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Title: Varenicline versus placebo for waterpipe smoking cessation: A double-blind randomised-controlled trial

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Clinical trial Registration

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Declaration of competing interests:

The trial was funded from GRAND 2014, supported by Pfizer, an annual grants programme independently reviewed and awarded.

Abstract

Background and Aims

Waterpipe tobacco smoking is a growing public health concern. There is limited research using pharmacotherapy and no research using varenicline (established treatment for smoking cessation) in waterpipe-smokers. We tested the efficacy of varenicline in achieving abstinence from all tobacco use among waterpipe-smokers.

Design

Two-arm, parallel group, placebo-controlled, double-blind, multi-centre (n=4), individually randomised trial with follow-up to 25 weeks.

Settings

District General Hospitals and catchment communities within four districts of Punjab, Pakistan.

Participants

Adult daily waterpipe-smokers (N= 510; 253 in varenicline & 257 in placebo arms), who were interested in quitting, were recruited and analysed between March and November 2016. Of these, 220 (87%) in the varenicline and 239 (93%) in the placebo arms completed all follow-ups. Participants were on average aged 49 (SD 15.2) years, daily smokers and smoked for the last 27 (SD 15.9) years. More than half (261, 51.2%) also smoked cigarettes.

Intervention and comparator

All trial participants received two structured sessions of Behavioural Support (of 30 and 10 minutes) one at the time of registration and the other one week later. Participants were randomised to varenicline (active arm) and placebo (control arm) stratified on district, sex and concomitant cigarette smoking. Varenicline and placebo were dispensed as identical unlabelled tablets for 12 weeks: 0.5 mg for one week (once on days 1-3, twice on days 4-7) and 1mg for the subsequent 11 weeks (twice daily).

Measurements

The trial participants were followed-up for a period of 25 weeks post-randomisation. The primary outcome was 7-day repeated point prevalence abstinence from all forms of tobacco, self-reported at each of week 5, 12 and 25, verified by carbon-monoxide cut-off <10ppm.

Findings

No evidence of statistically significant difference in repeated point prevalence abstinence between the varenicline (12/253; 4·7%) and placebo (11/257; 4·3%) arms (RR = 1·11, 95%CI = 0·50-2·47, p=0·80) was observed (Bayes Factor = 0·048). Adverse events reported in 27 participants were 34 (15 in varenicline and 19 in placebo); none was serious.

Conclusions

Varenicline was not more effective than placebo in aiding cessation of tobacco use in long-term daily waterpipe smokers.

Funding

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Key words: smoking, waterpipe, hookah, shisha, cessation, addiction, behaviour, varenicline

Introduction

Use of a waterpipe (also known as hookah, shisha or narghile in various countries) to smoke tobacco is a major and growing public health concern (1). After remaining embedded within Middle-Eastern and South-Asian culture for over 400 years, waterpipe smoking has recently increased in popularity in these and other parts of the world (2). A waterpipe is a stemmed, water-containing apparatus in which tobacco is heated by burning charcoal. A mixture of tobacco and charcoal smoke is then inhaled through a hose attached to the apparatus. One waterpipe session can last a few minutes to several hours (3).

The recent emergence of waterpipe smoking is largely attributed to the introduction of tobacco flavourings, its commercialisation and social desirability particularly among youth (2, 4). Contrary to the commonly held beliefs that waterpipe smoking is a 'safer' alternative to cigarette smoking (5), evidence suggests that waterpipe smoking is harmful (6). As with other forms of tobacco, dependence is a key characteristic of waterpipe smokers, who exhibit cravings and withdrawal symptoms, even with an infrequent use pattern (7-9). The mixture of tobacco and charcoal smoke contains tobacco-specific nitrosamines, volatile aldehydes, heavy metals and other toxic substances, leading to illnesses commonly attributed to cigarette smoking (10, 11). A recent meta-analysis found a positive association between waterpipe smoking and lung (OR 4·6, 95%CI 2·6-8·0) and oesophageal cancers (OR 3·6, 95%CI 1·4-9·4) (12).

A recent systematic review on waterpipe prevalence globally found four studies from Pakistan (13). A national survey, assessing "ever daily waterpipe smoking", reported a prevalence of 2.2%. Three other studies reporting an unspecified measure of prevalence ranged between 3.9% among adults to 48.0% among university students. In line with the literature, Middle Eastern and south Asian adults are more likely to smoke waterpipe on a daily basis as compared to adolescents who smoke intermittently.

There is strong evidence for the success of cigarette smoking cessation interventions, including behavioural support and pharmacotherapies such as varenicline (14, 15). Varenicline, a high-affinity partial agonist for the α4β2 nicotinic acetylcholine receptors, has also shown to be more effective and cost-effective than nicotine replacement therapy (NRT) (16) (getting an additional 50-70% people to quit) or bupropion (17), respectively. Combining varenicline with behavioural support has further potential to increase cessation success (18). Annually, 18,000 premature deaths (7,000 cancer-related) are averted as a result of these interventions in England alone (19). The National Institute for Health and Care Excellence recommends use of behavioural support, NRT and varenicline in cigarette smoking cessation (20). However, the evidence to support the use of varenicline and other pharmacotherapies in waterpipe smoking cessation is absent (21). Two randomized controlled-trials on waterpipe cessation have been published so far. One assessed intense versus brief behavioural support in Syria and showed no difference in prolonged abstinence at 3 month follow up (relative risk (RR) 1.46 95% CI 0.69–3.09) (22). The second assessed buproprion plus behavioural support versus standard care in Pakistan, and showed an increase in smoking abstinence at 25 weeks in the intervention group (RR 2.3, 95% CI 1.3-4.7) (23). This paper presents the findings of the first randomised controlled trial to assess the effect of varenicline and the largest so far to evaluate any pharmacotherapy in waterpipe smoking cessation.

We tested the efficacy of varenicline in achieving six months abstinence from all forms of tobacco among waterpipe-smokers who were willing to quit. The specific aims were to compare varenicline with placebo to test the differences in: (a) six months repeated point prevalence abstinence, and (b) point abstinence at week 5, week 12 and week 25 from all forms of tobacco among water-pipe smokers. We also compared varenicline with placebo to test the differences in: (c) early and late relapse; (d) self-reported medication adherence at week 1, week 5 and week 12, and (e) adverse events.

Methods

Study design

This two-arm, double-blind, placebo-controlled, randomised trial was conducted in four large districts of Punjab, Pakistan. Based in three district hospitals (Chakwal, Khushab, Mandi Bahauddin districts) and a teaching hospital (Rawalpindi district), the study recruited participants from a large catchment population, based in both urban and rural settings. We obtained ethics approval from the respective research ethics committees at the Pakistan Health Research Council, all participating hospitals and the University of York. The trial protocol has been published elsewhere (24).

Participants

We recruited adults (18 years of age and above) who smoked waterpipe on a daily basis ($\geq$25 days in a month) for at least six months and were motivated to quit all forms of smoking. Participants were told that the purpose of the treatment was to help them quit permanently. We excluded people if they: had used any smoking cessation medications in the last 30 days; were pregnant, lactating, or planning to become pregnant; required hospitalisation; had an allergic reaction to varenicline in the past; or had unstable angina, untreated cardiac arrhythmia, myocardial infarction, cardiac procedure (in last three months), uncontrolled hypertension, stroke, chronic kidney disease, epilepsy or severe mental illnesses. We also excluded people who chewed smokeless tobacco and/or those with substances (including alcohol) misuse.

We identified potential participants either from hospitals' outpatient departments or from their catchment areas within community settings. We gave eligible participants verbal and written information about the trial, and 24 hours to consider participation, and obtained written consent from those interested.

Randomisation

In addition to behavioural support, we randomly assigned participants (1:1) to receive either varenicline or placebo, using a computer-generated allocation sequence at the University of York. The system, created in software R v3·2·2 (25), generated a permuted block randomisation list for each study site, with stratification factors including district, sex and concomitant cigarette smoking (derived from previous research) (23). Based on this random sequence, the system allocated each newly recruited participant either to varenicline or to the placebo arm. For treatment allocation, the researcher at each study site called the central research office. On receiving the basic information on recruiting district, sex, and concomitant smoking, the central research office generated a trial ID, by running a pre-specified code (for each random block). At allocation, research teams at the study sites and at the central office were unaware of the treatment condition associated with each trial ID. The trial ID corresponded to that on the treatment packs already made available at each of the participating hospital. To ensure double blinding, we used identical medication packs for both placebo and varenicline, which were labelled with a unique trial ID. All investigators, researchers and participants remained blinded to the allocation until the trial data were analysed.

Procedures

Once registered, we randomised trial-participants to receive either varenicline or placebo. In addition, we offered behavioural support to all participants.

Varenicline

Varenicline was manufactured and provided by Pfizer, Germany, in the form of unlabelled tablets. Once allocated to the varenicline arm, participants received their first week's supply to be taken prior to their quit date; the dosage was 0·5 mg tablet once daily on days 1-3 and twice daily on days 4-7. Another 11 weeks' supply was dispensed on day 8, coinciding with their quit date; the dosage was 1mg tablet twice daily. The participants were encouraged to complete the full course of medication treatment at the outset and the importance of treatment adherence was reinforced at

each follow up. Self-reported medication adherence was assessed using seven-day pill intake recall (at week 1, week 5 and week 12) by asking participants if they took their pills on each day of the previous week.

Placebo

Participants allocated to placebo were dispensed medication in exactly the same manner as described above for varenicline i.e. unlabelled pack of 0·5mg tablets in the first week and 1mg pack for the following 11 weeks.

Behavioural support

We offered behavioural support, consisting of two structured sessions, to all participants. Grounded in formative work (26), the sessions and the accompanying materials were designed to: (a) raise awareness about the harms of smoking (including waterpipe) and the advantages of quitting; (b) address common misperceptions specific to waterpipe smoking; (c) assist in planning a quit date, get social support and remove environmental cues; and (d) identify common triggers and withdrawal symptoms and suggest culturally appropriate coping strategies. A 30-minute session at enrolment encouraged participants to set a quit date and a 10-minute follow-up session a week later helped in reviewing progress and offering further support.

Data collection and follow-ups

On enrolment, we asked all participants about their age, sex, ethnicity, socio-economic status, smoking behaviour (including type(s), quantity, duration and frequency), motivation to quit, withdrawal symptoms using Mood and Physical Symptoms Scale (MPSS) (27) and dependency assessments using the Lebanon Waterpipe Dependency Scale (LWDS-11) (9). Follow-up at weeks 5, 12 and 25 assessed self-reported smoking status, carbon monoxide (CO) breath test, smoking urges using Strength of Urges To Smoke (SUTS) scale (9) and withdrawal symptoms and dependency using MPSS and LWDS, respectively. In addition, medication adherence and adverse events reviews were also carried out at all follow-ups.

Participants' phone numbers were obtained at the time of consent. The research staff remained in contact as they often delivered trial medications and conducted follow-ups during home visits. Where participants were recruited through community leaders, follow-ups were also arranged by first contacting them.

Outcomes

The primary outcome was six-months' repeated point prevalence (28) abstinence from all forms of tobacco, defined as self-reported point abstinence (not even a puff/chew/session in the previous 7 days) at each of week 5, 12 and 25 verified by CO cut-off <10ppm, measured by MicroCO (Micro Medical ltd., United Kingdom). Secondary outcomes included:

1. Point abstinence (not even a puff/chew/session in the previous 7 days) either at week 5, 12 or 25 verified by CO cut-off <10ppm.
2. Early-relapse, defined by a point abstinence at week 5 but a smoking status at week 12.
3. Late-relapse, defined by a point abstinence at week 5 and week 12 but a smoking status at week 25.

The MPSS (27) translated in Urdu and administered at baseline, week 5, 12 and 25, assessed withdrawal symptoms, including anxiety, depression, irritability, restlessness, hunger, concentration and sleep disturbance. The 11-item LWDS-11 (9), (also translated to Urdu), assessed waterpipe smoking dependence at baseline and weeks 5, 12 and 25. Its four subscales represented nicotine dependence, negative reinforcement, psychological craving and positive reinforcement.

We had procedures to identify, record, report and manage adverse events (24). All trial participants were encouraged to report and researchers were trained to enquire, record, report and assess (medically-qualified researcher only) any such events throughout the participants' follow-up. Once identified, all serious adverse events triggered urgent reporting (a cascade of phone calls and prescribed forms) and management protocol (involving a named hospital physician) within 24 hours.

We coded all clinical events using the Medical Dictionary for Regulatory Activities (MedDRA) (29), and collated and reported all adverse events data to the trial sponsors and the Independent Trial Steering Committee at six-monthly intervals. We also included checks to ensure data quality, which included calling 10% of all participants to validate the information provided to us by our field staff.

Statistical analysis

The sample size assumptions for this two-arm, double-blind, placebo-controlled, randomised trial were based on our previous clustered randomized controlled-trial in Pakistan (30) involving 1,955 participants (including waterpipe smokers), which gave an estimate of 37% continuous abstinence at 25 weeks for the behavioural support arm of the trial. Furthermore, we were interested in detecting a difference of an additional 13 percentage points in the varenicline group. This difference represents the median difference reported in the systematic review of Cahill et al. (15), which included trials looking at the effectiveness of varenicline. In order to detect an absolute difference of 13% in the varenicline versus the placebo group, with 80% power and 5% significance, 228 patients were required per arm. Allowing for a 10% dropout, a total of 508 patients were needed for recruitment.

Baseline data, including demographic variables, were summarised descriptively by trial arm but no formal statistical comparisons were undertaken. Continuous measures were reported as means and standard deviations (SD), while categorical data were reported as counts and percentages. The main analysis was based on intention-to-treat and hence all lost-to-follow-ups were imputed as smokers. We used log-binomial regression for the primary outcome, to estimate any difference in risks between the two arms of the study. A similar approach was used for the binary secondary outcomes; namely point abstinence at weeks 5, 12, and 25. Furthermore, we repeated the previous analyses adjusting for the stratification variables sex, concomitant smoking, and district, which we controlled for as a fixed effect in one instance and as a random effect in another. We also reported the Bayes factor for the primary outcome; put simply, the Bayes factor compares the likelihood of the observed data under the alternative hypothesis versus the null hypothesis (31-33).

A significance level of 0·05 was used for the primary analysis, whereas 0·10 was used for secondary analyses in order to allow for exploration of potential future hypotheses· All analyses were conducted using SAS, version 9·4 (SAS Institute, Cary, North Carolina). Due to this being a potentially low-risk trial, there was no separate Data Monitoring Committee. However, the Independent Trial Steering Committee performed the data-monitoring role. The trial was registered at the ISRCTN registry**:** ISRCTN94103375.

Role of Funding Source

The funder (Pfizer) of the study had no role in the 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.

Protocol Amendments

The following amendments were made in the protocol after the commencement of the trial. The primary outcome was defined as 'self-reported continuous abstinence for six-months' at the outset. However, our questionnaire design did not allow us to use the Russell Standard (as per protocol). Instead, we used 'repeated point prevalence abstinence' criteria as defined by the Society for Research on Nicotine and Tobacco (28). The design also did not allow us to measure 'early lapse' and 'late lapse'.

Results

Recruitment and Follow-up

Between March 8 and November 30, 2016, we screened 557 waterpipe smokers, out of which 553 (99%) were willing to quit smoking. Out of the 557 screened, 510 were recruited; 30 were not eligible, 11 did not consent and 6 could not participate for miscellaneous reasons (Figure 1). Of all 510 participants, 253 were assigned to the varenicline arm and 257 to the placebo arm. Of these, four did not receive allocated treatment. Repeated point prevalence abstinence, the primary outcome, was ascertained for 459 (90%) participants: 220 (87%) in the varenicline arm and 239

(93%) in the placebo arm. We lost 26 (10%) participants from the varenicline arm and 12 (5%) from the placebo arm at week 5 follow-ups. We lost 24 (9%) participants from the varenicline arm and 11 (4%) from the placebo arm at week 12 follow-up and we lost 22 (9%) participants from the varenicline arm and 12 (5%) from the placebo arm at week 25 follow-up. Overall, 19 participants in the varenicline arm and 24 participants in the placebo arm discontinued their medications before the end of 12 weeks (for details see Supplement 1).

Participant characteristics

Baseline characteristics did not differ between treatment groups (Table 1). Most trial participants were men (84·1%) and about a half smoked both waterpipe and cigarettes (51·2%), which was by design due to stratification on these variables. The mean age was 49 years (SD 15·2). All trial participants were daily and frequent waterpipe smokers and had been so on average for more than 27 years (SD: 15·9). Many participants smoked waterpipe six or more times a day (44·5%) with each session lasting 10 minutes (SD: 10·3), on average. Those who were concomitant smokers took on average 13 cigarettes per day (SD: 9·2) for at least 24 days (SD: 10·1) in the past month. The mean LWDS score was 19·2 (SD: 4·0) and only 19% ever attempted quitting in the past. Almost 95% participants reported no smoking restrictions in their households and 89% shared their waterpipe with others.

Outcomes

Table 2 presents the unadjusted repeated point prevalence abstinence, and self-reported and CO-verified point abstinence rates (secondary outcomes) at week 5, 12 and 25, as well as early and late relapse in both arms. No evidence of statistically significant differences between the varenicline and placebo arms was observed for the primary (repeated point prevalence abstinence) or secondary outcomes assessing point abstinence at different time-points. The Bayes factor associated with the main outcome (12/253 and 11/257) was 0·048. At the end of the 12-week medication phase, the CO-verified point abstinence rates were slightly higher in varenicline vs. the placebo arm. The early

relapse and late relapse rates were similar in the varenicline arm compared to the placebo arm. The results of the adjusted analyses as described in the methods section were similar to those presented in Table 2 (data not shown) albeit that for the CO-verified point abstinence at week-12 a statistically significant result was observed.

The analysis also showed that only 17.4% (44/253) and 15.9% (41/257) of all participants made at least one attempt to quit all forms of tobacco in the varenicline and in the placebo arms, respectively. Among those who reported smoking cigarettes as well as waterpipe at the baseline: 32.3% (41/127) in the varenicline arm and 27.6% (37/134) in the placebo arm attempted to quit cigarettes alone; 28.4% (36/127) in the varenicline arm and 30.6% (41/134) in the placebo arm attempted to quit waterpipe alone; but only 17.3% (22/127) in the varenicline arm and 14.9% (20/134) in the placebo arm attempted to quit both.

Based on a 7-day pill recall, no differences in the self-reported medication adherence between the varenicline and placebo arms at week 1 (mean pill count [SD] = 6·6 [1·22] vs 6·6 [1·25], p = 0·93), week 5 (mean pill count [SD] = 6·1 [2·05] vs· 6·1 [2·06], p >0·99) or week 12 (mean pill count [SD] = 6·2 [1·97] vs 6·1 [2·02], p = 0·53) were observed.

There were 34 adverse events reported in 27 individuals; similar rates were observed between the varenicline and placebo arms (Table 3). No serious adverse events were reported during the study.

Discussion

Our trial found no evidence of a difference between the varenicline arm and the placebo arm in achieving repeated point prevalence abstinence in adult daily waterpipe smokers, both with or without concomitant cigarette smoking. Ours was the first double-blind placebo-controlled, randomised trial evaluating any smoking cessation medication in waterpipe smokers. The only other medication RCT (open-label) in waterpipe smokers (conducted by our group) also did not indicate any advantage of adding bupropion to behavioural support in achieving six-months continuous abstinence from waterpipe smoking (23). A previous placebo-controlled trial, in which nicotine

patches were provided in addition to behavioural support, also did not show any significant effect on prolonged abstinence compared to placebo (34). There have been very few other non-pharmacological RCTs in waterpipe smokers (35). Two of the three trials in a recent Cochrane review (21) reported on the effect of individual behavioural support - one found it to be effective (23). Two other small RCTs - not eligible for inclusion in the above review - did not show any statistically significant effect of behavioural support in waterpipe smokers (22, 36). We also observed fewer gastrointestinal symptoms in the varenicline arm than the previous trials. While participants were advised to report all adverse events, our enquiry was open-ended and limited to our follow-up schedule, which could have contributed to the fewer reports.

Our trial has strengths and some limitations. This was a large, multi-centre trial, where we recruited 92% of those assessed for eligibility and retained 90% of them at six months for primary end point assessment. In addition to being a double blind, placebo-controlled, randomised trial, it complied with the highest standards of conducting clinical trials (MRC Guidelines for Good Clinical Practice in Clinical Trials) (37) and reported on medication adherence and adverse events. We also used a relatively strict measure of abstinence (compared to continuous abstinence) as we conducted repeated point prevalence assessments requiring CO-validation of self-reports at three time-points within six months (28). Any participant missing even one of the three follow-ups was considered as a smoker in an intention-to-treat analysis. Hence, our approach might have led to an under reporting of actual cessation events. In the absence of any other studies in our target population, we based our predicted abstinence rates in the control arm on the ASSIST trial (30). However, the participants in the assist trial were smokers with presumptive TB - a tobacco-related comorbidity. This is a key limitation of our trial planning, as our findings suggest that our assumption which was based on the participants in the ASSIST trial does not seem to represent our target population. Our trial was not able to assess several intermediate outcomes, including any changes in participants' knowledge of waterpipe related harms, perceived risks, motivation, attitudes, and self-efficacy in quitting. Given that ours was a medication trial, we decided against using these questions, in order to keep the

participants' assessment burden to a minimum. Our assessment of medication adherence, although using a valid 7-day recall approach (38), was subjective and may have over-estimated medication adherence (39). Our trial participants were generally older, smoked daily and frequently, and used traditional waterpipes (hookah) with unflavoured tobacco in social settings common in rural Punjab. Such characteristics and smoking behaviours are remarkably different from many other countries, where most waterpipe smokers are younger, use waterpipe tobacco mixed with flavoured molasses and often smoke intermittently in bars and cafes (2, 40). This limits the external validity of our trial findings.

Our trial findings are contrary to a well-established evidence base for the effect of varenicline in cigarette smoking cessation (14). In our trial, we observed very low abstinence rates in both arms despite offering behavioural support albeit limited to two sessions, which is well below the level of expert content, which is typically 4-6 sessions. Only a minority of our participants in both trial arms made serious attempts to quit all forms of tobacco smoking, which could explain why only a handful achieved abstinence. With so few making quit attempts, it also limited our trial's ability to demonstrate a difference between the two conditions, if there was any. This was an unexpected finding given that all participants took part in the trial willingly, showed an interest in quitting permanently and were explained about the objective of cessation treatment. However, it is understandable given the social context of waterpipe smoking in Pakistan, dual smoking and dependency patterns among the majority.

There are several indications to suggest that our participants were heavily dependent on nicotine and waterpipe smoking. All were daily and frequent smokers and many smoked cigarettes too. Most participants smoked within social environments without any indoor smoking restrictions, shared waterpipe with each other and hardly ever attempted to quit. It is not surprising that their dependency scores were almost double than those recorded in previous studies in Middle East and in the UK (40, 41).

While our findings are based on a single trial, they reinforce a widely held view among researchers in waterpipe smoking that there are profound differences between waterpipe and cigarette smoking behaviours and addiction patterns. While cigarette smoking is increasingly becoming a solitary behaviour, waterpipes are often shared and smoked in socially enjoyable settings, so there is a strong dimension of social dependence (9). In addition, the auditory, olfactory and visual aspects associated with waterpipe smoking add to its allure (42). In young waterpipe smokers, tobacco dependence develops even at low levels of consumption and low frequency of use (7). This calls for a distinct approach to waterpipe cessation that takes account of its specific social cues, which add to its dependency potential (21, 35).

Research on waterpipe smoking cessation, compared to cigarettes, is in its infancy. We, therefore, advocate for more evaluative research on waterpipe smoking cessation in Middle-Eastern and Western settings (35). In addition to nicotine dependency, future research should take account of the social dimension of waterpipe smoking (21, 35). There is some evidence to suggest that a community-based intervention may be effective in encouraging waterpipe smokers to quit (43). Such approaches need further development and adaptation to the specific socio-cultural context in which waterpipe smoking takes place. Further varenicline trials should consider testing extended treatment regimens and combinations with bupropion, as used in other highly dependent smokers (44, 45), or with more intensive behavioural (26) and community level approaches.

Our trial highlights the serious challenges in getting waterpipe smokers to quit successfully, especially in the absence of a conducive policy and social context. While waterpipe smoking is banned in restaurants and cafes in Pakistan, it is part of the country's social fabric, particularly in rural areas. Like other smokers, waterpipe smokers have a better chance of quitting if tobacco is more expensive, if public places are smoke-free and if social norms facilitate quitting behaviour. Our findings suggest that in the absence of strong policy measures and a societal change, most waterpipe smokers may not attempt to quit and those who do may not succeed even if they have access to cessation medications. We therefore make four suggestions: researchers need to continue

to find better ways to help people who are willing to quit waterpipe smoking; policy makers need to raise taxes and regulate all tobacco products including waterpipes, in accordance with the Framework Convention for Tobacco Control; health practitioners should offer support to waterpipe smokers who wish to quit, and tobacco control advocates need to continue to raise awareness about the negative consequences of waterpipe smoking, with an aim to reduce its popularity and consumption.

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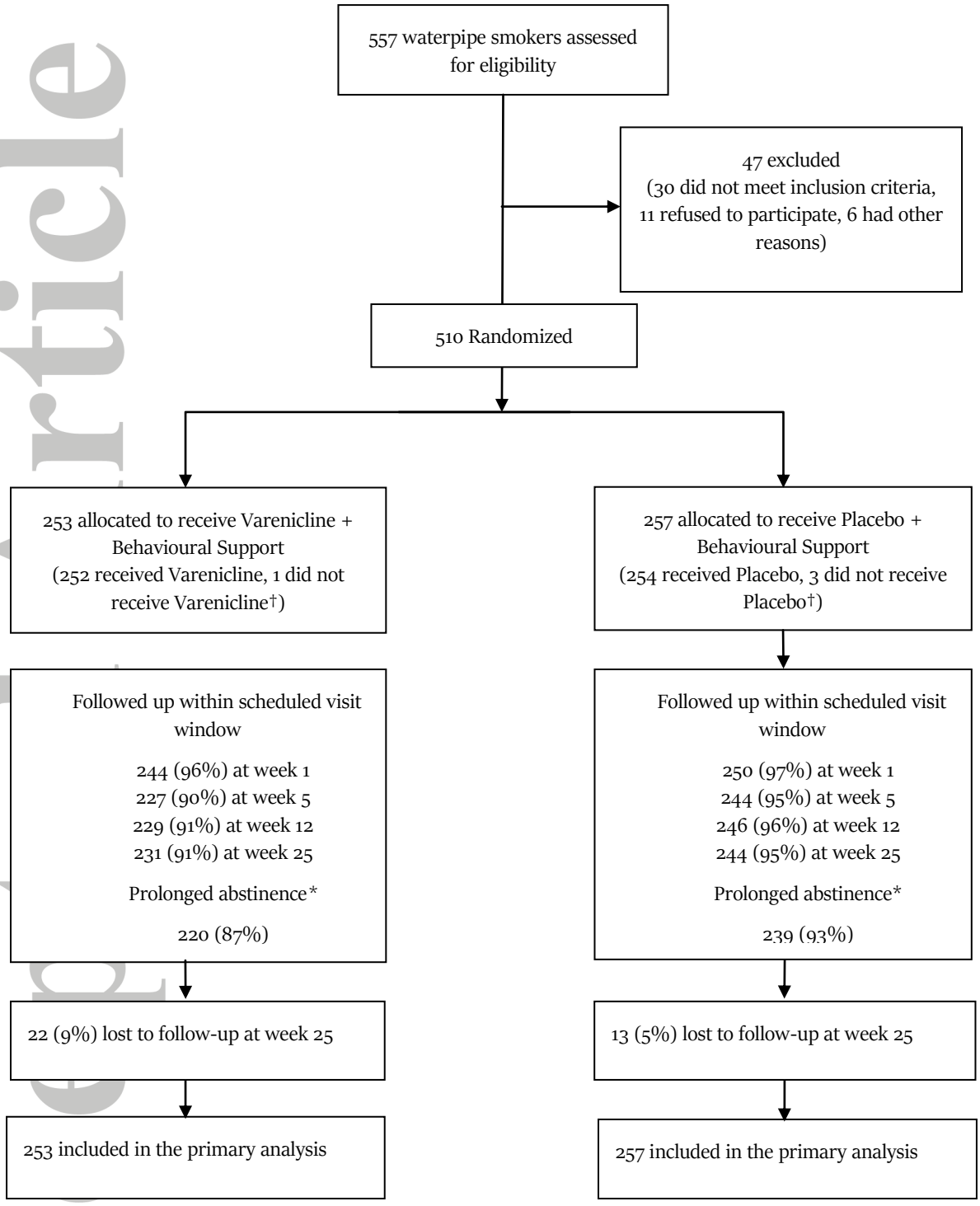
Figure 1. Trial profile in a CONSORT diagram



†The participants who did not receive varenicline and placebo, refused to take medicines after being enrolled in the trial.

*Numbers for which primary outcome (repeated point prevalence abstinence) data were available.

Table 1. Baseline characteristics

Characteristics	Varenicline group (n= 253)	Placebo group (n= 257)	All participants (n= 510)
Demographic history			
Age, years	49.9 (14·6)	48·4 (15·6)	49·2 (15·2)
≤ 37	58 (22·9%)	73 (28·4%)	131 (25·7%)
38-59	120 (47·4%)	114 (44·4%)	234 (45·9%)
≥ 60	75 (29·6%)	70 (27·2%)	145 (28·43%)
Women*	40 (15·8%)	41 (16·0%)	81 (15·9%)
Married	220 (87·0%)	220 (85·6%)	440 (86·3%)
Education			
≥ high school	36 (14·2%)	36 (14·0%)	72 (14·1%)
< high school	123 (48·6%)	128 (49·8%)	251 (49·2%)
No formal education	94 (37·2%)	93 (36·2%)	187 (36·7%)
Smoking history			
Duration of smoking, years	27·2 (15·2)	26·9 (16·6)	27·1 (15·9)
Age started smoking, years	22·5 (9·1)	21·4 (8·0)	22· 0 (8·6)
Days smoked waterpipe (in past 30 days)	29·1 (2·8)	29·2 (2·6)	29·1 (2·7)
Waterpipe sessions per day			
≤ 5 sessions	138 (54·6%)	145 (56·4%)	283 (55·5%)
6 – 10 sessions	46 (18·8%)	43 (16·7%)	89 (17·5%)
≥ 11 sessions	69 (27·3%)	69 (26·9%)	138 (27·1%)
Length of a waterpipe session, minutes	10·3 (11·3)	10·3 (9·4)	10·3 (10·3)
Share waterpipe with others	224 (88·5%)	230 (89·5%)	454 (89·0%)
Types of tobacco smoking*			
Waterpipe only	126 (49·8%)	123 (47·9%)	249 (48·8%)
Waterpipe + Cigarettes	127 (50·2%)	134 (52·1%)	261 (51·2%)
Days smoked cigarettes (in past 30 days)**	23·5 (10·4)	24·0 (9·8)	23·8 (10·1)
Cigarettes per day	12·3 (9·0)	12·7 (9·4)	12·5 (9·2)
Smoking restriction in household			
Not allowed	0 (0%)	2 (0· 8%)	2 (0·4%)
Some restriction	14 (5·5%)	12 (4·7%)	26 (5·1%)
No restriction	239 (94·5%)	243 (94·6%)	482 (94·5%)
Tobacco dependence			
LWDS-11 score†	19·2 (3·9)	19·1 (4·1)	19·2 (4·0)
MPSS score‡	10·1 (4·4)	10·1 (4·2)	10·1 (4·3)
Quit history			
Attempted quit in past	48 (19·0%)	47 (18·3%)	95 (18·6%)
Number of attempts to quit	2·1 (1·6)	2·0 (1·7)	2·0 (1·6)
Time since last quit attempt, years	5·6 (8·3)	4·1 (5·8)	4·9 (7·2)
Longest duration stayed abstinent in previous attempts, months	6·2 (14·3)	4·9 (7·5)	5·6 (11·4)

Data are n (%), or mean (SD)

* Stratifying variable

**Data on 261 participants who smoked cigarettes in addition to waterpipe

†Lebanon Waterpipe Dependence Scale: assessed physiological nicotine dependence, negative reinforcement, psychological craving and positive reinforcement of waterpipe use; possible total score ranges from 0 to 33

‡Mood and Physical Symptoms Scale: assessed feeling depressed, irritable, restless, hungry or poor concentration over the past 24 hours; possible total score ranges from 5 to 25.

Table 2. Repeated point prevalence abstinence, CO-verified and self-reported 7-day point prevalence abstinence rates†

	Varenicline, N= 253 n (%)	Placebo, N= 257 n (%)	RR (95% CI)	*P* value
Repeated point prevalence abstinence*	12 (4·7)	11 (4·3)	1·11 (0·50 - 2·47)	0·801
Point abstinence**				
CO verified (<10ppm) ‡				
Quit at week 5	22 (8·7)	26 (10·1)	0·86 (0·50 – 1·48)	0·583
Quit at week 12	31 (12·3)	26 (10·1)	1·21 (0·74 – 1·98)	0·445
Quit at week 25	29 (11·5)	26 (10·1)	1·13 (0·69 – 1·87)	0·625
Self-reported only				
Quit at week 5	23 (9·1)	32 (12·5)	0·73 (0·44 – 1·21)	0·224
Quit at week 12	31 (12·3)	28 (10·9)	1·13 (0·70 – 1·82)	0·632
Quit at week 25	29 (11·5)	27 (10·5)	1·09 (0·67 – 1·78)	0·73
Early relapse	6 (2·4)	9 (3·5)	-	0·466
Late relapse	4 (1·6)	6 (2·3)	-	0·557

† Participants lost to follow-up were imputed as smokers. Time-points reflect number of weeks following randomisation (day 0), target quit date occurred at week 1. Of the 510 participants, 253 randomised to varenicline group received 1 mg varenicline per day for the first week (0·5mg once daily for 3 days and then 0·5 mg twice daily), followed by 2mg varenicline per day for rest of the treatment course and 257 participants in the placebo group received matching placebo pills. Participants were instructed to begin taking study medication (varenicline or placebo) at randomisation for a total of 12 weeks. Week 12 reflects end of the medication phase. Week 25 signifies end of follow-up. CI = confidence interval; RR= Relative Risk.

*Primary outcome: self-reported point abstinence (not even a puff/chew/session in the last 7 days) at each of weeks 5, 12 and 25 (combined) verified by carbon monoxide (CO) cut-off <10ppm

**Secondary outcomes: point abstinence- in the last 7 days, early relapse, late relapse

‡CO breath test at weeks 5, 12 and 25 was used to confirm self-reported abstinence. A cut-off point of 10ppm was used to differentiate smokers from non-smokers.

Table 3. Adverse events

Adverse event†	Number of events in Varenicline group	Number of events in Placebo group
Respiratory disorders	1	3
Gastrointestinal disorders	3	9
General disorders (fever, hypertension)	2	1
Immune system disorders (allergic reaction)	1	3
Renal and urinary disorders	1	0
Nervous system disorders (dizziness, drowsiness)	5	2
Psychiatric disorders (anxiety)	2	1

† No serious adverse events occurred during the study. The non-serious adverse events occurred during the 12-week medication phase of the study. Events are reported by Medical Dictionary for Regulatory Activities (MedDRA) Dictionary (version 19·0) system organ class.