

Cytisinicline to Speed Smoking Cessation in the United States

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In 1984, the US Food and Drug Administration (FDA) approved nicotine gum as the first pharmacotherapy for cigarette smoking cessation. Other types of nicotine replacement therapy have followed (nicotine lozenges, transdermal patches,



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inhaler, and a nasal spray), and in 1997, the first non-nicotine pharmacotherapy, bupropion, was approved. The FDA has not approved a new drug with an indication for smoking cessation since varenicline was approved in 2006. For over a decade, more than 50% of US adults who smoke have attempted to quit at least once each year, with around 7% of those who smoke achieving abstinence each year for at least 6 months.¹ Many have tried more than 1 FDA-approved pharmacotherapy unsuccessfully and have begun trying to switch to less harmful tobacco products, which are not approved as smoking cessation medications (eg, electronic cigarettes, smokeless tobacco, or nicotine pouches).^{2,3} In a recent international study of smoking cessation attempts in the US, Canada, Australia, and England in 2020, nicotine replacement therapy was the most commonly used quit aid at the last attempt (28.8%), closely followed by nicotine vaping products at 28% (ie, electronic cigarettes).³ Only 10.8% used a nonnicotine pharmacotherapy, while 38.6% used no aid at all on their last quit attempt (ie, no counseling, physician advice, website, brochure, nicotine replacement therapy, electronic cigarette, medication, etc).³ Of the 4 countries studied, US participants who smoked were the most likely to use no form of assistance on their last quit attempt (40.2%).

It is against this background that the new study by Rigotti et al⁴ in this issue of *JAMA* provides hope that a new safe and effective drug regimen, cytisnicline, could become available for smoking cessation in the US in the near future (after FDA review of clinical trial data). The proposed mechanism of action of cytisnicline is 2-fold: (1) acting as a selective partial agonist, stimulating subtypes of nicotinic acetylcholine receptors in the brain, much as nicotine does, to reduce nicotine withdrawal and craving, and (2) acting as a temporary partial antagonist at these same receptors, blocking the effects of nicotine, and so reducing the reinforcing effects of a lapse cigarette. These effects are similar to, but not identical to, the effects of varenicline.^{5,6}

It has been a long journey for cytisnicline (also called cytisine), since being isolated from plants in the late 19th century, then developed as a smoking cessation aid and marketed in Eastern Europe since the 1960s.⁶ The study by Rigotti et al⁴ used a relatively new dosing schedule of 3 mg 3 times per day for 6 to 12 weeks that was developed after pharmacokinetic studies demonstrated that blood levels

peak 1 to 2 hours after each oral administration and then decline with a half-life of 4.8 hours.^{6,7} This dosing schedule promises better patient adherence due to fewer tablets required per day than the original dosing regimen used in eastern Europe and in some previous clinical trials (1.5 mg 6 times per day, reducing over 25 days).^{6,8} The results of the new trial by Rigotti et al⁴ show that 12 weeks of cytisnicline treatment has superior smoking cessation outcomes than 6 weeks of cytisnicline treatment (plus 6 weeks of placebo) or 12 weeks of placebo, with cigarette abstinence rates during weeks 9 to 12 of 32.6%, 22.3%, and 7%, respectively. It is common to all smoking cessation pharmacotherapies that some people relapse to smoking after stopping drug treatment. It is encouraging that in this new trial, the advantage of 12 weeks of treatment with cytisnicline remained clear at 24 weeks, when all participants had not taken the medication for at least 12 weeks (21.1% in the 12-week cytisnicline group vs 4.8% in the placebo group).

The smoking cessation rates with placebo in the trial⁴ were low, not reaching more than 12% 7-day point-prevalence cigarette abstinence at any point in the trial, despite regular access to smoking cessation counseling. This was possibly related to the fact that more than 60% of trial participants had previously tried nicotine replacement therapy, and more than 40% had previously tried varenicline. The trial participants had already tried to quit an average of 6 times, indicating that they were highly motivated to quit but addicted to the nicotine in their cigarettes.

It is not possible to make direct comparisons between outcomes from the new cytisnicline dosing schedule and the current most effective FDA-approved smoking cessation drug, varenicline, on the basis of this new trial because the trial did not include a varenicline comparison group. However, the more than 4-fold increase in the smoking cessation rate over placebo at 6 months in this trial is impressive. Two previous open-label randomized trials compared the older cytisnicline treatment regime (starting with 6 × 1.5 mg, then reducing over 25 days) with varenicline in direct head-to-head comparisons.^{8,9} Both of those trials found similar biochemically validated smoking cessation rates between varenicline and cytisnicline at 6 months, but adverse events were significantly less frequent with cytisnicline.⁸ In both of these trials, the varenicline group received the full dose for 12 weeks and the cytisnicline group either ended drug treatment at 25 days⁸ or dropped to a lower level (2 × 1.5-mg tablets per day) after 25 days,⁹ making direct comparisons of drug effects difficult to disentangle from duration of treatment.

The types of adverse event reports on cytisnicline are somewhat similar to those reported in trials of varenicline

(but possibly less frequent and severe), with insomnia and abnormal dreams being the most common (8%-10%) reported in the new trial⁴ and these were approximately twice as common as in the placebo-treated group. A higher proportion of those assigned to 12 weeks of cytisinicline took at least 90% of the tablets (79.3%) as compared with placebo (69.3%). This suggests that participants were generally not discouraged from taking the drug because of its adverse effects, relative to its perceived benefits. The fact that cytisinicline has been used for smoking cessation in some Eastern European countries for more than 50 years (including over the counter) without a serious problem with adverse events emerging is also reassuring regarding the safety profile of the drug.⁶

The rapid development and roll-out of numerous effective vaccines that protect against the more serious health effects of the COVID-19 virus has rightly been hailed as one of the greatest achievements in science and medicine, and has been described as “the most rapid scale-up of new life-saving technology” ever seen.¹⁰ However, it is worth considering that at its peak, the Centers for Disease Control and Prevention estimates that the virus caused around 472 000 deaths in the US in 2021.¹¹ That is almost as many deaths as the Centers for Disease Control and Prevention and others estimate die every year in the US because of cigarette smoking.¹² This has been happening for more than 50 years. It is unfortunate that there has

never been an “Operation Warp Speed” to prevent the more than 480 000 deaths each year caused by smoking. It is, however, a very positive development that another new and effective drug may be added to the limited list that clinicians and individuals who smoke can choose from to help end their deadly addiction to cigarettes. The US government is considering whether to implement decisive regulations to reduce the appeal and addiction to smoked tobacco products, by abolishing menthol as a characterizing flavor¹³ and requiring a 95% reduction in nicotine content in smoked tobacco products.^{14,15} Meanwhile, the government of New Zealand is already moving forward with its comprehensive plan to become a smoke-free country by 2025.¹⁶ The Smokefree Environments and Regulated Products (Smoked Tobacco) Amendment Act was signed into law in December 2022 and includes provisions to (1) ban the sale of tobacco to those born after 2008, (2) reduce the number of tobacco retailers by at least 90%, (3) reduce the permissible nicotine content in cigarettes by more than 90%, and (4) increase smoking cessation services, including continued adult access to approved electronic cigarettes.¹⁷ We hope that this decisive action by New Zealand might inspire countries like the US to tackle addiction to cigarettes with the vigor and speed that its effects on public health deserve. Until that happens, we hope that cytisinicline can help more people who smoke in the US to quit.

ARTICLE INFORMATION

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