

BRIEF REPORT

An uncontrolled trial of cytisine (Tabex) for smoking cessation

Witold Zatonski, Magdalena Cedzynska, Piotr Tutka, Robert West

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Objectives: Cytisine (Tabex) has been licensed in Eastern Europe as an aid to smoking cessation for 40 years. Cytisine is a partial agonist with high affinity binding to the $\alpha 4\beta 2$ nicotinic acetylcholine receptor believed to be central to the rewarding effect of nicotine. There is insufficient information on effectiveness to warrant licensing by modern standards. To assess whether full-scale controlled trials are warranted, this study sought to obtain an estimate of the 12-month continuous abstinence rates of smokers using cytisine with minimal behavioural support.

Design: An uncontrolled, open-label trial.

Setting: A smokers' clinic in an oncology centre in Warsaw, Poland.

Subjects: 436 consecutive attendees of the smokers' clinic of whom 191 were male. The mean dependence score (Fagerstrom Test for Nicotine Dependence) was 6.1.

Intervention: The standard regimen of Tabex (cytisine) was used, involving 25 days of treatment with minimal behavioural support.

Main outcome measure: Self-reported continuous abstinence for 12 months; with abstinence verified by carbon monoxide at the final follow up (after 12 months).

Results: 60 participants (13.8% of the total sample) were abstinent for 12 months. Of the 315 subjects, who had taken the drug, 49 (15.5%) stopped cytisine because of adverse effects (mostly gastric disturbances and nausea), although they were not serious. The frequency of the minor adverse effects, primarily gastric disturbance, was similar to that observed in previous studies with the drug.

Conclusions: The long-term abstinence rates were similar to those observed in smokers receiving nicotine replacement therapy. Full-scale randomised trials of cytisine (Tabex), conducted to the standards required by regulatory authorities, are warranted.

Nicotine replacement therapy (NRT) and bupropion increase 12-month continuous abstinence rates of smokers making a quit attempt by 5–14%, depending on the context.^{1–3} Other medications have also been found to aid cessation, most notably nortriptyline.² New medications in the pipeline are varenicline (Pfizer)⁴ and rimonabant (Sanofi-Aventis).⁵ Nicotine vaccines are undergoing clinical trials.⁶ Behavioural support can improve the chances of success of quit attempts by an estimated 2–7%.^{7–9}

The cost of smoking cessation treatments is an important issue. The cost per life-year gained compares very favourably with other medical treatments, but most healthcare systems and many smokers, even in richer countries, do not feel that they can afford the current forms of treatment. If a much cheaper form of treatment exists that is as effective, it is important to evaluate it. One such medication is Tabex.^{10–12}

The active ingredient of Tabex is cytisine (1.5 mg in each tablet). The cost for a full course of treatment in Poland is approximately the equivalent of £6 (US\$10, €8.90) and in Bulgaria it is about £2.50 (US\$ 5, €3.71) (for more information see: www.bpg.bg/tabex). This drug has been licensed for over 40 years in Eastern and Central Europe and many smokers in Poland use it. The total sales of Tabex in 2004 exceeded one million courses. It has been subjected to phase I and II studies and clinical trials (see below). However, it has not been subjected to sufficiently rigorous evaluation according to modern standards and would not receive a licence if submitted for approval today.

Cytisine is a compound derived from the plant, *Cytisus laburnum*. It is a nicotinic partial agonist binding with high affinity to a number of different subtypes of the neuronal nicotinic receptors, including receptors composed of $\alpha 4$ and $\beta 2$ subunits^{13 14} which are believed to be central to the effect of nicotine on the reward pathway.⁴ Because it has a high affinity for the receptor, cytisine prevents other ligands such as nicotine from attaching to it. However, once attached to the receptor, its effect is much less than that of nicotine. As a result, the drug would be expected to reduce the rewarding effects of nicotine and to decrease craving and attenuate nicotine withdrawal symptoms, but not be addictive itself or provide positive reward. Despite its properties there is no dissemination of the drug in western countries. However, cytisine has provided the starting point for a new medication for smoking cessation, varenicline, that has recently undergone clinical trials.⁴

Pharmacokinetic data derive mainly from animal studies.^{15 16} Applied orally in rabbits, cytisine is well absorbed in the gut. The elimination half-life after oral administration is 52 minutes. The drug is mainly excreted in unchanged form with the urine. Phase I studies show that cytisine has pharmacological effects that are somewhat similar to those of nicotine. Its toxicity is broadly similar though somewhat less.^{4 5 15 16} Clinical studies show that Tabex is well tolerated at the doses applied.¹⁷ Where side effects do occur, these include: changes in both taste and appetite, dryness in the mouth, headache, irritability, nausea, constipation, tachycardia, and mild elevation of the arterial blood pressure.^{10–12}

As regards efficacy, in one study reported in the documentation supporting registration in Poland, 366 smokers with "chronic bronchitis" were given Tabex and compared with 239 patients treated with placebo.¹⁷ Patients were smokers having a serious intention to stop smoking. At eight weeks follow-up, 55% of patients receiving Tabex were reported abstinent compared with 34% on the placebo ($p < 0.05$). However, abstinence was not adequately defined and allocation was not random. Another study was a randomised placebo-controlled trial of 1214 smokers followed up for two years.¹⁸ Follow-up was by post and reported abstinence rates were 21% in the active versus 13% in the placebo group ($p < 0.001$). Another placebo-controlled trial was carried out in the Federal Republic of Germany in which

2470 smokers were allocated to receive one of 16 drugs, of whom 520 were treated with Tabex or placebo. After three months 25% of those on Tabex reported abstinence in a postal questionnaire compared with 21% on placebo ($p > 0.05$).¹⁹ It was not clear how smokers were assigned to conditions.

No serious adverse effects were reported in the trials but the documentation and design of these studies would not be considered sufficient to support registration in European countries because of, among other things, lack of longer-term follow-up, clear definitions of sustained abstinence, and absence of biochemical verification. However, the data do suggest that the drug is safe and efficacious. There is a need to undertake a rigorous evaluation of its safety and efficacy using outcome criteria that are widely accepted in the field.

As a first step to this, we have undertaken an open label uncontrolled trial of use of the drug in a smokers' clinic in Warsaw. Smokers attending the clinic were prescribed the recommended course of treatment and followed up using Russell Standard criteria for 12 months. If 12-month continuous abstinence rates were observed that were substantially higher than the figure of 2–10% seen in placebo groups of other clinical trials¹ or in smokers attempting to stop unaided,²⁰ there would be a strong *prima facie* case for effectiveness and this would merit moving rapidly to full scale placebo-controlled randomised controlled trials. In an evaluation of the UK stop smoking services, a programme of weekly behavioural support for four weeks after the quit date plus NRT or bupropion yielded a continuous 12-month abstinence rate of 15% verified by carbon monoxide test.²¹ Clinical trials of NRTs with minimal support may provide a better comparison point because in the present trial, smokers usually only received one session of behavioural support. The >6 month continuous abstinence rates in the active treatment group of these NRT trials was 14%.¹ An abstinence rate similar to this would suggest therapeutic efficacy.

METHODS

This was an open, uncontrolled trial in the form of a clinical audit. A total of 438 consecutive attendees at the stop smoking clinic at the cancer institute in Warsaw between 17 November and 27 December 2003 took part. The stop smoking clinic provides a service to the local community and is provided free of charge. Smokers were considered for admission into the trial if they were seeking help with stopping smoking at the clinic. Smokers were excluded if they were judged by the consulting physician to be contraindicated for Tabex. The exclusion criteria were: active stomach ulcer, uncontrolled hypertension, adrenal hypertrophy, and receiving treatment for a psychiatric disorder. Two smokers were excluded by these criteria. Eligible patients were informed about the study and provided verbal consent. A total of 436 patients were included.

The treatment programme consisted of one session before quitting and the offer of other sessions to those that wanted it. The main session involved a nurse collecting demographic information and measuring blood pressure, heart rate, height, weight, and expired-air carbon monoxide concentration (CO). The patients then completed a questionnaire on nicotine dependence (Fagerstrom Test for Nicotine Dependence (FTND)²²). Then the patient was seen by a physician who took a smoking and medical history and obtained informed consent from eligible patients. The physician provided information about Tabex, including the usage regimen and side effects. Patients then received individually tailored advice on stopping smoking and written support materials. Patients were offered follow-up visits as required by the patient. The session lasted approximately 30 minutes in total. Follow-up visits, where they occurred,

lasted about 20 minutes and did not follow a formal structure.

Tabex is administered orally in a dose of 1 tablet every 2 hours (6 tablets daily) for three days while smokers reduce of the number of smoked cigarettes. The treatment then proceeds according to the following scheme: from the 4th to 12th day—1 tablet every 2.5 hours (5 tablets daily); from the 13th to 16th day—1 tablet every 3 hours (4 tablets daily); from 17th to 20th—1 tablet every 4 hours (3 tablets daily), from the 21st to 25th day—1 tablet every 6 hours, 1–2 tablets daily. Smokers were instructed that they should have stopped smoking completely by the fifth day. The average duration of taking medication was 22 days. The duration of the course of medication was shorter than for medication such as bupropion or nicotine replacement therapies, but this was a clinical audit of the treatment regimen currently licensed and it would not have been appropriate to operate outside the licence.

Participants were followed up at 12 weeks with up to one additional week needed to make contact. Those who reported being abstinent at 12 weeks were followed up at 12 months with up to an additional two months needed to make contact. The 12-week follow-up involved only telephone contact. Participants were asked whether they were currently smoking and whether they had smoked at all since the quit date, how far they had followed the treatment regimen and about any adverse events. The 12-month follow-up involved an initial telephone contact; participants who reported that they had not smoked since the 12-week follow-up were invited to attend the clinic for CO verification. Participants who were unable to attend the clinic were offered a home visit.

Outcome was assessed using the Russell Standard.²³ This standard is designed to facilitate comparison of outcome figures across studies. It involves 12 months of continuous abstinence recorded at the 12-month follow-up and supported at that follow-up by CO < 10 ppm. The Russell Standard allows reporting of up to five cigarettes during the follow-up window but in the present study only reports of complete abstinence were counted as successes. All smokers allocated to receive the treatment are included in the analysis and any participants that cannot be followed up are considered to have resumed smoking.

RESULTS

Table 1 shows the sample characteristics. The participants were similar in smoking and demographic profile to those found in clinical trials in the United States and United Kingdom.¹ Their FTND (dependence) score was slightly higher than that found in other clinical studies or the average for smokers attending the UK stop smoking services.²¹ However, the smokers had started smoking at a slightly older age than is typically found in US and UK studies. The majority of participants attended just one session.

Three hundred and forty-two smokers were successfully followed up by telephone at 12 weeks. Of these 315 indicated that they had taken at least one tablet of Tabex. One hundred and twenty participants (27.5%) of the total sample reported having not smoked at all since the quit date. When these participants were followed up at 12 months, 60 (13.8% of the original sample) reported having been abstinent for the preceding 12 months and were confirmed as abstinent by CO at the follow-up.

A total of 13.8% of those attending the smokers' clinic reported being continuously abstinent for 12 months at follow-up with their current smoking status confirmed by CO concentration. It may be noted that there were 27 participants who reported at follow-up that they had not taken any medication and all of these had returned to

Table 1 Sample characteristics and outcome

Total attending clinic	438
Number excluded	2
Total enrolled	436
Percentage (n) males	43.8 (191)
Mean (SD) age (years)	44.4 (13.1)
Percentage (n) smoking more than 10 cigarettes per day	95.0 (414)
Percentage (n) smoking more than 20 cigarettes per day	51.6 (225)
Mean (SD) FTND score (dependence)	6.1 (2.2)
Percentage (n) with post-secondary education	26.8 (117)
Mean (SD) age of starting to smoke regularly	18.9 (4.5)
Percentage (n) having tried to quit before	70.2 (306)
Percentage (n) attending one session	54.1 (236)
Mean (SD) number of visits to clinic	1.7 (0.9)
Number followed up at 12 weeks	342
Number of those followed up who reported taking ≥ 1 dose of medication	315
Percentage (n) abstinent at 12 weeks	27.5 (120/436)
Percentage (n) reporting gastric disturbance/nausea	10.4 (33/315*)
Percentage (n) stopping medication due to adverse events	15.5 (49/315*)
Number attempted to follow up at 12 months	120
Number followed up at 12 months	112
Number reporting abstinence	68
Percentage (n) confirmed abstinent at 12 months by CO	13.8 (60/436)

*The number reporting having taken medication.

CO, expired-air carbon monoxide concentration; FTND, Fagerstrom Test for Nicotine Dependence.

smoking; all participants (98) who could not be contacted were assumed to be smoking.

At the 12-week follow-up patients were asked about known nicotine withdrawal symptoms using a check list and any other adverse events using an open response format. The most frequently reported withdrawal symptoms were: irritability (36%), restlessness (23%), depression (15%), appetite increase (47%), and sleep disturbance (21%). Constipation occurred in less than 10% of patients but they were more frequently observed among those who quit (13% *v* 6%). The most frequently reported adverse events were mouth dryness (35%), and nausea and gastric disturbances (10%). Of the 315 subjects who had taken the drug, 49 (15.5%) reported that they stopped because of adverse effects, 31 due to nausea and gastric disturbances.

DISCUSSION

The 12-month success rate was similar to the figure observed in the evaluation of the UK smoking cessation services. This was despite the fact that the smokers were more dependent on average, as indicated by the FTND, and most only attended one session of psychological support.

There may be many reasons for the high success rate in the Polish study, other than treatment using Tabex, but the absolute percentage figure, together with clinical data used to register the product, give strong a priori grounds for believing that the drug is effective. The six-month sustained quit rates of the placebo group in NRT trials involving minimal behavioural support is 8%¹ but there were studies that had higher rates than this, so we cannot rule out a placebo response or chance as leading to the relatively high success rates in the present study.

There were no reported serious adverse events. The numbers reporting minor adverse events was higher than the figure for NRTs. However, without a direct comparison caution should be exercised in interpreting this figure.

Taken together with the results from earlier studies these findings support the argument for a drug evaluation programme undertaken to modern standards. This would include large scale clinical trials of this drug to a standard that would be acceptable by regulatory authorities around the world. More information is also required on the pharmacokinetic properties of the drug, its safety profile and ideally studies varying the dose and the duration of dose. The

What this paper adds

Cytisine, medication licensed in Eastern Europe for 40 years as an aid to smoking cessation, appears to improve abstinence rates in smokers attempting to stop. Existing studies, however, have not included long-term follow-up or have adopted inadequate abstinence criteria.

The 12-month carbon monoxide verified continuous abstinence rate following a standard course of treatment with cytisine with minimal behavioural support was found in 436 smokers to be similar (13.8%) to that observed following treatment with nicotine replacement therapy. Full scale randomised controlled trials could lead to widespread adoption of this drug which, because of its cost, could make effective treatment available to millions of smokers that would otherwise not be able to afford it.

obvious advantage of this medication is its cost. It offers the prospect of providing access to effective treatment to help with smoking cessation to millions of smokers who would not otherwise be able to afford it. For healthcare providers it offers the prospect of hugely reduced costs.

If Tabex is found to be more effective than placebo, the question will arise as to whether it is similar in effectiveness to other medication on the market or likely to become available soon, such as varenicline. At the time of writing there have been no published reports on the effectiveness of varenicline but data presented at conferences appear to show superiority over bupropion, with one year continuous abstinence rates of more than 20%. The mode of action of Tabex is similar, though the duration of treatment, precise pharmacology and dosing regimen may all lead to differences in effectiveness. A comparison between varenicline and Tabex may be worthwhile if placebo controlled trials show Tabex to have some efficacy.

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CONTRIBUTORS

Witold Zatonski: overall concept of the trial, planning, preparation and supervision of work done in trial, participation in analysis and editing the paper. Magdalena Cedzynska: participation in planning the observation, everyday controlling works doing in clinic, participation in analysis data and editing the paper. Piotr Tutka: participation in drafting and editing the paper. Robert West: participation in designing the follow-ups, analysis and drafting and editing the paper.

Authors' affiliations

W Zatonski, M Cedzynska, Department of Epidemiology & Cancer Prevention, The M Skłodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland

P Tutka, Department of Pharmacology and Toxicology, Medical University of Lublin, Poland

R West, Department of Epidemiology and Public Health, University College London, UK

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This study was a clinical audit and there was not at that time regulation in Poland to submit this kind of research to ethics committee. The manufacturer of the drug provided it free to the clinic but did not have any say on methods and data analysis

Correspondence to: Dr Witold Zatonski, Department of Epidemiology & Cancer Prevention, The M Skłodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland; zatonskiw@coi.waw.pl

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