Cytisine for Smoking Cessation
A Literature Review and a Meta-analysis

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Background: Cytisine is an agonist of nicotinic receptors; in particular, it binds strongly with α4β2 nicotinic receptors. Cytisine has been used to treat tobacco dependence for 40 years in Eastern Europe. The objective of this study was to review the literature on the effect of cytisine on smoking cessation.

Methods: Review of PubMed, EMBASE, Psychological Abstracts, BIOSIS, Google.com, and Scholar.google.com, using the keywords cytisine, cytisin, zytisin, cytisinum, Tabex, and smoking cessation. Experts and the manufacturer of Tabex were contacted. Placebo-controlled trials were included in a meta-analysis.

Results: Ten studies reported the effects of cytisine on smoking cessation, including 4 controlled studies (3 placebo controlled). Nine studies used the Bulgarian drug Tabex, containing 1.5 mg of cytisine per tablet, and one Russian study used buccal films containing either 1.5 mg of cytisine or 0.75 mg of anabasine. All studies were published between 1967 and 2005 in Bulgaria, Germany, Poland, and Russia. There were 4404 smokers treated with cytisine and 3518 in control conditions. The pooled odds ratio after 3 to 8 weeks in the 3 placebo-controlled trials (2 were double blind and 1 was randomized) was 1.93 (95% confidence interval, 1.21-3.06). For the 2 placebo-controlled double-blind trials with a longer follow-up, the pooled odds ratio after 3 to 6 months was 1.83 (95% confidence interval, 1.12-2.99). One placebo-controlled double-blind trial had follow-up after 2 years (odds ratio, 1.77; 95% confidence interval, 1.29-2.43). Some adverse effects were reported. Most trials were, however, of poor quality.

Conclusions: Cytisine may be effective for smoking cessation. This fact remained largely unnoticed in the English-language literature.

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Tobacco smoking is the first avoidable cause of deaths and morbidity in developed countries, yet available treatments for tobacco dependence are not very effective. Thus, new treatments are warranted. During World War II, the leaves of Cytisus laburnum (golden rain tree) were used by smokers as a tobacco substitute. A 1955 publication advised smoking C. laburnum or Ulex europaeus, which both contain cytisine, as a treatment for tobacco dependence. Cytisine (not to be confused with cytosine) is an alkaloid found in all parts of C. laburnum, particularly in its seeds. Like nicotine, cytisine is a natural insecticide. It has been used for decades as a smoking cessation drug in Eastern European countries. It is marketed for this purpose by a Bulgarian firm under the name of Tabex (information available at: http://www.tabex.net). Varenicline, a new and effective smoking cessation drug, was derived from cytisine. Cytisine has a molecular structure similar to that of nicotine and acetylcholine and it is an agonist of nicotinic receptors; in particular, cytisine has a high affinity for α4β2 nicotinic receptors. In 1978, the tobacco industry identified cytisine as the substance with the pharmacological action closest to that of nicotine. Because of its affinity to nicotinic receptors and its pharmacological similarities to nicotine, cytisine is being used as a starting material for the development of new drugs, and it is covered by several patents for its medical use.

See also pages 1547, 1561, and 1571

Despite the known affinity of cytisine for nicotinic receptors and despite the fact that cytisine has been used for decades as a smoking cessation drug, the clinical studies of cytisine are almost never cited in the English-language literature. In particular, cytisine is absent from recent reviews of smoking cessation drugs. This study reviews the literature on the efficacy of cytisine for smoking cessation and conducts a meta-analysis of placebo-controlled trials.
### METHODS

**SEARCH AND SELECTION OF STUDIES**

All studies of the effect of cytisine on smoking cessation were searched, in any language. PubMed, EMBASE, Psychological Abstracts, BIOSIS, Google.com, and Scholar.google.com were reviewed, using the keywords cytisine, cytisin, zyti- sin, cytisinum, Tabex, and smoking cessation. The manufacturer of Tabex (Sopharma, Sofia, Bulgaria) was contacted and provided scientific articles and reports on Tabex in several languages. Tobacco dependence specialists in Bulgaria, the Czech Republic, Germany, Poland, and Russia were contacted, and the reference lists of the retrieved articles were consulted. Professional translators provided English-language translations of all relevant articles in Bulgarian, German, Polish, and Russian. The original articles and their translations are available at http://www.stop-tabac.ch/cytisine. Placebo-controlled trials were included in a meta-analysis.

### DATA ABSTRACTION

Because, to my knowledge, this is the first review on this topic, results of all the retrieved studies are reported, controlled and uncontrolled, even though uncontrolled studies have less scientific value. No study was rejected. Smoking abstinence rates were calculated using as the denominator the total number of participants included at the start of the trial, and participants absent at follow-up were counted as smokers (intention-to-treat analysis), when these data were available. The smoking abstinence rates reported by the original authors were used, even though most of the time, no precise definition of smoking abstinence was provided. Only 1 trial\(^{20}\) reported that biochemical verification of smoking abstinence took place.

### META-ANALYSIS

Results of the placebo-controlled trials were included in a meta-analysis. The I\(^2\) statistic was used to assess heterogeneity; this statistic describes the percent-

### Table 1. Effect of Cytisine on Smoking Cessation, From Studies Without a Control Group*

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Source</th>
<th>Country</th>
<th>Type of Patients</th>
<th>Behavior Support</th>
<th>Drug</th>
<th>Duration of Treatment</th>
<th>At Baseline</th>
<th>At Follow-up</th>
<th>Who Were Abstinent</th>
<th>Quit Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Granatowicz,(^{26}) 1976</td>
<td>Poland</td>
<td>Smoking cessation clinic</td>
<td>573 (29%) received other drugs</td>
<td>Tabex</td>
<td>6 mo</td>
<td>27 d</td>
<td>1968</td>
<td>NA</td>
<td>1378 (based on 70%)</td>
</tr>
<tr>
<td>2</td>
<td>Kempe,(^{27}) 1967</td>
<td>Bulgaria</td>
<td>Addicted, men</td>
<td>NA</td>
<td>Tabex</td>
<td>1 mo</td>
<td>17 d</td>
<td>30</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Maliszewski and Straczynski,(^{31}) 1972</td>
<td>Poland</td>
<td>12 Men and 2 women</td>
<td>NA</td>
<td>Tabex</td>
<td>40 d</td>
<td>25 d</td>
<td>14</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Metelitsa,(^{18}) 1987</td>
<td>Russia (sample A)</td>
<td>Inpatients</td>
<td>NA</td>
<td>Films</td>
<td>15 d</td>
<td>15 d</td>
<td>41</td>
<td>NA</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Russia (sample B)</td>
<td>Outpatients, healthy</td>
<td>NA</td>
<td>Films</td>
<td>15 d</td>
<td>15 d</td>
<td>21</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Russia (sample C)</td>
<td>Hospital patients</td>
<td>NA</td>
<td>Films</td>
<td>6-14 mo</td>
<td>18</td>
<td>NA</td>
<td>5</td>
<td>27.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Russia (sample D)</td>
<td>Healthy plus psychiatric</td>
<td>NA</td>
<td>Films</td>
<td>6 mo</td>
<td>15 d</td>
<td>201</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Paun and France,(^{27}) 1994</td>
<td>East Germany (group F)</td>
<td>Group therapy patients</td>
<td>Weekly group sessions</td>
<td>Tabex</td>
<td>8 wk</td>
<td>17 d</td>
<td>130</td>
<td>NA</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>East Germany (group P1)</td>
<td>Patients with severe dependence</td>
<td>Group sessions for weeks</td>
<td>Tabex</td>
<td>8 wk</td>
<td>17 d</td>
<td>100</td>
<td>NA</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>East Germany (group P2)</td>
<td>Group therapy patients</td>
<td>Group sessions</td>
<td>Tabex</td>
<td>8 wk</td>
<td>17 d</td>
<td>100</td>
<td>NA</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>East Germany (group P1)</td>
<td>Group therapy patients</td>
<td>Group sessions</td>
<td>Tabex</td>
<td>26 wk</td>
<td>17 d</td>
<td>130</td>
<td>108</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>East Germany (group P2)</td>
<td>Group therapy patients</td>
<td>Group sessions</td>
<td>Tabex</td>
<td>26 wk</td>
<td>17 d</td>
<td>100</td>
<td>NA</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Stoyanov and Yanachkova,(^{30}) 1972</td>
<td>Bulgaria (sample A)</td>
<td>Healthy plus psychiatric</td>
<td>NA</td>
<td>Tabex</td>
<td>NA</td>
<td>20 d</td>
<td>70</td>
<td>NA</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bulgaria (sample B)</td>
<td>Psychiatric patients</td>
<td>NA</td>
<td>Tabex</td>
<td>“A short period of time”</td>
<td>20 d</td>
<td>17</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Zatonski et al,(^{13}) 2005</td>
<td>Poland</td>
<td>Patients from the smoking cessation clinic</td>
<td>Visits to clinic</td>
<td>Tabex</td>
<td>3 mo</td>
<td>25 d</td>
<td>436</td>
<td>342</td>
<td>120</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data not available.

*Available at: http://www.stop-tabac.ch/cytisine.
age of variability due to true heterogeneity rather than error or chance. Because there was heterogeneity, a random-effects model was used to estimate the pooled weighted average of odds ratios (ORs) using computer software (Review Manager, version 4.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

STUDY CHARACTERISTICS

Ten studies were found, reported in 16 articles, that tested the effect of cytisine on smoking cessation in 17 different samples of smokers. The Bulgarian drug Tabex was used in 9 of these studies. Each tablet of Tabex contains 1.5 mg of cytisine. These tablets are swallowed, and the manufacturer recommends using 6 tablets per day (total, 9 mg of cytisine) during the first 3 days after smoking cessation, then decreasing the dosage gradually down to 2 tablets per day until the 25th day, when the treatment is stopped. All studies of Tabex more or less followed this regimen, although some used a shorter course of treatment. Tabex also contains calcium dihydrogenophosphate, lactose, wheat starch, microcrystalline cellulose, t alc, and magnesium stearate (data available at: http://www.tabex.net/41814_packageinsert.htm). One Russian study used films of 0.4 cm² placed between the gum and lip, containing either 1.5 mg of cytisine or 0.75 mg of cytisine plus 0.75 mg of anabasine. Patients took 4 to 6 of these films per day for 5 days after quitting smoking, and a decreasing dose thereafter until the 15th day. These films dissolve entirely in the mouth over 1½ hours and were developed to obtain buccal absorption of cytisine, with the aim of eliminating the digestive adverse effects produced by cytisine pills when they are swallowed.

All studies of the efficacy of cytisine for smoking cessation were conducted in Bulgaria, East and West Germany, Poland, and Russia. Tabex was tested for the first time for smoking cessation in Bulgaria and East Germany in 1965,21,22 and the most recent study16 was presented in 2005. One randomized controlled trial of Tabex is under way in Poland.16 Cytisine has also been tested for the treatment of depression, and positive results have been reported.33

CONTROL GROUPS

There were 7 uncontrolled studies18,19,22-31 and 4 controlled studies22-24 of cytisine for smoking cessation (1 study22 included controlled and uncontrolled samples). One Russian study compared films containing cytisine with films containing anabasine, but did not report results separately for these 2 drugs.18-20 Three controlled studies22-24 compared Tabex with a placebo, and 1 controlled study25 compared Tabex plus autogenic training with autogenic training alone. Only 2 of the 3 placebo-controlled studies24,28 reported that the trial was double blind, and only 1 included a clear indication that randomization took place.28

Authors of the other double-blind trial reported that “subjects received a numbered pouch with 100 Tabex or placebo tablets,”25(p2093)from which we can presume, but not definitively conclude, that subjects were randomized. The latter study was reported in 4 different articles.24-27 In one double-blind randomized trial conducted in West Germany, Tabex was compared with placebo and with 12 other substances (Aatabakko [a compound of caffeine and theobromine], Citotal, Nicobre-vin, Nicocortyl, Ni-Perlen, Pempidil, potassium, Radix levistici, Rau-cer stop 5 HT, Targophagin, Unilobin, and Viotil).28 Finally, slow-release cytisine tablets are under development in Bulgaria, but, to my knowledge, no trial of the efficacy of these new tablets has been published.34,35

EFFECT OF FILMS CONTAINING CYTISINE

One Russian study18-20 tested 0.4-cm² films containing cytisine, anabasine, or cytisine and anabasine. The effect of these 3 types of films was studied in 281 smokers across 4 different samples.18 First, a clinical sample of 41 smokers (inpatients with cardiovascular diseases) received these films for 15 days, and 56.0% of them quit smoking after an unspecified time, apparently at the end of treatment. Quit rates by group were not reported. Second, a sample of 21 healthy smokers (outpatients) tested the same films for 15 days, and 28.6% quit smoking at the end of treatment. Third, 18 healthy smokers were treated for 6 to 14 months, and 5 (27.8%) remained abstinent at the end of the study (results by group were not given). Fourth, a sample of 201 smokers, including some psychiatric patients, were treated with these films and followed up after 6 months. An “absolute effect” (ie, smoking abstinence) was obtained in 50.0% of patients.18 Two more articles19,20 reported on the same first 2 samples of 62 smokers, providing more details and a longer follow-up. These 2 articles indicated the number of subjects receiving each type of film: 1.5 mg of cytisine (n=23), 0.75 mg of cytisine plus 0.75 mg of anabasine (n=16), or 1.5 mg of anabasine (n=23). In these 2 articles, these 62 people were followed up for 6 to 14 months, when 6 (21%) of the 29 short-term quitters had relapsed, leaving a 37.1% abstinence rate (23/62) at 6 to 14 months. None of these articles indicated whether smokers were randomly assigned to receiving these 3 films, nor did they indicate the numbers and proportions of quitters per group. In all 3 articles, the authors nevertheless stated that films containing cytisine or cytisine in combination with anabasine were more effective than films containing anabasine. Two articles19,20 reported data on the pharmacodynamics of these films in 78 patients.

EFFECT OF TABEX

Nine studies reported on the effect of the Bulgarian preparation Tabex, including 6 uncontrolled studies16,21,22,30,32 and 4 controlled studies.22,27-29 A German study22 reported data from several sites, but only 1 site (Potsdam Rehbrücke, group R) included a control group that received placebo; the other groups were uncontrolled (groups F, P1, and P2). In these 9 studies, a total of 4146 smokers were treated with Tabex and 3518 were included in control conditions. Smoking abstinence rates at the end of treatment (usually 4 weeks) in smokers using Tabex ranged from 29.0% to 76.0%, and abstinence rates after 3 to 12 months ranged from 13.8% to 70.0% (Table 1).
META-ANALYSIS

The 3 placebo-controlled studies of Tabex were included in a meta-analysis. (The flow diagram for the meta-analysis is given in the Figure.) No behavioral support was provided to participants in any of these 3 studies. In one study, smoking abstinence was assessed in mailed surveys, based on replies to the following: “I have completely stopped smoking” and “Are you a smoker or a non-smoker?” In the article by Schmidt, abstinence was determined from answers in a mail survey to an unspecified question on “complete abstinence.” In the study by Paun and Franze, abstinence was determined by physicians using an unspecified criterion. A first meta-analysis was conducted on data collected after 4 weeks, after 8 weeks, and at the end of treatment (apparently a few weeks) for the placebo-controlled group only in the article by Schmidt. In these 3 placebo-controlled trials, there was significant heterogeneity for short-term outcomes ($I^2=75.1\%$, heterogeneity $P=.04$), and the pooled effect for these 2 studies after 3 to 6 months was as follows: OR, 1.83 (95% confidence interval, 1.12–2.99) (random-effects model). Only 1 placebo-controlled study reported long-term results after 2 years (OR, 1.77; 95% confidence interval, 1.29–2.43) (Table 2).

ADVERSE EFFECTS

Smokers need a medical prescription to obtain Tabex. The manufacturer of Tabex specifies that “the following adverse effects are rather often observed at the beginning of Tabex treatment: changes in both taste and appetite, dryness in the mouth, headache, irritability, nausea, constipation, tachycardia, light elevation of the arterial pressure” and that Tabex is contraindicated for people with arterial hypertension and advanced atherosclerosis (data available at: http://www.tabex.net/41814_packageinsert.phtml).

In published studies, the adverse effects that were slightly more frequent in subjects using cytisine than in those using placebo were weight gain, headache, and heartburn. Nausea, vertigo, diarrhea, and digestive problems were reported in some studies, with no comparison with placebo or at the same rate as placebo. One uncontrolled study reported a decrease in blood pressure after 15 minutes; another reported, on the contrary, an increase of 10 mm Hg in blood pressure; and 2 others reported no effect on blood pressure. One study reported tachycardia in 62 (16%) of 388 patients, 2 reported light tachycardia in 3 (4%) of 70 patients and an “insignificant” effect on heart rate, and 1 reported no effect on the electrocardiogram and blood pressure.

TOXICITY

There are numerous reports of people getting poisoned with seeds of *C. laburnum*, which contain cytisine. One fatal case was reported in a psychiatric patient who also used the antipsychotic drug chlorpromazine hydrochloride (Largactil). This patient absorbed 23 pods of *C. laburnum*, corresponding to 35 to 50 mg of cytisine. The lethal dose in humans is, however, unknown. Poisoning in children who eat laburnum seeds is frequent. It was reported that “in an average summer, over three thousand children are admitted to hospitals in England and Wales because of laburnum poisoning” but that “laburnum is not as dangerous as has been thought and that many of these admissions are unnecessary.”

Poisoning symptoms with cytisine resemble poisoning symptoms with nicotine and include nausea, abdominal pain, vomiting, muscular weakness, and respiratory stimulation, soon followed by respiratory depression. One report described 2 non-lethal suicide attempts by the same patient, a pharmacist who swallowed 40 to 50 Tabex tablets (containing 60 to 75 mg of cytisine) on her first suicide attempt and 90 tablets (containing 135 mg of cytisine) on her second attempt. Poisoning with laburnum is probably due to the short-term nicotinelike effect of cytisine on the central nervous system. In the rat, the lethal dose of cytisine (median lethal dose, the dose at which half the animals die) is 1.7 mg/kg intravenously and 101 mg/kg per os. In the animal, there are reports of fatal accidental poisoning with seeds of *C. laburnum*. Incidentally, there are more reports of fatal poisoning in...
<table>
<thead>
<tr>
<th>Study No.</th>
<th>Source</th>
<th>Country</th>
<th>Control Group, Placebo, double blind</th>
<th>Behavioral Support</th>
<th>Duration of Tabex Therapy</th>
<th>Total No. of Patients</th>
<th>Cytisine Group Present at Follow-up</th>
<th>Cytisine Group</th>
<th>Control Group</th>
<th>Quit Rate, %</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Benndorf et al, 1968</td>
<td>East Germany (first 314 subjects only)</td>
<td>Placebo, double blind</td>
<td>None, “we avoided suggestive influence”</td>
<td>20 d</td>
<td>4-6 wk</td>
<td>157</td>
<td>157</td>
<td>NA</td>
<td>120</td>
<td>48</td>
<td>76.4</td>
<td>30.6</td>
</tr>
<tr>
<td>Benndorf et al, 1969</td>
<td>East Germany</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>20 d</td>
<td>4-6 wk</td>
<td>607</td>
<td>607</td>
<td>NA</td>
<td>395</td>
<td>246</td>
<td>65.1</td>
<td>40.5</td>
</tr>
<tr>
<td>Benndorf et al, 1970</td>
<td>East Germany (only 395 Tabex-treated subjects abstinent at 4-6 wk)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>20 d</td>
<td>5-12 mo</td>
<td>607</td>
<td>NA</td>
<td>204</td>
<td>143</td>
<td>NA</td>
<td>23.6</td>
<td>NA</td>
</tr>
<tr>
<td>Scharfenberg et al, 1971</td>
<td>East Germany (4 wk)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>20 d</td>
<td>4 wk</td>
<td>607</td>
<td>607</td>
<td>1214</td>
<td>395</td>
<td>246</td>
<td>65.1</td>
<td>40.5</td>
</tr>
<tr>
<td>East Germany (6 mo)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>20 d</td>
<td>6 mo</td>
<td>607</td>
<td>607</td>
<td>801</td>
<td>185</td>
<td>97</td>
<td>30.5</td>
<td>16.0</td>
<td>2.30 (1.73-3.07)</td>
</tr>
<tr>
<td>East Germany (2 y)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>20 d</td>
<td>2 y</td>
<td>607</td>
<td>607</td>
<td>801</td>
<td>127</td>
<td>79</td>
<td>20.9</td>
<td>13.0</td>
<td>1.77 (1.29-2.43)</td>
</tr>
<tr>
<td>Marakulin et al, 1984</td>
<td>Russia</td>
<td>Autogenic training, 12-14 sessions</td>
<td>Individual and group sessions</td>
<td>3 wk</td>
<td>3 wk</td>
<td>388</td>
<td>232</td>
<td>NA</td>
<td>272</td>
<td>123</td>
<td>70.1</td>
<td>53.0</td>
</tr>
<tr>
<td>Paun and France, 1968</td>
<td>East Germany (groups R plus placebo)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>17 d</td>
<td>8 wk</td>
<td>36</td>
<td>239</td>
<td>NA</td>
<td>15</td>
<td>80</td>
<td>41.7</td>
<td>33.5</td>
</tr>
<tr>
<td>Schmidt, 1974</td>
<td>West Germany (3-4 wk)</td>
<td>Placebo, double blind</td>
<td>None (by mail)</td>
<td>3 wk</td>
<td>3-4 wk</td>
<td>250</td>
<td>270</td>
<td>Cytisine group, 181; placebo group, 239</td>
<td>103</td>
<td>84</td>
<td>41.2</td>
<td>31.1</td>
</tr>
<tr>
<td>West Germany (3 mo)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>3 wk</td>
<td>3 mo</td>
<td>250</td>
<td>270</td>
<td>Cytisine group, 181; placebo group, 239</td>
<td>68</td>
<td>57</td>
<td>27.2</td>
<td>21.1</td>
<td>1.40 (0.91-2.13)</td>
</tr>
<tr>
<td>West Germany (3-4 wk, all 12 other drugs in trial, including placebo, excluding lime tea)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>3 wk</td>
<td>3-4 wk</td>
<td>250</td>
<td>270</td>
<td>Cytisine group, 181; placebo group, 239</td>
<td>103</td>
<td>74</td>
<td>41.2</td>
<td>34.1</td>
<td>1.35 (1.03-1.78)</td>
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<tr>
<td>West Germany (3 mo, all 12 other drugs in trial, including placebo, excluding lime tea)</td>
<td>Placebo, double blind</td>
<td>None</td>
<td>3 wk</td>
<td>3 mo</td>
<td>250</td>
<td>2170</td>
<td>1994</td>
<td>103</td>
<td>740</td>
<td>41.2</td>
<td>34.1</td>
<td>1.35 (1.03-1.78)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data not available.
*Available at: http://www.stop-tabac.ch/cytisine.
Research conducted during the past 40 years suggests that cytisine is effective for smoking cessation. Thus, an apparently effective smoking cessation drug that has been used for decades in Germany and Eastern European countries remained unnoticed in other countries. Most of the articles reviewed herein were never cited in the English-language literature. Despite the existence of 3 placebo-controlled trials, recent reviews of the efficacy of smoking cessation drugs omitted cytisine\(^2,14,15\) and little research on cytisine has been conducted in recent years.

This omission is probably explained because studies of the efficacy of cytisine were not published in English and because the available evidence is based on studies that do not conform to current standards in conducting and reporting drug trials. In particular, only 1 recent study\(^16\) used biochemical verification of smoking status, and most studies did not indicate which criterion was used to define smoking abstinence. Only 1 of the 3 placebo-controlled studies clearly indicated that randomization took place, and only 2 were double blind. Most studies were short term, and the number of participants present at follow-up was not always reported. This research probably also remained unnoticed because all studies except 2\(^ {10,28}\) were conducted in Eastern European countries before democratization. However, the only randomized, double-blind, placebo-controlled study\(^ {28}\) was conducted in West Germany, and it showed statistically significant effects of cytisine. Research conducted in the West during the same period (1960s and 1970s) was also often of poor quality, because current methodological standards were not widely adopted at that time, even in the West.\(^6\) Probably because of their poor quality, several studies reported unrealistically high quit rates (60%-70%) and should be interpreted with caution. However, quit rates and ORs in the 3 placebo-controlled trials are well in the range of short-term outcomes in studies of other smoking cessation drugs (nicotine replacement therapy and bupropion).\(^2\) These 3 studies seem, therefore, to be credible, if considering in addition that cytisine binds strongly with nicotinic receptors and that varenicline is effective for smoking cessation.

Few adverse effects of cytisine were reported in the studies reviewed herein, which does not mean that cytisine is innocuous. Cytisine causes poisoning, and toxicity tests of cytisine in humans were conducted and results published as internal industry reports in Bulgarian; however, despite repeated attempts, I was unable to obtain these reports. Thus, it is apparently not known whether cytisine has any effect on organ damage or whether it is carcinogenic, teratogenic, or genotoxic in humans. Apart from the relatively short-term adverse effects reported in smoking cessation trials, it is unknown whether the recommended dose of Tabex and cytisine films (9 mg/d) carries any risk and what would be the consequences if children swallowed these tablets.\(^3\) There is some discrepancy between the adverse effects reported in published studies and the list of adverse effects in the manufacturer’s leaflet. In particular, more weight gain using cytisine than using placebo was reported in 1 study,\(^ {25}\) and vertigo was mentioned in some studies but not in the manufacturer’s leaflet. On the other hand, increases in blood pressure and heart rate are listed in the manufacturer’s list of adverse effects, but were not consistently reported in published studies.

One limitation of this review is that it was conducted by only 1 person. A duplication of the data search and extraction processes by a second person would have been preferable, but the search process was, nevertheless, extensive and comprehensive. The available data suggest that cytisine may be effective for smoking cessation. This result is all the more interesting considering that no behavioral support was provided to participants in any of the 3 placebo-controlled trials. It is necessary to conduct state-of-the-art clinical trials to confirm these results. However, given the uncertainties about the toxicity of cytisine, it may not be ethical to conduct phase 3 clinical trials before more is known about the toxicity and tolerability of cytisine in humans, at the dosage recommended by the manufacturer. An apparently effective treatment for the first avoidable cause of death in developed countries remained largely unnoticed, despite research published during the past 40 years. How many other effective drugs are there for which efficacy remained unnoticed because existing trials were not published in English in Western countries?

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