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A Double-Blind, Randomised, Placebo-Controlled Trial of Cytisine for Smoking Cessation in Medium-Dependent Workers

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Among many studies on cytisine only a few have been controlled trials, and the aim of this study was to assess the efficacy of cytisine in a randomized controlled double-blind trial compared to placebo in medium-dependent smoking men working in mining industry. *Materials and methods:* 171 middle-aged smokers were randomised to either cytisine (25-days regimen) or placebo; both groups received individual counseling with brochure. Self-reported continuous abstinence was assessed at 8 and 26 weeks. *Results:* At the end of week 8 there were no differences in number of abstinent subjects, but at 26 weeks 10.6% of subjects were abstinent in cytisine group compared to 1.2% in placebo (p = .01). In both groups, we did not find any weight increase, but quality of life improved in both groups, and physical and social functioning improved in cytisine group. *Conclusions:* Cytisine may be an effective medication to help smokers quit even for those working in difficult working conditions with high relapse rate.

In order to prevent lung cancer, chronic obstructive pulmonary disease and other smoking-related illnesses, comprehensive tobacco control should comprise the process of successful quitting by current smokers. Self-aid has been shown to have a very little effect, but behavioural support, along with one of the medication alternatives, could help up to 30% of quitters abstain from smoking at least for the first 6 months (Silagy et al., 2004). Various forms of nicotine-replacement therapy (NRT) are available, and more than 100 double-blind, randomised controlled trials have been published showing that NRT doubles success rate of quitters (West et al., 2007). New medications with evident effect have been introduced, and their potential for smoking cessation has been demonstrated in large studies.

However, individual counseling along with NRT or varenicline still remain an expensive choice for people leaving in the low-income countries. In a study done by the authors (unpublished) up to 83% of current smokers said they would like to cease smoking within the next 6 months, but 88.5% admitted they would only rely on their willpower because of very poor awareness and unavailability of the NRT and varenicline. For a low-income country the absolute cost of medication for smoking cessation is an important matter for the majority of smokers. That is why cytisine has been in use for several years in some countries of Central Asia. Its 25-day course is 5 to 15 times cheaper than the 25-day treatment with NRT (Etter, 2006).

This medication is the active substance in 'Tabex'. It is a natural extract from the seeds of Cytisus Laburnum tree, and a partial agonist of α 4β 2-nicotinic acetylcholine receptors, which are responsible for reinforcing effects of nicotine. Being an agonist of these receptors, it reduces negative withdrawal symptoms of cigarette abstinence and cravings. Additionally, by preventing the nicotine binding to these receptors, it decreases its reinforcing effects. In Bulgaria, this medication has been used for about 40 years, but it has never been included into any recommendations or guidelines because of very few publications describing the use of this medication to treat tobacco dependence in English (Karam-Hage et al., 2007).

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Among many studies on cytisine only a few have been controlled, and the majority of these were done long time ago (Etter et al., 2007). In a recent uncontrolled trial (Zatonski et al., 2006), authors reported that of 315 patients, 27.5% had reported they did not smoke at 6 months and 13.8% — at 12 months, verified by exhaled CO. The pooled OR from two double-blind, placebo-controlled trials was 1.83 at 3 and 6 months compared with placebo, and in another trial they reported OR 1.77 at 12 months (Etter, 2006).

The efficacy of this medication is still disputable due to limitations in the studies undertaken. The other problem with smoking cessation treatment is that poor data are available on real-life efficacy of medications and interventions, because the studies have been done in clinics with more compliant patients and excellent readiness to quit. With the current study, we aimed to investigate the efficacy of cytisine in a randomised controlled double-blind trial compared to placebo in medium-dependent smoking men working in the mining industry.

Materials and Methods

Patients

Participants were drawn from current daily smokers without any serious chronic diseases. Subjects were 20 years old and older, smoked at least 15 cigarettes a day during the year prior to inclusion into the trial, had claimed high motivation to quit smoking and readiness to do so immediately and had not had any experience of cytisine use before.

We recruited all our patients from the staff of the mining company in Kyrgyzstan, mainly men, who either had taken part in group cessation programs at the workplace before, but unsuccessfully, or were invited into this trial as the first attempt to stop smoking. They were recruited via an advertisement at their workplace, and 350 subjects expressed their wish to participate. First, they were screened if they met the inclusion criteria; those who did not were counselled individually for 15 minutes, received a targeted brochure on how to quit smoking and left. Otherwise people were subjected to initial testing using their smoking history, anthropometric measurements, Fagerstrom test for nicotine dependence (FTND ; Fagerstrom et al., 1991), health-related quality of life (QL), exhaled carbon monoxide (CO) measurement and lung function testing. Data were verified with exhaled carbon monoxide.

We excluded patients having serious or unstable disorders, and the data were checked using their annual screening data profiles. Usually, they all have to undergo annual screening, chest X-ray, electrocardiogram, cardiac ultrasonography upon indications, lung function testing, blood cell count, and blood biochemical assay. Patients contra-indicated for cytisine use were excluded. Those contraindications were ischemic heart disease, severe arrhythmias, severe atherosclerosis, schizophrenia, tumors, pregnancy and breastfeeding. Patients were advised to abstain from the use of other medications, if no acute or chronic diseases required their use.

Study Design

We planned this study in parallel groups as randomised, double-blind and placebo-controlled. It consisted of 2-weeks screening and counselling of patients, followed by initial administration of medication, with 6 months follow-up. We included all the requirements of the Russell standard for smoking cessation trials (West et al., 2005), and the study design was approved by the Ethical Committee of Ministry of Health of Kyrgyz Republic and was done in accordance with Declaration of Helsinki. All patients signed an informed consent to participate in this trial in their native language.

Within the screening phase, patients were randomly divided into two groups. One group received cytisine tablets according to the manufacturer's instructions: (1) first 3 days smoking should be reduced by half, and each tablet should be taken every 2 hours (6 tablets a day); (2) days 4–12 — smoking must be discontinued, and each tablet should be taken every 2.5 hours (5 tablets a day); (3) days 13–16 — each tablet must be taken every 3 hours (4 tablets a day); (4) days 17–20 — each tablet must be taken every 4 hours (3 tablets a day); (5) days 21–22 — each tablet must be taken every 6 hours (2 tablets a day); and (6) days 23–25 — one tablet a day. The second group was taking placebo tablets using the same regimen. Randomisation was done using randomisation code made by a sided statistical scientist, and the code was kept with him.

Subjects were instructed not to enrol in any other consultations or treatment programs, and stop smoking on the fifth day of cytisine use, and the day of treatment inception was chosen individually. Participants were screened at the end of week 8 and week 26. At each visit, we measured continuous abstinence since the quit date, measured their bodyweight, asked about the reasons to resume smoking and side effects of the medication. Then we measured their exhaled CO level with the use of piCO Smokerlyzer (Bedfont, United Kingdom), and asked patients to fill in the SF-8 questionnaire. All those procedures were undertaken by a trained physician.

The primary efficacy measures were continuous abstinence since the smoking discontinuation from day 5 to the end of week 8 and from day 5 to end of week 26. That was defined as no cigarettes at all and verified with exhaled CO level. Those patients that reported continuous abstinence but had exhaled CO level 9 ppm or more along with those who missed at least one visit were considered smokers. As secondary efficacy measures we used exhaled CO and change in health-related QL.

To follow the Russell standard, we defined (1) duration of abstinence 6 months (26 weeks); (2) full

abstinence at examination points. The question we used was 'Have you smoked even a single cigarette during the last 4/22 weeks since you discontinued the use of the medication?'; (3) biochemical verification was done with exhaled CO monitor; (4) we did intention-to-treat analysis — patients who did not take medication at all were excluded from the analysis, and those patients who withdrew from the trial and moved to an unreachable place (totally 13 subjects) were excluded from the analysis; (5) protocol violators that did not come to follow-up or were abstinent with CO higher or equal to 9 ppm were considered smokers; (6) follow-up was blind.

Statistical Analysis

Data were processed using Statistica 6.0 (StatSoft) and NCSS 2002. Data are shown as percentages or means ± standard deviation. Within the groups, changes in continuous variables (CO level, number of cigarettes, etc.) were compared using the Wilcoxon test or analysis of variance. The primary outcome measures were evaluated using a logistic regression analysis.

Results

Of all 350 patients initially screened, 171 were enrolled and took at least one dose of medication (figure 1). Patients of both groups were similar to each other in their smoking histories, and there were mostly men participating, smoking one pack of cigarettes a day on average (table 1). Only a quarter of our patients had used any medication previously to quit smoking, but the majority tried to quit a few times before. Our smokers had medium tobacco dependence.

The rates of continuous abstinence at the end of week 8 of treatment did not differ between the groups ($p = .38$) and generally were low. Nine patients in the cytisine group remained abstinent at this time compared with five patients in the placebo group (see Table 2). However, by the end of the 26th week of treatment only one patient in placebo group was a non-smoker with low exhaled CO level, whereas those nine abstinent patients in cytisine group were still nonsmokers ($p = .01$).

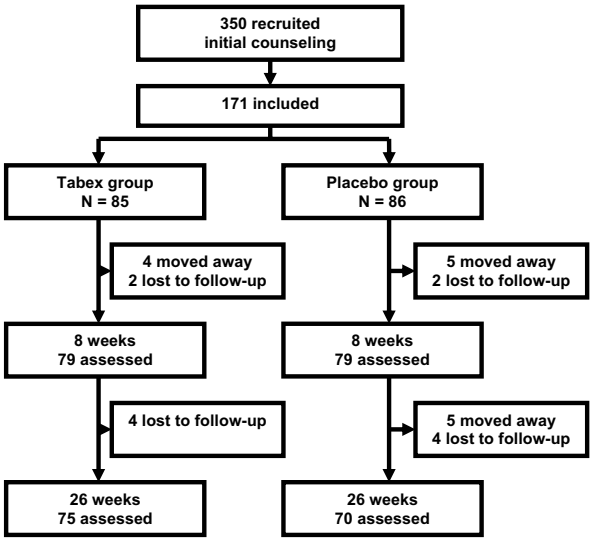

Figure 1
Trial profile.

Table 1
Baseline Characteristics of Subjects

	Cytisine group (n = 85)	Placebo group (n = 86)
Characteristics of patients		
Male/female	84 (99%) / 1 (1%)	82 (95%) / 4 (5%)
Mean (*SD*) age, years	38.3 (7.7)	39.4 (9.5)
Smoking status		
Mean (*SD*) cig per day	21.7 (6.9)	21.9 (7.0)
Mean (*SD*) smoking years	19.8 (7.7)	17.7 (7.5)
Attempted to quit previously, %	87.7	84.0
Mean (*SD*) number of attempts	3.4 (3.3)	3.2 (3.2)
Used medications to quit, %	27.1	27.3
Mean (*SD*) FTND score (0–10)	5.3 (1.4)	5.3 (1.7)
Mean (*SD*) exhaled CO, ppm	26.7 (8.7)	26.1 (12.1)

The main effects logistic regression was used in the analysis to study the probability of continuous abstinence at weeks 5 to 26. We analysed the effect of cytisine use, age, cigarettes smoked, smoking duration, previous attempts to quit, FTND score and exhaled carbon monoxide, and the frequencies of the variables are shown in Table 3. Previous attempts to stop smoking and the use of medications to stop smoking before had no association with the abstinence, and other analysed variables are shown in Table 3. We also analysed if answers to FTND questions could have association with abstinence. We found that OR of abstinence for subjects who find it not difficult to abstain from smoking in places where smoking was prohibited was 2.01 (0.50–8.07).

In general, we saw a reduction in exhaled CO level in the entire group from 26.4 ± 10.5 to 20.8 ± 12.0 ppm ($p < .001$). In the cytisine group, CO reduced from 26.7 ± 8.7 to 19.3 ± 11.0 ppm ($p < .001$), but in the placebo group we did not find a statistically significant lessening of CO (from 26.1 ± 12.1 to 22.5 ± 12.7 ppm).

Table 2
Continuous Abstinence Rates*During Treatment and Follow-Up

Weeks	Cytisine	Placebo	p
5–8	9 (10.6%)	5 (5.7%)	0.36
5–26	9 (10.6%)	1 (1.2%)	0.01

Note: *No cigarettes at all, verified by exhaled CO.

Table 3
Logistic Regression Model for the Abstinence Predictors

Variable	OR	95% CI
Cytisine use	8.93	1.06–75.28
Age	1.11	0.91–1.37
Weight	1.02	0.96–1.1
Number of cigarettes	1.06	0.89–1.26
Smoking duration	0.95	0.77–1.18
FTND score	1.13	0.60–2.14
Exhaled CO level	0.99	0.91–1.09

Treatment with both cytisine and placebo did not change the subjects' bodyweight. Initially our patients weighed 73.4 ± 10.2, and 26 weeks after their weight was 73.1 ± 10.2 kg. Cytisine use did not change bodyweight (74.6±10.5 at baseline and 73.8 ± 10.3 kg in the end) as did placebo use (72.2 ± 9.7 vs. 72.4 ± 10.2 kg). In nine abstinent subjects in cytisine group we did not see any weight gain — 70.7 ± 6.3 kg at baseline and 69.4 ± 6.4 kg at 26 weeks.

All patients were asked about their health-related quality of life using eight questions from the general SF-8 questionnaire. Initially, there were no differences in QL between those receiving cytisine and those receiving placebo. Treatment with cytisine led to improvement of physical activity (PA), social activity (SA), role physical (RP), mental health (MH), physical pain (PP) and general health (GH) scores (from 47.5 ± 6.3 to 50.2 ± 5.0; from 48.2 ± 5.6 to 49.9 ± 4.1; from 49.0 ± 5.7 to 51.6 ± 5.0; from 48.9 ± 7.3 to 51.5 ± 6.0; from 55.8 ± 5.8 to 57.8 ± 5.2 and from 46.0 ± 7.0 to 48.8 ± 6.0 respectively). But treatment with placebo also led to improvement of four scores — MH, VT, PP and GH (see Figure 2). In verified abstinent subjects of both groups (N = 10), there was a significant improvement of only two scores — RP and GH, and the latter increased from 45.5 ± 6.8 to 53.0 ± 5.3.

Eight patients from the entire group experienced side effects and stopped using either cytisine or placebo because of side effects — 4 in the cytisine group (4.7%) and 4 (4.7%) in the placebo group. The most common adverse effects were dyspepsia (in one cytisine and two placebo patients), nausea (in two cytisine and one placebo patient), headache in one cytisine and one placebo patient, and other effects (in one cytisine and one placebo). There was not enough evidence to relate these effects to study medication in both groups.

Discussion

Our study showed that cytisine was effective in smoking cessation when delivered as part of individual counselling compared to placebo in medium-dependent smoking men. In this study it increased the cessation rate by 8 times compared to placebo. Meanwhile, the overall cessation rate for this medication in this study was low compared with other trials.

In our study we invited smokers who might have been different from the subjects of other studies on cytisine. We studied the medication with medium- dependent men working in the mining industry, and not attending specialised clinic for smoking cessation. The working conditions of these people predisposed them to heavier smoking in a stressful environment, where relapse was more probable. In conditions of heavy physical load in real life, craving would be the most probable reason for relapse, as it is in a usual setting (Killen et al., 1997). The majority of subjects in our study, both on medication and placebo, explained their relapse as a strong craving for smoking, which in their working conditions might play a greater role. This may explain why the abstinence rate in the placebo group was so unexpectedly low — only one patient, even after the individual counselling, remained abstinent after 6 months.

This study may shed more light on the real-world efficacy of cytisine. In the previous studies, the medication doubled the cessation rate, but the placebo group patients showed only two times lower abstinence rates, and it was around 10%. In our study we got an OR of smoking cessation of 8.9 with cytisine because of very low cessation rate in placebo group. Apart from the high placebo relapse rate, the other fact possibly explaining such low abstinence in placebo group could be the absolute prevalence of working men in the study group. In spite of the fact women are generally harder to quit (Bjornson et al., 1995), working men in the mining industry are still a very difficult subpopulation of smokers. This was a limitation of our study, and we assume abstinence rates in the active group could be different if more women were included in the group.

Another limitation of this study could be the short timing of for the follow-up period. Although the Russell Standard recommends 6 months for a follow-up period, it could be valuable to observe patients after 12 months and even longer.

In this trial we measured health-related quality of life as an indicator of the impact of smoking cessation or reduction. We used short questionnaire, and we found that certain indices changed in both groups. In general, both interventions led to improvement of QL, and this was due to counseling offered to subjects of both groups. So even individual counselling was sufficient to improve mental and general health and some other indices. But only cytisine group showed significant improvement of physical and social activities.

Overall, this study showed that cytisine was an effective medication to help smokers quit, even for those working in difficult working conditions with high relapse rate. This medication, probably, has less efficacy compared to other medication options, but due to low cost it may become a medication of choice for low-

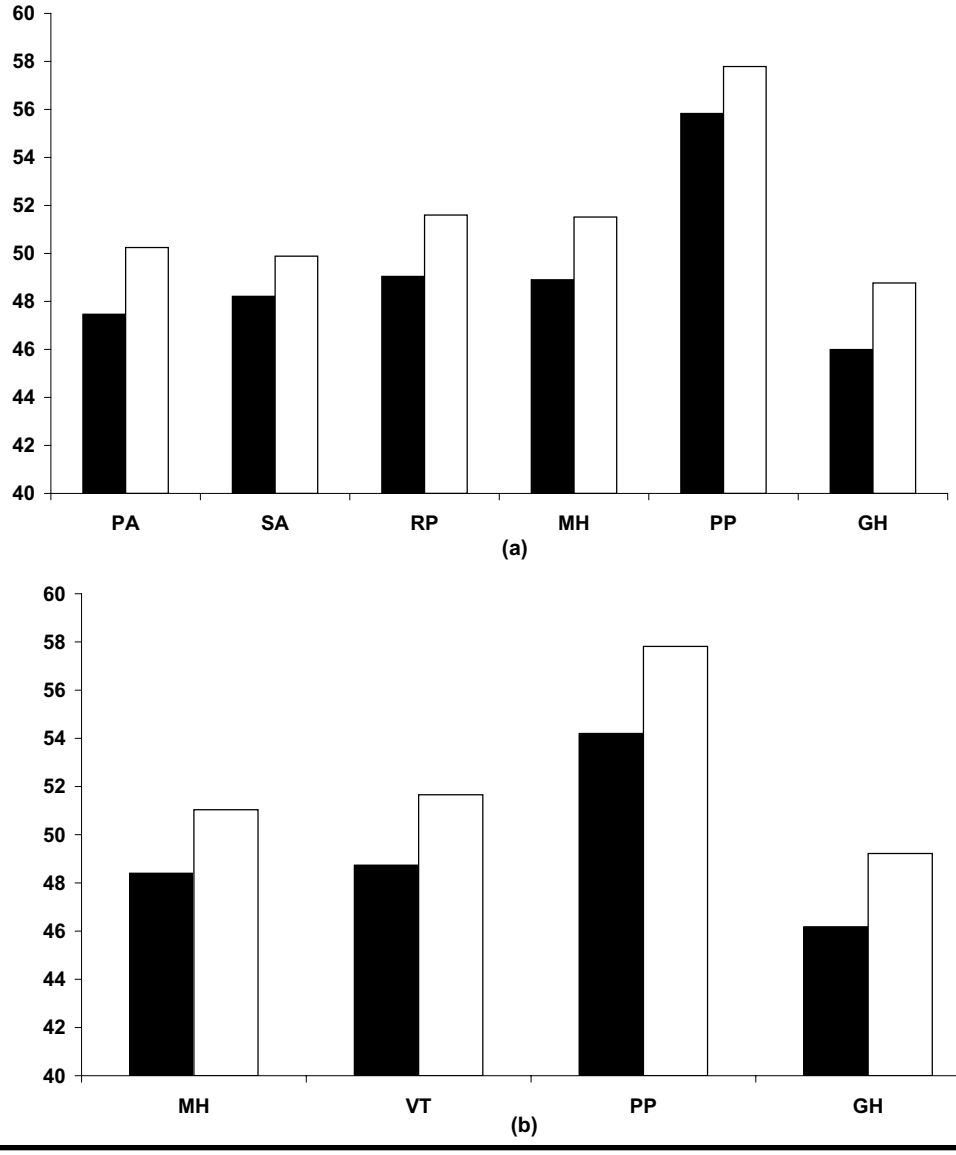

Figure 2

Change in QL of patients treated with cytisine (a) and placebo (b)

Note: PA – physical activity, SA – social activity, RP – role physical, MH – mental health, PP – physical pain, GH – general health, VT – vitality.

income smokers willing to quit. It is well tolerated and could be a good alternative for medication-aid cessation in countries where the high cost of smoking cessation medication hampers the wide use of other options.

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