Appendix A

Summary of results from search for published studies in the period April 2022 to January 2024

RCTs of cytisine compared to varenicline

Tindle 2022 – Included 400 participants in Russia with HIV, who were described as engaging in "risky drinking and smoking". They were randomised to 4 groups: active varenicline and placebo nicotine replacement therapy (NRT, group 1), placebo varenicline and active NRT (group 2), active cytisine and placebo NRT (group 3), or placebo cytisine and active NRT (group 4). There were no significant differences at 6 months between groups in smoking abstinence, including group 1 vs 2 (15 of 100 vs 17 of 99; odds ratio (OR) 0.89, 95% confidence interval (CI) 0.38 to 2.08), group 3 vs 4 (19 of 100 vs 19 of 101; OR 1.00, 95% CI 0.46 to 2.17), and group 1 vs 3 (OR 0.79, 95% CI 0.35 to 1.78). This study recruited participants which may not be generalisable to the wider population, although it does provide a useful comparison of cytisine with varenicline and NRT.

Oreskovic 2023 – Recruited 377 smokers from the general population, 186 received cytisine and 191 received varenicline. The cessation rate after 24 weeks was 32.46% in the varenicline group and 23.12% in the cytisine group. Participants assigned to cytisine experienced fewer adverse events (incidence rate ratio (IRR) 0.59, 95% CI 0.43 to 0.81) and fewer severe or more extreme adverse events (IRR 0.72, 95% CI 0.35 to 1.47). The 4-week cytisine treatment was shown to be less effective than the 12-week varenicline treatment for smoking cessation. This study would not be included in the NICE evidence review or Cochrane review due to the short follow-up period.

RCT of cytisine compared to placebo

Rigotti 2023 (ORCA-2) – This double blind trial recruited 810 adults who smoked regularly and randomised them to 3 groups, it was funded by Achieve Life Sciences. All received treatment for 12 weeks, the first group received

cytisine for 6 weeks followed by placebo for 6 weeks (n=269), the second group received cytisine for 12 weeks (n=270) and the third received placebo for 12 weeks (n=271). For the 6 week course of cytisine vs placebo, continuous abstinence rates were 25.3% vs 4.4% during weeks 3 to 6 (OR 8.0, 95% CI 3.9 to 16.3) and 8.9% vs 2.6% during weeks 3 to 24 (OR 3.7, 95% CI 1.5 to 10.2). For the 12 week course of cytisine vs placebo, continuous abstinence rates were 32.6% vs 7.0% for weeks 9 to 12 (OR 6.3, 95% CI 3.7 to 11.6) and 21.1% vs 4.8% during weeks 9 to 24 (OR 5.3, 95% CI 2.8 to 11.1). Nausea, abnormal dreams, and insomnia occurred in less than 10% of each group. Sixteen participants (2.9%) discontinued cytisine due to an adverse event. No drug-related serious adverse events occurred.

Phusahat 2022 – Participants were recruited from a community pharmacy in Thailand and randomly assigned to receive cytisine (n=67) or placebo (n=65), with both groups receiving 5 sessions of counselling by a community pharmacist. The primary outcome was continuous abstinence rate at week 48 these were 14.93% and 6.15% for cytisine and placebo, respectively. The relative risk was 2.41 (95% CI 0.80–7.35).

Pastorino 2022 – This study enrolled 869 heavy tobacco users and randomised them to receive cytisine plus counselling (n=470) or counselling alone (n=399). At the 12 month follow-up, the rate of smoking cessation was 32.1% in the cytisine arm and 7.3% in the control arm. Self-reported adverse events occurred more frequently in the cytisine arm (399 events among 196 participants) than in the control arm (230 events among 133 participants). The most common adverse events were gastrointestinal symptoms, comprising abdominal swelling, gastritis, and constipation.

RCT of cytisine compared to NRT

Tavakoli-Ardakani 2023 – Hospitalised patients were randomised to receive nicotine gum (n=30) for 8 weeks or the standard dose of cytisine for 25 days (n=17). The outcome of smoking cessation at 6 months occurred in 2 of the 30 (6.66%) in the nicotine gum group, and 3 of the 17 (17.61%) in the cytisine group. Although a small study it suggests that cytisine has potential for increasing the likelihood of smoking cessation.

Cost Utility analysis

Li 2022 – An incremental cost utility analysis was undertaken in Bangladesh and Pakistan based on a 12 month RCT. Participants who were newly diagnosed with pulmonary tuberculosis (TB) were randomised to cytisine (n=1,239) or placebo (n=1,233). Cytisine for smoking cessation among patients with TB was not cost-effective compared with placebo.

Summary of systematic reviews of cytisine compared to varenicline, nicotine replacement and placebo

De Santi 2023 – This systematic review identified 12 RCTs, 8 of these compared cytisine to placebo across 5,922 participants. The results showed a higher smoking cessation in the cytisine groups with a risk ratio (RR) of 2.25 (95% CI 1.42 to 3.56). The authors reported this as moderate-quality evidence. Two RCTs compared cytisine to NRT with the results being described as 'modest results in favour of cytisine'. Non-serious adverse events were slightly higher in cytisine groups than placebo with RR of 1.24 (95% CI 1.11 to 1.39).

Ofori 2023 – 14 RCTs were included involving 9,953 adults. It reported 5 study that compared cytisine to placebo. The results identified a superior primary outcome of 6 month biochemically verified continuous abstinence in the cytisine group (RR 2.25, 95% CI 1.13 to 4.47). When compared to varenicline in 2 RCTs the results favoured varenicline (RR 1.13, 96% CI 0.65 to 1.95). Adverse events were higher in cytisine groups than placebo or NRT, but less than varenicline (RR 0.67, 95% CI 0.48 to 0.95)

Ongoing studies

RCT of cytisine compared to nicotine containing e-cigarettes

Walker 2023 – an RCT based in New Zealand will recruit 800 adults who smoke. They will randomise to 3 groups, receiving nicotine containing e-cigarettes plus cytisine, nicotine containing e-cigarettes alone or cytisine alone. All groups will receive a 6 month text message based support

programme. The primary outcome is self-reported, biochemically verified, continuous abstinence at 6 months post-quit date.

ORCA-3 – is an RCT based in the US, funded by Achieve Life Sciences, aiming to recruit 792 adults who smoke. Randomisation to 3 groups covering cytisine for 6 or 12 weeks, or placebo for 12 weeks, with all receiving behavioural support by a qualified staff member. The length of follow-up is not currently available.

Centre for Addiction and Mental Health – this Canadian RCT will recruit 48 participants to evaluate the safety and effectiveness of cytisine as a smoking cessation treatment in individuals with concurrent alcohol use disorder. The 2 groups will be comprised of cytisine and placebo interventions, following the standard cytisine dosing schedule. The length of follow-up is not currently available.

ISBN: 978-1-4731-5737-8