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EDITORIALS

Cytisine, the world's oldest smoking cessation aid

Growing evidence for its use as an affordable treatment globally

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Nearly 50 years ago, and before any smoking cessation aids were approved in the Western world, cytisine was being used in eastern and central Europe to help people quit smoking. An alkaloid with high affinity for the α4β2 nicotinic acetylcholine receptor subtype, cytisine is derived from the plant *Cytisus laburnum*. It was discovered in 1818, first isolated in 1865,[1] and its actions were documented as "qualitatively indistinguishable from that of nicotine" in 1912.[2] It was smoked as an accessible and cheap tobacco substitute by German and Russian soldiers during the second world war, and it was brought to market in 1964 as a cessation aid under the brand name Tabex, now produced by Sopharma, a Bulgarian drug company. Currently, the recommended course of treatment starts at one tablet every two hours (six in total per day) for one to three days, tapered gradually, with a scheduled quit date at day 5, and ending with one to two tablets daily by days 21-25. Optimal doses and duration of treatment, however, are as yet undetermined because no human pharmacokinetic data have been published.

The first data from clinical trials on the beneficial effects of cytisine for quitting smoking were published in the late 1960s to early 1970s in non-English, eastern European journals. Quit rates, self reported and collected by mail, ranged from 41% to 65% at the end of treatment and 21% to 30% at six months or longer of follow-up.[3] The trials' methods, some with uncontrolled designs, did not meet Western regulatory standards.

In 2011, a more rigorously designed trial of cytisine was published in the *New England Journal of Medicine*,[4] and in 2013 a meta-analysis in *Thorax* synthesized the findings across all controlled trials.[3] The summary estimate of efficacy was significant and comparable to published effects for nicotine replacement, bupropion, nortriptyline, and clonidine, with a relative risk of abstinence of 1.57 (95% confidence interval 1.42 to 1.74). In a Cochrane meta-analysis restricted to the two most recent and higher quality studies, the relative risk of abstinence was even stronger (3.98; 2.01 to 7.87; table⇓).[5] The absolute sustained long term quit rates, however, were modest: 8.5% for cytisine versus 2.1% for placebo at one year. The low quit rate in both groups was attributed to the minimal behavioral support provided and the study locales: Poland and Kyrgyzstan. These nations are still fairly permissive to smoking in public places and 37% to 45% of men, respectively, smoke.[6] Furthermore, the course of treatment for cytisine (25 days) is shorter than for other cessation aids, and a longer course of treatment might reduce relapse.[7]

Cytisine's dosing schedule seems safe as tested. Reported side effects are mainly gastrointestinal and include stomach ache, dry mouth, dyspepsia, and nausea. Contraindications for use include pregnancy, breast feeding, severe atherosclerosis, and uncontrolled hypertension.

Former socialist countries have withdrawn cytisine since joining the European Union, which has not approved its use. In 2012, five of 126 surveyed nations participating in the World Health Organization's Framework Convention on Tobacco Control reported access to cytisine—all were in eastern and central Europe.[8] Regulatory approval in the West would require serious investment (upward of $1bn; £0.64bn; €0.75bn) for research into the pharmacokinetics and pharmacodynamics of cytisine in humans and a second phase III trial.[9] The drug industry is unlikely to finance such research because of the high cost-profit ratio. Realistic to the counter economic forces, Aveyard and West called for the UK to approve cytisine for use anyway.[10] Such a move would require an entirely new regulatory standard.

Because cytisine is inexpensive, governments should consider funding proper phase I and randomized controlled comparative effectiveness trials, with appropriate pharmaco-economic analysis. If governments are unwilling, then the US Food and Drug Administration and other similar regulatory bodies should evaluate the benefit versus risks of approving cytisine for smoking cessation.

The pharmacology of cytisine analogues is also being explored. Cytisine inspired Pfizer's development of varenicline, which putatively has a similar mechanism of action for smoking cessation and reached annual sales of $755m worldwide.[11] RJ Reynolds and its spinoff Targacept are interested in cytisine

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derivatives as potential nicotine alternatives and therapeutic agents for neurodegenerative and psychiatric disorders.[12 13]

Naturally grown, inexpensively produced, and generically available, cytisine is a half to a twentieth of the cost of other cessation drugs. On the basis of existing efficacy data it should be considered as a cessation aid in low income countries where other treatments are unavailable or unaffordable.

There is currently an international online market for cytisine for smoking cessation—a Google search of "buy Tabex" yielded 5470 results. Online vendors claim a 76-80% quit rate, and some sites sell a dissolvable cytosine strip, which has even fewer data or studies available. For this editorial, we purchased a box of 100 1.5 mg cytisine tablets for $31.20 (including US shipping) from a website that marketed natural products and herbs. When production is unregulated, however, buyers risk obtaining poor quality or counterfeit formulations.

Cytisine's initial evidence of efficacy and clear affordability are strong indicators for continued studies. In the meantime, cyber buyers beware.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JJP has served on ad hoc scientific advisory and grant review boards for Pfizer and has a Pfizer funded investigator initiated research award. SD has not received any industry support. NLB is a former member of the FDA tobacco products scientific advisory committee; serves on a Pfizer smoking cessation medication advisory board; and has been an occasional consultant to GlaxoSmithKline and McNeil, which market smoking cessation drugs.

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Table

Table 1| Comparison of smoking cessation drugs

Variable	Drug						
	Cytisine	Varenicline	Bupropion	Nicotine patch	Patch+acute NRT*	Nortriptyline	Clonidine
Year of first publication for cessation	1964	2006	1994	1982	1995	2002	1988
No of controlled clinical trials (no of participants)	2 (911)	14 (6166)	27 (9157)	32 (15 517)	3 (1456)	2 (171)	3 (504)
Relative risk of abstinence (95% confidence interval)†	3.98 (2.01 to 7.87)	2.48 (1.92 to 3.21)	1.39 (1.19 to 1.61)	1.53 (1.35 to 1.73)	1.37 (1.07 to 1.75)	1.68 (0.91 to 3.09)	1.55 (1.03 to 2.33)
12 month quit rates (%)†:							
Active drug	8.5	21.5	25.8	17.5	17.9	25.6	21.1
Placebo	2.1	8.7	18.0	11.8	13.1	5.3	12.6
Side effects	Common: dry mouth, dyspepsia, stomach ache, and nausea (12%)	Common: nausea (33%), headache, insomnia; uncommon: neuropsychological symptoms	Common: insomnia, dry mouth, nausea, headache; uncommon: seizure, neuropsychological symptoms	Common: skin reaction, headache, sleep disturbance, cough, hiccups		Common: dry mouth, drowsiness, dizziness, constipation; can be lethal in overdose	Common: dry mouth, dizziness, sedation; dose dependent: postural hypotension
Cost and duration of treatment	$20-30; 25 days	$474-501; 12 weeks	$228-521; 12 weeks	$112-238; 8-10 weeks	$186-685; 8-10 weeks	$95; 12 weeks	$76; 12 weeks
Counties available in (N)‡	5	55	52	74	74	3	1

*NRT=nicotine replacement (available as transdermal patch, lozenge, gum, nasal spray, and inhaler).

†Trials data, relative risk of abstinence and 12 month follow-up quit rates from Mills and colleagues[14] (varenicline, bupropion, nicotine patch, patch+acute NRT) and *Cochrane Database of Systematic Reviews* [15] (cytisine, nortriptyline—calculated for 2 trials with 12 month follow-up outcomes comparing arms with drug management only and standard course of nortriptyline *v* placebo; clonidine—calculated for 3 trials with 12 month follow-up outcomes).

‡Awareness of availability for smoking cessation, as reported in 2012 by 126 member nations of the WHO Framework Convention on Tobacco Control.

$1=£0.64; €0.75.