NICE National Institute for Health and Care Excellence

2024 exceptional surveillance of tobacco: preventing uptake, promoting quitting and treating dependence (NICE guideline NG209)

Surveillance report

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Surveillance decision

We will update recommendations 1.12.2, 1.12.7, 1.12.8 and 1.12.9 in the NICE guideline on tobacco.

The update will focus on the inclusion of cytisine as a medicinally licensed product to be used as a stop-smoking intervention. The guideline currently states that varenicline, nicotine-containing e-cigarettes and nicotine replacement therapies (NRT) are more likely to result in people successfully stopping smoking. The available evidence confirms that cytisine has a comparable effect, safety and cost to these recommended products.

Reason for the exceptional review

A Cochrane review on nicotine receptor partial agonists for smoking cessation was published in September 2023. This presented results of moderate-certainty evidence that cytisine helps more people to quit smoking than placebo. The data from this review was used in a Cochrane component network meta-analyses (NMA) on pharmacological and e-cigarette interventions for smoking cessation in adults, which was also published in 2023 and reported high-certainty evidence that cytisine was associated with higher quit rates than placebo. Cytisine was made available in the UK for the first time in January 2024. It was approved in the UK by the Medicines and Healthcare Regulatory Agency (MHRA) in 2019 but has not previously been brought to market despite its use in Eastern Europe since the 1970s. The removal of varenicline from the market in July 2021 has led to increased interest in the use of cytisine for smoking cessation.

Methods

The exceptional surveillance process consisted of:

- Literature searches to identify relevant evidence published since the searches of the Cochrane review were conducted. Medline, Embase, Cochrane CENTRAL and the Cochrane database of systematic reviews were searched.
- Considering the new evidence in the Cochrane reviews that triggered the exceptional review.

- Considering relevant information from previous surveillance reviews of the guideline.
  - 2023 surveillance review investigated a study on the use of e-cigarettes in pregnant women which is not relevant to the topic under review here.
  - 2020 surveillance review assessed the effectiveness of Allen Carr's programme on stopping smoking which resulted in a partial update of the guideline. This effected the recommendations being considered here but is not relevant to the intervention under investigation in this review.
- Considering the evidence used to develop the guideline in 2021 (evidence review K).
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for ongoing research on cytisine was completed on ClinicalTrials.gov, the ISRCTN Registry, and the Cochrane CENTRAL database.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Search and selection strategy

We searched for new evidence related to the use of cytisine for smoking cessation. Cytisine is the intervention of interest due to the change in licencing and recently published evidence within the Cochrane review on nicotine receptor partial agonists. The dates of the search were from April 2022 to January 2024 to cover the period since the Cochrane review search. The Cochrane NMA utilised the results from the same search.

See appendix A for details of all evidence considered, and references.

Information considered in this exceptional surveillance review

Evidence that triggered the exceptional review

Cochrane review on nicotine receptor partial agonists – a total of 8 studies were included that assessed the efficacy of cytisine for smoking cessation in adults. Four studies comparing cytisine to placebo which showed that cytisine helped people to quit smoking, with a moderate-certainty of evidence (risk ratio [RR] 1.30, 95% confidence interval [CI] 1.15 to 1.47). A further 2 studies randomised people to receive either cytisine or varenicline, these showed that more people in the varenicline arm quit smoking (RR 0.83, 95% CI 0.66 to 1.05). This showed a moderate-certainty of evidence, limited by the fact that the confidence intervals incorporated the potential for benefit from either cytisine or varenicline. One study compared cytisine to NRT and found that more people in the cytisine arm successfully quit than in the NRT arm (RR 1.43, 95% CI 1.13 to 1.80). The final study compared 40 days and 84 days of cytisine, and found that more people successfully quit on the longer treatment, the standard duration of treatment is 25 days. None of these studies were set in a UK population. There was no evidence of a difference between cytisine and placebo in the number of reported serious adverse events.

Cochrane component NMA – this assessed pharmacological and e-cigarette interventions for smoking cessation in adults. The studies described in the nicotine receptor partial agonists review described above were included in this analysis. In total 322 studies were included covering nicotine e-cigarettes, cytisine, varenicline, NRT, bupropion, nortriptyline and non-nicotine e-cigarettes. The authors concluded that the most effective interventions were nicotine e-cigarettes, varenicline and cytisine (all with high-certainty). The hierarchy of results of the NMA when comparing smoking cessation rates at 6 months or longer, in comparison to placebo were:

- nicotine e-cigarettes (odds ratio [OR] 2.37, 95% credible interval [CrI] 1.73 to 3.24; 16 randomised controlled trials [RCTs], 3,828 participants),
- varenicline (OR 2.33, 95% CrI 2.02 to 2.68; 67 RCTs, 16,430 participants),
- cytisine (OR 2.21, 95% CrI 1.66 to 2.97; 7 RCTs, 3,848 participants),
- bupropion (OR 1.43, 95% CrI 1.26 to 1.62; 71 RCTs, 14,759 participants).

There was no clear difference in the number of people reporting serious adverse events (SAEs) for nicotine e-cigarettes, varenicline, cytisine or NRT when compared to no pharmacotherapy/e-cigarettes or placebo, this was classed as low-certainty evidence. Bupropion may slightly increase rates of SAEs.

Details on potential costs of cytisine

A National Institute for Health and Care Research (NIHR) funded economic analysis from 2014 (ScHARR) reported that cytisine was estimated to be more cost-effective than varenicline. The outputs from the economic model estimated more mean life-years and quality of life-adjusted years, and lower mean lifetime costs, for cytisine than varenicline treatment.

The costs of cytisine to the NHS is not currently listed in the BNF but reports suggest that a course may be available for £115 (25 days). This appears to compare favourably with varenicline, which cost £230 for a full course when it was available in the UK, and bupropion having an estimated price for a standard 7 week course of £134.

Results of update of search

We searched for studies investigating cytisine that were published since the searches conducted for the Cochrane review in April 2022. We found 6 RCTs and 4 systematic reviews, 2 of these being the Cochrane reviews already identified. These are reported in detail in appendix A. There was also 1 cost-utility analysis and 1 publication was a report of the methods used to develop a Spanish guideline on smoking cessation. The studies we found agree with the results of the Cochrane reviews.

There were 2 studies comparing cytisine and varenicline. The first of these was an RCT located in Russia which included 400 participants and concluded that cytisine had equivalent efficacy to varenicline at 6 months. The participants had HIV and showed behaviour of high drinking and smoking, which questions the external validity of this study. The second study recruited 377 participants in Croatia and Slovenia, from the general population, and reported results at 24 weeks, which would limit this study's inclusion in the guideline evidence review and the Cochrane review, both of which stipulated a minimum follow-up of 6 months. The results showed the cytisine group to have a lower cessation rate and a lower rate of adverse events.

Two studies randomised participants to receive cytisine or placebo. A study from the US

randomised 810 adults and reported 'abstinence rates' were higher in cytisine groups than placebo at 24 weeks. The second study was set in Thailand (n=132) and all participants received counselling in addition to cytisine or placebo. The results stated that the 'abstinence rates' at week 48 were higher in cytisine than placebo groups.

One Italian RCT recruited 869 participants from a lung cancer screening programme, they were described as heavy tobacco users. Cytisine and counselling or counselling alone were provided. At 12 months the 'quit rate' was higher for the cytisine group than counselling alone group.

One study, set in Iran, randomised 47 hospitalised patients to receive cytisine or nicotine gum. Showing favourable results for cytisine, but was limited by the low number of participants.

The 2 systematic reviews were both published after the Cochrane review and included a higher number of trials on cytisine than the Cochrane reviews. The results of both confirmed that cytisine had a positive impact on smoking cessation when compared to placebo. When compared to varenicline the results favoured varenicline but were not significant with the confidence intervals crossing the line of no effect.

Results of ongoing trials searches

The results of the searches of the clinical trial registries identified 3 studies. One of these is set in New Zealand (n=800) and compares cytisine and nicotine containing e-cigarettes, with a follow-up period of 6 months. This is due for completion in 2024. A US based study comparing cytisine to placebo in 792 adults is expected to publish in 2024. A Canadian RCT recruited 48 participants, comparing cytisine to placebo, and is due for completion in 2024. The two larger studies will be monitored and have been added to the NICE event tracker.

Information considered when developing the guideline

Cytisine was not licensed for use when the NICE guideline was developed in 2021 and was therefore not included in the evidence review (evidence review K: smoking cessation and harm reduction treatments). During the guideline development the committee did not consider it appropriate to rank the individual treatments according to the results of the

NMA. Instead preferring to offer a choice of treatments, and an informed choice be arrived at, that had considered the benefits and harms of each option.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

An equalities and health inequalities assessment was completed during this surveillance review. See appendix B for details.

Overall decision

After considering the available evidence and the impact on current recommendations, we decided that an update of recommendations 1.12.2, 1.12.7, 1.12.8 and 1.12.9 is required. The change in the availability of cytisine in the UK means that it should be considered alongside other interventions for smoking cessation. Given the evidence provided in the Cochrane review and more recently published trials, it is apparent that cytisine should be listed in the medicinally licensed product recommendations as an option for people who smoke.

There is evidence that the level of adverse events is less than those reported for varenicline and the costs of cytisine do not appear to be prohibitive to the recommendation.

Topic expertise is required on whether cytisine is recommended to people who smoke as a product that is 'more likely to result in them successfully stopping smoking' (recommendation 1.12.7) or 'less likely to result in them successfully stopping smoking' (recommendation 1.12.8).

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