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A.38 Varenicline – smoking cessation – EML
A.5 Bupropion – smoking cessation – EML

As clinicians, public health specialists, academics, and researchers we are committed to the WHO Framework Convention on Tobacco Control (WHO FCTC). The WHO 2021 campaign aims to support 100 million people around the world to quit tobacco use (i.e., the WHO is focusing this year on the O of the six MPOWER measures). We therefore thank the WHO for the opportunity to make a statement in support of the tobacco cessation medications varenicline and bupropion to be added to the WHO Model List of Essential Medicines (WHO EML). However, in this submission we argue for cytisine to also be added.

Varenicline belongs to a class of pharmacotherapies called nicotinic acetylcholine receptors (nAChRs) partial agonists, which combat nicotine addiction by reducing nicotine withdrawal symptoms and cravings through activation of dopaminergic pathways in the brain.[1] Varenicline also competitively inhibits nicotine from binding to nAChRs, thus reducing the reward obtained from tobacco consumption.[1] A Cochrane systematic review of nAChRs partial agonists for smoking cessation found varenicline to be the most effective single-form pharmacotherapy for smoking cessation.[2]

We believe that if varenicline is added to the WHO EML, then cytisine should also be added. Like varenicline, cytisine is structurally similar to nicotine and acts as a partial agonist at nAChRs,[3] although the medications have different half-lives (cytisine: 4.8 hours[4]; varenicline: 17 hours[1]), and dosing regimens.

Cytisine is a plant-derived alkaloid found in the Golden Rain (*Laburnum anagyroides*) and other members of the Fabaceae family.[3] Cytisine is one of the oldest smoking cessation medications, being available since the 1960s in Eastern and Central Europe. An extensive summary of the evidence base for cytisine as a smoking cessation medication can be found in the review by Tutka et al (2019), which includes a summary of research currently underway.[3]

Cytisine appears to be an ideal smoking cessation treatment when assessed using the APEASE criteria proposed by Michie et al (2014) as part of their framework for identifying suitable behaviour change interventions.[5] Specifically, cytisine is effective, cost-effective, safe, affordable, practicable, acceptable, and equitable.

- **Efficacy/Effectiveness:** A recent systematic review found cytisine to be superior to placebo (abstinence at longest follow-up: Relative Risk = 1.74, 95% Confidence Intervals [CI] 1.38 - 2.19) based on data from eight trials (N=4,216).[3] A pragmatic non-inferiority trial also found 25 days of cytisine to be superior to combination Nicotine Replacement therapy (NRT: Patch plus gum or lozenges for eight weeks) at supporting smoking abstinence (self-reported continuous abstinence [CA] at one month: 40% vs 31% respectively, Risk Difference [RD]= 9.3, 95% CI 4.2 - 14.5, N=1,310).[6] This finding is supported by a cross-sectional study from a nationally representative household survey of 1403 adults in Russia, suggesting that, after adjusting for age and gender, cytisine was more effective than NRT for 90-day abstinence (adjusted Odds Ratio=2.91, 95% CI=1.28 - 6.59, p=0.011) among those who tried to quit smoking in the past year.[7] A pragmatic non-inferiority trial found 12 weeks of cytisine to be at least as effective as varenicline (12 weeks) at supporting smoking abstinence (verified CA at six months: 12.1% vs 7.9% respectively, RD=4.3, 95% CI -0.22 - 8.79, N=679) in indigenous New Zealand Māori or extended family of Māori.[8] As yet unpublished post-hoc Bayesian analysis of this trial indicates cytisine may be superior to varenicline. A clinical trial (N=2388) of cytisine has also been undertaken in two low-income

countries (Bangladesh and Pakistan) in tuberculosis patients who smoked,[9] and a cytisine versus nortriptyline for smoking cessation trial is currently underway in Thailand (a middle-income country). These trials are important given approximately 80% of all tobacco users are in low- and middle-income (LMIC) countries.

- **Cost-effective:** Research has shown cytisine to have the lowest cost per quality-adjusted-life-year of all tobacco cessation medications,[10] and modelling suggests cytisine may be more cost-effective than varenicline.[11-12]

- **Safe:** Like nicotine (and many other medications), cytisine is toxic in animals and people when ingested in large amounts. However, when used at its current therapeutic dose (1.5–9 mg per day for 25 days) cytisine appears to be well tolerated**,** with few adverse events compared to a placebo (pooled RR=1.09, 95% CI 0.94-1.26),[3] NRT (incidence rate ratio [IRR]: 1.67, 95% CI 1.38-2.01, p<0.001)[6] or varenicline (IRR=0.56, 95% CI 0.49- 0.65, p<0.001).[8] Adverse reactions to cytisine are generally non-serious and self-limiting, and are predominantly related to nausea, vomiting and sleep disturbance. Importantly, nausea occurs less frequently in people taking cytisine than in people taking varenicline,[8] likely due to cystine's lower potency at 5-HT_3 receptors.[13] Cytisine is also well tolerated in Tuberculosis patients who smoke and want to quit.[9] Observed adverse reactions are like those reported in a periodic safety update report provided to European authorities (based on more than seven million exposed persons).[3]

- **Affordable:** The cost of smoking cessation interventions is important to both tobacco users and healthcare funders. Yet, even in wealthy countries, current forms of cessation treatment are often considered unaffordable. A major advantage of cytisine (for governments/healthcare providers and individuals) over other pharmacological cessation products on the market is its current low cost[3, 14] and affordability (based on the WHO criteria).[15] For example, in Poland cytisine is 1.5% of the average monthly salary, compared to NRT (17.7% - 24.6% of the average monthly salary), varenicline (24.8% of the average monthly salary) or bupropion (27.3% of the average monthly salary).[3] Varenicline is now off-patent in many countries and thus the presence of an in-class competitor in the market will likely exert a downward pressure on the price of both cytisine and varenicline once cytisine become more widely marketed. In many LMIC countries, the high cost of widely available NRT results in less-than-optimal dosing even in the instances it is used. A low cost cytisine treatment could also potentially also exert a downward pressure on the price of NRT products. It will be important that strategies are put in place to stop anti-competitive practices that block price competition for varenicline and cytisine, and to identify strategies to ensure a transparent and sustainable drug supply chain, particularly for LMIC countries.

- **Practicable:** Cytisine has been approved for use on prescription and/or over-the-counter (OTC) in 18 European Union (EU) countries (as an OTC product in Bulgaria, Czech Republic, Latvia, Lithuania and Poland), eight non-EU countries (Azerbaijan, Armenia, Ukraine, Belarus, Georgia, Moldova, Russia and Serbia), and five Central Asian countries (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan),[3] although not all of these countries have cytisine available for people wanting to quit smoking. More recently cytisine has been approved in Canada as an OTC natural health product for smoking cessation.[3] Note that of the two nAChRs partial agonists available, only cytisine is available in the OTC category, helping to ensure greater access for people wanting to quit. Cytisine has a long history of use, there is a large safety database with few adverse events reported,[3] and compliance with the current treatment regimen (1.5mg 25-day titration schedule) if not optimal, is acceptable when used in a community-based setting.[6, 8] A dose-ranging study has just been published showing efficacy and tolerability of a higher dosage and simplified dosing schedule, which is now been explored in a phase 3 trial.[16]

- **Acceptable:** The public health impact of a tobacco cessation product not only depends on its efficacy and effectiveness, but also on its acceptability and reach in the population. Cytisine's 'natural' product status (i.e., it is sourced from plants grown in plantations, not synthesized in a

laboratory, like varenicline) could increase its acceptability and use among indigenous people, tobacco users in countries where the use of herbal medicines is widespread (e.g., China, India), and in those who do not want to use NRT, varenicline or anti-depressants to help them quit tobacco use. For example, qualitative research suggests cytisine (in its currently marketed form) would be appealing to indigenous New Zealand Māori and people from the Pacific islands if it were promoted in a culturally appropriately manner.[17-18]

- **Equitable:** If cytisine was available at relatively low cost, given its appeal and wide margin of safety, cessation outcomes for tobacco users who live in countries where cytisine is licensed are likely to be equitable. However, despite calls for cytisine to be licensed worldwide[9, 14, 19-20] it is relatively unknown outside Central/Eastern Europe (although some manufacturers of cytisine are working to license their product in other countries, including the USA).

We support the addition of varenicline and bupropion to the WHO EML, but we also strongly recommend that cytisine should be added and available OTC to offer choice. If varenicline and bupropion are not added to the WHO EML, cytisine certainly should be. Quitting tobacco is difficult and people who are tobacco dependent benefit from a choice to assist their quit attempts. The addition of cytisine alongside bupropion and varenicline will improve access to tobacco cessation medications, particularly for tobacco users in low- and middle-income countries (where people are motivated to quit smoking but have no/limited access to cessation medications), and potentially also for indigenous people; and will support 1.3 billion people around the world to quit tobacco use.

Signed

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