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Cytisine for smoking cessation in patients with tuberculosis: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial

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Summary

Background Smoking cessation is important in patients with tuberculosis because it can reduce the high rates of treatment failure and mortality. We aimed to assess the effectiveness and safety of cystine as a smoking cessation aid in patients with tuberculosis in Bangladesh and Pakistan.

Methods We did a randomised, double-blind, placebo-controlled, trial at 32 health centres in Bangladesh and Pakistan. Eligible patients were adults (aged >18 years in Bangladesh; aged >15 years in Pakistan) with pulmonary tuberculosis diagnosed in the previous 4 weeks, who smoked tobacco on a daily basis and were willing to stop smoking. Patients were randomly assigned (1:1) to receive behavioural support plus either oral cytisine (9 mg on day 0, which was gradually reduced to 1·5 mg by day 25) or placebo for 25 days. Randomisation was done using pregenerated block randomisation lists, stratified by trial sites. Investigators, clinicians, and patients were masked to treatment allocation. The primary outcome was continuous abstinence at 6 months, defined as self-report (of not having used more than five cigarettes, bidis, a water pipe, or smokeless tobacco products since the quit date), confirmed biochemically by a breath carbon monoxide reading of less than 10 parts per million. Primary and safety analysis were done in the intention-to-treat population. This trial is registered with the International Standard Randomised Clinical Trial Registry, ISRCTN43811467, and enrolment is complete.

Findings Between June 6, 2017, and April 30, 2018, 2472 patients (1527 patients from Bangladesh; 945 patients from Pakistan) were enrolled and randomly assigned to receive cytisine (n=1239) or placebo (n=1233). At 6 months, 401 (32·4%) participants in the cytisine group and 366 (29·7%) participants in the placebo group had achieved continuous abstinence (risk difference 2·68%, 95% CI –0·96 to 6·33; relative risk 1·09, 95% CI 0·97 to 1·23, p=0·114). 53 (4·3%) of 1239 participants in the cytisine group and 46 (3·7%) of 1233 participants in the placebo group reported serious adverse events (94 events in the cytisine group and 90 events in the placebo group), which included 91 deaths (49 in the cytisine group and 42 in the placebo group). None of the adverse events were attributed to the study medication.

Interpretation Our findings do not support the addition of cytisine to brief behavioural support for the treatment of tobacco dependence in patients with tuberculosis.

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For the Bengali translation of the Abstract see **Online** for appendix 1

For the Urdu translation of the Abstract see **Online** for appendix 2

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Introduction

Tuberculosis is one of the most common chronic infectious diseases in the world: in 2018, an estimated 10 million people had tuberculosis and around 1·5 million deaths were attributed to the disease.[1] In 2017, about 85% of tuberculosis deaths occurred in Africa and southeast Asia where the prevalence of smoking is high.[1] In the absence of smoking cessation services to treat nicotine dependence, the general population in these regions remain at risk of premature death and disabilities due to smoking. Assuming that the relative prevalence of smoking and tuberculosis remain stable, it is estimated that more than 40 million potentially avoidable tuberculosis-related deaths will be attributable to smoking by 2050.[2] Many smokers in low-income and middle-income countries (LMICs) have access to health services and each contact with these services provides an opportunity to incorporate smoking cessation treatment to help them quit. The integration of smoking cessation interventions within national and regional tuberculosis services in LMICs offers a viable solution to reduce the tuberculosis and tobacco-related disease burden.[3]

A tuberculosis treatment period of at least 6 months offers opportunities for health-care professionals to treat tobacco dependence alongside tuberculosis. Newly diagnosed patients with tuberculosis might be more motivated to stop smoking than smokers without

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See Online for appendix 3

Research in context

Evidence before this study

We searched CINAHL, Embase, MEDLINE, the Cochrane Controlled Trials Register from inception to June 1, 2020, for randomised controlled trials of smoking cessation interventions in low-income and middle-income countries (LMICs) in adult smokers with tuberculosis published in English. Two quasi-experimental studies indicated that offering behavioural support to patients with tuberculosis might result in high rates of smoking cessation and improve clinical outcomes. Our previous smoking cessation trial of behavioural support with and without bupropion in a large sample of patients with suspected and confirmed tuberculosis in Pakistan found that patients given behavioural support were seven to eight times more likely to have stopped smoking than those given usual care at 6 months. A higher cessation rate was observed in patients with confirmed tuberculosis than those with suspected tuberculosis. However, the addition of bupropion to the behavioural support intervention had no significant effect on the number of patients who had stopped smoking at 6 months. Our search yielded no other trials of pharmacological treatment (eg, nicotine replacement therapy, varenicline, or cytisine) for smoking cessation in patients with tuberculosis. Although evidence indicates that behavioural support is effective for smoking cessation in patients with tuberculosis, to the best of our knowledge, no randomised trials have been done investigating the effect of cytisine for smoking cessation in such patients.

Added value of this study

We recruited a large sample of patients with tuberculosis in Bangladesh and Pakistan to assess the effectiveness of cytisine with behavioural support for smoking cessation compared with behavioural support alone. To the best of our knowledge, this is the largest trial of cytisine for smoking cessation to date, and it is the first such trial to be done across two countries. Although the proportion of patients who achieved abstinence at 6 months was high in both groups, cytisine had no clinically or statistically significant advantage for smoking cessation when added to behavioural support in patients with tuberculosis.

Implications of all the available evidence

When offered behavioural support, a large proportion of patients with tuberculosis quit smoking, often more readily than general smokers. Patients who stop smoking are also more likely to recover from tuberculosis than those who do not. Compelling evidence supports advising and counselling patients with tuberculosis to quit smoking. However, current evidence does not support supplementation of behavioural support with pharmacological treatment in patients with tuberculosis. More research on strategies for the implementation of behavioural support for smoking cessation in routine tuberculosis care in LMICs is needed.

tuberculosis because of concerns about their illness and associated consequences.[4] By reducing the risk of tuberculosis relapses and deaths and by preventing other tobacco-related chronic conditions, the potential health benefits of smoking cessation might be even higher among patients with tuberculosis than among smokers in the general population.[5] Offering smoking cessation interventions to patients with tuberculosis should be routine and has been shown to be feasible in many contexts, although such interventions are rarely provided in LMICs.[6,7] The scarcity of low-cost, effective, and safe smoking cessation treatment options in patients with tuberculosis, in addition to several other barriers, is widely acknowledged.[8,9]

Individual counselling, alone and in combination with pharmacotherapy, is an effective strategy for smoking cessation.[10] In our previous trial of 1955 patients attending tuberculosis clinics in Pakistan, we found that two-fifths of smokers attained continuous abstinence at 6 months with behavioural support offered by health professionals.[5] However, the challenges of delivering 30–40 min of behavioural support within routine tuberculosis care including resource constraints,[9] led to the development of a shorter optimised behavioural support intervention. In addition to the provision of behavioural support, substantial evidence indicates that nicotine replacement therapy and treatment with nicotine receptor partial agonists (bupropion, cytisine, and varenicline) are effective strategies to aid smoking cessation in the general population.[11] The plant-based alkaloid cytisine is recommended as an affordable intervention, especially for LMICs.[12] The cost of cytisine is five to ten times lower than nicotine replacement therapy and varenicline, and has been found to be effective in moderate-to-heavy smokers.[12] However, the effectiveness of cytisine in patients with tuberculosis in LMICs remains unknown. We aimed to investigate the effectiveness and safety of cytisine when given in combination with brief behavioural support in patients with tuberculosis in Bangladesh and Pakistan.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled, trial at 32 health centres in Bangladesh and Pakistan. Sites were designated tuberculosis treatment centres run by the national tuberculosis control programmes of Bangladesh and Pakistan and were chosen on the basis of having the required resources and ability to recruit participants and take part in the research. The sites were 17 subdistrict hospitals in Bangladesh and 15 secondary care hospitals in Pakistan located in urban and rural areas.

Eligible patients were adults (aged >18 years in Bangladesh; aged >15 years in Pakistan, defined per the

national tuberculosis control programmes of respective countries) with pulmonary tuberculosis diagnosed in the previous 4 weeks, who smoked tobacco on a daily basis and were willing to stop smoking. Patients with extrapulmonary tuberculosis, tuberculosis complications (retreatment or any drug resistance), those receiving streptomycin or para-aminosalicylic acid, and patients using tobacco dependence medication were excluded. Patients who were pregnant or lactating, had a history of myocardial infarction, stroke, or severe angina within the previous 2 weeks, had uncontrolled high blood pressure, severe renal impairment requiring dialysis or known diagnosis of schizophrenia or epilepsy were also excluded.[13]

The study protocol (appendix 3 p 36)[13] was approved by the Ethics Committee of the University of York (York, UK) and the national ethics committees in Bangladesh and Pakistan. The trial was done in accordance with the Declaration of Helsinki and the national regulatory requirements. The trial was overseen by an Independent Steering Committee and Data Monitoring Committee (appendix 3 pp 2, 3). All participants provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive cytisine plus behavioural support or placebo plus behavioural support for 25 days using permuted blocks of eight, stratified by trial sites. Randomisation lists were pregenerated by the trial statistician at York Trials Unit (University of York) and held securely at the offices of the study partners (ARK Foundation [Dhaka, Bangladesh] and The Initiative [Islamabad, Pakistan]) for sequential allocation by masked trial coordinating staff. Investigators, clinicians, and patients were masked to treatment allocation. To maintain masking, medication packs were identical and cytisine and placebo capsules were identical in appearance, smell, and taste. Code-break envelopes were prepared separately for each medication pack, which contained the true allocation, for emergency unmasking as per the protocol.[13]

Procedures

A brief behavioural support intervention for smoking cessation was offered to all patients (appendix 3 p 5). The intervention was delivered by tuberculosis health workers in two face-to-face sessions: a 10-min session on the day of enrolment (day 0) and a 5-min session on the quit date (±2 days). The starting study drug dose was 9 mg cytisine (Desmoxan; Aflofarm, Pabianice, Poland) or placebo administered orally as six 1·5 mg capsules per day, which was gradually reduced to 1·5 mg (one capsule) by day 25, with a quit date set for day 5. The complete dosing schedule is shown in appendix 3 (p 10). The trial medication was dispensed for free by site researchers in two batches: patients were provided medication for 7 days on day 0 (at enrolment), followed by medication for 18 days on day 5, to complete the course. Clearly labelled colour-coded boxes were used for each block of varying dosing regimen (days 1–3, 4–7, 8–12, 13–16, 17–20, 21–24, and 25) and blister packs were cut out to contain the exact daily dosage. To further simplify the dosing regimen, scheduling cards were completed in the patient's presence to assist them in remembering when to take the trial medication.

Patients were followed up on day 5, weeks 5, 9, and 12, and at 6 and 12 months. These timepoints were designed to correspond to routine tuberculosis clinic visits, with the exception of visits on day 5 (to monitor for adverse drug reactions) and 12 months (to assess secondary outcomes), which were supplementary to the routine visits. Participants were not paid any incentives to attend follow-up visits, but they were reimbursed for travel expenses to attend visits that were not part of routine tuberculosis care.

Outcomes

The primary endpoint was continuous abstinence at 6 months.[14] Continuous abstinence was defined as self-report (of not having used more than five cigarettes, bidis, a water pipe, or smokeless tobacco products since the quit date), verified biochemically by a breath carbon monoxide reading of less than 10 parts per million (ppm). A negative urine cotinine test (NicAlert test strip [Nymox Pharmaceutical, Quebec, QC, Canada]; One Step urine test strip [Home Health UK, Bushey, UK]) was also required for participants who reported smokeless tobacco use at baseline.

Secondary outcomes were continuous abstinence at 12 months; point abstinence at weeks 5 and 12, and 6 and 12 months; early lapses (defined by a self-report of tobacco use [even once] after the quit date, but having point abstinence at week 5) and late lapses (defined by a self-report of tobacco use [even once] between week 5 and week 12, but showing point abstinence at week 5 and week 12); clinical tuberculosis score;[15] chest X-ray grade; sputum smear microscopy; adherence to tuberculosis treatment; tuberculosis treatment outcome (success, failure, default, relapse, or death; appendix 3 pp 58–59); Mood and Physical Symptoms Scale score; Strength of Urges To Smoke scores; and time to first use of tobacco product of the day (from the Heaviness of Smoking Index[16]).[17] Full details for all secondary outcomes are included in appendix 3 (pp 58–59). Medication adherence was measured using a pill count and a 7-day recall approach.[18] Information about supplemental smoking cessation advice sought by the patients, during the 6 months since quit date, was also reported to provide context for interpretation of study findings.

For more on the **face-to-face sessions** see https://tbandtobacco.org/

We did sensitivity analyses of the primary outcome by adjusting for baseline nicotine dependency, age, sex, and type of tobacco use, and did a complete case analysis, excluding patients who had died, were lost to follow-up, had missing self-reported abstinence data or either missing or invalid biochemical test data. We also did

exploratory subgroup analyses of the primary outcome by age, sex, type of tobacco use, tuberculosis severity, country of residence, and socioeconomic status.

Safety was assessed through adverse event collection up to week 9 and adverse events were collected through self-reports completed by patients using checklists based on common adverse events reported in the product insert of Desmoxan and previous studies of cytisine.[13] Patients who reported any moderate-to-severe symptoms were reviewed by the site-designated independent clinician, to determine the severity and expectedness, and to ascertain whether the event was associated with study treatment. The country coordinating office was notified of all serious adverse events within 24 h of site researchers becoming aware of an event, who in turn notified the York trial team within 24 h. Medically qualified staff at the country coordinating centres confirmed the causality and expectedness of events, and classified adverse events according to the Medical Dictionary for Regulatory Activities (MedDRA).[13]

For more on **Desmoxan** see www.desmoxan.pl

Data were initially collected on paper case report forms and then checked and entered at the country level through a web interface into a central trial database with inbuilt validation rules, hosted by York Trials Unit. Data were extracted periodically by the trial statisticians for the purpose of trial coordination and reporting to the independent oversight committees. Queries were resolved with country trial teams on an ongoing basis.

Statistical analysis

On the basis of cessation rates reported in previous trials,[7,19] assuming an attrition rate of 10%,[7] we calculated that a sample size of 1074 patients in the cytisine group and 1074 patients in the placebo group would provide 80% power to detect a 6% difference in the proportion of patients who had achieved continuous abstinence rates at 6 months between cytisine and placebo groups. Thus, we aimed to recruit 1194 patients in each group.

The number and proportion of abstinent participants were reported by treatment group. The between-group difference was presented as the risk difference and relative risk (RR) with 95% CIs. A p value for the effect of allocation was derived using logistic regression, with trial sites included as random-effects using robust SEs. Missing primary outcome data were treated as a negative outcome (ie, not abstinent). Any primary outcome data collected more than 4 weeks before or after the 6-month follow-up were also treated as a negative outcome. Secondary outcomes were analysed in the same manner. Since a carbon monoxide cutoff of less than 10 ppm was used for biochemical verification of self-reports of abstinence, participants reporting continuous abstinence at 6 months post-randomisation with a carbon monoxide reading of 10 ppm or more, could not be verified. We regarded these participants as not abstinent; their high carbon monoxide reading indicated that they were most likely still smoking despite reporting abstinence.

Continuous tuberculosis outcomes and nicotine dependency were analysed using linear mixed-effect regression models for all available timepoints. The number of adverse events (serious and non-serious), patients with any adverse event, and adverse events per patient in the two groups was compared using a χ^2 test. Adherence to study medication was categorised as good (≥80%), moderate (≥50%) and poor (<50%),[13] on the basis of the number of days participants self-reported to have taken medications as prescribed.

The costs of treatment for behavioural support and trial medications were collected in local currencies and converted to purchasing power parity (PPP) to pool the results across the two countries. Placebo medications were considered at zero cost. Costs were presented as purchasing power parity US$ (PPP US$) 2017 values. Missing values were imputed using multiple imputation. The imputation model included other health-care costs and quality of life for economic evaluation, which will be reported elsewhere.

All prespecified primary, secondary and safety analyses were done by intention to treat whereby patients were analysed according to their allocated treatment group regardless of their compliance with the study drug schedule. Two-sided p values of less than 0·05 were considered to indicate statistical significance. All statistical analysis were done using Stata (version 16.0).

This trial is registered with the International Standard Randomised Clinical Trial Registry, ISRCTN43811467.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 6, 2017, and April 30, 2018, of 13 934 (18%) patients with tuberculosis assessed, 2472 patients (1527 patients from Bangladesh; 945 patients from Pakistan) were enrolled and randomly assigned to receive behavioural support plus either cytisine (n=1239) or placebo (n=1233; figure; appendix 3 p 12). 11 462 (82%) patients with tuberculosis were excluded, predominantly because they were not daily smokers. Of the 2472 patients enrolled, 1142 (92%) of 1239 patients in the cytisine group and 1130 (92%) of 1233 patients in the placebo group completed the 6-month follow-up assessment (figure).

Baseline characteristics were balanced between the two treatment groups (table 1). Most participants were men (2448 [99%] of 2472 patients) and had smoked a mean of 11·1 cigarettes per day (SD 8·6) for the previous 23 years, with a quarter reporting they had previously attempted to quit.

At 6 months, 675 (54·5%) of 1239 participants in the cytisine group and 644 (52·2%) of 1233 participants in the

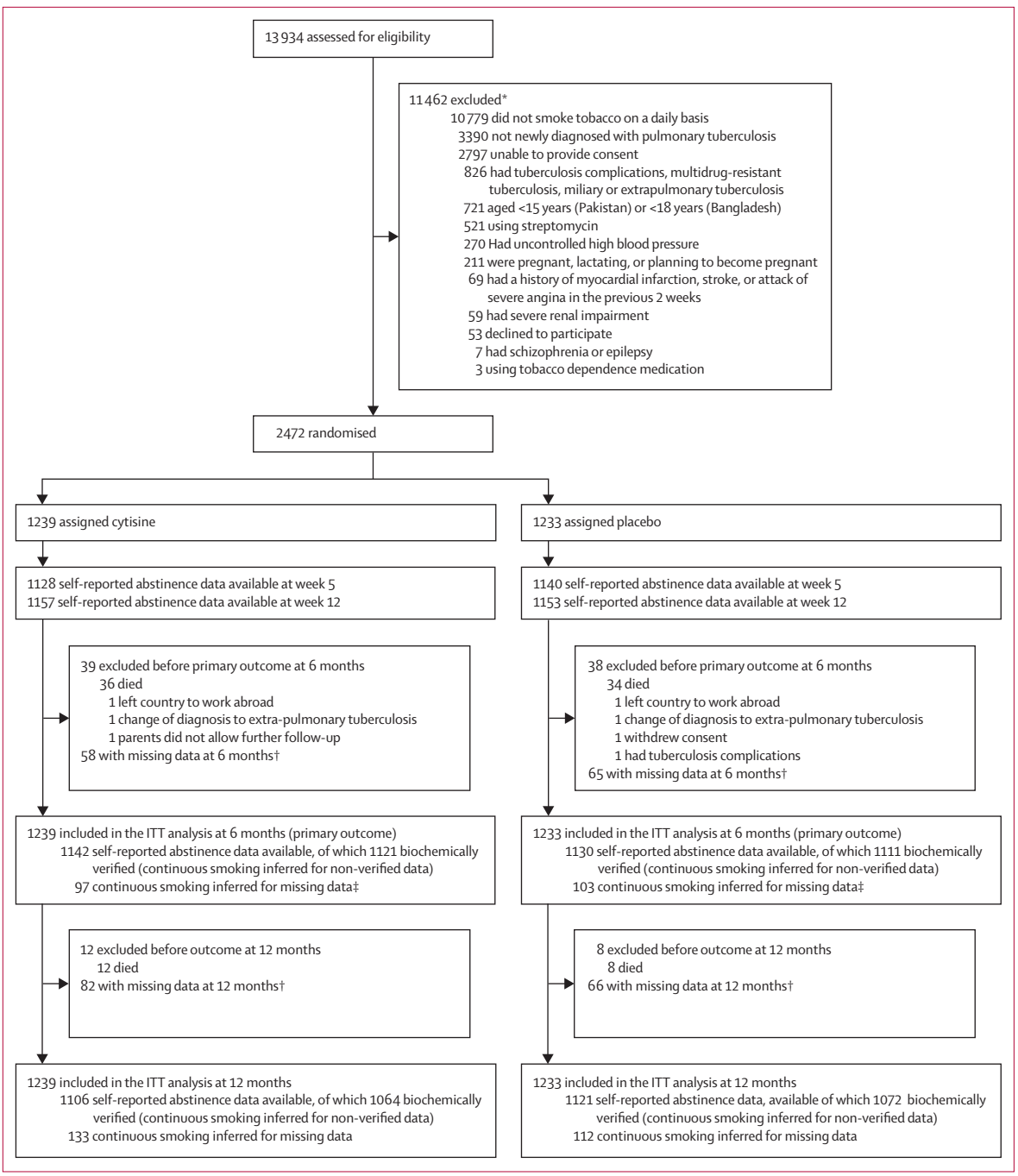

Figure: **Trial profile**
ITT=intention-to-treat. *Exclusions before randomisation could be for more than one reason. †Numbers of patients with missing data were not mutually exclusive across the 6 month and 12 month analyses; 47 patients receiving cytisine had missing data at both months 6 and 12 and 43 patients receiving placebo had missing data at months 6 and 12. ‡A status of continued smoking was inferred for any missing data.

placebo group reported continuous abstinence, which was biochemically-verified in 401 (32·4%) of 1239 participants in the cytisine group and 366 (29·7%) of 1233 participants in the placebo group (table 2). We found no difference in the proportion of patients achieving biochemically-verified continuous abstinence between the groups (risk difference 2·68%, 95% CI –0·96 to 6·33; RR 1·09, 95% CI 0·97 to 1·23). Overall, of the 1322 patients who self-reported continuous abstinence at 6 months, 767 (58%) were biochemically verified.

The analysis remained robust to additional adjustments for baseline level of nicotine dependence, age, sex, and

	Cytisine (n=1239)	Placebo (n=1233)
Age, years	42·5 (14·3)	42·4 (14·2)
Sex		
Female	12 (1·0%)	12 (1·0%)
Male	1227 (99·0%)	1221 (99·0%)
Body-mass index*	18·5 (3·1)	18·6 (3·3)
Marital status		
Single	155 (12·5%)	163 (13·2%)
Separated	2 (0·2%)	6 (0·5%)
Married	1067 (86·1%)	1044 (84·7%)
Divorced	1 (0·1%)	3 (0·2%)
Widowed	14 (1·1%)	17 (1·4%)
Tuberculosis severity score†		
Class 1	130 (10·5%)	134 (10·9%)
Class 2	587 (47·4%)	570 (46·2%)
Class 3	508 (41·0%)	514 (41·7%)
Class 4	14 (1·1%)	15 (1·2%)
Tobacco use‡		
Cigarettes	1152 (93·0%)	1149 (93·2%)
Bidi	129 (10·4%)	130 (10·5%)
Hookah	46 (3·7%)	48 (3·9%)
Electronic cigarettes	1 (0·1%)	2 (0·2%)
Smokeless tobacco	82 (6·6%)	88 (7·1%)
Other	35 (2·8%)	28 (2·3%)
Cigarettes smoked per day§	11·1 (8·1)	11·0 (9·0)
Duration of smoking, years	23·4 (14·2)	23·3 (13·8)
Previously attempted to quit	324 (26·2%)	330 (26·8%)
Strength of urges to smoke score¶‖	2·8 (1·1)	2·8 (1·1)
Time to first daily smoke, min**††		
<5 min	348 (28·1%)	332 (26·9%)
5–30	426 (34·4%)	418 (33·9%)
31–60	217 (17·5%)	220 (17·8%)
>60	246 (19·9%)	262 (21·2%)

Data are mean (SD) or n (%). Some percentages might not sum to 100 because of rounding. *Data missing for two patients in the cytisine group and one patent in the placebo group. †Based on the presence of eight tuberculosis related signs and symptoms (eg, chest pain or being underweight), summarised into four severity classes: class 1 (0–1 symptoms), class 2 (2–3 symptoms), class 3 (4–7 symptoms), and class 4 (8 symptoms).[15] ‡Categories were not mutually exclusive—ie, some patients reported more than one type of tobacco use. §Data missing for 91 patients in the cytisine group and 84 patients in the placebo group. ¶Data missing for one patient in the cytisine group. ‖Urge to smoke in the past 24 h was scored on a scale from 0 to 5, whereby 0 indicated no urge to smoke and 5 indicated a continuous urge to smoke. **Tobacco dependence was measured using the time to first use of tobacco product after waking component of the Heaviness to Smoke Index.[17] ††Data missing for two patients in the cytisine group and one patient in the placebo group.

Table 1: **Baseline characteristics**

type of tobacco use; excluding the 70 patients who died before 6 months follow-up and for whom a trial outcome of continued smoking status was imputed; and a complete case analysis further excluding 170 patients with missing data (comprising seven patients excluded for other reasons, 123 patients lost to follow-up and 40 patients who indicated self-reported quitting but for whom no biochemical verification was available; appendix 3 p 17). Reasons for missing data were primarily associated with loss to follow-up or missing biochemical verification data.

The proportion of patients who had achieved self-reported abstinence was higher in the cytisine group than the placebo group at 5 weeks (risk difference 4·40, 95% CI 0·54 to 8·27), 12 weeks (3·14, –0·79 to 7·07), 6 months (4·42, 0·58 to 8·26), and 12 months (3·32, –0·38 to 7·02; table 2), but these differences were not statistically significant. However, we found no difference between the groups in the proportion of patients with biochemically-verified continuous abstinence at 12 months (2·64, –0·71 to 5·98). Of the participants who were abstinent at 5 weeks, a similar proportion had early lapses in the two groups (0·78, –1·21 to 2·77; appendix 3 p 18). The proportion of patients who had late lapses between weeks 5 and 12 were also similar between the groups (0·05, –1·63 to 1·72). Of the 839 patients who reported smoked tobacco use only at baseline and self-reported some form of tobacco use at 6 months, 717 (85%) remained tobacco smokers only (n=347 in the cytisine group; n=370 in the placebo group), 61 (7%) reported smoked and smokeless tobacco use (n=31 in the cytisine group; n=30 in the placebo group) and 61 (7%) reported use of smokeless tobacco only at 6 months (n=31 in the cytisine group; n=30 in the placebo group).

At 6 months, 1007 (89·5%) of 1125 patients in the cytisine group and 1018 (91·2%) of 1116 patients in the placebo group had achieved tuberculosis treatment success (ie, cured or had completed treatment) and at 12 months, 899 (81·4%) of 1105 had achieved treatment success in the cytisine group compared with 927 (83·0%) of 1117 patients in the placebo group (table 3). Mean clinical tuberculosis scores decreased from 3·4 (SD 1·6) at baseline to 1·0 (1·3) at 12 months in both treatment groups (appendix 3 pp 13, 19–20). We observed no significant differences in the outcomes of sputum smear microscopy, tuberculosis treatment adherence, and chest x ray grade between the groups (appendix 3 pp 21–23). Mood and Physical Symptoms Scale and Strength for Urges To Smoke scale scores were similar between the groups (appendix 3 pp 14, 24). Self-reported medication compliance was high (>90%) and similar in both treatment groups (appendix 3 p 25). Reasons for withdrawals from treatment and non-compliance are listed in appendix 3 (pp 26, 27).

An insufficient number of women (n=24) were enrolled to enable meaningful subgroup analysis by sex. Among individuals who were exclusive smokers (ie, not dual tobacco users), a small absolute difference was identified in the proportion of patients who had achieved continuous abstinence at 6 months between the cytisine and placebo groups, but this difference was not statistically significant (399 [34%] of 1157 patients in the cytisine group *vs* 356 [31%] of 1145 patients in the placebo group; RR 1·11,

95% CI 0·99 to 1·25; appendix 3 p 15). In the placebo group, the proportion of patients who had achieved continuous abstinence at 6 months was higher among dual users (ie, those who smoked and reported smokeless tobacco at baseline) than those who only smoked tobacco (p=0·024 for the interaction with allocated treatment; appendix 3 p 15). However, differences in abstinence rates between dual users and exclusive smokers were not consistent at earlier timepoints, and the number of participants was small (12 [7%] of 170 dual users were abstinent at 6 months). The difference in the proportion of participants who had achieved continuous abstinence at 6 months between the cytisine and placebo groups was slightly larger in Pakistan than Bangladesh, but this difference was not statistically significant (6% in Pakistan [157 (33%) of 476 patients in the cytisine group and 127 (27%) of 469 patients in the placebo group] *vs* 1% in Bangladesh [244 (32%) of 763 patients in the cytisine group and 239 (31%) of 764 patients in the placebo group]); p=0·118 for the interaction term; appendix 3 p 15).

The mean cost of cytisine was PPP US$48·27 (SE 0·36) per participant in the cytisine group. The mean costs of training health-care workers and delivering behavioural support were similar between the two groups (PPP US$60·65 [SE 0·41] in the cytisine group *vs* PPP US$12·37 (SE 0·08) in the placebo group; between-group difference PPP US$48·28 [95% CI 47·71–48·80]).

53 (4·3%) of 1239 participants in the cytisine group and 46 (3·7%) of 1233 participants in the placebo group reported serious adverse events (94 events in the cytisine group and 90 events in the placebo group), but this difference was not statistically significant (RR 1·07, 95% CI 0·89 to 1·29; p=0·488; table 4). Serious adverse events included 91 deaths (49 in the cytisine group and 42 in the placebo group). Other serious adverse events reported more than twice were breathing difficulties (n=4 events in the cytisine group; n=6 events in the placebo group), fever (n=1 cytisine group; n=3 placebo group), lung cancer (n=9 cytisine group; n=6 placebo group), myocardial infarction (n=8 cytisine group; n=5 placebo group), stroke (n=3 cytisine group; n=2 placebo group), chest pain (n=1 cytisine group; n=2 placebo group), and haemoptysis (n=2 cytisine group, n=1 placebo group). None of these serious adverse events (including deaths) were attributed to the study medication. Expected and other reported non-serious adverse events are summarised in appendix 3 (pp 29, 30). 98 (7·9%) of 1239 patients in the cytisine group and 86 (7·0%) of 1233 patients in the placebo group had one or more non-serious adverse events (RR 1·13, 95% CI 0·86 to 1·50). A full list of serious and non-serious adverse events are shown in appendix 3 (pp 33–35).

594 (24%) of 2472 enrolled patients sought supplemental smoking cessation advice (appendix 3 p 35), the majority of the supplemental smoking cessation advice was provided by public hospitals; the mean number of times a patient sought advice was similar between the cytisine group (2·5 times [SD 1·6]) and the placebo group (2·5 times [2·0]). The proportion of patients who sought supplemental smoking cessation advice was similar between the cytisine (n=299 [26%]) and placebo (n=295 [26%]) groups.

	Cytisine (n=1239)	Placebo (n=1233)	Risk difference (95% CI)	Risk ratio (95% CI)
Continuous abstinence at 6 months				
Self-reported	675 (54·5%)	644 (52·2%)	2·25% (–1·68 to 6·18)	1·04 (0·97 to 1·12)
Biochemically verified*	401 (32·4%)	366 (29·7%)	2·68% (–0·96 to 6·33)	1·09 (0·97 to 1·23)
Continuous abstinence at 12 months				
Self-reported	600 (48·4%)	585 (47·4%)	0·98% (–2·96 to 4·92)	1·02 (0·94 to 1·11)
Biochemically verified	309 (24·9%)	275 (22·3%)	2·64% (–0·71 to 5·98)	1·12 (0·97 to 1·29)
Self-reported point abstinence				
5 weeks	762 (61·5%)	704 (57·1%)	4·40% (0·54 to 8·27)	1·08 (1·01 to 1·15)
12 weeks	685 (55·3%)	643 (52·1%)	3·14% (–0·79 to 7·07)	1·06 (0·99 to 1·14)
6 months	509 (41·1%)	452 (36·7%)	4·42% (0·58 to 8·26)	1·12 (1·01 to 1·24)
12 months	426 (34·4%)	383 (31·1%)	3·32% (–0·38 to 7·02)	1·11 (0·99 to 1·24)

Data are n (%). *Primary outcome (continuous abstinence at 6 months, defined as self-report [of not having used more than five cigarettes, bidis, waterpipe sessions, or smokeless tobacco products since the quit date], confirmed biochemically by a breath carbon monoxide reading of less than 10 parts per million).

Table 2: **Primary and key secondary tobacco cessation outcomes**

	Cytisine (n=1239)		Placebo (n=1233)	
	Patients with available data	All randomly assigned patients	Patients with available data	All randomly assigned patients
Cured or completed treatment at 6 months	1007/1125 (89·5%)	1007 (81·3%)	1018/1116 (91·2%)	1018 (82·6%)
Cured or completed treatment at 12 months	899/1105 (81·4%)	899 (72·6%)	927/1117 (83·0%)	927 (75·2%)

Data are n/N (%) or n (%).

Table 3: **Tuberculosis treatment success**

	Cytisine (n=1239)	Placebo (n=1233)
Total number of severe adverse events	94	90
Possibly/probably related to study drug	0	0
Patients with one or more severe adverse events	53 (4·3%)	46 (3·7%)
Severe adverse events in ten or more individuals		
Deaths	49 (4·0%)	42 (3·4%)
Lung cancer	9 (0·7%)	6 (0·5%)
Myocardial infarction	8 (0·6%)	5 (0·4%)
Difficulty breathing	4 (0·3%)	6 (0·5%)

Data are n or n (%).

Table 4: **Serious adverse events**

Discussion

The proportion of patients who achieved abstinence at 6 months did not significantly differ between the cytisine and placebo groups, which shows that cytisine

had no additional benefit for smoking cessation in patients with tuberculosis. The risk difference in 6-month continuous abstinence rates between the two treatment groups (2·68%) was less than the difference of 6% that would represent a clinically significant difference. Moreover, the observed risk difference was not statistically significant, although the upper limit of the 95% CI was above 6%. This finding was consistent across all secondary tobacco cessation outcomes. The number of adverse events were balanced between the two groups. No serious adverse events were attributed to study medication, and cytisine seemed to be well-tolerated. The proportion of patients with available data for continuous abstinence (92%) was high and similar in both groups.

A 2018 meta-analysis of all cytisine trials (n=4216; sample size range 150–1214) showed that smoking cessation rates among patients given cytisine improved by 75% compared with patients given placebo.[12] Additionally, a non-inferiority trial found cytisine to be more effective than nicotine replacement therapy.[20] However, the absolute difference in cessation rates between cytisine and placebo in our trial was lower than that reported in previous trials, possibly due to certain contextual and population differences. In subgroup analyses, a non-significant difference in cessation rates in favour of cytisine was noted in those who smoked exclusively (34% in the cytisine group *vs* 31% in the placebo group). By contrast to our trial, previous trials recruited healthy participants. The participants included in our study were recently diagnosed with pulmonary tuberculosis and, as part of behavioural support, learned about the association between smoking and their condition. The proportion of patients in the placebo group who met the primary endpoint (29·7%) indicates that the participants had a strong motivation to quit. In our previous trial of patients presenting with tuberculosis symptoms, 41% of participants achieved abstinence by 6 months with behavioural support; however, the sessions were longer in duration (30–45 min) than those in the current study.[7] This difference in intrinsic motivation between specific groups and the general population is also exemplified during pregnancy when high quit rates are achieved with behavioural support alone.[21] Another key difference between our participants and those included in the previous cytisine trials is the extent of nicotine addiction. The mean number of cigarettes smoked per day in previous cytisine trials were higher (19·3 cigarettes per day [SD 11·9];[20] 23·0 cigarettes per day [8·7][22]) than in our trial (11·1 cigarettes per day [8·1]). Generally, heavy smokers with high nicotine dependence are more likely to benefit from medication[23] by attenuating their withdrawal symptoms than are light smokers.[12] However, the proportion of participants in Pakistan (who smoked a mean 12·9 cigarettes per day) who had achieved abstinence by 6 months (33% in the cystine group *vs* 27% in the placebo group) did not significantly differ from the proportion in Bangladesh (mean 9·8 cigarettes per day; 32% achieved abstinence in the cystine group *vs* 31% achieved abstinence in the placebo group). Moreover, our pragmatic trial was done in clinical settings where some loss of effectiveness is expected when compared with explanatory trials.

To the best of our knowledge, this is the largest trial of cytisine for smoking cessation to date, and is the first such trial to be done across two countries. Bangladesh and Pakistan were selected because of existing partnerships with academics and tuberculosis programmes, local knowledge, and previous experience of doing trials in these countries. With the exception of a small trial (n=171) in Kyrgyzstan,[24] this is the first trial of cytisine and one of the few smoking cessation trials to be done in LMIC settings. Other strengths of this study were the rigor and quality with which the trial was done and the assessment of abstinence at 12 months, which represents a longer follow-up than is usually done in smoking cessation trials, and tuberculosis outcomes. Approximately, 42% of participants who self-reported continuous abstinence at 6 months could not be verified biochemically. This finding is consistent with the accuracy of self-report from other smoking cessation clinical trials[25] and our previous trial[7] in patients suspected to have tuberculosis in Pakistan, where about half (49%) of the self-reports could be biochemically validated. This difference could be explained by multiple factors including social desirability in response to participation in a smoking cessation trial or wanting to avoid stigma that might be associated with continued smoking considering that it will worsen tuberculosis outcomes,[25] and poor air quality that is likely to be a contributor to higher carbon monoxide levels than the cutoff used.[26]

Our trial had some limitations. First, our assessment of adherence to the trial medication was self-reported.[27] Considering the complexity of the cytisine dosing schedule and anti-tuberculosis comedication, adherence to study medication might have been lower than reported. Although a lower level of adherence would not influence the difference between the cytisine and placebo groups, it might have resulted in a lower proportion of patients achieving abstinence across the two groups. Second, the stability and pharmacovigilance of cytisine have not yet been assessed in non-European climates. Although we ensured medication storage conditions were within the manufacturer's recommendations, exposures to high temperatures or humidity might have led to instability and loss of efficacy. Third, our trial was not powered to detect differences in secondary tuberculosis outcomes or for subgroup analysis. Fourth, only a small number of women were recruited, which might limit the generalisability of our findings; however, this is likely to be due to low smoking prevalence among women in south Asia and might also

be due to sex-specific barriers in seeking cessation support (eg, stigma), which requires further exploration.[28] The effectiveness of cytisine requires assessment when administered using simplified dosing schedules, in combination with other medications, with intensive behavioural support or without behavioural support. Pharmacovigilance studies are also needed to assess the stability of cytisine in a variety of geographical regions. Affordable smoking cessation aids such as cytisine are currently under consideration for licensing in high-income countries, thus a need exists to assess such options for smoking cessation in LMICs and in smoking-attributable disease groups.

The addition of cytisine to brief behavioural support was not effective for smoking cessation in routine tuberculosis care. Health professionals should continue to question patients with tuberculosis about their smoking status and offer interventions to support smoking cessation, consistent with current national or international guidance.

Contributors

OD drafted the manuscript, contributed to study design, study conduct, and interpretation of findings. AKe contributed to methods and results sections of the manuscript, data management, and statistical analysis. AR and AMM managed the study and contributed to interpretation of findings. DK, EK, MB, and HE provided insights to study design with regard to aspects of behavioural support implementation, evaluation of its delivery, and interpretation of findings. RH, DB, RF, AKh, RZ, and SM conducted the study in Bangladesh and Pakistan, collected and managed the data, and provided important input for data analysis and interpretation. RG contributed to study design, study conduct, and interpretation of results, and provided supervision and provided crucial input for the analysis. SP and JL designed and completed the cost analysis. AS oversaw study design, trial conduct, interpretation of findings, and drafting of the discussion. KS conceptualised the study, contributed to the study design, study conduct, interpretation of findings, and writing of the manuscript. All authors provided critical revisions and approved the final manuscript.

Declaration of interests

DK reports an unrestricted grant from Pfizer in 2009 for an investigator-initiated trial on the effectiveness of practice nurse counselling and varenicline for smoking cessation in primary care (Dutch Trial Register NTR3067). EK reports participation in clinical studies by Pfizer, and has received grants from Pfizer, before and during the conduct of the study. KS reports a research grant from Pfizer to study the effects of varenicline on waterpipe smoking cessation. All other authors declare no competing interests.

Data sharing

Partial anonymised datasets will be made available upon request for the purpose of academic research. Requests should first be directed to Kamran Siddiqi (Chief Investigator), so that a data request form can be sent to the York Trials Unit to ascertain details of the research proposed and enable appropriate datasets to be shared. Data will be available once all planned secondary papers are published. The protocol is available in appendix 3 (p 36) and the statistical analysis plan will also be provided on request.

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