Cytisine — A Tobacco Treatment Hiding in Plain Sight
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A randomized, controlled trial published in this issue of the Journal brings renewed attention to cytisine, a potentially useful pharmacotherapy for smoking cessation that has been hiding in plain sight. A naturally occurring plant alkaloid, cytisine has been sold in Eastern Europe as an inexpensive smoking-cessation aid for 50 years but is unavailable elsewhere.

Two events brought it to broader attention in 2006. First, Etter’s review of overlooked, older studies suggested a potential efficacy of cytisine for smoking cessation, although a firm conclusion could not be drawn because previous trials did not meet contemporary standards. Second, varenicline, a drug with a similar mechanism of action, was licensed as a new smoking-cessation aid. Cytisine, like varenicline, is a partial agonist that binds selectively to the \( \alpha_4\beta_2 \) nicotinic acetylcholine receptor subtype that appears to mediate nicotine dependence.

Subsequently, two randomized trials and two meta-analyses incorporating them provided better evidence of cytisine’s efficacy as compared with placebo. The study reported here is noteworthy for its direct comparison of cytisine with an established, first-line smoking-cessation pharmacotherapy. In this randomized, noninferiority trial, cytisine was not just similar to nicotine-replacement therapy but actually superior to it for continuous tobacco abstinence at 1 month, the trial's primary outcome measure. This is only an end-of-treatment intermediate outcome, but cytisine remained superior to nicotine-replacement therapy at a 6-month follow-up in one of two typical measures of long-term efficacy.

Conducted as a pragmatic clinical trial, the study recruited smokers seeking treatment in a real-world setting. New Zealand’s national telephone quitline provided minimal behavioral support and had few exclusion criteria. The advantage of this design is that an intervention found to be truly effective is likely to work in many settings. In contrast with the tightly controlled conditions used in standard efficacy (or explanatory) trials to maximize internal validity, in this study, participants were aware of the study treatment and there was no biochemical verification of their self-reported tobacco abstinence at follow-up.

Although cytisine was associated with a higher rate of adverse events than nicotine-replacement therapy, only 5% of patients discontinued cytisine because of side effects. The most common symptoms, nausea and vomiting and sleep disorders, had previously been observed and mirror patients’ experience with varenicline. The psychiatric side effects reported in postmarketing surveillance of varenicline were not observed, but the study was too small to detect rare events. These symptoms did not emerge during decades of use of cytisine in Eastern Europe, but the extent of monitoring for these effects is unclear.

Several features of the trial may have biased the results against nicotine-replacement therapy. More than 20% of participants had used nicotine-replacement therapy in their most recent attempt to stop smoking and were already nonresponders to nicotine-replacement therapy. Both groups received vouchers to subsidize the purchase of nicotine-replacement therapy, and 4% of the participants in the cytisine group used these vouchers along with their assigned drug. Nicotine-replacement therapy is more effective when users combine the skin patch with an orally absorbed treatment such as gum or lozenges. Nicotine-replacement therapy might have produced a better outcome if different means of
delivery had been combined, but combination therapy was not part of the protocol for the trial.

Overall, the study shows that cytisine is at least equivalent to nicotine-replacement therapy, since both were used in real-world practice. Further trials will be needed to determine whether cytisine is truly superior to nicotine-replacement therapy and how it compares with other first-line pharmacotherapies that help smokers achieve long-term tobacco cessation. Studies could also explore whether the efficacy of cytisine could be improved with alternative dosing regimens.

A more urgent issue with regard to cytisine concerns public health. Cytisine is an inexpensive drug that has been used for decades and for which there are now current data showing its safety and effectiveness. There are millions of smokers worldwide who might benefit from it. The compelling rationale for bringing cytisine to market is not that its efficacy is superior to that of current pharmacotherapies but that current pharmacotherapies are unavailable to so many smokers — especially those in low-income and middle-income countries — because of their cost. Stakeholders in high-income countries seeking to contain health care costs would also benefit from a lower-cost pharmacotherapeutic option.

The challenge is to protect public health while retaining cytisine’s affordability for consumers. Unfortunately, in the United States and Western Europe there is now no direct pathway through the regulatory and pharmaceutical market structure for a potentially useful drug with cytisine’s unconventional history. The solution will require creative collaboration among a range of stakeholders. These include regulators, pharmaceutical companies, government agencies that fund research, and both public and private organizations whose mission is to improve global public health. A first step might be to convene these stakeholders and challenge them to identify a way forward.

The need is urgent. Tobacco use is now the leading preventable cause of death worldwide. Smoking cessation benefits virtually every smoker, and the use of pharmacotherapy improves the likelihood of success for those who attempt to quit. We can save lives by making effective treatments available to all smokers.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Out of Africa — Caring for Patients with Ebola

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Although the Ebola virus was recognized in 1976, until now Ebola virus disease (EVD) had been confined to remote areas in Africa, occurring in discrete outbreaks. Even with the thousands of cases in the current outbreak, most cases occur in areas where tragically few resources are available to care for affected patients — in Guinea, Liberia, and Sierra Leone. However, a small number of patients have been transferred to hospitals with modern technology. In addition,