JAMA | Original Investigation

Effect of Cytisine vs Varenicline on Smoking Cessation
A Randomized Clinical Trial

Ryan J. Courtney, PhD; Hayden McRobbie, PhD; Piotr Tutka, MD; Natasha A. Weaver, PhD; Dennis Petrie, PhD; Colin P. Mendelsohn, MBBS; Anthony Shakeshaft, PhD; Saki Talukder, MPH; Christel Macdonald, BPsych; Dennis Thomas, PhD; Benjamin C. H. Kwan, PhD; Natalie Walker, PhD; Coral Gartner, PhD; Richard P. Mattick, PhD; Christine Paul, PhD; Stuart G. Ferguson, PhD; Nicholas A. Zwar, PhD; Robyn L. Richmond, DSc; Christopher M. Doran, PhD; Veronica C. Boland, PhD; Wayne Hall, PhD; Robert West, PhD; Michael Farrell, MB

IMPORTANCE Cytisine is more effective than placebo and nicotine replacement therapy for smoking cessation. However, cytisine has not been tested against the most effective smoking cessation medication, varenicline, which is associated with adverse events known to lead to discontinuation of therapy.

OBJECTIVE To examine whether standard cytisine treatment (25 days) was at least as effective as standard varenicline treatment (84 days) for smoking cessation.

DESIGN, SETTING, AND PARTICIPANTS This noninferiority, open-label randomized clinical trial with allocation concealment and blinded outcome assessment was undertaken in Australia from November 2017 through May 2019; follow-up was completed in January 2020. A total of 1452 Australian adult daily smokers willing to make a quit attempt were included. Data collection was conducted primarily by computer-assisted telephone interview, but there was an in-person visit to validate the primary outcome.

INTERVENTIONS Treatments were provided in accordance with the manufacturers' recommended dosage: cytisine (n = 725), 1.5-mg capsules taken 6 times daily initially then gradually reduced over the 25-day course; varenicline (n = 727), 0.5-mg tablets titrated to 1 mg twice daily for 84 days (12 weeks). All participants were offered referral to standard telephone behavioral support.

MAIN OUTCOMES AND MEASURES The primary outcome was 6-month continuous abstinence verified using a carbon monoxide breath test at 7-month follow-up. The noninferiority margin was set at 5% and the 1-sided significance threshold was set at .025.

RESULTS Among 1452 participants who were randomized (mean [SD] age, 42.9 [12.7] years; 742 [51.1%] women), 1108 (76.3%) completed the trial. Verified 6-month continuous abstinence rates were 11.7% for the cytisine group and 13.3% for the varenicline group (risk difference, −1.62% [1-sided 97.5% CI, −5.02% to ∞]; P = .03 for noninferiority). Self-reported adverse events occurred less frequently in the cytisine group (997 events among 482 participants) compared with the varenicline group (1206 events among 510 participants) and the incident rate ratio was 0.88 (95% CI, 0.81 to 0.95; P = .002).

CONCLUSIONS AND RELEVANCE Among daily smokers willing to quit, cytisine treatment for 25 days, compared with varenicline treatment for 84 days, failed to demonstrate noninferiority regarding smoking cessation.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12616001654448

Visual Abstract

JAMA Patient Page page 96

Supplemental content

CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ryan J. Courtney, PhD, National Drug and Alcohol Research Centre, University of New South Wales, R1 Building, 22-32 King St, Randwick, NSW, Australia (r.courtney@unsw.edu.au).

JAMA. 2021;326(1):56-64. doi:10.1001/jama.2021.7621

Varenicline is the most effective sole pharmacotherapy for smoking cessation,[1,2] but it is associated with some adverse events known to lead to early discontinuation of treatment.[3] Cytisine is a plant-based alkaloid that, like varenicline, is a selective partial agonist at nicotinic acetylcholine receptors.[4] Cytisine has been licensed for use in some eastern and central European and central Asian countries for more than 50 years,[4] and it has recently been approved as a natural health product by Health Canada,[5] but it is not currently approved by the US Food and Drug Administration for smoking cessation. Randomized clinical trials (RCTs) have found cytisine to be more effective than placebo and nicotine replacement therapy in aiding smoking cessation for at least 6 months.[6-9]

A direct comparison between varenicline and cytisine has been identified as a significant evidence gap.[4,10] The purpose of this RCT was to examine the hypothesis that cytisine is noninferior to varenicline for smoking cessation.

Key Points

Question Is cytisine noninferior to varenicline regarding smoking cessation?

Findings In this noninferiority randomized clinical trial that included 1452 participants, verified 6-month continuous abstinence rates were 11.7% for the cytisine group vs 13.3% for the varenicline group, a difference that did not meet the noninferiority margin of 5%.

Meaning The study findings failed to demonstrate noninferiority of cytisine compared with varenicline regarding smoking cessation.

Methods

Design

This noninferiority, open-label RCT was undertaken in New South Wales and Victoria, Australia.[11] The trial was approved by the University of New South Wales human research ethics committee (HC16888). A clinical trial notification was submitted to the Australian Therapeutic Goods Administration (Application ID: CT-2016-CTN-04676-1). All participants provided verbal informed consent. The trial protocol and statistical analysis plan appear in Supplement 1 and Supplement 2, respectively.

Screening, consenting procedures, and check-in calls were completed by staff at the trial coordinating center located at the University of New South Wales (the sole study site for the trial). The RCT was conducted primarily by telephone and the study drugs were delivered by mail. To verify the primary outcome of continuous smoking cessation, an in-person visit was required to administer the carbon monoxide breath test. Baseline and follow-up computer-assisted telephone interviews were completed by employees of an independent organization (social research center) who were blinded to treatment allocation. Participants and trial coordinating center staff were not blinded to treatment allocation.

Participants

Individuals were recruited from advertisements (print [ie, newspapers and posters], radio, and digital media [ie, Facebook and Google]) and from a smoking cessation telephone quit line that provided behavioral support. The study procedures and further details on the trial design appear in the eFigure and in the eMethods in Supplement 3.

Participants were eligible for inclusion if they were: at least 18 years of age; a current daily smoker; willing to make a quit attempt by taking either medication; able to provide verbal informed consent; and had access to a telephone for interviews. Due to the significant differences in smoking rates that exist between ethnic groups in Australia, particularly among the indigenous Aboriginal and Torres Strait Islander peoples, respondents were asked to self-identify which ethnic groups they belonged to via a fixed-category question.

The exclusion criteria were women who were pregnant, breastfeeding, or planning to get pregnant within the next 7 months; individuals who were currently using smoking cessation medications; those who were participating in another smoking cessation program; those with a known hypersensitivity to any of the active substances or excipients; those with a hospitalization within the previous 3 months for arrhythmia, myocardial infarction, stroke, or severe angina; and those with a known diagnosis of pheochromocytoma or hyperthyroidism.

All participants were screened by a study physician. Further details on precautionary conditions for the study treatments and the screening process appear in the eMethods in Supplement 3.

Randomization and Masking

A data management system (UNICOM Intelligence) located at the social research center was used to assign a unique randomization number to study participants using a pregenerated randomization list embedded in the system. Only an independent statistician located at the social research center had access to the pregenerated randomization list. After the baseline computer-assisted telephone interview, the data management system was used to randomly assign each participant to 1 of the treatment groups in a 1:1 ratio (**Figure 1**). The permuted block randomization used unequal block sizes of 12 and 16.

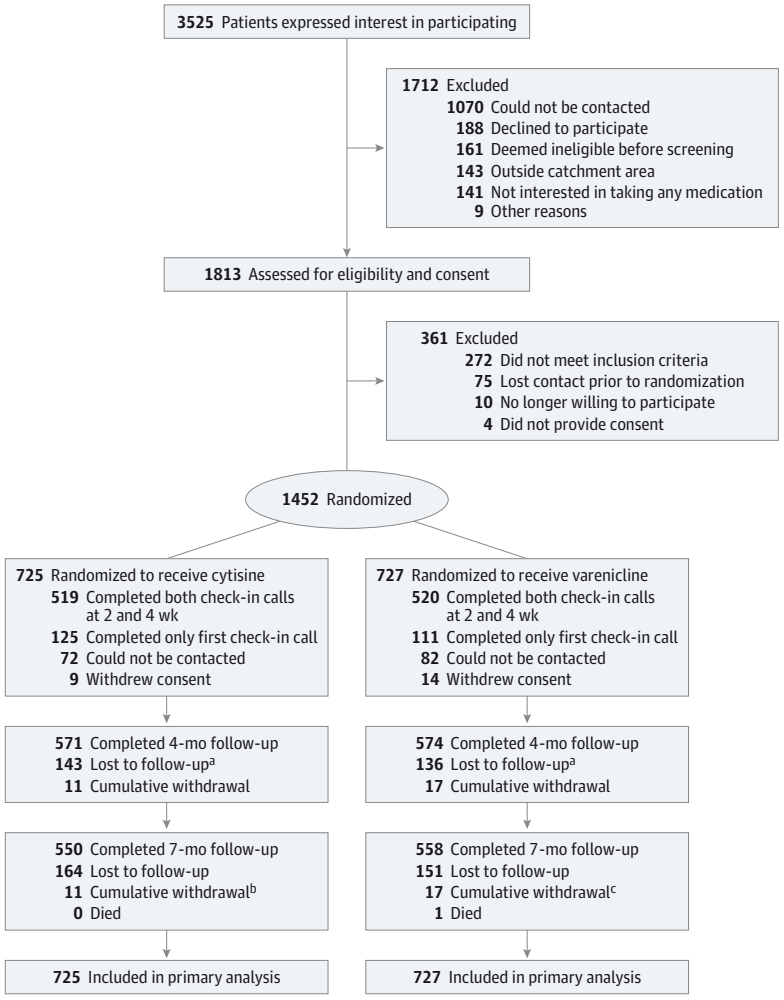
Due to the nature of the intervention, only single blinding (ie, outcome assessment by the independent social research center) was possible. Because the 2 treatments looked different (capsule vs tablet) and had a contrasting dosing regimen and length of treatment, the participants could not be blinded.

Treatments

Participants in the cytisine group received 1.5-mg/d capsules for a 25-day standard course of treatment and quit smoking on day 5. For days 1-3, participants in the varenicline group received one 0.5-mg tablet and then 2 tablets for days 4-7; on day 8, they quit smoking and started taking one 1-mg tablet taken twice daily for an 84-day (12 weeks) course of treatment (eTable 1 in Supplement 3). Treatments were mailed to participants by a central pharmacy at no cost and included instructions on product use. Participants were advised to follow the manufacturer's recommendations included with the

jamanetwork/2021/jama/06jul2021/joi210053 PAGE: right 2 SESS: 43 OUTPUT: Jun 15 17:11 2021

Figure 1. Screening, Randomization, and Follow-up of Participants in the Trial



[a] Lost contact or participant did not respond.

[b] The reasons for withdrawal were not provided (n = 8), not interested in taking medication (n = 1), experienced adverse event (n = 1), and not interested in continuing the study (n = 1).

[c] The reasons for withdrawal were not provided (n = 8), not interested in taking medication (n = 4), experienced adverse event (n = 3), and not interested in continuing the study (n = 2).

product. All participants were offered standard quit line support, which consisted of a free telephone-based call-back service for smokers, providing up to 6 behavioral support calls and a kit containing written information about quitting smoking. The trial coordinating center staff completed an online quit line referral form on behalf of consenting participants.

Baseline, Check-in Calls, and Follow-up Interviews

The social research center completed computer-assisted telephone interview assessments at baseline and at 4 and 7 months after randomization. Participants were reimbursed A$40 for completing each interview.

The baseline computer-assisted telephone interview collected sociodemographic information, smoking history, and health status (Supplement 1).[11] Participants received 2 check-in calls from the trial coordinating center staff within the first month of active treatment to capture data on adverse events and treatment adherence.

At 4 and 7 months, self-reported abstinence and adverse event data were collected using computer-assisted telephone interviews. At 4-month follow-up, participants who discontinued treatment early were asked the reason for doing so.

Participants who met the self-reported secondary outcome of 6-month continuous abstinence were asked to perform a carbon monoxide breath test (Micro+ Smokerlyzer; Bedfont Scientific Ltd) to determine if they met the primary outcome. Participants were reimbursed A$40 for test completion. Participants elected to either visit the trial coordinating center or have a trial staff member come to their home to perform this test.

All adverse events were evaluated by medically trained investigators and summarized using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Adverse event severity was assessed using version 4.0 of the Common Terminology Criteria for Adverse Events. Causality was assessed using criteria from the World Health Organization.

Primary and Secondary Effectiveness Outcomes

The primary outcome was continuous abstinence from smoking (self-report of not having smoked >5 cigarettes during the 6-month period preceding the 7-month follow-up)[12] that was verified by a carbon monoxide breath test (expired carbon monoxide level of ≤9 ppm). Participants who were lost to follow-up, who reported abstinence but did not complete the carbon

monoxide test, or for whom the carbon monoxide level was greater than 9 ppm were classified as still smoking.[13]

The secondary abstinence outcome measures were self-reported: 3- and 6-month continuous abstinence; 7-day point prevalence abstinence measured at the second check-in call (approximately 4 weeks after baseline – the post hoc analysis) and at 4-month and 7-month follow-up; and cigarette consumption at each follow-up. Because of the potential for type I error due to multiple comparisons, the findings for the analyses of the secondary end points should be interpreted as exploratory.

Primary Adverse Event Outcome

The adverse event analyses included all participants who had taken at least 1 dose of cytisine or varenicline. The primary adverse event outcome was the difference in the rate of adverse events between the treatment groups.

Statistical Analysis

The statistical analysis was guided by a prespecified statistical analysis plan (Supplement 2). Most of the primary and secondary effectiveness outcomes were preplanned per the statistical analysis plan. The post hoc analyses of 7-day point prevalence abstinence assessed at the second check-in call and the use of informative priors for the bayesian analysis were not prespecified in the statistical analysis plan. An additional post hoc analysis comparing the adverse event outcome was undertaken. This analysis was similar to the primary adverse event outcome analysis, but evaluated adverse event occurrence up until 28 days after the baseline interview completion date to facilitate comparison of adverse events across treatment groups close to the end of the treatment period for cytisine.

The study was designed to have 90% power at the 1-sided significance level of .025 to detect a noninferiority margin of 5% in 6-month biochemically verified continuous abstinence rates between the groups at 7-month follow-up (1266 participants; 633 per group). A pragmatic RCT[8] showed cytisine use resulted in a 6-month self-reported continuous abstinence rate of 22%. Given the more stringent outcomes in this study, a quit rate of 19% in the cytisine group was assumed. For the varenicline group, a quit rate of 17% was assumed. This rate was based on pragmatic evaluations of varenicline that show lower quit rates and varying heterogeneity in the relative effect according to clinical practice and the population treated[14] than the quit rates observed in controlled trial environments.[1] For example, a study (n = 3116) assessing enrollees via a quit line and taking varenicline identified a continuous cessation rate of 17% at 6 months.[15]

To account for the projected attrition rate of 15%, the sample size calculation was revised prior to reaching the original projected targeted sample size and the recruitment period was subsequently extended. This decision was approved by members of the trial steering committee and each investigator. This change to extend recruitment was approved by the University of New South Wales human research ethics committee on April 4, 2019. At this point in the trial, 1259 participants had been randomized and 314 participants had completed 7-month follow-up. To account for a lost to follow-up rate of 15%, 1450 total participants (725 per group) were required to be randomized.

A noninferiority margin of 5% was chosen because it was considered acceptable from a clinical point of view.[16] In addition, the noninferiority margin was set at 5% per guidelines from the US Food and Drug Administration and the European Medicines Agency.[17,18] The trial investigators deemed the 5% noninferiority margin an effectiveness difference relevant for clinicians and policy makers when considering the shorter treatment duration of cytisine, the potentially enhanced safety profile, and lower cost. Additional information on the design and noninferiority margin justification appear in the eMethods in Supplement 3.

To estimate treatment effectiveness, 1-sided 97.5% CIs and credible intervals (CrIs) were used for the between-group difference in the proportion with continuous abstinence (verified by the carbon monoxide breath test). For the noninferiority analysis, a 1-sided level of .025 was used to determine statistical significance of the treatment effect in the frequentist analysis and a posterior probability $Pr\ (p_{cytisine} - p_{varenicline} > -0.05)$ greater than .975 to determine statistical significance in the bayesian analysis. The bayesian analysis was secondary to the main frequentist analysis and it allowed for direct calculation of the probability of noninferiority given the current trial data and consideration of prior information (ie, previously published data on both treatments).[1]

The primary effectiveness analysis was conducted with participants analyzed according to randomization groups. All randomized participants were included in the analysis set and were classified as still smoking unless self-reported continuous abstinence was verified by the carbon monoxide breath test. Sensitivity analyses were conducted in which alternative missing data assumptions were made and those with protocol violations were excluded. The bayesian analysis used 2 types of conjugate priors. For the primary analysis, an uninformative β prior was used that corresponded to the uniform distribution.

Secondary post hoc analyses were conducted using informative conjugate β priors based on available active comparator trial data.[1] The distributions for the informative priors appear in eTable 2 in Supplement 3 and were derived from the abstinence rates and sample sizes of previous varenicline trials (23.8%; combined sample size of 6171) and 1 cytisine trial (21.8%; n = 655).[1] Logistic regression was used to estimate the odds ratios for the treatment effect that were both unadjusted and adjusted for age, nicotine dependence, and recently diagnosed mental illness. These variables were identified a priori from the literature as potential factors that may influence smoking cessation. The self-reported secondary outcomes were assessed for superiority with 2-sided tests at the .05 level. Planned subgroup analyses were conducted for age (<40 years vs ≥40 years), sex (male vs female), nicotine dependence (low or medium vs high), and recently diagnosed mental illness within the last 12 months (yes vs no) as well as for treatment group × subgroup interactions.

A data and safety monitoring board provided oversight of adverse event data on a periodic basis. For the primary adverse event outcome, the proportion of reported adverse events occurring between treatment initiation and 7-month follow-up were compared between the treatment groups. The most

Table 1. Baseline Characteristics of the Participants

Characteristics[a]	Cytisine	Varenicline
No. of participants	725	727
Age, mean (SD), y	42.8 (13.1)	42.9 (12.3)
Sex, No. (%)		
Female	362 (49.9)	380 (52.3)
Male	363 (50.1)	347 (47.7)
Ethnicity, No. (%)[b]		
Aboriginal or Torres Strait Islander	37 (5.1)	33 (4.5)
Non-Aboriginal or non-Torres Strait Islander	683 (94.2)	689 (94.8)
Country of birth, No. (%)		
Australia	538 (74.2)	569 (78.3)
United Kingdom	55 (7.6)	44 (6.1)
New Zealand	31 (4.3)	24 (3.3)
All other countries	101 (13.9)	90 (12.4)
Highest level of education, No. (%)[c]		
No schooling	0	1 (0.1)
Primary school	157 (21.7)	144 (19.8)
High school	119 (16.4)	146 (20.1)
College	449 (61.9)	435 (59.8)
Age when first started smoking, mean (SD), y[d]	16.2 (3.8)	16.3 (4.0)
No. of cigarettes smoked, mean (SD), /d	18.3 (8.0)	17.7 (8.0)

[a] Additional baseline characteristics appear in eTable 3 in Supplement 3.

[b] Ethnicity was missing for 5 participants in each treatment group. Aboriginal or Torres Strait Islanders are indigenous Australians; all others are non-Aboriginal or non-Torres Strait Islander.

[c] Highest level of education was missing for 1 participant in the varenicline group.

[d] Includes any type of tobacco product.

frequent adverse events (occurrence of ≥5%) were presented by MedDRA term and compared between treatment groups. Pharyngitis and influenza were excluded because these are common ailments unlikely to be caused by use of the study medications. These exclusions were prespecified and align with the approach taken in an active comparator trial of cytisine.[8] All serious adverse events were presented by MedDRA term, event type, and treatment group. A post hoc analysis of adverse event occurrence between cytisine and varenicline also was conducted for participants reporting an adverse event start date within 28 days after the baseline interview.

The between-group difference for the rate of adverse events was modeled using negative binomial regression. The analysis of the adverse events was summarized using the incidence rate ratio (IRR) and 95% CI for the cytisine group compared with the varenicline group. This analysis was 2-sided and used a significance threshold of .05.

Most of the analyses were performed using Stata version 15 (StataCorp); however, the bayesian analysis was performed using R version 4.0.2 (R Foundation for Statistical Computing).

Results

The first trial participant was randomized on November 16, 2017, and the last on May 22, 2019. The final computer-assisted telephone follow-up interview was completed on January 31, 2020.

The sample consisted of 1452 participants (725 in the cytisine group and 727 in the varenicline group; Figure 1). The baseline characteristics were balanced across both treatment groups (mean [SD] age, 42.9 [12.7] years and 742 [51.5%] were women; **Table 1** and eTable 3 in Supplement 3). Quit line referrals were similar (76.6% for the cytisine group and 75.3% for the varenicline group). A total of 1108 participants (76.3%) completed the trial at 7-month follow-up and the retention rate was similar across both treatment groups (75.9% for the cytisine group and 76.8% for the varenicline group).

Primary Abstinence Outcome

The verified 6-month continuous abstinence rates were 11.7% for the cytisine group and 13.3% for the varenicline group (**Table 2**). This primary analysis did not confirm noninferiority of cytisine compared with varenicline at the 2.5% level of significance (risk difference, −1.62% [1-sided 97.5% CI, −5.02% to ∞]; $P = .03$ for noninferiority). The lower bound was −5.023% for the risk difference, which extended below the lower bound of −5.0% required for noninferiority.

The bayesian analysis supported this result (**Figure 2**). A risk difference of −1.6% (1-sided 97.5% CrI, −5.0% to 100%) and a probability of 97.4% for noninferiority was calculated based on a uniform prior. The post hoc informative priors analysis demonstrated a risk difference of −6.2% (1-sided 97.5% CrI, −8.3% to 100%) and a probability of 15.2% for noninferiority.

Sensitivity Analyses

The sensitivity analyses for the primary outcome showed a nonsignificant result when participants with missing smoking status were excluded (18.6% vs 21.5%; risk difference, −2.9% [1-sided 97.5% CI, −8.1% to ∞]; $P = .21$ for noninferiority) (Table 2 and eTable 4 in Supplement 3). In the sensitivity analysis in which participants were excluded if they reported use of a non-allocated medication (protocol deviation), noninferiority was established (12.0% vs 13.4%; risk difference, −1.4% [1-sided 97.5% CI, −4.9% to ∞]; $P = .02$ for noninferiority).

Table 2. Verified Abstinence and Self-reported Abstinence at Different Time Points[a]

Outcome[b]	No. (%)		Risk difference, % (1-sided 97.5% CI)	*P* value
	Cytisine	Varenicline		
No. of participants	725	727		
Primary outcome				
Verified 6-mo continuous abstinence at 7-mo follow-up	85 (11.7)	97 (13.3)	−1.62 (−5.02 to ∞)	.03[c]
Sensitivity analysis				
Missing or unconfirmed status, No./total (%)[d]	85/457 (18.6)	97/452 (21.5)	−2.9 (−8.1 to ∞)	.21[c]
Secondary outcomes				
Self-reported 6-mo continuous abstinence at 7-mo follow-up	102 (14.1)	133 (18.3)	−4.2 (−8.0 to −0.4)[e]	.03[f]
Self-reported 3-mo continuous abstinence at 4-mo follow-up	111 (15.3)	131 (18.0)	−2.7 (−6.5 to 1.1)[e]	.17[f]
7-d point prevalence for self-reported abstinence at 7-mo follow-up	137 (18.9)	168 (23.1)	−4.2 (−8.4 to 0.0)[e]	.05[f]
7-d point prevalence for self-reported abstinence at 4-mo follow-up	167 (23.0)	219 (30.1)	−7.1 (−11.6 to −2.6)[e]	.002[f]

[a] Abstinence was defined as not having smoked more than 5 cigarettes for the entire 6-month period preceding the 7-month follow-up, which was verified biochemically by an expired carbon monoxide level of 9 ppm or less.

[b] An assumption was made that all participants with missing data for smoking status were still smoking.

[c] Calculated using a 1-sided *Z* test for noninferiority at the significance level of .025.

[d] Did not self-report a status or did not complete a required carbon monoxide test and were excluded.

[e] Data are expressed as risk difference, % (2-sided 95% CI).

[f] Calculated using a 2-sided *Z* test for superiority at the significance level of .05.

Secondary Abstinence Outcomes

Cytisine was inferior regarding self-reported continuous abstinence at 7 months (14.1% vs 18.3% for the varenicline group; risk difference, −4.2% [2-sided 95% CI, −8.0% to −0.4%], *P* = .03; Table 2). Logistic regression analysis was used to estimate the intervention effect yielding the unadjusted odds ratio of 0.86 (95% CI, 0.63 to 1.18; *P* = .35) and the adjusted odds ratio of 0.89 (95% CI, 0.65 to 1.21; *P* = .45). Subgroup analyses found no significant differences for any of the prespecified subgroups (eTable 5 in Supplement 3). No significant differences in cigarette consumption per day at either the baseline visit or any of the follow-up visits were identified for cytisine vs varenicline (eTable 6 in Supplement 3).

In the post hoc analysis, the 7-day point prevalence for abstinence at the second check-in call was significantly higher in the cytisine group (42.5%; 308 of 725) than in the varenicline group (32.3%; 235 of 727) (risk difference, 10.2% [95% CI, 5.2%-15.1%]; *P* < .001).

Treatment Adherence

By the second check-in call, 88.8% (n = 644) of the cytisine group and 87.3% (n = 635) of the varenicline group had self-reported starting treatment. For participants in the cytisine group who had started taking the medication, a median number of 33 capsules (interquartile range, 23-45 capsules) had been taken by the first check-in call. For participants in the varenicline group who had started taking the medication, a median number of 13 tablets (interquartile range, 8-20 tablets) had been taken at the same time point. The expected number of doses taken by 2 weeks after randomization (assuming 4 days to start treatment from the delivery date) was 53 capsules for the cytisine group and 17 tablets for the varenicline group. At 4-month follow-up, the proportion of participants who reported discontinuing treatment because of an adverse event was lower in the cytisine group compared with the varenicline group (16.5% vs 34.3%, respectively; *P* < .001).

Adverse Event Outcomes

Self-reported adverse events for participants who reported any treatment use (ie, a single dose) occurred less frequently in the cytisine group (997 events reported by 482 participants) compared with the varenicline group (1206 events reported by 510 participants; **Table 3**) and the IRR was 0.88 (95% CI, 0.81-0.95; *P* = .002). The most frequently reported adverse events (abnormal dreams and nausea) were less commonly reported by participants in the cytisine group.

The severity of all adverse events was comparable. One participant in the varenicline group, who had a history of mental illness, attempted suicide approximately 1 month after starting varenicline. This participant was taking varenicline in the days up to this serious adverse event, was hospitalized following the event, and was subsequently discharged with appropriate management. There was no significant between-group difference in the occurrence of serious adverse events for the cytisine group (n = 17) and the varenicline (n = 32) group (Table 3 and eTable 7 in Supplement 3) and the IRR was 0.97 (95% CI, 0.55-1.73, *P* = .92).

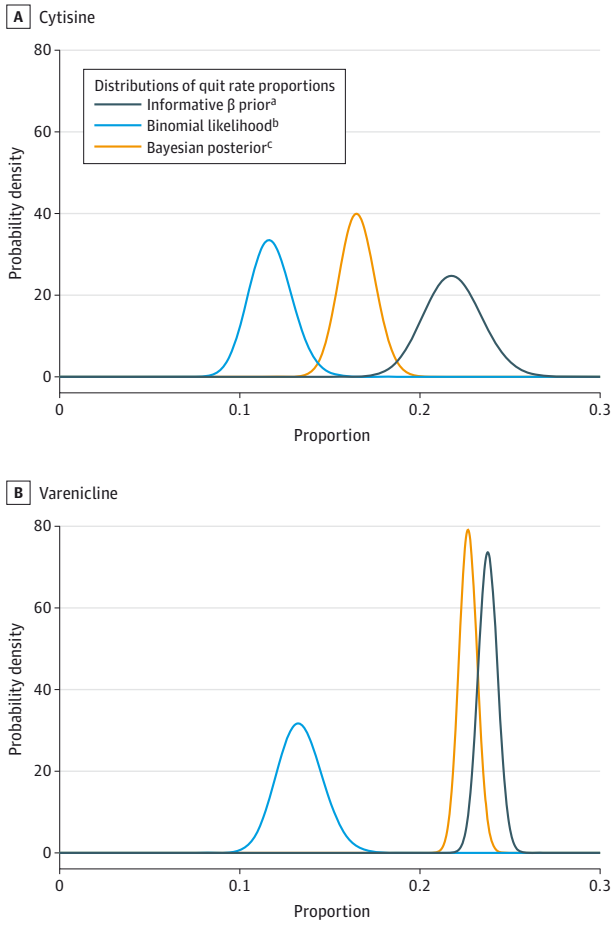
The post hoc analysis of adverse events occurring within the first 28 days showed that there were fewer adverse events in the cytisine group (733 events reported by 419 participants) compared with the varenicline group (913 events reported by 452 participants) and the IRR was 0.87 (95% CI, 0.79-0.95; *P* = .004)

Discussion

This RCT failed to demonstrate that cytisine at standard dosing and treatment length was noninferior to varenicline for smoking cessation. The risk difference was −1.6% (in favor of varenicline) and the lower bound of the 1-sided 97.5% CI was −5.023%, which exceeded the 5% predefined noninferiority margin.

jamanetwork/2021/jama/06jul2021/joi210053 PAGE: right 6 SESS: 43 OUTPUT: Jun 15 17:11 2021

Figure 2. Distributions of Quit Rates for Cytisine and Varenicline



Each curve represents the frequency distribution for the corresponding quit rate proportion and is centered at the expected value of the quit rate. The taller and narrower the distribution, the less uncertainty there is around the quit rate. For cytisine, the posterior distribution is located around halfway between the prior and likelihood distributions because of available data from only 1 previous trial with a similar sample size as the current trial. For varenicline, the posterior distribution is located closer to the prior distribution because of available data from previous trials that generated a larger combined sample size.

[a] The prior distribution incorporates data from the previous trials.

[b] The likelihood distribution is based only on the observed quit rate from the current trial.

[c] The posterior distribution is the combination of the prior and likelihood distributions under a bayesian framework (see Methods for details).

Table 3. Adverse Events and Serious Adverse Events Among Those Who Reported Taking at Least a Single Dose[a]

	No. (%)	
	Cytisine	Varenicline
No. of participants[b]	675	663
Adverse events		
Participants with any	482 (71.4)	510 (76.9)
Total No. of events	997	1206
Severity		
Severe	30 (3.0)	35 (2.9)
Moderate	255 (25.6)	309 (25.6)
Mild	712 (71.4)	862 (71.5)
Most frequent (≥5% of all events)		
Abnormal dreams	120 (16.6)	185 (25.4)
Nausea	79 (10.9)	198 (27.2)
Sleep disturbance	135 (18.6)	137 (18.8)
Headache	67 (9.2)	59 (8.1)
Serious adverse events		
Participants with any	17 (2.5)	32 (5.0)
Total No. of events[c]	17	33
Died	0	1 (<1.0)
Life-threatening	0	1 (<1.0)[d]
Required hospitalization	16 (2.4)	31 (4.7)
Medically important	1 (<1.0)	0

[a] Nasopharyngitis and influenza were excluded.

[b] Among those who reported taking at least a single dose.

[c] Of the 50 events, 2 occurred in the same person.

[d] Was possibly related to the study medication.

A post hoc bayesian analysis that incorporated previous trial data found a probability of 15% for cytisine being noninferior to varenicline. A per-protocol analysis excluding those who had taken nonallocated study medication demonstrated noninferiority. This finding, however, is likely an artifact of treatment crossover with a higher number of participants in the cytisine group (n = 35) taking varenicline (an approved and accessible medication in Australia) compared with those in the varenicline group (n = 3) taking cytisine.

The number of participants lost to follow-up was higher than anticipated, although retention was balanced across treatment groups (76.3% overall). Biochemically verified continuous abstinence outcomes in this trial were low for both groups (11.7% in the cytisine group vs 13.3% in the varenicline group) but were comparable with other trials providing minimal behavioral support.[19]

A possible reason why noninferiority was not achieved in the current trial is that the standard dosing and treatment length for cytisine may not be optimal. Closer scrutiny of phase 2 varenicline studies provided some insights into how optimal dosing was established and transitioned through phase 3 and 4 studies.[1,20] The same level of investment in research and development has not occurred for cytisine because the majority of trials have been publicly funded.[4] There is now some private research investment in cytisine following the commercialization and patent of cytisinicline succinate salt as a new drug product,[21] but market competition and the costs of drug development will be challenges as generic varenicline becomes more widely available.

Cytisine was well tolerated in this trial and had significantly fewer adverse events compared with varenicline and significantly fewer cases of treatment discontinuation for adverse events. Abnormal dreams and nausea were more commonly reported by those allocated to the varenicline group, which is a finding supported by the Cochrane review of nicotine receptor partial agonists for smoking cessation.[1] Cytisine has been found to have a lower binding affinity to 5-HT_{3A} receptors than varenicline (activation of 5-HT_{3A} is associated with nausea).[22]

This finding may partially explain why study participants were less likely to report nausea in association with cytisine.

Two previous pragmatic, active comparator, noninferiority trials of cytisine have been reported from New Zealand.[8,23] The first of these trials compared cytisine (25 days) vs nicotine replacement therapy (8 weeks) among quit line enrollees and demonstrated effectiveness of cytisine for self-reported continuous smoking abstinence at 1 week, 1 month (primary outcome), and at 2-month and 6-month follow-up (22% for cytisine vs 15% for nicotine replacement therapy at 6-month follow-up).[8] The second trial (cytisine vs varenicline) used a noninferiority margin of 10% and had carbon monoxide-verified 6-month abstinence rates (imputation was used for missing data) of 12.1% for cytisine and 7.9% for varenicline (risk difference, 4.29 [95% CI, −0.22 to 8.79]; $P = .17$).[23] Consistent findings were identified for the sensitivity analysis of the primary outcome and across various time points (3, 6, and 12 months) for both measures (continuous and point prevalence) of smoking abstinence.[23]

Methodological differences may be relevant to the interpretation of this trial and previous trials.[8,23] For example, a lower proportion of participants in this trial identified as indigenous. The perception of cytisine as a "natural product" may appeal to some indigenous groups.[24] Second, for the only other active comparator trial vs varenicline, the cytisine treatment regimen differed compared with the current trial (25 days vs 12 weeks).[23] The post hoc analysis of self-reported 7-day point prevalence at 28 days in the current trial suggests that quit rates at this time point may be higher for cytisine compared with varenicline; however, further study of extended cytisine dosing with verified continuous abstinence outcomes is warranted.

Limitations

This study has several limitations. First, this trial used minimal behavioral support and participants were offered quit line referral. Telephone counseling is known to be an effective treatment,[25] but previous studies have found low use and acceptance of quit line support among Australian smokers.[26,27]

Second, quit line staff knowledge and skill in supporting people taking cytisine or varenicline was not measured despite the study team providing quit line staff with training about the trial medications. Because cytisine is a novel medication, and currently not available in Australia, quit line staff may have been less knowledgeable and comfortable providing advice about cytisine than varenicline. Nonetheless, the standard quit line support that was provided reflects a routine clinical practice setting.

Third, this study was open label. Even though the design could have included placebo in both groups to standardize the dosage regimen, this would have added significant cost and complexity to the trial. Fourth, smoking cessation was only verified via the carbon monoxide breath test for the primary continuous abstinence outcome. Carbon monoxide testing typically identifies recent smoking (ie, within 24 hours of last cigarette) and cotinine measurement can identify smoking exposure for a longer time frame.

Fifth, even though both treatments were provided as per standard dosing, they do differ in treatment duration and this should be considered when interpreting adverse events. Sixth, cytisine was compared with varenicline in this trial but not with other smoking cessation therapies. In previous trials, cytisine was found to be more effective for smoking cessation than nicotine replacement therapy.[8]

Conclusions

Among daily smokers willing to quit, cytisine treatment for 25 days, compared with varenicline treatment for 84 days, failed to demonstrate noninferiority regarding smoking cessation.

ARTICLE INFORMATION

Accepted for Publication: April 28, 2021.

Author Affiliations: National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia (Courtney, McRobbie, Shakeshaft, Talukder, Macdonald, Mattick, Boland, Farrell); Department of Experimental and Clinical Pharmacology, University of Rzeszow, Rzeszow, Poland (Tutka); School of Medicine and Public Health, University of Newcastle, Newcastle, Australia (Weaver, Paul); Centre for Health Economics, Monash Business School, Monash University, Clayton, Australia (Petrie); No affiliation (Mendelsohn); Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia (Thomas); St George and Sutherland Clinical School, University of New South Wales, Sydney, Australia (Kwan); National Institute for Health Innovation, School of Population Health, University of Auckland, Auckland, New Zealand (Walker); School of Public Health, University of Queensland, Herston, Australia (Gartner); Tasmanian School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, Australia (Ferguson); Faculty of Health Sciences and Medicine, Bond University, Robina, Australia (Zwar); School of Population Health, University of New South Wales, Sydney, Australia (Richmond); Cluster for Resilience and Wellbeing, Appleton Institute, Central Queensland University, Brisbane, Australia (Doran); National Centre for Youth Substance Use Research, University of Queensland, Herston, Australia (Hall); Department of Behavioural Science and Health, University College London, London, England (West).

Author Contributions: Drs Courtney and Farrell had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Courtney, McRobbie, Tutka, Petrie, Shakeshaft, Thomas, Walker, Gartner, Mattick, Paul, Ferguson, Zwar, Richmond, Doran, Boland, Hall, West, Farrell.
Acquisition, analysis, or interpretation of data: Courtney, McRobbie, Weaver, Petrie, Mendelsohn, Shakeshaft, Talukder, Macdonald, Thomas, Kwan, Walker, Paul, Ferguson, Doran, Farrell.
Drafting of the manuscript: Courtney, McRobbie, Tutka, Petrie, Kwan, Walker, Ferguson, Doran, Farrell.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Courtney, Weaver, Petrie.
Obtained funding: Courtney, McRobbie, Petrie, Shakeshaft, Walker, Gartner, Mattick, Paul, Ferguson, Richmond, Doran, Farrell.
Administrative, technical, or material support: Courtney, McRobbie, Shakeshaft, Talukder, Macdonald, Thomas, Kwan, Mattick, Ferguson, Richmond, Boland, Farrell.
Supervision: Courtney, McRobbie, Tutka, Thomas, Kwan, Mattick, Paul, Ferguson, Richmond, Boland, Farrell.

Conflict of Interest Disclosures: Dr McRobbie reported receiving honoraria from Pfizer for speaking at smoking cessation meetings and attending advisory board meetings. Drs McRobbie and Walker reported previously receiving cytisine from Sopharma for the conduct of a noninferiority trial of cytisine vs nicotine replacement therapy. Dr Tutka reported serving as consultant to Aflofarm, which is a manufacturer of cytisine. Dr Mendelsohn reported receiving funding from Pfizer Australia, GlaxoSmithKline, and Johnson & Johnson Pacific for teaching, consulting, serving on an advisory board, and conference expenses. Dr Kwan reported receiving speaking fees from Pfizer. Dr Walker reported receiving cytisine from Achieve Life Sciences for the conduct of

a noninferiority trial of cytisine (Tabex) vs varenicline; receiving investigator-initiated grants and smoking cessation medication (varenicline) and matching placebo from Pfizer for the conduct of a relapse prevention trial in patients with chronic obstructive pulmonary disease who smoke; and serving as a consultant for and receiving honoraria and travel support for speaking at research meetings from Achieve Life Sciences and Pfizer (manufacturers of smoking cessation medications). Dr Gartner reported receiving grants from the Australian Research Council, Metro South Health Service, Central Queensland Hospital and Health Service, Arthritis Australia, and the HIV Foundation Queensland. Dr Ferguson reported previously serving as a consultant to Pfizer and GlaxoSmithKline Consumer Healthcare on matters relating to smoking cessation and harm minimization; having been a member of a scientific advisory board for Johnson & Johnson; receiving researcher-initiated project grant funding from Pfizer (through the Grand initiative); and having provided consulting services to JUUL Labs Inc while working as a consultant for Pinney Associates. Dr Zwar reported receiving honoraria from Pfizer and GlaxoSmithKline for advice on smoking cessation education programs and for conference expenses. Dr West reported serving as a consultant to Pfizer, which manufactures varenicline, and receiving grants from Pfizer. Dr Farrell reported receiving unrestricted research funding from Mundipharma, Seqirus, and Indivior. No other disclosures were reported.

Funding/Support: This research was funded by project grant 1108318 and career development fellowship grant 1148497 (awarded to Dr Courtney) from the Australian National Health and Medical Research Council. The University of New South Wales National Drug and Alcohol Research Centre is supported by grant funding from the Australian government under the Substance Misuse Prevention and Service Improvements Fund. All study medications were purchased by the research team.

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank the study participants, the individuals at the social research center who conducted the baseline and follow-up interviews, the individuals at the Chemist Warehouse pharmacy for storing and dispensing medications (central pharmacy), Josephine Pang, MBBS (compensated study physician), staff at the University of New South Wales trial coordinating center, and the uncompensated data and safety monitoring board members (Julia Lappin, PhD, Jason Grebely, PhD, and Kathy Petoumenos, PhD [all 3 with the University of New South Wales], and Daniel Barker, PhD [University of Newcastle]). We also thank Mohammad Siahpush, PhD (University of Nebraska Medical Center), for uncompensated contributions to the overall trial and for input on the statistical analysis plan, and Alan Melrose, LLB (University of New South Wales), for uncompensated support with other trial-related inquiries.

REFERENCES

1. Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;5(5):CD006103.

2. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation. *Cochrane Database Syst Rev*. 2013;5(5):CD009329.

3. Drovandi AD, Chen CC, Glass BD. Adverse effects cause varenicline discontinuation: a meta-analysis. *Curr Drug Saf*. 2016;11(1):78-85.

4. Tutka P, Vinnikov D, Courtney RJ, Benowitz NL. Cytisine for nicotine addiction treatment. *Addiction*. 2019;114(11):1951-1969.

5. Karnieg T, Wang X. Cytisine for smoking cessation. *CMAJ*. 2018;190(19):E596.

6. Scharfenberg G, Benndorf S, Kempe G. Cytisine (Tabex) as a pharmaceutical aid in stopping smoking. Published in German. *Dtsch Gesundheitswesen*. 1971;26(10):463-465.

7. Vinnikov D, Brimkulov N, Burjubaeva A. A double-blind, randomised, placebo-controlled trial of cytisine for smoking cessation in medium-dependent workers. *J Smok Cessat*. 2008;3(1):57-62. doi:10.1375/jsc.3.1.57

8. Walker N, Howe C, Glover M, et al. Cytisine versus nicotine for smoking cessation. *N Engl J Med*. 2014;371(25):2353-2362.

9. West R, Zatonski W, Cedzynska M, et al. Placebo-controlled trial of cytisine for smoking cessation. *N Engl J Med*. 2011;365(13):1193-1200.

10. Leaviss J, Sullivan W, Ren S, et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? a systematic review and economic evaluation. *Health Technol Assess*. 2014;18(33):1-120.

11. Thomas D, Farrell M, McRobbie H, et al. The effectiveness, safety and cost-effectiveness of cytisine versus varenicline for smoking cessation in an Australian population. *Addiction*. 2019;114(5):923-933.

12. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials. *Addiction*. 2005;100(3):299-303.

13. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. 2002;4(2):149-159.

14. Brose LS, West R, Stapleton JA. Comparison of the effectiveness of varenicline and combination nicotine replacement therapy for smoking cessation in clinical practice. *Mayo Clin Proc*. 2013;88(3):226-233.

15. Biazzo LL, Froshaug DB, Harwell TS, et al. Characteristics and abstinence outcomes among tobacco quitline enrollees using varenicline or nicotine replacement therapy. *Nicotine Tob Res*. 2010;12(6):567-573.

16. Mulla SM, Scott IA, Jackevicius CA, et al. How to use a noninferiority trial: Users' Guides to the Medical Literature. *JAMA*. 2012;308(24):2605-2611.

17. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on the choice of the non-inferiority margin. Published July 27, 2005. Accessed May 26, 2021. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf

18. US Food and Drug Administration. Non-inferiority clinical trials to establish effectiveness; guidance for industry; availability. *Fed Regist*. 2016;81(216):78605-78606.

19. Yingst JM, Veldheer S, Hrabovsky S, et al. Pilot randomized trial of an automated smoking cessation intervention via mobile phone text messages as an adjunct to varenicline in primary care. *J Health Commun*. 2018;23(4):370-378.

20. Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist. *Arch Intern Med*. 2006;166(15):1561-1568.

21. Achieve Life Sciences. Achieve announces patent granted in the US for novel formulation of cytisinicline. Accessed December 15, 2020. https://achievelifesciences.com/2019/05/30/achieve-announces-patent-granted/

22. Clarke A, Price KL, Lummis S. Cytisine's lower potency at 5-HT3 receptors may explain its lower incidence of nausea and vomiting than varenicline. Presented at: Society for Research on Nicotine and Tobacco; September 17-18, 2020; European online conference.

23. Walker N, Smith B, Barnes J, et al. Cytisine versus varenicline for smoking cessation in New Zealand indigenous Māori: a randomized controlled trial. Published online March 24, 2021. *Addiction*. doi:10.1111/add.15489

24. Thompson-Evans TP, Glover MP, Walker N. Cytisine's potential to be used as a traditional healing method to help indigenous people stop smoking: a qualitative study with Māori. *Nicotine Tob Res*. 2011;13(5):353-360.

25. Matkin W, Ordóñez-Mena JM, Hartmann-Boyce J. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019;5:CD002850.

26. Boland VC, Mattick RP, McRobbie H, et al. "I'm not strong enough; I'm not good enough. I can't do this, I'm failing. *Int J Equity Health*. 2017;16(1):196.

27. Clare P, Slade T, Courtney RJ, et al. Use of smoking cessation and quit support services by socioeconomic status over 10 years of the national drug strategy household survey. *Nicotine Tob Res*. 2014;16(12):1647-1655.