Cytisine vs Varenicline for Smoking Cessation in a Primary Care Setting: A Randomized Non-Inferiority Trial

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Abstract

Introduction

A smoking-cessation program was implemented as a randomized non-inferiority trial in primary care practices in Croatia and Slovenia to investigate whether a standard 4-week treatment with cytisine was at least as effective and feasible as a standard 12-week treatment with varenicline in helping smokers quit.

Methods

Out of 982 surveyed smokers, 377 were recruited to the non-inferiority trial: 186 were randomly assigned to cytisine and 191 to varenicline treatment. The primary cessation outcome was 7-day abstinence after 24 weeks, while the primary feasibility outcome was defined by adherence to the treatment plan. We also compared the rates of adverse events between the two treatment groups.

Results

The cessation rate after 24 weeks was 32.46% (62/191) in the varenicline group and 23.12% (43/186) in the cytisine group (odds ratio [OR]: 0.63, 95% credible interval [CI]: 0.39 to 0.98). Of 191 participants assigned to varenicline treatment 59.16% (113) were adherent, while 70.43% (131 of 186) were adherent in the cytisine group (OR: 1.65, 95% CI: 1.07 to 2.56). Participants assigned to cytisine experienced fewer total (incidence rate ratio [IRR]: 0.59, 95% CI: 0.43 to 0.81) and fewer severe or more extreme adverse events (IRR: 0.72, 95% CI: 0.35 to 1.47).

Conclusion

This randomized non-inferiority trial (n = 377) found the standard 4-week cytisine treatment to be less effective than the standard 12-week varenicline treatment for smoking cessation. However, adherence to the treatment plan, ie, feasibility, was higher, and the rate of adverse events was lower among participants assigned to cytisine treatment.

Implications

The present study found the standard 12 weeks of varenicline treatment to be more effective than the standard 4 weeks of cytisine treatment for smoking cessation in a primary care setting in Croatia and Slovenia. Participants assigned to cytisine, however, had a higher adherence to the treatment plan and a lower rate of adverse events. Estimates from the present study may be especially suitable for generalizations to high-smoking prevalence populations in Europe. Given the much lower cost of cytisine treatment, its lower rate of adverse events, and higher feasibility (but its likely lower effectiveness with the standard dosage regimen), future analyses should assess the cost-effectiveness of the two treatments for health policy considerations.

Introduction

Varenicline (trade name: Champix) and cytisine (a generic agent; trade name: Tabex) are medications used to treat nicotine addiction by reducing craving for smoking cigarettes and other tobacco products and attenuating withdrawal symptoms caused by smoking cessation[1,2]. Several studies have shown that pharmacotherapies using varenicline and cytisine are effective for smoking cessation[3-6]. Varenicline has been estimated to successfully help between 15% and 27% of the treated remain abstinent from smoking for one year, substantially and significantly more than bupropion and placebo[7-9]. A trial comparing cytisine to nicotine replacement therapy (NRT) similarly found the former to be more effective (relative risk [RR]: 1.4), with a 22% quit rate six months after beginning treatment[5]. Placebo-controlled trials also found cytisine to be more effective[10,11]. However, the two randomized non-inferiority trials conducted thus far to compare the two medications directly have produced mixed evidence: The first trial[12], conducted in New Zealand among participants from an indigenous Māori or whānau (extended-family) of Māori population, has found cytisine to be more effective (12.1% compared to 7.9%; relative risk [RR]: 1.55; 95% CI: 0.97 to 2.46). The second trial — conducted in Australia[13] among volunteers recruited through advertisements, digital media, radio and a smoking cessation telephone quit line — has estimated a lower 6-month abstinence in the cytisine group and a risk difference estimate of -1.62% (11.7% and 13.3%; 1-sided 97.5% CI, −5.02% to ∞), narrowly failing to demonstrate noninferiority at a 5% margin. Given the paucity and ambiguity of existing evidence, head-to-head comparisons are still scant and additional studies are needed[14]. Our study aimed to implement a smoking cessation program using pharmacotherapy in a real-life setting — primary care practices in Croatia and Slovenia — as a non-inferiority trial to investigate whether treatment with cytisine was at least as effective and feasible as treatment with varenicline in helping smokers.

Methods

The study was conducted in 50 family medicine primary care practices: 26 in Croatia and 24 in Slovenia. A clinical trial notification was submitted to the Croatian and Slovenian administration and research ethics approvals were obtained from the Croatian National Ethical Committee (UPI/I-530-09/19-06/13) and from Commission for Medical Ethics of the Republic of Slovenia (0120-133/2019/4) following the guidelines of the European Medical Agency and Committee for Proprietary Medicinal Products: "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95). All participants provided written informed consent. Trial participants received no reimbursement for their time, but medication was provided free of charge at the expense of the research team. Travel expenses incurred by the participants to reach the family medicine primary care practices were reimbursable up to a maximum of HRK 120 or EUR 15. An insurance policy was contracted covering all medical expenses and other expenses arising from adverse events during the research.

Each practice had between 1,275 and 2,375 adult patients. General medicine doctors specialized in family medicine (MDs) from the 50 primary care practices involved in the study were trained in the administration of both varenicline and cytisine, in recognizing adverse events and in managing them (e.g., nausea, insomnia, abnormal dreams, constipation, dyspepsia, sleep disorder, vomiting, and flatulence) as well as in providing behavioral support. We also hired research assistants (RAs), who received brief training in smoking cessation counseling.

The trial protocol and guidance for staff are provided in Supplement 1. The consent sheet with information for participants is provided as Supplement 2. The baseline interview questionnaire on smoking habits, the Fagerström test for nicotine dependence[15], attitudes about smoking as a cause of diseases, interest in pharmacotherapy, and sociodemographic information is provided as Supplement 3.

Study population

The MDs surveyed 982 smokers across 50 primary care practices to assess smoking behavior and interest in pharmacotherapy for smoking cessation. Only people meeting the following criteria were eligible to participate in the study: 1) had a primary care MD at one of the 26 participating primary care practices in Croatia or at one of 24 primary care practices in Slovenia; 2) were aged 18 or older; 3) were then smoking at least one cigarette per day and indicated a desire to quit via survey; 4) did not have contraindications to the use of the medicines being tested (according to the summary of product characteristics for varenicline and cytisine); 5) indicated an interest in pharmacotherapy via the survey. Ineligible for the study were people: 1) with a cognitive impairment according to the records of the field investigator (their primary care family medicine MD); 2) with a mental disorder, according to the same records; 3) considered by the MDs to be insufficiently collaborative to participate in the trial; 4) considered by MDs to have frequent adverse reactions to multiple drugs in the previous treatment of acute and chronic diseases; 5) who were pregnant or breastfeeding; 6) who participated in another smoking cessation program. MDs assisted by primary care nurses performed the screening. Respondents meeting the above criteria were invited to participate in the study. Due to significant complications amid the then-emergent COVID-19 pandemic (spring and summer of 2020), we aimed to recruit 380 participants (the number specified by the original protocol), which was deemed a realistic upper bound by staff of the participating primary care practices.

Randomization

A random number generator was used to allocate varenicline or cytisine treatment in a 1:1 ratio stratified by practice and based on the order of enrollment. The pre-specified random allocation was uploaded to REDCap (a data management tool). Due to differences in the duration and dosages of the treatments as well as the medications' different shape, neither the participants nor the MDs and RAs could be blinded.

Treatment

The varenicline treatment was given by standard protocol, starting one week prior to the patient's target quit date at 0.5 mg once daily and was increased to 0.5 mg twice daily on day 4. On the target quit date (day 8), the dose was increased to 1 mg twice daily and maintained for 12 weeks[16].

We also followed the standard manufacturer's dosage protocol[17] for participants assigned to cytisine treatment, who were given a 25-day supply and asked to reduce their smoking during the first 4 days of treatment with an aim to quit on the 5th day. Days 1 through 3, they were instructed to have one tablet every 2 hours through the waking day (up to six tablets per day). Days 4 through 12, the dosage was one tablet every 2.5 hours (up to five tablets per day). Days 13 through 16, it was one tablet every 3 hours (up to four tablets per day); days 17 through 20, one tablet every 4 to 5 hours (three tablets per day); and days 21 through 25, one tablet every 6 hours (two tablets per day).

Baseline and follow-up

MDs and RAs asked all the study participants to fill out the Fagerström test for nicotine dependence as part of the baseline interview prior to starting treatment[18]. We also collected data on the participants' sex, age, educational attainment, smoking history (number of cigarettes/day), attitudes toward smoking, and intentions to quit. Participants were given medication, explained how it was to be taken, and a phone number to call with any questions. Either during participants' in-person visits to their MDs or via calls with RAs, the follow-up started with the first day of the treatment, followed by weekly calls or visits for the first 4 weeks, then every two weeks, until the 12th week, and finally twice more, after 16 and 24 weeks. At each time point, RAs or MDs motivated the patients to continue taking medications, encouraged them to stop smoking, and recorded the outcomes.

Effectiveness, feasibility, and adverse events outcomes

The primary effectiveness outcome was smoking status defined by self-reported 7-day abstinence 24 weeks after starting treatment. Smoking status was also recorded after 4, 8, and 12 weeks. We considered participants lost to follow-up not to have reported 7-day abstinence after 24 weeks.

We defined the primary feasibility outcome was adherence: whether the participant reported taking ≥80% of the medication by the end of the treatment plan (25 days for cytisine, 12 weeks for varenicline). Adherence was recorded on day 1 and after weeks 1, 2, 3, 4, as well as, for varenicline, after weeks 6, 8, 10, and 12. Participants lost to follow-up were considered non-adherent.

Finally, MDs classified adverse events according to The Common Terminology Criteria for Adverse Events (CTCAE - version 5.0)[19] into mild, moderate, severe, and life-threatening events, and death. The two outcomes of interest were defined as the number of total adverse events of any severity experienced by a participant and the total number of severe or more extremely adverse events (life-threatening events and deaths). Adverse events were recorded on day 1 and after weeks 1, 2, 3, and 4 (for cytisine treatment), as well as after weeks 6, 8, 10, and 12 (for varenicline treatment).

Statistical analyses

The statistical analyses followed a pre-specified analysis plan (Supplement 4). Additional, post-hoc analyses are so described. We analyzed self-reported 7-day abstinence after 24 weeks as the primary effectiveness outcome using a Bayesian logistic regression with a single binary independent variable indicating with value 1 that the assigned treatment was with cytisine and with 0 that the assigned treatment was with varenicline. We chose a weakly informative prior to reflect the expectation of the treatment group coefficient estimate of close to 0, i.e. to an odds ratio (OR) of close to 1, but some chance of a more extreme coefficient. For the treatment coefficient, we chose a Student's t distribution with a mean of 0, 7 degrees of freedom and a standard deviation (SD) of 2.5 divided by the standard deviation of the treatment variable; for the intercept term, a Student's t distribution with a mean of 0, 7 degrees of freedom and an SD of 2.5[20]. This selection is slightly more conservative than the default of the 'rstanarm' R package[21]: the Student's t distribution has heavier tails than the normal, allowing for the possibility of more extreme values while still avoiding an uninformative prior[20,22].

We considered the estimated proportion of the posterior distribution (of the treatment group) above or below 0 (i.e., above or below an odds ratio of 1) to indicate the probability that cytisine was at least as effective as varenicline (or less effective than varenicline, respectively)[23]. The median of the posterior distribution was exponentiated to obtain the point estimate of the odds ratio of cessation at 24 weeks with cytisine treatment compared to with varenicline treatment. The central 95% of the posterior distribution were taken as the 95% credible interval. To obtain the relative risk estimate (for ease of interpretation)[24], we divided the median of 10,000 posterior draws of the linear predictor assuming cytisine treatment by the equivalent median of 10,000 draws assuming varenicline treatment, where the posterior draws of the linear predictor were implied by the Bayesian logistic regression model estimated from the trial data (analogously for 95% credible intervals).

We conducted effectiveness analyses according to an intention-to-treat perspective based on the assigned treatment, regardless of whether participants had been lost to follow-up or had not adhered to the treatment for any reason. Existing instrumental variable approaches estimating the causal effect among adherent participants ("compliers") in non-inferiority trials do not account for the possibility of non-adherence (rather than treatment crossover)[25]. Hence, to avoid biases stemming from non-random non-adherence, we did not conduct sensitivity analyses among the subset of participants who adhered to the treatment plan to avoid estimates biased by non-random non-adherence[26].

We performed a secondary, multivariable analysis to adjust the treatment coefficient estimate for the participants' pre-treatment Fagerström test for nicotine dependence category (treated as a continuous variable of range 1-4 for power considerations), as well as age, sex, and educational attainment (also treated as a continuous variable, of range 1-5). We also employed a multilevel Bayesian logistic regression with varying intercept terms in a secondary analysis, to take into account the hierarchical nature of the data collected across 50 family medicine primary care practices[27,28]. Cessation after 12, 8, and 4 weeks were assessed in further secondary, post-hoc effectiveness analyses.

A final post-hoc, secondary effectiveness analysis was performed using summarized data on the primary cessation outcome (6 months after baseline) from the two previous non-inferiority trials. These estimates were used in a random-effects meta-analysis (using the 'metafor' R package[29]) to obtain an informative prior for a univariable Bayesian logistic regression analysis. The meta-analytic log odds estimate of the treatment was set as the mean and the corresponding standard error was taken as the scale parameter of a Student's t distribution with 7 degrees of freedom.

We conducted the primary feasibility analysis with adherence as the outcome in an univariable Bayesian logistic regression with the above-described weakly informative priors. We added a multivariable analysis as a secondary analysis.

In post-hoc analyses, we compared the total number of adverse events and the number of severe or more extreme adverse events using Bayesian negative binomial regressions with weakly informative Student's t distribution priors equivalent to those described above. Unlike in the intention-to-treat approach adopted in the analyses of effectiveness and feasibility of the two treatments, we considered only participants who took at least one dose of the assigned medication in the adverse event analyses. Markov chain convergence for all the Bayesian models was assessed by default checks that the diagnostic statistic $\hat{R} < 1.01$[30].

Results

The trial began on 14 July 2020 with the first participants' randomization and ended on 4 November 2022 with the final follow-up call with the final participant. Nine hundred eighty-two potential participants from 26 primary care practices in Croatia and 24 in Slovenia completed a survey about their smoking habits and interest in pharmacotherapy and 377 enrolled in the trial (Figure 1). The baseline characteristics were balanced across the varenicline (n=191) and cytisine (n=186) groups (Table 1). Only 13.72% of the participants (48/377) were lost to follow-up by the final 24-week call (Figure 1) and participants withdrew consent. All the Markov chains for all Bayesian models (discussed below) converged.

Effectiveness of cytisine vs. varenicline therapy

The self-reported 7-day abstinence rate after 24 weeks was 32.46% (62/191) in the varenicline group (12 weeks of treatment) and 23.12% (43/186) in the cytisine group (4 weeks of treatment). The exponentiated median of the posterior distribution from the univariable Bayesian logistic regression, i.e., the odds ratio (OR), was 0.63 (95% credible interval [CI]: 0.39-0.98), indicating that participants assigned cytisine treatment — compared with those assigned varenicline — had 37% lower odds of not smoking 24 weeks after the treatment began. The estimated proportion of the posterior distribution of the cytisine treatment coefficient below 0 (i.e., below and OR of 1) was 97.81%. Using posterior draws of the linear predictor of the estimated model, we estimated the relative risk (RR) to be 0.71 (95% CI: 0.51-0.99).

In a secondary, multivariable Bayesian logistic analysis of the 24-week cessation outcome adjusted for the participants' Fagerström nicotine dependence category, age, sex, and educational attainment, the estimated OR for cytisine treatment (compared to varenicline) was 0.60 (95% CI: 0.37-0.96). The proportion of the posterior distribution of the cytisine treatment coefficient estimated to be below 1 was

98.29%, and the estimated RR was 0.70 (95% CI: 0.47-0.97). Estimates for the covariates are reported in Figure 2A. Estimates from the multilevel analysis incorporating the hierarchical structure of participants treated at primary care practices are similar to those from pooled models and reported along with practice-specific intercept estimates in Supplement 5 Figure 1A-C.

Secondary, post-hoc univariable analyses for the cessation outcome at earlier time points yielded OR estimates of 0.64 (95% CI: 0.41-0.98; RR: 0.73, 95% CI: 0.53-0.99) after 12 weeks; 0.69 (95% CI: 0.44-1.08; RR: 0.77, 95% CI: 0.55-1.05) after 8 weeks; and 0.97 (95% CI: 0.62-1.50; RR: 0.97, 95% CI: 0.71-1.32) after 4 weeks (Figure 2B). The estimates for all covariates from the corresponding multivariable models (pooled, not multilevel) are reported in Supplement 5 Figure 2A-C. The proportion of participants reporting 7-day abstinence in each group at all the time points is reported in Figure 1.

The post-hoc random-effects meta-analysis of previous studies' estimates produced an OR of 1.14 (95% confidence interval: 0.62-2.10; Q: 4.23; p-value=0.04; I^2 =76.35%). This estimate was used as the informative prior in a Bayesian logistic regression. The median OR from draws from the posterior distribution was 0.76 (95% CI: 0.50-1.10; RR: 0.82, 95% CI: 0.61-1.07), and 92.67% of the distribution was below 1.

Feasibility of cytisine vs. varenicline therapy

Among the participants assigned to varenicline treatment, 113 of 191 (59.16%) were adherent (≥80% of the medication had been taken at the end of the treatment plan), while 131 of 186 (70.43%) were adherent in the cytisine group (Figure 1 contains adherence data at earlier time points). The univariable Bayesian logistic regression yielded an OR of 1.65 (95% CI: 1.07-2.56) and the corresponding estimated RR was 1.19 (95% CI: 1.03-1.39). The proportion of the posterior distribution estimated to be above 0 was 99.02%. The estimates from the secondary, multivariable analysis of feasibility are reported in Figure 2C.

Adverse events

Figure 1 reports the number of participants assigned to each treatment who not to commence with the therapy out of a fear of adverse events (and separately, for any reason). It also reports the number of participants who were no longer adherent to the treatment plan due to adverse events by the 2nd, 4th, 8th, and 12th week after baseline.

Table 2 reports the total, mild, moderate, severe, and life-threatening adverse events and the number of participants who experienced them in each treatment group. The univariable negative binomial Bayesian regression analysis of the total adverse events yielded an incidence rate ratio (IRR) of 0.59 (95% CI: 0.43-0.81) for cytisine treatment. The corresponding analysis of severe or more extreme adverse events produced an IRR of 0.72 (95% CI: 0.35-1.47). There was only one life-threatening event: a stroke occurred in the varenicline group. Restricting the adverse events only to those recorded by the end of week 4 of treatment, we estimated an IRR of 0.70 (95% CI: 0.52-0.92) for total adverse events and 0.85 (95% CI: 0.39-1.85) for severe or more extreme adverse events.

Discussion

This trial estimated a standard 4-week treatment with cytisine to be less effective than a standard 12-week treatment with varenicline for smoking cessation: 32.46% (62/191) of participants in the varenicline group and 23.12% (43/186) in the cytisine group reported 7-day abstinence after 24 weeks, yielding an odds ratio of 0.63 (and a relative risk of 0.71). The corresponding uncertainty of the estimate allowed us to reject the hypothesis that treatment with cytisine was non-inferior, an inference supported by the 95% credible interval (0.39-0.98) of the OR and the proportion of the posterior distribution below 1 (97.81%).

We estimated cytisine to be the more feasible of the two treatments. 70.43% of the participants assigned to cytisine were adherent to the treatment plan, compared with 59.16% in the varenicline group. This finding is consistent with those from the previous two non-inferiority studies[12,13]. Furthermore, participants reported substantially fewer total adverse events in the cytisine group (IRR: 0.59; 95% CI: 0.43-0.81). Though the difference was not as clear, there were also fewer severe adverse events reported in the cytisine group (18 vs. 25; IRR: 0.72; 95% CI: 0.35-1.47). The direction of the findings persisted after restricting the adverse events only to those recorded by the end of week 4 of treatment, suggesting that they were not driven simply by the shorter length of the cytisine treatment (which is regardless an important characteristic of any treatment, and especially so with respect to adverse events). The previous two non-inferiority studies produced similar estimates.

Further considering the effectiveness of the two treatments, post-hoc analyses of cessation outcomes at earlier time points exhibited a noteworthy trend. The estimated effectiveness of the two treatments was indistinguishable after 4 weeks, as 32.46% and 31.72% participants reported abstinence in the varenicline and cytisine groups, respectively (RR: 0.97; 95% CI: 0.62-1.50). By the 8-week point, the proportion of participants assigned to cytisine who reported 7-day abstinence dropped to 25.81%, and the estimate resembled that of the primary outcome, after 24 weeks. The previous non-inferiority study conducted in Australia reported a result yet more favorable to cytisine-treatment effectiveness after 4 weeks[13]. That trial shared the (standard) dosage with the present one and likewise did not show non-inferiority 6 months after the baseline interview. In the earlier non-inferiority trial comparing the two treatments among indigenous Māori or whānau (extended family) of Māori in New Zealand, 12 weeks of cytisine treatment were assigned instead of the standard 25 days, thus matching the length of the assigned varenicline treatment: that study found cytisine to be at least as effective as varenicline after 6 months[12]. Courtney et al.[13] have argued in light of these previous results that the shorter standard regimen of cytisine may not be optimal, possibly due to comparatively less research having been devoted to determining optimal dosage[2,7]. The effectiveness comparison at 4 weeks in the present study was consistent with this interpretation and warrants further research.

The more notable difference between the effectiveness estimates of the present study and those of the previous two trials is the result in favor of varenicline's comparative effectiveness. While the first of the previous trials mentioned above narrowly failed to demonstrate non-inferiority after 24 weeks, its relative risk estimate for cytisine treatment would have been 0.88 (95% confidence interval: 0.67-1.15), compared to 0.71 (95% CI: 0.51-0.99) in the present study. In contrast, the earlier trial estimated a relative risk of 1.55 (95% confidence interval: 0.97-2.46) for cytisine treatment. Possibly as important is the substantially higher proportion of participants reporting 7-day abstinence after 24 weeks in the present trial, at 32.46% for the varenicline group, compared to 13.3% and 7.9% in the previous two trials, and 23.12% in the cytisine group, compared to the previously estimated 11.7% and 12.1%.

These differences may partly be due to differences between the study populations. Despite the implementation of tobacco control policies set forth by the WHO in Croatia and Slovenia[31,32], as well as drug reimbursement policies[33], the much higher smoking prevalence rates in Croatia (36.9%) and Slovenia (22.3%) than in Australia (13.6%) may imply that smokers in Australia differ from those in the former two countries[34]. The earlier of the two previous trials was conducted among Māori or whānau of Māori, where prevalence is higher than in the general population in New Zealand[35]. However, following several interventional studies and smoking-cessation promotion projects[36-38], as the first smoking-cessation randomized pharmacotherapy trial in Croatia and Slovenia, the present study may provide a more suitable basis for generalization to high smoking prevalence areas in Europe. Another feature of the present study that may aid generalizability is its primary care setting, where participants would normally receive treatment from their medical care providers.

Given the differences in contexts discussed above, interpreting the totality of the evidence produced by the present study together with that of the two previous studies is challenging. Nevertheless, we attempted to quantitatively synthesize the evidence in a post-hoc Bayesian analysis using an informative prior, constructed from a random-effects meta-analysis of the two previous studies' estimates. The

median of the posterior distribution of the relative risk was 0.82 (95% CI: 0.61-1.07), with 92.67% of the distribution still below 1, suggesting that varenicline is more effective. Interpretations of this post-hoc analysis should take into account the differing duration of the treatments across the studies.

Finally, the main effectiveness estimates of the present study, favoring the 12-week varenicline treatment compared with the 4-week cytisine treatment, should also be considered bearing in mind the substantially lower cost of cytisine compared to varenicline, as well as its higher feasibility and lower rate of adverse events[14]. Future cost-effectiveness analyses, given the now available estimates from head-to-head comparisons as well as the introduction of generic varenicline options, may have important population health implications.

Limitations

There are several limitations to the present study. First, with regards to the primary cessation outcome, self-reported 7-day abstinence alone may be less reliable than when verified by a carbon monoxide breath test, which was not available. On the other hand, while higher than the cessation rates in the previous two non-inferiority trials, the cessation rates estimated in this trial were consistent with those of previous placebo-controlled trials. The fact that participating MDs had been regular care providers for the trial participants should lend additional confidence in self reports, though this remains a limitation of the study.

Second, blinding was not viable, since the standard treatment lengths for and appearance of cytisine and varenicline differed. Third, while the primary care setting and sample of the present study may be conducive to relevant generalizations, the MDs participating in this study were working in family medicine primary care practices in large cities, some of which were affiliated with academic medical centers. Results may hence be different in populations served by family medicine primary care practices in rural settings or those without academic affiliations.

Fourth, during critical periods for this trial both Slovenia and Croatia were living under "lockdown" due to the COVID-19 pandemic[39,40]: many of the participating MDs were preoccupied with COVID-19 patients, and the general population was under increased stress and reluctant to leave their homes to visit family medicine primary care offices[41]. These circumstances prevented us from expanding the sample size target (beyond 380) and may have impacted the participants' smoking behavior[42].

Conclusion

This randomized non-inferiority trial (n=377) found **a standard 4-week** cytisine **treatment** to be less effective than **a standard 12-week** varenicline **treatment** for smoking cessation. However, adherence to the treatment plan, i.e., feasibility, was higher, and the rate of adverse events lower among participants assigned to cytisine treatment.

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Declaration of interests

In the interest of transparency, the authors wish to declare the following roles and relationships: SO, SPL, HT, JMA, JR, and ZKK received the grant. The cytisine (Tabex®)30 was purchased for the trial

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Research materials transparency

To encourage a higher enrollment rate, the consent sheet used in this study has guaranteed to all participants that individual data collected during the trial would not be shared with researchers not involved in the present study. Supplements 1-5 contain the study protocol, consent sheet, survey questionnaire, statistical analysis plan, and supplementary figures. Sample R code used for the statistical analyses described in the methods section is available **at github.com/tinoreskovic/cytisine_varenicline**. **The complete analysis code (the corresponding, equivalent code for other outcomes) is available upon request.**

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Tables

Table 1. Baseline characteristics of the trial participants

Variable [mean, standard deviation (SD); or count (percentage)]	Varenicline (N=191)	Cytisine (N=186)	Overall (N=377)
Age			
Mean (SD)	49.2 (11.5)	48.7 (13.0)	49.0 (12.3)
Sex			
Male	82 (42.9%)	77 (41.4%)	159 (42.2%)
Female	109 (57.1%)	109 (58.6%)	218 (57.8%)
Fagerström test for nicotine dependence category			
Low dependence (1)	31 (16.2%)	21 (11.3%)	52 (13.8%)
Low to moderate dependence (2)	55 (28.8%)	67 (36.0%)	122 (32.4%)
Moderate dependence (3)	88 (46.1%)	84 (45.2%)	172 (45.6%)
High dependence (4)	16 (8.4%)	13 (7.0%)	29 (7.7%)
NA	1 (0.5%)	1 (0.5%)	2 (0.5%)
Number of cigarettes per day			
Mean (SD)	18.9 (8.82)	18.6 (9.05)	18.8 (8.92)
Age when first started smoking			
Mean (SD)	19.0 (4.81)	18.6 (3.71)	18.8 (4.30)
NA	1 (0.5%)	1 (0.5%)	2 (0.5%)
Educational attainment			
Elementary school or less (1)	19 (9.9%)	18 (9.7%)	37 (9.8%)
Some high school / vocational school (2)	11 (5.8%)	9 (4.8%)	20 (5.3%)
Completed high school / vocational school (3)	104 (54.5%)	95 (51.1%)	199 (52.8%)
Some higher education (4)	15 (7.9%)	20 (10.8%)	35 (9.3%)
Completed higher education program (5)	42 (22.0%)	43 (23.1%)	85 (22.5%)
NA	0 (0%)	1 (0.5%)	1 (0.3%)

Table 2. Adverse events among participants who reported taking at least one dose of the medication

Number of participants who took at least one dose	Varenicline (N=180)	Cytisine (N=173)
Total adverse events (number of participants who experienced at least one adverse event)	677 (131)	326 (93)
By CTCAE severity category:		
Mild	335 (92)	173 (63)
Moderate	316 (81)	135 (55)
Severe	25 (20)	18 (13)
Life-threatening	1 (1)	0 (0)
Death	0 (0)	0 (0)

CTCAE: The Common Terminology Criteria for Adverse Events version 5.0.

Figure captions and titles

Figure 1 title: Trial participant flow diagram: screening, randomization, follow-up; adherence and cessation outcomes.

Figure 1 caption: Self-reported adherence: ≥80% of the medication taken as specified by the treatment plan. All percentages are with respect to the total number of participants assigned to each treatment.

Figure 2A title: Effectiveness of cytisine treatment vs varenicline treatment for smoking cessation after 24 weeks: univariable and multivariable analyses.

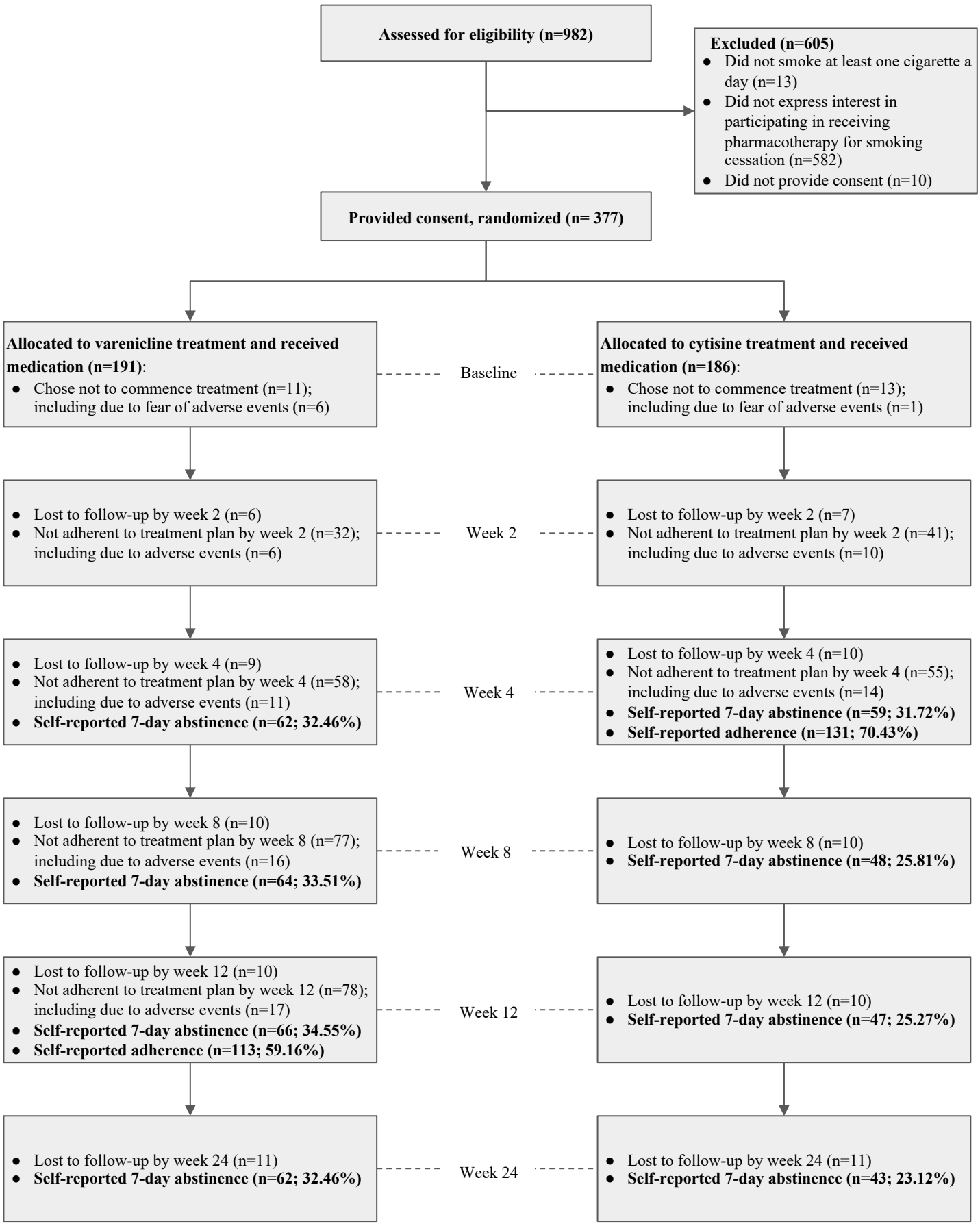
Figure 2A caption: Smoking cessation is defined as self-reported 7-day abstinence. For statistical power considerations, the Fagerström test category is treated as a continuous variable of range 1-4, indicating dependence level. Educational attainment is treated as a continuous variable of range 1-5.

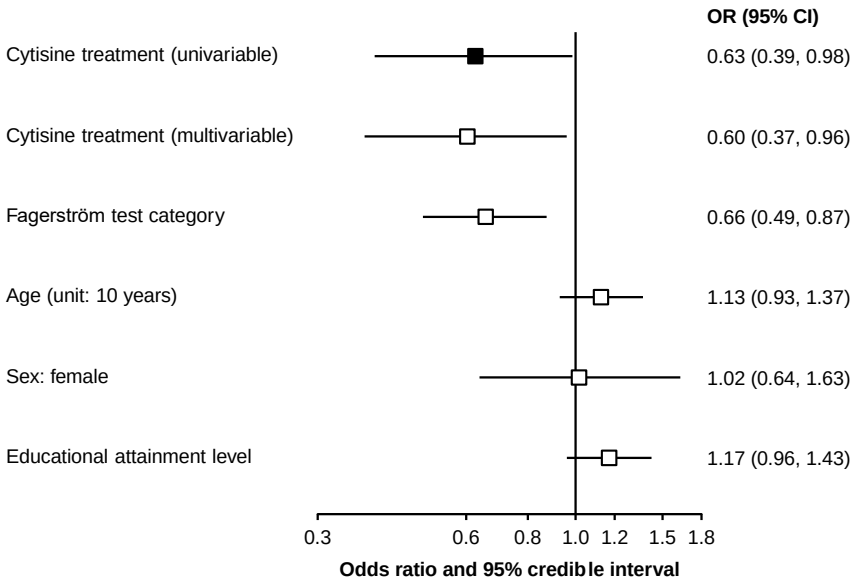
Figure 2B title: Effectiveness of cytisine treatment compared to varenicline treatment for smoking cessation over time.

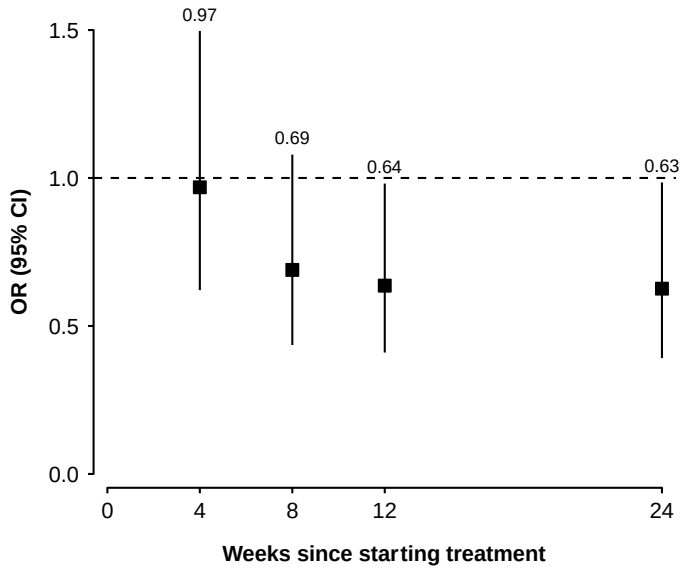
Figure 2B caption: Odds ratio estimates are written above the vertical bars indicating the 95% credible intervals.

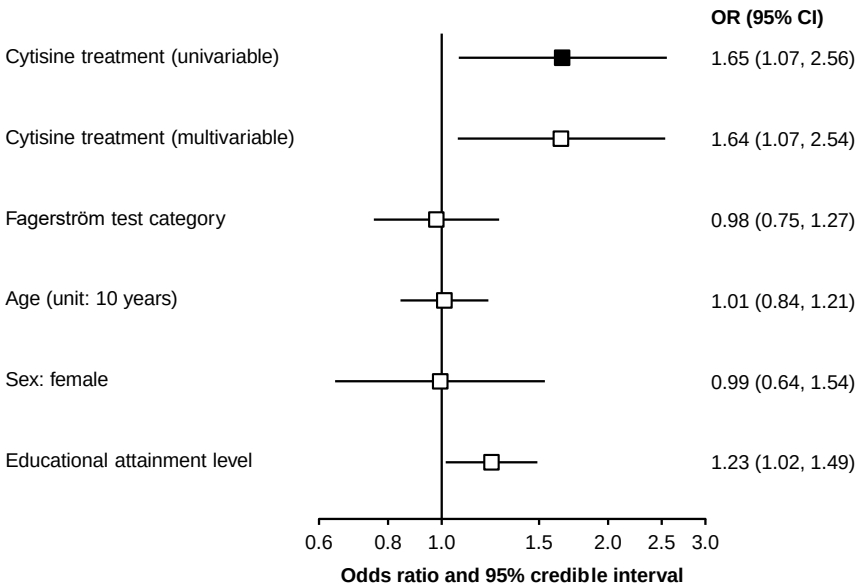
Figure 2C title: Feasibility of cytisine treatment compared to varenicline treatment: univariable and multivariable analyses.

Figure 2C caption: Feasibility is defined as self-reported adherence, that is, ≥80% of the medication taken as specified by the treatment plan.


Assessed for eligibility (n=982)
Excluded (n=605)
Did not smoke at least one cigarette a day (n=13)
Did not express interest in participating in receiving pharmacotherapy for smoking cessation (n=582)
Did not provide consent (n=10)
Provided consent, randomized (n= 377)
Allocated to varenicline treatment and received medication (n=191):
Chose not to commence treatment (n=11); including due to fear of adverse events (n=6)
Baseline
Allocated to cytisine treatment and received medication (n=186):
Chose not to commence treatment (n=13); including due to fear of adverse events (n=1)
Lost to follow-up by week 2 (n=6)
Not adherent to treatment plan by week 2 (n=32); including due to adverse events (n=6)
Week 2
Lost to follow-up by week 2 (n=7)
Not adherent to treatment plan by week 2 (n=41); including due to adverse events (n=10)
Lost to follow-up by week 4 (n=9)
Not adherent to treatment plan by week 4 (n=58); including due to adverse events (n=11)
Self-reported 7-day abstinence (n=62; 32.46%)
Week 4
Lost to follow-up by week 4 (n=10)
Not adherent to treatment plan by week 4 (n=55); including due to adverse events (n=14)
Self-reported 7-day abstinence (n=59; 31.72%)
Self-reported adherence (n=131; 70.43%)
Lost to follow-up by week 8 (n=10)
Not adherent to treatment plan by week 8 (n=77); including due to adverse events (n=16)
Self-reported 7-day abstinence (n=64; 33.51%)
Week 8
Lost to follow-up by week 8 (n=10)
Self-reported 7-day abstinence (n=48; 25.81%)
Lost to follow-up by week 12 (n=10)
Not adherent to treatment plan by week 12 (n=78); including due to adverse events (n=17)
Self-reported 7-day abstinence (n=66; 34.55%)
Self-reported adherence (n=113; 59.16%)
Week 12
Lost to follow-up by week 12 (n=10)
Self-reported 7-day abstinence (n=47; 25.27%)
Lost to follow-up by week 24 (n=11)
Self-reported 7-day abstinence (n=62; 32.46%)
Week 24
Lost to follow-up by week 24 (n=11)
Self-reported 7-day abstinence (n=43; 23.12%)


OR (95% CI)
Cytisine treatment (univariable)
0.63 (0.39, 0.98)
Cytisine treatment (multivariable)
0.60 (0.37, 0.96)
Fagerström test category
0.66 (0.49, 0.87)
Age (unit: 10 years)
1.13 (0.93, 1.37)
Sex: female
1.02 (0.64, 1.63)
Educational attainment level
1.17 (0.96, 1.43)
0.3
0.6
0.8
1.0
1.2
1.5
1.8
Odds ratio and 95% credible interval


0.97
0.69
0.64
0.63
1.5
1.0
0.5
0.0
OR (95% CI)
0
4
8
12
24
Weeks since starting treatment


OR (95% CI)
Cytisine treatment (univariable)
1.65 (1.07, 2.56)
Cytisine treatment (multivariable)
1.64 (1.07, 2.54)
Fagerström test category
0.98 (0.75, 1.27)
Age (unit: 10 years)
1.01 (0.84, 1.21)
Sex: female
0.99 (0.64, 1.54)
Educational attainment level
1.23 (1.02, 1.49)
0.6
0.8
1.0
1.5
2.0
2.5
3.0
Odds ratio and 95% credible interval