIT-C score, and number of cigarettes smoked per day over time was assessed by means of repeated-measures mixed models adjusted for baseline value. Kaplan–Meier curves, the log rank test, and Cox proportional hazards regression analysis were used to measure time to first lapse from quit date (return to daily smoking).

Table 1. Baseline Characteristics of the Participants.*

Characteristics	Cytisine (N=655)	NRT (N=655)
Female sex — no. (%)	372 (57)	372 (57)
Age — yr	37.8±11.8	38.4 (11.9)
Ethnic group — no. (%)†		
New Zealand Maori	215 (33)	213 (33)
Non-Maori	440 (67)	442 (67)
Less than 12 years of schooling — no. (%)	344 (53)	329 (50)
Cigarettes smoked per day‡	19.3±11.9	19.0 (10.0)
Cigarette dependence§	5.4±2.1	5.3 (2.3)

* Plus–minus values are means ±SD. No significant differences were observed between groups in baseline characteristics. NRT denotes nicotine-replacement therapy.
† Ethnic group was self-reported. Maori are indigenous New Zealanders; all others are non-Maori.
‡ The number of cigarettes smoked per day includes hand-rolled cigarettes.
§ Cigarette dependence was measured with the Fagerström Test of Cigarette Dependence. On a scale of 1 to 10, a score above 5 indicates high cigarette dependence and a score of 5 or below indicates low cigarette dependence.

RESULTS

OUTCOMES

Among 3001 people assessed, 1310 were eligible for study participation and underwent randomization, 655 in each group (Fig. 1). Loss to follow-up at 1 month was 12% in both groups (Fig. 1). Baseline characteristics were evenly balanced between the treatment groups (Table 1; and Table S1 in the Supplementary Appendix, available at NEJM.org).

Cytisine was not only noninferior to nicotine-replacement therapy but had superior effectiveness: 1-month continuous abstinence rates were significantly higher in the cytisine group (40%, 264 of 655) than in the nicotine-replacement therapy group (31%, 203 of 655) (risk difference, 9.3 percentage points; 95% confidence interval [CI], 4.2 to 14.5; number needed to treat, 11) (Table 2). Complete case and per-protocol analyses revealed similar findings (Table 2). Adjusted logistic-regression analysis produced an odds ratio of 1.5 for abstinence with cytisine (95% CI, 1.2 to 1.9; P=0.003). Prespecified analyses conducted according to sex showed a significantly higher 1-month continuous abstinence rate with cytisine in women and showed no significant difference (noninferiority) in men (P=0.011 for heterogeneity), with no significant differences noted for other subgroups (Fig. S1 in the Supplementary Appendix). The secondary cessation outcomes at 1 week and at 1, 2, and 6 months were consistent with the primary outcome, with the exception of 6-month, 7-day point-prevalence abstinence rates (which were not statistically significant) (Table 2).

At 1 week, 66% (392 of 596) of participants in the nicotine-replacement therapy group were using nicotine-replacement therapy obtained through the voucher system as compared with 4% (26 of 600) in the cytisine group. In the cytisine group, at 1 week after the quit date, 63 tablets should have been taken, but participants reported taking a mean (±SD) of 49±24 tablets. At 1 month after the quit date, all 100 tablets should have been taken, but participants reported taking a mean of 72±34 tablets. Overall, 53% (344 of 655) of participants were in compliance with the guidelines for cytisine treatment (i.e., they had taken 80 or more tablets), whereas 67% (437 of 655) in the nicotine-replacement therapy group were in compliance with treatment guidelines (i.e., they had used nicotine-replacement therapy at both 1 week and 1 month). At 1 month after the quit date, 22% of participants in the cytisine group and 55% of those in the nicotine-replacement

Table 2. Continuous Abstinence and 7-Day Point-Prevalence Abstinence According to Treatment Group, According to the Intention-to-Treat Analysis.

Abstinence	Cytisine (N=655)	NRT (N=655)	Relative Risk (95% CI)	Risk Difference (95% CI)	P Value
	no./total no. (%)				
Continuous					
Quit rate*					
1 Wk	394 (60)	303 (46)	1.3 (1.2 to 1.4)	13.9 (8.5 to 19.2)	<0.001
1 Mo	264 (40)	203 (31)	1.3 (1.1 to 1.5)	9.3 (4.2 to 14.5)	<0.001
2 Mo	202 (31)	143 (22)	1.4 (1.2 to 1.7)	9.0 (4.3 to 13.8)	<0.001
6 Mo	143 (22)	100 (15)	1.4 (1.1 to 1.8)	6.6 (2.4 to 10.8)	0.002
Sensitivity analyses for 1-mo quit data					
Complete cases only†	264/565 (47)	203/560 (36)	1.3 (1.1 to 1.5)	10.5 (4.8 to 16.2)	<0.001
Per protocol					
Population with protocol violations excluding noncompliance‡	252/537	199/551	1.3 (1.1 to 1.5)	10.8 (5.0 to 16.6)	<0.001
Population with protocol violations including noncompliance§	189/330	167/407	1.4 (1.2 to 1.6)	16.2 (9.1 to 23.4)	<0.001
7-Day point prevalence					
Quit rate*					
1 Wk¶	266 (41)	199 (30)	1.3 (1.2 to 1.6)	10.2 (5.1 to 15.4)	<0.001
1 Mo	273 (42)	215 (33)	1.3 (1.1 to 1.5)	8.9 (3.7 to 14.1)	<0.001
2 Mo	246 (38)	206 (32)	1.2 (1.0 to 1.4)	6.1 (1.0 to 11.3)	0.020
6 Mo	206 (31)	196 (30)	1.1 (0.9 to 1.2)	1.5 (−3.5 to 6.5)	0.549

* Data for the quit rate are based on the assumption that all participants for whom data on smoking status were missing were smoking.
† Complete cases refers to participants for whom data on smoking status were complete at 1 month.
‡ This population excluded participants with missing data at 1 month and protocol violations, which were defined as death, pregnancy, withdrawal, loss to follow-up, use of non-NRT cessation products, use of antipsychotic medication, and crossovers.
§ This population excluded the same participants as described directly above, but protocol violations also included noncompliance with treatment.
¶ Point-prevalence abstinence at 1 week is lower than continuous abstinence at 1 week because the definition of continuous abstinence allows for a slip of up to five cigarettes, whereas the general definition used for point-prevalence abstinence does not.

therapy group continued their allocated treatment. In the cytisine group, there were 19 participants who used cytisine and nicotine-replacement therapy concomitantly.

ADVERSE EVENTS

Self-reported adverse events occurred more frequently in the cytisine group (288 events reported by 204 participants) than in the nicotine-replacement-therapy group (174 events reported by 134 participants), with an incidence rate ratio of 1.7 (95% CI, 1.4 to 2.0; P<0.001) (Table 3). Similar findings were observed for participants who were compliant with treatment (161 events reported by 107 participants in the cytisine group vs. 113 events reported by 88 participants in the nicotine-replacement-therapy group; incidence rate ratio, 1.4; 95% CI, 1.1 to 1.8; P=0.003) (Table 3). In the cytisine group, 67% of adverse events were reported between randomization and 1 month after the quit date, as compared with 49% in the nicotine-replacement-therapy group. The majority of adverse events were nonserious and were mild to moderate in severity (Table 3). The most frequent adverse events in the cytisine group were nausea and vomiting and sleep disorders (Table 3, and Table S4 in the Supplementary Appendix). Serious adverse events are listed in Table S5 in the Supplementary Appendix. Among participants in the cytisine group who reported an ad-

verse event, 89% at 1 week (2 missing) and 82% at 1 month after the quit date (13 missing) said they would recommend cytisine to someone who wanted to stop smoking.

Overall, 21% of participants in the cytisine group and 34% of those in the nicotine-replacement-therapy group did not quit on the quit day. The median time to relapse (resumption of smoking) after the quit day was significantly longer in the cytisine group than in the nicotine-replacement therapy group: 53 days (95% CI, 36 to 100) versus 11 days (95% CI, 6 to 22) (P<0.001 for log-rank test; hazard ratio, 0.8 [95% CI, 0.7 to 0.9, P=0.001]); 348 participants in the cytisine group relapsed within 6 months versus 389 participants in the nicotine-replacement therapy group (Fig. 2). A greater difference was observed for those who were compliant with treatment (Fig. 2). Other outcome data are presented in the Supplementary Appendix.

Table 3. Summary of All-Cause Adverse Events.

Event	Cytisine (N=655)	NRT (N=655)
Participants with any adverse event — no. (%)	204 (31)	134 (20)
Adverse events — no.		
Any	288	174
In those who complied with treatment*	161	113
In those who did not comply with treatment	127	61
Participants with serious adverse event — no. (%)	45 (7)	39 (6)
Serious adverse events — no.†‡	56	45
Deaths§	1	1
Life-threatening events	0	1¶
Hospitalizations	18	18
Otherwise medically important events	37	25
Severity of all adverse events — no.‖		
Mild	139	78
Moderate	111	77
Severe	38	19
Most frequent adverse events (≥5% of all events) — no. **		
Nausea and vomiting (ICD-10 R11)	30	2
Sleep disorders (ICD-10 G47.0 and G47.8)	28	2

* In the cytisine group, compliance was defined as having taken 80% or more of the required number of tablets within 1 month after the quit date (i.e., 80 or more tablets). In the NRT group, compliance was defined as having used NRT at 1 week and 1 month after the quit date. It was assumed that participants with missing data were not compliant.

† A serious event was defined as death, a life-threatening event, an event requiring hospitalization, or otherwise medically important event (i.e., the event does not belong in any of the other categories but may jeopardize the patient and may require medical or surgical intervention to prevent the occurrence of one or more other serious adverse events).

‡ The categories are mutually exclusive.

§ There were two deaths: one participant in the cytisine group died from alcohol-related asphyxiation during the treatment period, and one in the NRT group died of a heart attack during follow-up.

¶ This event was development of a brain tumor.

‖ The severity of events was not medically verified.

** The list of most frequent adverse events excludes signs and symptoms of cold and influenza. Adverse events were categorized in accordance with the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), Australian Modification.

DISCUSSION

Cytisine was superior to nicotine-replacement therapy for smoking cessation among dependent smokers motivated to quit. Self-reported adverse events over 6 months were almost twice as common in the cytisine group than in the nicotine-replacement-therapy group. Types of adverse events in the cytisine group were similar to those seen in previous placebo-controlled trials of cytisine.[6-9] Our trial was neither large enough nor long enough to assess the occurrence of uncommon adverse events or those with a long time to onset. Compliance with allocated treatment was modest. Time to relapse was delayed in the cytisine group. During treatment, participants in the cytisine group reported fewer symptoms of tobacco withdrawal, found smoking less rewarding, and reduced the number of cigarettes smoked per day. The higher quit rate observed in women taking cytisine has not been previously reported in studies of nAChR partial agonists. This finding could be the result of chance (since data were not adjusted for multiplicity) but warrants further investigation, since several reviews of nicotine-replacement therapy have reported lower quit rates in women than in men,[23,24] possibly as a result of biologic and psychosocial differences.

We chose a noninferiority design on the basis of data available at the time, before publication of the placebo-controlled trial by West et al.[25] Our trial population was similar to that of New Zealand Quitline callers overall[26] (although Asian, Pacific Islander, and male smokers are slightly underrepresented among Quitline users),[26,27] New Zealand smokers overall,[28,29] and three previous

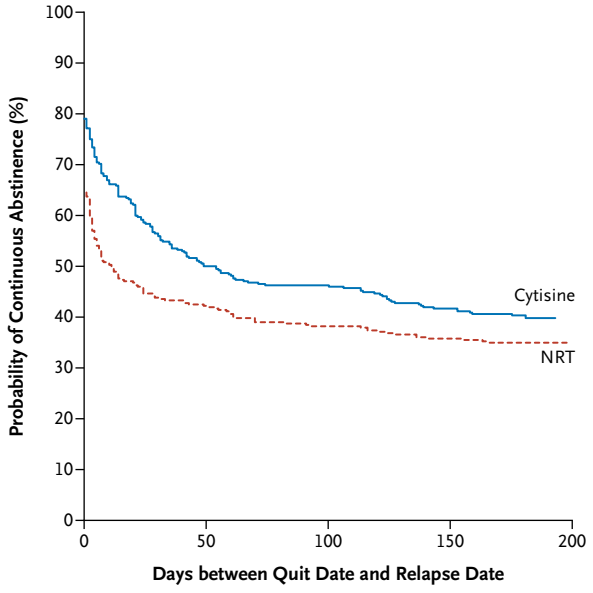

Figure 2. Kaplan–Meier Curve for Time to First Relapse.

Twenty-one percent of participants in the cytisine group and 34% of participants in the NRT group did not quit on the quit date (Day 0). Time to relapse was defined as the number of days to return to regular (daily) smoking of cigarettes. In the cytisine group, the median time to relapse was significantly longer among those who complied with treatment (177 participants) than among those who did not (171 participants): 127 days (95% CI, 62 to unable to estimate) versus 20 days (95% CI, 8 to 25); P<0.001 by the log-rank test.

trial populations recruited through Quitline.[30-32] The trial was pragmatic, with broad entry criteria. The criteria for exclusion on the basis of medical conditions reflected the manufacturer's precautions for the use of cytisine and Quitline's policy regarding contraindications for nicotine-replacement therapy. As a precaution, we excluded people who reported that they had schizophrenia, given cytisine's similarity to varenicline (which has a boxed warning related to severe mental health problems). Users of noncigarette tobacco products were not excluded but were probably few in number given that such products are rarely used in New Zealand and that the sale of snus (a moist tobacco powder that is placed under the upper lip) is illegal. We followed the manufacturer's recommended dosing regimen for cytisine, although we are not aware of any published studies that support the regimen.

Our study had several limitations. First, since researchers were aware of treatment allocation, there may have been a reporting bias in favor of cytisine. Second, although adverse events were medically reviewed, they were self-reported. The higher proportion of adverse events in the cytisine group may be due to reporting bias, since the known side effects of nicotine-replacement therapy could have been regarded as "normal" by participants in the nicotine-replacement therapy group who had previously received such therapy and could therefore have gone unreported. We did not collect long-term safety data; in the placebo-controlled trial by West et al.,[25] adverse events reported during a 12-month follow-up period were predominantly related to gastrointestinal effects. Third, because participants were unlikely to have prior knowledge of cytisine, some of the treatment effect might be explained by its novelty. Fourth, verification of self-reported abstinence was not undertaken owing to both the broad geographic dispersal of the study population and budget constraints. In addition, at 1 month participants in the nicotine-replacement-therapy group would have received positive test results for cotinine, a metabolite of nicotine, even if they were not smoking. Abstinence rates may therefore be overreported or underreported (see the Supplementary Appendix for an estimate of validated abstinence), but there should not be a difference in the nature of reporting between groups. Fifth, smokers who call Quitline may be more motivated to quit than other populations of smokers.[33] Sixth, the treatment periods for the two interventions were different; the selection of a 1-month primary outcome should help to ensure comparability. There was also a between-group difference in participants' access to treatments (i.e., cytisine was delivered free, whereas nicotine-replacement therapy was obtained from a pharmacy at a small cost). In a previous trial with 1410 participants in which the same recruitment method was used, participants were randomly assigned either to receive free delivery of nicotine-replacement therapy by courier or to use of the voucher system.[31] No between-group differences in continuous absti-

nence at 3 weeks, 3 months, or 6 months were observed.

The trial shows that cytisine is an effective smoking-cessation aid for use as a first-line treatment for tobacco dependence. The most common adverse events were nausea and vomiting and sleep disorders. The effect sizes in this trial were similar to those observed in a trial of varenicline versus nicotine-replacement therapy.[34] Given the large difference in the market prices of varenicline and cytisine,[11] a head-to-head, noninferiority trial that includes cost-effectiveness analyses is justified.

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