







Cytisine versus varenicline for smoking cessation in New Zealand indigenous Māori: a randomized controlled trial

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ABSTRACT

Aim To determine whether cytisine was at least as effective as varenicline in supporting smoking abstinence for ≥ 6 months in New Zealand indigenous Māori or *whānau* (extended-family) of Māori, given the high smoking prevalence in this population. **Design** Pragmatic, open-label, randomized, community-based non-inferiority trial. **Setting** Bay of Plenty, Tokoroa and Lakes District Health Board regions of New Zealand. **Participants** Adult daily smokers who identified as Māori or *whānau* of Māori, were motivated to quit in the next 2 weeks, were aged ≥ 18 years and were eligible for subsidized varenicline. Recruitment used multi-media advertising. **Interventions** A total of 679 people were randomly assigned (1 : 1) to receive a prescription for 12 weeks of cytisine or varenicline, plus low-intensity cessation behavioural support from the prescribing doctor and community stop-smoking services or a research assistant. Day 5 of treatment was the designated quit date. **Measurements** The primary outcome was carbon monoxide-verified continuous abstinence at 6 months, analysed as intention-to-treat (with multiple imputation for missing data). Secondary outcomes measured at 1, 3, 6 and 12 months post-quit date included: self-reported continuous abstinence, 7-day point prevalence abstinence, cigarettes per day, time to (re)lapse, adverse events, treatment adherence/compliance and acceptability, nicotine withdrawal/urge to smoke and health-care utilization/health-related quality of life. **Findings** Verified continuous abstinence rates at 6 months post-quit date were 12.1% (41 of 337) for cytisine versus 7.9% (27 of 342) for varenicline [risk difference 4.29%, 95% confidence interval (CI) = -0.22 to 8.79; relative risk 1.55; 95% CI = 0.97–2.46]. Sensitivity analyses confirmed that the findings were robust. Self-reported adverse events over 6 months occurred significantly more frequently in the varenicline group (cytisine: 313 events in 111 participants; varenicline: 509 events in 138 participants, incidence rate ratio 0.56, 95% CI = 0.49–0.65, $P < 0.001$) compared with the cytisine group. Common adverse events were headache, nausea and difficulty sleeping. **Conclusion** A randomized controlled trial found that cytisine was at least as effective as varenicline at supporting smoking abstinence in New Zealand indigenous Māori or *whānau* (extended-family) of Māori, with significantly fewer adverse events.

Keywords Cytisine, indigenous, non-inferiority, smoking, trial, varenicline.

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INTRODUCTION

Combination nicotine replacement therapy (NRT) and varenicline are currently the most effective smoking cessation medications available, and are approved for use by many of the world's regulatory authorities [including the European Medicines Agency (EMA), the UK Medicines

and Healthcare Products Regulatory Agency (MHPR) and the US Food and Drug Administration (FDA)]. A less well-known medication is cytisine, a plant-based alkaloid which was first authorized for use as a smoking cessation medication in Bulgaria in 1964 [1]. Cytisine is currently available over-the-counter and/or on prescription as a smoking cessation treatment in 18 central/eastern

European countries, but does not have regulatory approval for use in the United Kingdom, western Europe, the United States or countries that follow the regulatory approval processes of these nations [for example, New Zealand (NZ)] [2]. However, cytisine has been sold in Canada as an over-the-counter herbal product for smoking cessation since 2017 [1].

Like varenicline, cytisine is structurally similar to nicotine and acts as a partial agonist at nicotinic acetylcholine receptors [1,3], although the two medications have different half-lives (cytisine: 4.8 hours [4]; varenicline: 17 hours [5]) and dosing regimens. Cytisine has been found in clinical trials to be superior to both placebo [1,6–9] and nicotine replacement therapy (NRT) [10] at supporting smoking abstinence, with mild and self-limiting adverse events reported [1,6–10]. No trials have yet been published directly comparing cytisine with varenicline, despite observed effect sizes in a trial comparing cytisine to NRT [10] being similar to those in a trial comparing varenicline to NRT [11]. A major advantage of cytisine over varenicline is the current large price difference between the two drugs in markets where currently approved [12], the much lower cost per quality-adjusted life-years for cytisine [13] and modelling suggesting that cytisine may be considerably more cost-effective than varenicline [14,15]. Furthermore, as a natural product, cytisine may be appealing to certain populations, e.g. indigenous people who smoke [16].

We aimed to investigate whether cytisine was at least as effective as varenicline in supporting smoking cessation among the indigenous Māori people of NZ [17], who comprise 16.5% of the NZ population [18]. In 2018/19 Māori had a high prevalence of daily smoking (30.9%) compared with the general population (12.5%) [19]. NZ smoking cessation trials indicate that Māori are just as likely to quit smoking as non-Māori [10,20]. We hypothesized that 12 weeks of cytisine plus low-intensity behavioural support (BHS) would be at least as effective as 12 weeks of varenicline plus low-intensity BHS for smoking cessation at 6 months post-quit date.

METHODS

Study design

We undertook a parallel-group, randomized, controlled, pragmatic non-inferiority trial. A pragmatic design was chosen to ensure that the study findings were as generalizable as possible, reflecting real-world access to varenicline (and probably cytisine, if it receives marketing approval in NZ). The trial was conducted and monitored according to good clinical practice guidelines and is reported with fidelity to the final version of the protocol and statistical analysis plan. An earlier version of the protocol has been published [17]. Key differences between the published

protocol and the final protocol relate to expansion of the recruitment region and use of multiple imputation analysis to account for missing data. The protocol was approved by the NZ Multi-Region Ethics Committee and the HRC Standing Committee on Therapeutic Trials (SCOTT), which assesses trials of new medicines that require approval under Section 30 of the Medicines Act 1981. The trial was undertaken in the Lakes District Health Board region of NZ, then expanded to the Bay of Plenty and Tokoroa regions.

Participants

Participants were recruited via multi-media advertising and promotion by community-based smoking cessation services and health professionals. Advertisements directed potential participants to register via the study website (and be called back by a researcher) or to call/text a researcher directly. Registered participants were provided with further trial information and assessed for eligibility. All participants provided verbal consent. Inclusion criteria were: self-identified as Māori or *whānau* of Māori (including people who are not themselves Māori by *whakapapa* (genealogy) but live in a Māori *whānau*, such as in a household by marriage); aged ≥ 18 years; smoked tobacco daily; motivated to quit in the next 2 weeks; eligible for government-subsidized varenicline via the special authority process; able to provide verbal consent; and had daily access to a mobile phone/internet. Exclusion criteria were: pregnant/breastfeeding; currently using smoking cessation medication (including e-cigarettes); enrolled in another cessation programme/study; had used varenicline or cytisine in the previous 12 months; had a known hypersensitivity to cytisine or varenicline; self-reported moderate/severe renal impairment; treatment for active/latent tuberculosis; experienced a heart attack, stroke or severe angina within the previous 2 weeks; uncontrolled high blood pressure (> 150 mmHg systolic, > 100 mmHg diastolic); and/or a history of seizures.

Randomization/masking

Eligible participants were randomly allocated (1 : 1) to receive a prescription for a 12-week course of cytisine (Tabex[®]) or varenicline (Champix[®]). Block randomization was undertaken, with varying block sizes. The randomization sequence was prepared by the trial statistician using R and loaded into the REDCap database, which was then accessed by the study doctor via a computer at the point of randomization. The trial was open-label, as participants and researchers collecting outcome data were not masked to treatment allocation. Although a double-blind trial would have been ideal, participants were not blinded given the different dosing regimens for the medications and their different appearance. Two of the six lead investigators

(M.V., S.P.) were blinded to treatment allocation until after data lock and analysis. Three lead investigators (N.W., C.B., J.B.) were unblinded when assessing and assigning causality for serious adverse events, and the trial statistician was required to create unblinded reports for the trial Data Safety Monitoring Committee (DSMC).

Procedures

Participants were advised to visit their preferred community pharmacy for dispensing of their allocated medicine. Prescriptions were uploaded by the study doctor to a secure website for pharmacists to access. In line with current access to varenicline in NZ, pharmacists dispensed allocated treatment in three allotments over 8 weeks. Access to study medications was free for participants.

To ensure comparability, both groups were asked to reduce their smoking as much or as often as necessary or desired over the first 4 days of treatment so that they were smoke-free by day 5 ('quit date'), and to follow the dosing regimen for their allocated product. The quit date at day 5 was the same for both medications and was in line with standard instructions for use of cytisine (note: in NZ, packet instructions for varenicline suggest that users adopt a flexible quit date between 8 and 35 days, and do not explicitly promote a cut-down to quit process). The two study treatments have very different dosing regimens. For cytisine, the standard 25-day dosing regimen was followed: days 1–3: one tablet (1.5 mg) every 2 hours through the waking day (six tablets/day); days 4–12: one tablet every 2.5 hours (five tablets/day); days 13–16: one tablet every 3 hours (four tablets/day); days 17–20: one tablet every 4–5 hours (three tablets/day); and days 21–25: one tablet every 6 hours (two tablets/day). A maintenance dose of cystine was added for day 26 to week 12 (one tablet every 6 hours: two tablets/day) to match the treatment duration of varenicline. This choice was supported by repeat-dose pharmacokinetic data and modelling provided by Achieve Life Sciences, demonstrating adequate steady-state plasma concentrations of cytisine during the maintenance period. For varenicline, the dosing regimen was according to the approved recommendations for Champix: days 1–3: one tablet (0.5 mg) per day; days 4–7: one tablet (0.5 mg) twice a day; and day 8–week 12: one tablet (1.0 mg) twice a day. A full prescription consisted of 219 tablets for cytisine and 165 tablets for varenicline.

Participants were offered smoking cessation BHS, to replicate support available in NZ when cessation medications are prescribed by a medical doctor; namely: (1) brief advice delivered by the study doctor immediately after writing the prescription (post-randomization) and (2) referral to community-based cessation services for additional free BHS (delivered through telephone, text, face-to-face, or group counselling). If participants refused referral, they

were offered 6 weeks of BHS telephone calls (one call per week, 10–15 minutes per call) delivered by the trial research assistants. This support encouraged positive engagement to ensure that participation in the study aligned with their *tūmanako* (aspirations).

The majority of outcome data were collected by telephone interview at baseline, then 1, 3 and 6 months (and 12 months in an early cohort of participants) post-quit date. Adverse event (AE) data were collected via self-report at each follow-up call, via a prompted participant-completed web-based AE diary, and/or reported by community pharmacists, general practitioners and/or community-based smoking cessation providers. Verification of smoking abstinence at 6 and 12 months post-quit was undertaken face-to-face at a site convenient to the participant.

Outcomes

Baseline data included age, gender, *iwi* (tribe), connectedness to *iwi* and education (as a proxy for socio-economic status). Residential address was also used to determine neighbourhood socio-economic status based on the NZ Index of Multiple Deprivation (NZDep) [21]. Other baseline data included: smoking history; cigarette dependence [Fagerström Test of Cigarette Dependence (FTCD); score between 1 and 10, with scores > 5 indicating high cigarette dependence and ≤ 5 indicating low dependence] [22,23]; tobacco withdrawal symptoms and urge to smoke [mood and physical symptoms scale (MPSS) for seven symptoms: 1 = not at all, 5 = extremely, with a total score of 5–25, urge to smoke scored 0–10: the higher the score the greater the urge] [24]; motivation to quit (1 = very low, 5 = very high); alcohol use [Alcohol Use Disorders Identification Test (AUDIT-C), scale of 0–12, the higher the score the greater the risk of alcohol dependence] [25]; and health-related quality of life using the EQ-5D instrument (<https://euroqol.org/>); health-care utilization [26]; and concomitant medication.

The primary outcome was continuous smoking abstinence 6 months post-quit (self-reported abstinence since quit date, allowing ≤ 5 cigarettes in total but none in the last week [27]), analysed as intention-to-treat (ITT) (with multiple imputation for missing data). Abstinence was verified by a researcher or community-based cessation provider, using standardized exhaled carbon monoxide (CO) measurement with a Bedfont Smokerlyzer (Bedfont Scientific Ltd, Kent, UK), with a reading of ≤ 9 parts per million (p.p.m.) signifying abstinence [27,28].

Secondary outcomes included: self-reported treatment adherence (picking up their prescription from the pharmacy) and treatment compliance (taking their assigned medication); tobacco withdrawal symptoms and urge [24]; self-reported continuous abstinence; 7-day point

prevalence abstinence (no cigarettes, not a single puff, in the previous 7 days) [27]; time to first cigarette smoked from the quit date, even a single puff (lapse); time to first relapse (time to smoking more than five cigarettes a day for 3 or more days in a row); number of cigarettes smoked per day; product acceptability at end of treatment; other cessation support used during the trial; concomitant medication; health-related quality of life (3 and 6 months); and health-care utilization [26]. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Serious AEs (SAEs) were classified by three authors and the study doctor as non-serious or serious (death, life-threatening, hospitalization, persistent or sustained disability/incapacity, congenital abnormality/birth defect, significant medical event). Likelihood of causality was assessed using the World Health Organization (WHO) Standardized Case Causality Assessment Tool (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable) [29].

Statistical analysis

A planned sample size of 2140 people (1070 per group) assumed 28% loss to follow-up [10] and 90% power at the one-sided significance level of 2.5% to detect a non-inferiority margin of 10% between the two groups at 6 months. The 6 month quit rate was estimated to be 22% in the cytosine group, based on data from a national NZ Quitline trial ($n = 1310$) [10]. A 6-month quit rate of 28% was reported in a varenicline trial ($n = 714$) undertaken in participants with stable cardiovascular disease [30]; however, we chose to be more conservative, and assumed a 25% quit rate given the pragmatic community-based nature of our trial.

Analyses using SAS version 9.4 followed a pre-specified plan, and the trial had an independent DSMC. Non-inferiority for the primary outcome was evaluated by observing whether the lower bound of the two-sided 95% confidence intervals (CI) for risk difference in quit rates between the groups was above the non-inferiority limit of minus 10. This margin of error was chosen as it was the smallest value that is clinically relevant [31]. If non-inferiority was evident, we planned assessment as to whether cytosine had superior effectiveness to varenicline, using the same approach but comparing to a zero difference. The primary analyses were carried out on ITT basis, with multiple imputation analysis performed to account for missing data using the fully conditional specification logistic regression method (data were assumed to be missing at random). Fifty multiple imputed data sets were created, and the imputation model included baseline age, sex, NZDep [21] and treatment group. The imputed data sets were analysed using log-binomial regression and combined

to output one inference. Quit rates, relative risk and risk difference were calculated.

To check robustness of the results various sensitivity analyses were performed. Analyses addressing the impact of different limits for CO measurements (i.e. at ≤ 3 , ≤ 5 and ≤ 8 p.p.m.) were undertaken. Groups were compared using χ^2 tests for the following analyses: complete case analysis, assuming that participants with missing smoking status data were smokers, and per-protocol analysis excluded participants with major protocol violations (e.g. death, pregnancy, withdrawals, loss to follow-up, non-adherence, non-compliance). Self-reported adherence was defined as having collected all 12 weeks' study medication from a pharmacy. Self-reported medication compliance was defined as having collected all 12 weeks' study medication from a pharmacy and taken most or all of their tablets. A second measure of medication compliance was defined as having taken $\geq 80\%$ of study medication 3 months post-quit date.

In pre-specified subgroup analyses, the consistency of effects was assessed in the primary outcome for age ($< 40/\geq 40$ years), sex and education (< 12 years of schooling or no qualification/ ≥ 12 years of schooling), type of cigarettes smoked (factory-made only/roll-your-own only/both), extent of cigarette dependence (Fagerström score: low, high) and AUDIT-C score (low/high: high = AUDIT-C score ≥ 4 for men and ≥ 3 for women), using tests for heterogeneity. We assessed change from baseline in symptoms of tobacco withdrawal symptoms (for abstainers) and number of cigarettes per day (for smokers) over time using 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 smoking relapse (time to first lapse and relapse from quit date) in those with data available.

Role of the funding source

This research was supported by a contract from the Health Research Council of NZ. The funder had no role in development of the study design, data collection, analysis and interpretation or writing of the publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Indigenous data sovereignty is managed by the RAUORA Māori (*Kaitiaki*) governance group, with support from members of the NIHI Māori Research Advisory Committee. Requests for access to the data or study documents will be considered by these groups where the proposed use aligns with public good purposes, does not conflict with other

requests or planned use by the study authors, and the requestor is willing to sign a data access agreement. Contact is through the corresponding author.

RESULTS

The first randomization occurred on 18 September 2017, and the last follow-up occurred on 10 October 2019. Of 1105 people assessed, 679 were eligible and randomized, 337 in the cytisine group and 342 in the varenicline group (Fig. 1). This sample size was less than planned: we

experienced delays in obtaining ethics and regulatory approvals and recruitment was slower than anticipated, so recruitment could not continue without additional resources.

Twenty-three participants were excluded from the trial because they did not want to use varenicline, but no one was excluded because they did not want to use cytisine. Nine participants allocated varenicline withdrew from the study immediately after being randomized or by the first behavioural support call, compared to zero participants allocated cytisine. Differential withdrawal was still evident by 6 months: 31 (9%) participants in the cytisine group

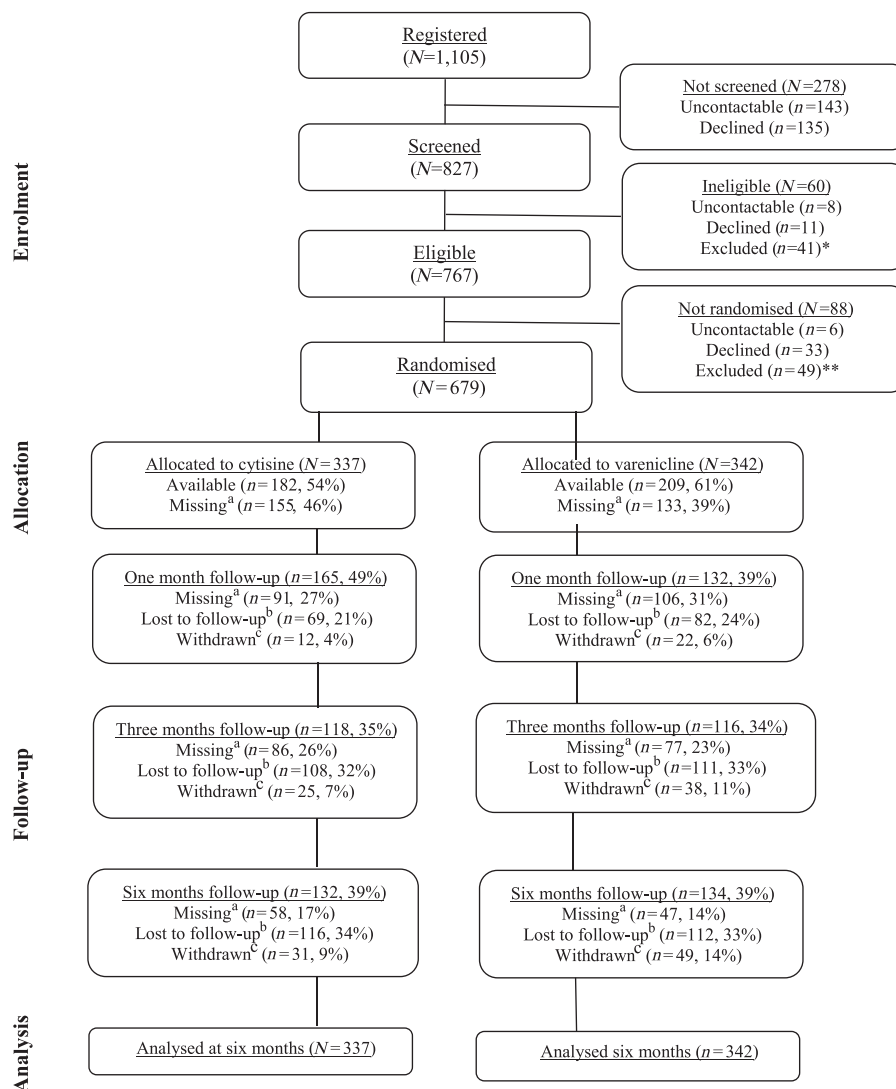


Figure 1 Trial profile: *not eligible for varenicline under special authority ($n = 13$), high risk/history of epilepsy ($n = 5$), outside study region ($n = 5$), not Māori or *whānau* of Māori ($n = 5$), currently using smoking cessation medication ($n = 3$), non-daily smoker ($n = 3$), breastfeeding ($n = 2$), other trial participant in household ($n = 2$), severe renal disease ($n = 1$), contraindication to varenicline ($n = 1$), did not want to use varenicline ($n = 1$). **Did not want to use varenicline ($n = 22$), not eligible for varenicline under special authority ($n = 11$), high risk/history of epilepsy ($n = 4$), outside study region ($n = 3$), contraindication to varenicline ($n = 3$), unstable hyperthyroidism ($n = 3$), currently using smoking cessation medication ($n = 1$), breastfeeding ($n = 1$), no national health index number, which was required for the prescription ($n = 1$). ^aMissing: the number of participants who were contacted but did not provide data (this includes a subset where data had not been handled in accordance with the protocol, which were therefore counted as missing). ^bLost to follow-up: the number of participants who could not be contacted at this follow-up time-point. ^cWithdrawn: the number of participants who withdrew from the trial (no further data were available)

withdrew, compared with 49 (14%) participants in the varenicline group, primarily due to adverse events [66% (35 of 53) of participants who provided a reason for withdrawal]. Loss to follow-up at 6 months was 34% overall, and similar in both groups (Fig. 1). Missing data ranged between 14 and 46%, depending on the variable and time-point of measurement (this included a subset of data at each time-point that had not been handled in accordance with the protocol, which was, therefore, counted as missing).

Baseline characteristics were evenly balanced between treatment groups (Table 1, Supporting information, Tables S1 and S2). Participants had a mean age of 43 years [standard deviation (SD) = 11.9, range = 8–82], a strong motivation to quit, and were predominantly women (69.7%).

Cytisine was non-inferior to varenicline, but not clearly superior: 6 month continuous abstinence rates were

12.1% (41 of 337) for cytisine versus 7.9% (27 of 342) for varenicline (risk difference = 4.29; 95% CI = -0.22 to 8.79, risk ratio = 1.55; 95% CI = 0.97–2.46; Table 2). Sensitivity (Table 2) and subgroup (Supporting information, Table S3) analyses yielded results that were consistent with the primary findings. Secondary cessation outcomes at 3, 6 and 12 months were also consistent with the primary outcome (Table 2).

Overall, 96% of participants (225 of 234 with available data) collected all or some of their 12-week prescription: 50% (117) collected all their medication, 27% (64) collected only two of the three medication instalments and 19% (44) collected only the first medication allotment (Supporting information, Table S4). No difference in medication collection was observed between the groups, even when those lost to follow-up or withdrawn were assumed to be non-adherent (Supporting information, Table S4). Of the 117 participants with available data who said they had collected their full prescription, 84 (72%) reported that they took most or all of their study medication, with no difference between groups (Supporting information, Table S4).

Self-reported AEs occurred less frequently in the cytisine group (313 events in 111 participants) compared with the varenicline group (509 events in 138 participants), with an incidence rate ratio of 0.56, 95% CI = 0.49–0.65, $P < 0.001$. The on-line participant diary was the most common source of AE reporting (66%), followed by participant interview (30%, Table 3). Forty-one per cent (128) of AEs in the cytisine group were assessed as certain or probably/likely related to treatment, compared to 57% (290) in the varenicline group (Table 3). Thirty-five SAEs were reported (cytisine: 16 events in 16 participants; varenicline: 19 events in 17 participants), with none assessed as certain or probably/likely related to treatment (Table 3, Supporting information, Table S6). Two SAEs were assessed as possibly related to treatment: one in the cytisine group (depression) and one in the varenicline group (cholecystectomy). The most frequently reported AEs in both groups were headache, nausea, difficulty sleeping, vivid dreams, tiredness, stomach-ache and dry mouth (Table 4).

Eighty-eight per cent (104 of 118) of participants allocated cytisine stated at 3 months that they would recommend their allocated treatment to others to help them quit smoking, compared to 74% (86 of 116) allocated varenicline ($P = 0.037$). There were no between-group differences for other secondary outcomes (Supporting information).

DISCUSSION

Cytisine was at least as effective as varenicline for smoking cessation among Māori and *whānau* of Māori who smoked daily and were motivated to quit. These findings were

Table 1 Baseline characteristics of participants.

Variables	Cytisine <i>n</i> = 337	Varenicline <i>n</i> = 342
Gender		
Female (<i>n</i> , %)	223 (66.2)	250 (73.1)
Male (<i>n</i> , %)	114 (33.8)	92 (26.9)
Age (years)		
Mean (SD)	43.1 (11.9)	43.5 (11.8)
Ethnicity		
New Zealand Māori (<i>n</i> , %)	322 (95.5)	318 (93.0)
<i>Whānau</i> of Māori (<i>n</i> , %)	15 (4.5)	24 (7.0)
Neighbourhood deprivation ^a		
1 Least deprived (<i>n</i> , %)	7 (2.1)	3 (0.9)
2	16 (4.7)	23 (6.7)
3	45 (13.4)	41 (12.0)
4	51 (15.1)	45 (13.2)
5 Most deprived (<i>n</i> , %)	218 (64.7)	230 (67.3)
Motivation to quit ^b	<i>n</i> = 182	<i>n</i> = 210
Score ≥ 4	142 (78.0)	157 (74.8)
Median (IQR)	4.5 (4–5)	5 (3–5)
Cigarette dependence ^c	<i>n</i> = 181	<i>n</i> = 207
Mean (SD)	5.2 (2.5)	5.2 (2.2)
Cigarettes per day ^d	<i>n</i> = 193	<i>n</i> = 220
Mean (SD)	15.5 (7.8)	15.5 (7.8)
Alcohol use ^e	<i>n</i> = 179	<i>n</i> = 206
Female (mean, SD)	3.5 (3.3)	3.2 (3.0)
Male (mean, SD)	4.2 (3.6)	4.8 (3.3)

SD = standard deviation. IQR = interquartile range. ^aBased on the New Zealand Index of Multiple Deprivation, which measures deprivation at the neighbourhood level [21]. ^bMeasured on a scale of 1–5: 1 very low, 5 very high. ^cCigarette dependence measured using the Fagerström Test of Cigarette Dependence [22,23], which is on a scale of 1–10, with scores > 5 indicating high cigarette dependence and ≤ 5 indicating low cigarette dependence. ^dIncluding roll-your-own tobacco. ^eAlcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT-C), on a scale of 0–12, where the higher the score the greater the risk of alcohol dependence. For men, a score ≥ 4 indicates an increased risk of hazardous drinking or alcohol dependence, while in women it is a score of ≥ 3 [25].

Table 2 Continuous abstinence and 7-day point prevalence abstinence by treatment group (intention-to-treat analysis).

	Cytisine N = 337 (n/N, %)	Varenicline N = 342 (n/N, %)	Relative risk (95% CI)	Risk difference (95% CI)	P-value
Continuous abstinence					
Self-reported 1-month quit rate ^b	200 ^a /337 (59.3)	216 ^a /342 (63.1)	0.94 (0.83–1.06)	-3.81 (-11.14 to 3.52)	0.46
Self-reported 3-month quit rate ^b	124 ^a /337 (36.7)	102 ^a /342 (29.7)	1.23 (0.99–1.53)	6.93 (-0.13 to 14.00)	0.18
Self-reported 6-month quit rate ^b	77 ^a /337 (22.9)	60 ^a /342 (17.5)	1.31 (0.97–1.77)	5.41 (-0.62 to 11.44)	0.16
CO-verified 6-month quit rate ^b	41^a/337 (12.1)	27^a/342 (7.9)	1.55 (0.97–2.46)	4.29 (-0.22 to 8.79)	0.17
Self-reported 12-month quit rate ^b	60 ^a /264 (22.6)	49 ^a /257 (19.0)	1.19 (0.85–1.66)	3.59 (-3.37 to 10.56)	0.36
CO-verified 12-month quit rate ^b	43^a /264 (16.3)	32^a/257 (12.4)	1.32 (0.86–2.02)	3.97 (-2.03 to 9.98)	0.31
Sensitivity analyses for 6-month quit data					
Complete cases only (CO verified) ^c	21/170 (12.4)	13/176 (7.4)	1.67 (0.87–3.23)	4.97 (-1.31 to 11.24)	0.12
Complete cases only (not CO verified) ^c	45/194 (23.2)	34/197 (17.3)	1.34 (0.90–2.00)	5.94 (-2.01 to 13.88)	0.14
Per protocol ^d	20/111 (18.0)	11/113 (9.7)	1.85 (0.93–3.68)	8.28 (-0.72 to 17.28)	0.07
Missing assumed to be smoking	21/337 (6.2)	13/342 (3.8)	1.64 (0.83–3.22)	2.43 (-0.85 to 5.71)	0.15
Varying CO cut-off ^b					
≤ 3 p.p.m.	36 ^a /337 (10.7)	23 ^a /342 (6.7)	1.60 (0.97–2.65)	4.03 (-0.20 to 8.27)	0.15
≤ 5 p.p.m.	40 ^a /337 (11.8)	26 ^a /342 (7.5)	1.58 (0.98–2.54)	4.34 (-0.10 to 8.77)	0.18
≤ 8 p.p.m.	41 ^a /337 (12.1)	27 ^a /342 (7.9)	1.55 (0.97–2.46)	4.29 (-0.22 to 8.79)	0.17
7-day point prevalence abstinence					
1-month quit rate ^b	154 ^a /337 (45.6)	171 ^a /342 (50.0)	0.91 (0.78–1.07)	-4.39 (-11.90 to 3.12)	0.40
3-month quit rate ^b	173 ^a /337 (51.2)	162 ^a /342 (47.2)	1.08 (0.93–1.29)	3.99 (-3.53 to 11.50)	0.34
6-month quit rate ^b	140 ^a /337 (41.4)	112 ^a /342 (32.9)	1.26 (1.03–1.54)	8.55 (1.31 to 15.79)	0.12
12-month quit rate ^b	115 ^a /264 (43.6)	111 ^a /257 (43.2)	1.01 (0.83–1.23)	0.61 (-7.90 to 9.12)	0.91

^aCalculated using *n* and % (obtained from the log binomial regression model which does not output the *n*, numbers rounded). ^bMultiple imputation analysis. ^cThose participants with full (non-imputed) data. ^dPer protocol analysis excluding participants with protocol violations (pregnancy, withdrew at 6 months, lost to follow-up at 6 months, cross-over, people who self-reported that they had quit at 6 months but were not visited for CO verification). Bold type was to highlight the verified quit rate data at 6 and 12 months. CI = confidence interval; CO = carbon monoxide; p.p.m. = parts per million.

Table 3 Summary of all-cause adverse events.

Total adverse events and SAEs	Cytisine <i>n</i> = 313	Varenicline <i>n</i> = 509
Source of adverse event and SAE reporting (<i>n</i> , %) ^a		
On-line study diary	195 (62.3)	350 (68.8)
Study interview	102 (32.6)	141 (27.7)
Pharmacist	26 (8.3)	23 (4.5)
Other ^b	16 (5.1)	26 (5.1)
Event type (<i>n</i> , %)		
Adverse event	297 (94.9)	490 (96.3)
SAEs: death	0	0
SAEs: life-threatening ^c	0	1
SAEs: hospitalization	13 (4.2)	13 (2.6)
SAEs: congenital abnormality ^d	0	1
SAEs: otherwise medically important	3	4
Causality assessment outcome for all adverse events and SAEs (<i>n</i> , %) ^e		
Certain	98 (31.3)	223 (43.8)
Probable/likely	30 (9.6)	67 (13.2)
Possible	45 (14.4)	71 (13.9)
Unlikely	69 (22.0)	74 (14.5)
Conditional/unclassified	71 (22.7)	74 (14.5)
Unassessable/unclassifiable	0	0
Causality assessment outcome for SAEs only (<i>n</i> , %) ^e		
Certain	0	0
Probable/likely	0	0
Possible ^c	1	1
Unlikely ^f	3	1
Conditional/unclassified	12 (75.0)	17 (89.5)
Unassessable/unclassifiable	0	0

SAE = serious adverse event ^aPercentages do not tally as adverse events could be reported from more than one source. ^bGeneral practitioners (*n* = 1), community-based smoking cessation providers (*n* = 5), other (*n* = 36). ^cCardiac arrest. ^dHeart disease. ^eDepression (cytisine group) and cholecystectomy (varenicline group). ^fDizziness, gall bladder inflammation, stroke (cytisine group) and cardiac arrest (varenicline group). ^gWorld Health Organization standardized case causality assessment tool [29].

consistent among the various sensitivity and subgroup analyses, and at 3, 6 and 12 months post-quit. Self-reported AEs over 6 months occurred less frequently in the cytisine group than in the varenicline group. Self-reported medication adherence and compliance with allocated treatment was similar between the groups, despite the different dosing regimens.

A strength of this trial is its pragmatic design, reflecting real-world access to varenicline in NZ (and potentially cytisine, if granted a marketing authorization in NZ). The trial highlights the benefits of working in partnership with indigenous communities to support positive behaviour change. Broad inclusion criteria and absence of incentive payments to participants to improve medication adherence and trial retention contribute to the generalizability of the study findings to the 'real world'. High participation by Māori women (who have higher daily smoking rates than Māori men: 33% versus 29%, respectively, in 2018/19) [19] suggests strong motivation among this group to quit. Medical exclusion criteria reflected the manufacturers' precautions for use of cytisine and varenicline. We followed the manufacturers' recommended dosing regimens for both medications, although this trial is the first, to our

knowledge, to use an extended cytisine treatment. This prolonged treatment (which is approximately three times longer than the recommended dosing regimen) could be a driver of the observed treatment effect. The trial had high internal validity: we controlled for selection bias by undertaking computer randomization, and the doctor randomizing participants did not know what the next treatment allocation was. The moderate level of medication adherence and compliance reflects how these behaviours impact upon smoking abstinence rates in the population, although some performance bias may exist. On first impression, it appears that the more complex dosing regimen for cytisine was not a barrier to use. However, the research assistants interacting with participants reported (but did not formally record) that for many participants the cytisine dosage regimen was a barrier, but one that was mitigated by some participants' preference for cytisine and delivery of behavioural support in the first 6 weeks of treatment (which highlighted the importance of medication adherence and compliance). Our use of ITT analysis gave a conservative treatment effect. No one type of analysis is perfect to address the biases arising from loss to follow-up, withdrawal and missing data in a trial of this nature. We chose multiple

imputation as our preferred method to address this issue, although we acknowledge that participants lost to follow-up in smoking cessation trials are usually considered to have resumed smoking. It is possible that some loss to follow-up in this trial was due to adverse events, given that participants withdrawing from the trial primarily cited side effects as a reason. Thus, the assumption that participants lost to follow-up have resumed smoking may not be valid and would bias the effect sizes downwards [32]. However, we still undertook sensitivity analyses with missing participants assumed to be smoking and found a similar finding to our primary analysis. We took a person-centred approach to AE reporting, with participants encouraged to report 'health events' during and following treatment using their own words. Finally, the observed self-reported 6-month continuous abstinence rate for cytosine (22%) was consistent with our previous pragmatic trial, where people calling the NZ Quitline received a free 25-day course of cytosine delivered at no cost to their home [10].

The study had a number of limitations. First, the smaller than anticipated sample size is reflected in the wide CIs and restricted our ability to undertake some comparisons. Based on the sample size obtained and the effect sizes observed, the trial had just under 60% power, indicating an increased likelihood of type 2 error. Secondly, higher than expected loss to follow-up and missing data reduced the power of the trial to test the hypothesis with precision and could have resulted in under- or overestimation of treatment effects. To increase precision, we used multiple imputation for missing data while adjusting for the uncertainty of the missing data. To assess the robustness of findings for plausible alternative assumptions about the missing data, we undertook sensitivity analyses that produced similar and consistent results to the ITT analysis. Thirdly, treatment allocation and delivery of behavioural support was not blinded, so some reporting bias in favour of one treatment or the other could have occurred. Fourthly, treatment-related AEs may have reduced the likelihood of quitting (i.e. some participants reported stopping medication because of AEs), or contributed to loss to follow-up or the higher withdrawal rate seen in the varenicline group. Early nausea during varenicline treatment may reduce adherence and be associated with lower likelihood of smoking cessation [33], so should be anticipated and managed in people taking cytosine or varenicline. The lower incidence of nausea in the cytosine group is probably due to cytosine's slower potency at 5-HT₃ receptors [34]. Fifthly, users of non-cigarette tobacco products were not excluded but were likely to be few, because smokeless tobacco and heat-not-burn products were not available for sale in NZ prior to March 2018. Sixthly, there may be some preference bias in favour of cytosine because of its novelty (e.g. some participants may have preferred cytosine over varenicline because it was new, and they may have used varenicline in the past

and experienced an AE and/or did not quit), as well as its 'natural' status (important for many Māori, given their strong connection with the land). We tried to mitigate this bias by carefully describing the two medications to participants, to highlight their equipoise. However, as part of the ethics process we had to explain in the participant information sheet (see Supporting information) the source of both medications (i.e. cytosine being plant-based and found in several NZ plants, while varenicline was not plant-based, but developed from cytosine), and present available AE information for the two medications. It was evident that some members of the study population preferred to be allocated cytosine, given: (1) the numbers of potential participants not wanting to engage in the trial if they could not have access to this medication and (2) the differential withdrawal noted in the first week post-randomization in those allocated varenicline. Future cytosine trials should quantify the potential effect of participants' treatment preference on the primary outcome by asking about preference at baseline then stratifying the primary analyses accordingly [35]. Finally, although AEs were self-reported, medically reviewed and, like those reported in previous cytosine [1] and varenicline research [8], the trial was neither large enough nor long enough to assess occurrence of uncommon AEs nor those with a long time to onset. Given the above, it is important that the trial findings be considered exploratory and subject to validation from additional trials comparing cytosine to varenicline, and meta-analysis of such trials.

Future analysis of the data set includes a cost-effectiveness analysis to aid adoption decisions in NZ and beyond, and *post-hoc* Bayesian analysis of the primary outcome. Strategies to optimize medication adherence and compliance for both medications to increase quitting success should be investigated, plus further research on the extended treatment regimen for cytosine is justified. Research should also focus upon the impact of cytosine on smoking abstinence in other population groups who have high smoking prevalence, such as people with psychiatric disorders. Finally, further studies are needed to provide more comprehensive data on the safety profile of cytosine, and to examine approaches to maximizing its effectiveness, such as use in combination with NRT and extended treatment to prevent relapse.

Clinical trial registration

The trial is registered at [Clinicaltrials.gov](https://clinicaltrials.gov): NCT02957786.

Declaration of interests

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Table 4 Most common types of adverse events.

	Cytisine	Varenicline
Number of participants with most frequent adverse events ^a (n, %)	n = 111	n = 138
Headache	35 (31.5)	40 (29.0)
Nausea	25 (22.5)	54 (39.1)
Difficulty sleeping	15 (13.5)	28 (20.3)
Vivid dreams	8 (7.2)	24 (17.4)
Tiredness	9 (8.1)	19 (13.8)
Stomach-ache	10 (9.0)	18 (13.0)
Dry mouth	9 (8.1)	5 (3.6)
Total number of events, for most frequent adverse events (n, %)	n = 297	n = 490
Headache	55 (18.5)	76 (15.5)
Nausea	30 (10.1)	97 (19.8)
Difficulty sleeping	19 (6.4)	32 (6.5)
Vivid dreams	9 (3.0)	31 (6.3)
Tiredness	10 (3.4)	28 (5.7)
Stomach-ache	10 (3.4)	25 (5.1)
Dry mouth	9 (3.0)	19 (3.9)

^aIn participants who had ≥ 1 event.

W., C.B. and M.V. V.P. report grants from Pfizer, grants from the Health Research Council of New Zealand, outside the submitted work; and has previously undertaken two trials of e-cigarettes for smoking cessation [with e-cigarettes purchased from a NZ e-cigarette on-line retailer (NZVAPOR, <https://www.nzvapor.com/>), e-liquid for one trial purchased from Nicopharm, Australia (<https://www.nicopharm.com.au/>) and nicotine patches supplied by the NZ Government via their contract with Novartis (Sydney, Australia)]. Neither NZVAPOR nor Nicopharm have links with the tobacco industry. C.B. also reports personal fees from the Moffat Cancer Center, University of Florida, USA, and personal fees from Virginia Commonwealth University, USA outside the submitted work. J.B. also reports personal fees from New Zealand Ministry of Health Natural Health Products (NHPs) Regulations Subcommittee on the Permitted Substances List (member of subcommittee 2016–17), non-financial support from Uppsala Monitoring Centre, Sweden (who manages the technical and scientific aspects of the WHO Programme for International Drug Monitoring); honorary consultant and herbal safety signal reviewer (2004–current), outside the submitted work. None of the above parties had any role in the design, conduct, analysis or interpretation of the trial findings or writing of the resulting publication.

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Author contributions

Natalie Walker: Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization. **Barry Smith:** Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; visualization. **Joanne Barnes:** Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization. **Marjolein Verbiest:** Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization. **Varsha Parag:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; resources; software; supervision; validation; visualization. **Subhash Pokhrel:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision;

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information.