Editorial

**Getting cytisine licensed for use worldwide: a call to action**

Natalie Walker, Chris Bullen, Joanne Barnes, Hayden McRobbie, Piotr Tutka, Martin Raw, Jean-François Etter, Kamran Siddiqi, Ryan Courtney, João Mauricio Castaldelli-Maia,Nancy Rigotti, Peter Selby, Janie Sheridan, Robert West

Summary

Most tobacco users live in low and middle income countries where stop smoking medicines are unavailable or unaffordable. A low cost and effective cessation medication, cytisine, would be ideal for these populations but remains unavailable as current regulatory structures unreasonably impede access.

Editorial

Effective tobacco cessation medicines are needed in low- and middle-income countries (LMICs), where most tobacco users live, but are often unavailable or unaffordable.[[1](#_ENREF_1)] Cytisine (an alkaloid found in some plants belonging to the Leguminosae family) could be a solution to this problem. Cytisine, like varenicline, is a partial agonist at nicotinic acetylcholine receptors (nAChRs)[[2](#_ENREF_2)]with high affinity for the alpha-4 beta-2 nAChRs subtype, and aids cessation by reducing the severity of withdrawal and the satisfaction associated with tobacco use.[[3](#_ENREF_3)] However, there are a number of key differences between the two medications (Table 1).

**Table 1: Cytisine compared to varenicline**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Half life** | **Treatment period** | **Cost for full course (US$)**[[4](#_ENREF_4)] |
| Cytisine | 4.8 hours[[5](#_ENREF_5)] | Titrated down over 25 days | $15-$20 |
| Varenicline | 17 hours[[6](#_ENREF_6)] | Titrated up over 12 weeks | $474-501 |

Evidence for cytisine’s efficacy and effectiveness comes from several sources. Four systematic reviews (five trials, undertaken in Central/Eastern Europe, n=3,250) have found cytisine to be superior to placebo for short- and long-term abstinence from smoking,[[7-10](#_ENREF_7)] with a pooled relative risk at ≥ six months of 3.29 (95% confidence intervals 1.84 - 5.90).[[8](#_ENREF_8)] A New Zealand non-inferiority trial (n=1,310) found cytisine was more effective than combination nicotine replacement therapy (NRT) at increasing six-month quit rates.[[11](#_ENREF_11)] Cytisine is well-tolerated when taken according to the recommended dose: adverse events reported in trials are typically non-serious and self-limiting gastrointestinal and sleep disturbances.[[7-11](#_ENREF_7)] Cytisine is cheaper than varenicline (Table 1), nortriptyline (~US$95 for a 12-week course), NRT (~US$112-$685 for a 8-10 week course), and bupropion (~US$228-521 for a 12-week course).[[4](#_ENREF_4)] Cytisine is affordable (even in LMICs),[[12](#_ENREF_12)] it has the lowest cost per quality-adjusted-life-year of all smoking cessation medications,[[13](#_ENREF_13)] and may be more cost-effective than varenicline.[[14](#_ENREF_14)]

Since the 1960s cytisine has been available as a prescription-only or non-prescription smoking cessation treatment in Central and Eastern Europe. Cytisine is manufactured according to the principles of European Union (EU)-Good Manufacturing Practice standards by two companies: Sopharma (Bulgaria) andAflofarm (Poland). Yet cytisine is currently only authorised by regulatory authorities for smoking cessation in four EU countries (Bulgaria, Poland, Latvia, Lithuania) and 13 non-EU countries (Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Serbia, Tajikistan, Turkmenistan, Uzbekistan, Ukraine). Many LMICs will not licence cytisine unless it is first licensed in a reference country (namely, Australia, Austria, Belgium, Canada, Denmark, Germany, Finland, Iceland, France, Ireland, Luxemburg, Holland, New Zealand, Norway, Sweden, Switzerland, USA, UK, Japan, Italy, Spain, Portugal) or is on the World Health Organization (WHO) Essential Medicines List.

If cytisine is effective, cost-effective, affordable and well-tolerated, why isn’t it licensed more widely?[[4](#_ENREF_4), [13](#_ENREF_13), [15](#_ENREF_15)] A key reason is that Sopharma andAflofarm have not actively sought regulatory approval outside Central and Eastern Europe. This could be because regulatory authorities such as the UK Medicines and Healthcare Products Regulatory Agency (MHRA), the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA) may require further placebo-controlled trials of cytisine to be undertaken in Western European and/or North American populations. However, there is little incentive for pharmaceutical companies to conduct such research since cytisine is a generic drug. Potential investors may not see the opportunity for substantial return unless a patent can be attached; this would almost certainly increase the cost to consumers.[[15](#_ENREF_15)] Interestingly, Extab has recently obtained the rights from Sopharma to market a “new patent-protected version of Tabex (cytisine)” outside Central and Eastern Europe, and is currently seeking regulatory approval in the USA, Japan and other major markets (http://extabpharma.com/). Extab’s website states: “Following discussions with FDA and MHRA, a further large-scale clinical trial is in planning”. If regulatory approval is obtained, it remains unknown where the new version of Tabex will be priced in the market.

What can be done now to promote wider marketing authorisation and availability of the existing low-cost cytisine? Without pharmaceutical industry investment, trials required by the MHRA, EMA and FDA will rely on public good funding to progress; such funding is difficult to obtain in a highly competitive research environment and is often insufficient to cover the costs of studies that would meet regulatory standards. For many LMICs, where cytisine has the potential to have the greatest impact, there are additional barriers to accessing tobacco cessation products. For example, tobacco cessation is not listed among the WHO ‘best buys’ - a priority list of cost-effective interventions to tackle non-communicable diseases (NCDs)[[16](#_ENREF_16)] - despite being a leading risk factor in the WHO target of a 25% relative reduction in NCD mortality by 2025.[[17](#_ENREF_17)] Furthermore, tobacco control is key to achieving Goal 3 (Good Health and Well-Being) of the United Nations Sustainable Development Goals (http://www.un.org/sustainabledevelopment/health/). To date, international health donors have shown limited interest in tobacco cessation. In response, we propose the following:

1. We recommend to regulatory authorities that further placebo-controlled trials of cytisine in its current form are unnecessary (sufficient placebo-controlled trial data exist and additional long-term safety data would become available through post-marketing surveillance) and unethical (people motivated to quit will be denied a cessation treatment if randomised to placebo).
2. We encourage companies to explore alternative regulatory routes to licensing of cytisine, such as the ‘well-established use’ procedure in Europe.[[18](#_ENREF_18)]
3. We plan to facilitate access to all relevant trial data. The website [www.stop-tabac.ch/cytisine](http://www.stop-tabac.ch/cytisine) contains the original trial articles and English translations (where needed). An up-to-date evidence summary for cytisine is available at this website (<http://www.treatobacco.net/en/page_485.php>), and clinical study reports from the two most recent trials[[11](#_ENREF_11), [19](#_ENREF_19)] can be obtained from the trial authors.
4. We encourage the WHO to update its position on tobacco cessation to include cytisine.
5. We advocate that all governments signatory to the WHO Framework Convention on Tobacco Control prioritise implementation of Article 14.
6. We encourage donors to support wider provision of low-cost tobacco cessation interventions (like cytisine) in LMICs.

If cytisine became more widely available, the presence of an in-class competitor to varenicline (which comes off patent in 2020) could exert a downward pressure on the price of both drugs. Bringing cytisine ‘in from the cold’ at an affordable price would benefit millions of tobacco users throughout the world.

**References**

1. Piné-Abata, H., McNeill, A., Murray, R., et al. A survey of tobacco dependence treatment services in 121 countries. *Addiction* 2013; **108:** 1476–84.

2. Coe, J.W., Brookes P.R., Veteline, M.G., et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005; **48**: 3474-7.

3. Tutka, P., Zatonski, W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep* 2006; **58**: 777-98.

4. Prochaska, J., Das, S., Benowitz, N. Cytisine, the world's oldest smoking cessation aid. *BMJ* 2013; **347**: f5198.

5. Jeong, S-H., Newcombe, D., Sheridan, J., Tingle, M. Pharmacokinetics of cytisine, an α4β2 nicotinic receptor partial agonist, in healthy smokers following a single dose. *Drug Test Anal* 2014; first published online: 17 Sept 2014; doi: 10.1002/dta.1707.

6. Obach, R., Reed-Hagen, A., Krueger, S., et al. Metabolism and disposition of varenicline, a selective alpha4beta2 acetylcholine receptor partial agonist, in vivo and in vitro. *Drug Meta Dispos* 2006; **34**: 121-30.

7. Etter, J.F. Cytisine for smoking cessation: a literature review and a meta-analysis. *Arch Intern Med* 2006; **166**: 1553-9.

8. Hajek, P., McRobbie, H., Myers, K. Efficacy of cytisine in helping smokers to quit: systematic review and meta analysis. *Thorax* 2013; **68**: 1037-42.

9. Cahill, K., Stead, L.F., Lancaster, T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews, The Cochrane Library,* 2012: Art. No.: CD006103.

10. McRobbie, H., Hajek, P., Bullen, C., Feigen, V. Rapid review of non-NHS treatments for smoking cessation. *National Institute of Clinical Excellence*, London, 2006.

11. Walker, N., Howe, C., Glover, M., et al. Randomized comparison of cytisine versus nicotine for smoking cessation. *New Engl J Med* 2014; **371**: 2353-62.

12. West, R., Raw, M., McNeill, A., et al. Healthcare interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. *Addiction* 2015; **110**: doi: 10.1111/add.12998.

13. Stapleton, J. The case for licensing cytisine now for smoking cessation is overwelming [letter]. *BMJ* 2013; **347**: f5736.

14. Leaviss, J., Sullivan, W., Ren, S., et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. *Health Technol Assess* 2014; **18**: 1-119.

15. Aveyard, P., West, R. Cytisine and the failure to market and regulate for human health. *Thorax* 2013; **68**: 989.

16. World Health Organization and World Economic Forum, From burden to “best buys”: reducing the economic impact of non-communicable diseases in low- and middle-income countries.2011, *World Health Organization and World Economic Forum* ([www.who.int/nmh/publications/best\_buys\_summary](http://www.who.int/nmh/publications/best_buys_summary), accessed 21 March 2016). Geneva.

17. Kontis, V., Mathers, C., Rehm, J, et al. Contribution of six risk factors to acheiving the 25 x 25 non-communicable disease mortality reduction target: a modelling study. *Lancet* 2014; **384**: 427–37.

18. Borg, J., Laslop, A., Pani, L., Maciulaitis, R., Melchiorri, D. Reflections on decisions made on the well-established use of medicinal products by EU Regulators and the ECJ. *Sci Pharm* 2014; **82**: 655-63.

19. West, R., Zatonski, W., Cedzynska, M., et al. Placebo-controlled trial of cytisine for smoking cessation. *New Engl J Med* 2011; **365**: 1193-1200.