NICE National Institute for Health and Care Excellence

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Tobacco: preventing uptake, promoting quitting and treating dependence (update)

Evidence review Q for cytisinicline for smoking cessation

NICE guideline NG209

Evidence underpinning recommendations 1.12.2, 1.12.4, 1.12.5, 1.12.8 and 1.12.10

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FINAL

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The effectiveness of cytisinicline as an intervention to aid smoking cessation

1.1 Review question

What is the effectiveness of the nicotine receptor partial agonist cytisinicline as a means of smoking cessation?

1.1.1 Introduction

Smoking remains a significant public health concern, with tobacco use continuing to be a leading cause of preventable death and disease worldwide. Despite the availability of various smoking cessation interventions, many smokers still struggle to quit successfully. The current NICE guideline on tobacco dependence (NG209) recommends several pharmacological and behavioural interventions to support smoking cessation. However, new evidence suggests that cytisinicline, a plant-based alkaloid with a mechanism of action similar to varenicline, may offer an additional effective option for smokers attempting to quit.

This review question was selected to evaluate the effectiveness of cytisinicline as a potential new pharmacotherapy for smoking cessation in adults. Cytisinicline has been marketed as a smoking cessation aid since 1960. The inclusion of cytisinicline in this guideline update was prompted by emerging clinical trial data and its recent consideration for regulatory approval. As cytisinicline is not currently part of standard smoking cessation practice in the UK, this review aims to assess its efficacy and safety profile compared to existing treatments. The findings will inform whether cytisinicline should be recommended as an additional option for adults who smoke and want to quit, potentially expanding the range of effective smoking cessation interventions available to healthcare providers and patients.

1.1.2 Summary of the protocol

Table 1: Summary of the protocol

Population	Inclusion: • Adults who smoke tobacco and want to stop smoking Exclusion: • People who do not smoke • Pregnant and breastfeeding women • People aged 17 and under • People who want to stop using smokeless tobacco but not smoking
Interventions	• Cytisinicline • Cytisinicline in combination with behavioural support

Comparator	• Placebo
	• No medication
	• Other smoking cessation pharmacotherapies with or without behavioural support:
	  ○ Nicotine replacement therapy (single-mode or multi-mode)
	  ○ Bupropion
	  ○ Varenicline
	  ○ Electronic cigarettes
	• These pharmacotherapies may be used in combination with each other

Outcomes	Primary outcomes (critical outcomes): • Smoking abstinence at 6 months. • Smoking abstinence at longest follow-up, at least 6 months from study baseline • Smoking abstinence at more than 1 month but less than 6 months from study baseline. • Adverse events • Health related QoL For the abstinence outcomes we will use the strictest definition of abstinence reported in each study (e.g. prolonged or continuous over point prevalence), and where available, we will favour biochemically validated over self-reported abstinence.
Study type	We will include: • Systematic reviews of RCTs

	• RCTs • cRCTs

Abbreviations: QoL, quality of life; RCTs, randomised controlled trials; cRCTs, cluster randomised controlled trials

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.. The review builds upon the high-quality systematic review by Livingstone-Banks et al. (2023), which assessed the effectiveness of nicotine receptor partial agonists, including cytisinicline and varenicline, for smoking cessation. This Cochrane review is directly applicable to this review question.

For outcomes not covered in the Cochrane review (smoking abstinence at >1 month but <6 months, and at 6 months), we conducted additional data extraction from the primary studies included in the Cochrane review. In line with the previous review in this area, the minimal important differences (MID) used for smoking cessation was the line of no effect, as any intervention that shows effectiveness in helping to stop smoking is making a clinically meaningful difference - where confidence intervals crossed the line of effect we downgraded once for imprecision in line with the previous review in this area and due to the known harmful effects of smoking any increase in smoking would be clinically meaningful. For adverse events which were dichotomous outcomes, the default MIDs (RR 0.80-1.25) were used and for quality of life which were continuous outcomes default MIDs of 0.5 of the median standard deviation of the control group were used.

Additional searches were run from April 2022 onwards to identify new evidence published since the Cochrane review. Declarations of interest were recorded according to NICE's conflicts of interest policy.

The protocol can be found in appendix A.

1.1.3.1 Protocol deviations

The protocol specified using the Cochrane Risk of Bias 2.0 tool for newly identified RCTs and extracting and presenting data from the Livingstone-Banks et al. (2023) review separately from any newly identified studies. However, two protocol deviations were made:

1. To maintain consistency with the Livingstone-Banks et al. (2023) review which used Risk of Bias 1.0, the review used Risk of Bias 1.0 for all RCTs including newly identified studies. This deviation was made to ensure consistency in risk of bias assessment across all included studies.

2. Rather than presenting data from the Livingstone-Banks et al. (2023) review separately from the newly identified studies, all data were combined in new meta-analyses. This decision was made because:

    - there were a substantial amount of new data that could significantly impact the results

    - A combined analysis incorporating all available evidence would provide the most useful assessment of effectiveness

1.1.3.2 Search methods

Searches were run on August 28, 2024, for the effectiveness review and September 2, 2024, for the cost-effectiveness review.

The searches covered the period from April 2022 onwards, building on the existing Cochrane review by Livingstone-Banks et al 2023 which covered literature up to April 2022. Cost-effectiveness searches were limited to publications from 2009 onwards.

Searches were limited to English language publications. Animal studies, conference abstracts, and trial registry records were excluded.

For effectiveness searches, the Cochrane RCT classifier was used in EPPI Reviewer v5 to identify randomised controlled trials. References with

abstracts from Medline, Embase and PsycInfo were classified using this tool if they were not indexed as RCTs at source. References indexed as RCTs at source and those with no abstract went straight to sifting without being run through the RCT classifier.

Epistemonikos and the Cochrane Database of Systematic Reviews were used as the sole sources to identify systematic reviews. These databases were searched separately from the RCT searches and the RCT classifier was not applied to these searches.

Full search strategies for each database are provided in appendix B.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Study selection

A systematic search carried out to identify potentially relevant records found 305 references. Of those, 105 references were removed as duplicates. The remaining 200 references were screened at title and abstract level against the review protocol, with 175 excluded leaving 25.

In accordance with the protocol, 10% of references were screened separately by 2 reviewers with 100% agreement. No discrepancies required resolution.

The full texts of 25 studies were ordered for closer inspection. These included 1 systematic review (Livingstone-Banks et al 2023) as specified in the protocol, and 24 studies published after the Cochrane review's search date of April 2022. Of these, 20 studies were excluded at the full-text review stage (see appendix J for more details).

The included systematic review (Livingstone-Banks et al 2023) was assessed against our protocol criteria. From this review, 8 RCTs met our inclusion criteria. Together with the 4 new RCTs identified from our updated searches, this gave a total of 5 studies included in our review (1 systematic review and 4

RCTs). For a summary of included studies see Table 2 and for full references see the list of included studies (section 1.1.14.1).

The study process selection is presented as a PRISMA diagram in appendix C.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion, are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of the Cochrane systematic review Livingstone-Banks 2023

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
Livingstone-Banks 2023 Systematic review of RCTs N=45,049 Follow-up time: At least 6 months from study baseline	Setting: Various Setting: Community pharmacies, smoking cessation clinics, hospitals, tuberculosis treatment centres, lung screening clinics, and national quitline services. Settings were across multiple studies including: • Community pharmacy settings (Walker 2021) • Lung screening clinic (Pastorino 2022) • Tuberculosis treatment centres (Dogar 2020) • National quitline service (Walker 2014) • Mining company occupational health service (Vinnikov 2008)	Adult tobacco smokers	Cytisinicline, with various dosing regimens: Standard dose: 9 mg per day for 20 to 25 days Some studies tested longer durations (40 and 84 days)	Placebo No medication Nicotine replacement therapy (NRT) - both monotherapy and combination Bupropion Electronic cigarettes	Smoking abstinence at longest follow-up (at least six months from study baseline) Number of participants experiencing adverse events (nausea, insomnia, abnormal dreams, headache, depression, suicidal ideation) Number of participants experiencing serious adverse events Number of participants experiencing neuropsychiatric serious adverse events Number of participants experiencing cardiac serious adverse events	Low risk of bias

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
	• Smoking cessation clinics (West 2011, Scharfenberg 1971) Location: Multiple countries Funding source: National Institute for Health Research (NIHR), via Cochrane Infrastructure and Cochrane Programme Grant funding to the Cochrane Tobacco Addiction Group					

Abbreviations:

RCT: Randomised controlled trial

Table 3 Summary of studies included in the effectiveness evidence from Livingstone-Banks 2023

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
Courtney 2021 N=1452	Setting: community Location: Australia Funding: Global Research Awards for Nicotine Dependence (GRAND), supported by Pfizer	Adult tobacco smokers recruited via adverts and smoking cessation phone line	Cytisinicline 1.5mg x6/day, reducing over 25 days Interactive behavioural support (7 scheduled counselling calls during treatment	Varenicline 0.5mg x2/day, titrated to 1mg x2/day Interactive behavioural support (7 scheduled counselling calls during treatment period + follow-up support calls)	Continuous abstinence at 6months (CO verified)	Low risk of bias

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
			period + follow-up support calls)			
Dogar 2020 N=2472	Setting: Tuberculosis (TB) centres and home Location: Bangladesh and Pakistan Funding: European Union Horizon 2020 research and innovation programme	Adult tobacco smokers - daily tobacco smokers with pulmonary TB Authors defined eligible adult patients as aged >18 years in Bangladesh and aged >15 years in Pakistan	Cytisinicline 9mg/day, reduced to 1.5mg/day by day 25 Behavioural support (4 face-to-face sessions and 2 phone calls during 25-day treatment period)	Placebo Behavioural support (4 face-to-face sessions and 2 phone calls during 25-day treatment period)	Continuous abstinence at 6 months (CO confirmed) Continuous abstinence at 12 months (self-report)	Low risk of bias
Pastorino 2022 N=869	Setting: community Location: Italy Funding: multiple cancer research funding bodies	Adult tobacco smokers in a lung-screening trial. Participants described as 'heavy smokers' defined as more than or equal to 30 pack-years (20-cigarette packs smoked per day multiplied by the number of years smoked).	Cytisinicline 40 days with behavioural support Cytisinicline 84 days with individual behavioural support sessions during treatment period	Individual behavioural support sessions during treatment period	Continuous abstinence at 12 months (CO verified)	High risk of bias (unclear risk for random sequence generation, allocation concealment, incomplete outcome data; high risk for blinding)

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
Scharfenberg 1971 N=1214	Setting: smoking cessation clinic Location: East Germany Funding: Not reported	Adult tobacco smokers recruited via smoking clinics and press releases	Cytisinicline 20 days 1.5mg does increasing to 4.5mg No behavioural support	Placebo No behavioural support	Abstinence 4weeks (self-report), 6 months (self-report), 2 years (self-report)	Unclear risk of bias (unclear for all domains)
Vinnikov 2008 N=197	Setting: mining company Location: Kyrgyzstan Funding: Not reported	Adult tobacco smokers - smoking>15 cigarettes/day who claimed they were motivated to quit	Cytisinicline 25 days. 9mg/day reducing to 1.5mg/day Behaviour counselling with brochure	Placebo Behaviour counselling with brochure	Continuous abstinence rate from day 5 to 8 weeks (CO validated); Continuous abstinence from day 5 to 26 weeks (CO validated).	Unclear risk of bias (unclear risk for incomplete outcome data, mostly male population limits generalisability)
Walker 2014 N=1310	Setting: national Quitline Location: New Zealand Funding: Health Research Council of New Zealand, manufacturer supplied the treatments free of charge	Adult tobacco smokers – daily smokers who had called the NZ National Quitline and who identified as motivated to quit	Cytisinicline 25 days NRT (patch, gum or lozenge) if needed after completing the Cytisinicline course Quitline support (low-intensity telephone behavioural support - average	Usual care, 8-week course of NRT (patch, gum or lozenge) Quitline support (low-intensity telephone behavioural support average 3 x 10-15-min calls over 8 weeks)	Continuous Abstinence Rate at 1 week (self-report), 1 months (self-report), 2 months (self-report), 6 months (self-report)	High risk of bias (high risk for blinding)

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
			3 x 10-15-min calls over 8 weeks)			
Walker 2021 N=679	Setting: community pharmacy Location: New Zealand Funding: Health Research Council of New Zealand, manufacturer supplied the treatments free of charge	Adult tobacco smokers who were of indigenous Māori origin.	Cytisinicline 9mg/day reducing to 3mg/day, 25 days with maintenance dose for day 26 to week 12 (3mg/day every) to match the treatment duration of varenicline. Low-intensity behavioural support during treatment period	Varenicline 3mg/day, 12 weeks Low-intensity behavioural support during treatment period	Continuous abstinence at 6 months (CO verified); 12 months (CO verified)	High risk of bias (high risk for incomplete outcome data and open-label design)
West 2011 N=740	Setting: smoking cessation clinic Location: Poland Funding: UK National Prevention Research Institute, Cancer Research UK, NIHR	Adult tobacco smokers >10 cigarettes/day	Cytisinicline 9mg/day reducing to 3mg/day, 25 days Minimal behavioural support	Placebo Minimal behavioural support	Abstinence 6 months (CO verified); 12 months (CO verified)	Low risk of bias

Abbreviations:

RCT: Randomised controlled trial

Table 4 Summary of studies included in the effectiveness evidence from updated searches

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
Oreskovic 2023 RCT N=377 Follow-up time: 24weeks	Setting: primary care practices Location: Croatia and Slovenia Funding: Global Research Awards for Nicotine Dependence, supported by Pfizer	Adults who had indicated a desire to quit smoking	Cytisinicline, standard dosing protocol, 25 days Behavioural support from trained doctors and research assistants during treatment period	Varenicline standard dosing protocol, 12 weeks Behavioural support from trained doctors and research assistants during treatment period	Abstinence 6 months (self-report) Abstinence at longest follow-up (self-report) Adverse events	High risk of bias (high risk for blinding)
Phusahat 2022 RCT N=132 Follow-up time: 48 weeks	Setting: Community pharmacy at the Faculty of Pharmaceutical Sciences, Khon Kaen University Location: Thailand Funding source: Government Pharmaceutical Organization, Thailand (grant No. 4/2561)	Adult smokers aged 18-65 years, smoking >10 cigarettes/day, willing to quit smoking, without serious medical conditions or psychiatric disorders	Cytisinicline tablets with tapering 25-day regimen (9mg/day reducing to 3mg/day) plus five sessions of smoking cessation counselling by trained community pharmacists using the 5As model (ask, advise, assess, assist, arrange) during treatment period	Matching placebo tablets plus five sessions of smoking cessation counselling by trained community pharmacists using the 5As model during treatment period	Continuous abstinence rate at 48 week (CO verified) Continuous abstinence rate at 24 week (CO verified) Adverse events Health-related quality of life	High risk of bias (high risk for attrition bias)
Rigotti 2023 RCT N=810 Follow-up time: 24 weeks	Setting: 17 sites across the US, with the largest number in the Southeast Location: United States Funding source: Achieve Life Sciences	Adult smokers aged 18 years or older, currently smoking 10 or more cigarettes per day, with expired air	Cytisinicline 3 mg taken orally 3 times daily for 12 weeks Cytisinicline 3 mg taken orally 3 times daily for 6 weeks	Placebo taken orally 3 times daily for 12 weeks, with the same brief smoking cessation behavioural support as the intervention groups. (Brief smoking	Smoking abstinence at 12 weeks (CO verified) Smoking abstinence at 24 weeks (self-report) Adverse events	Low risk of bias

Study details	Setting, location, funding	Population	Intervention	Comparator(s)	Outcomes	Risk of bias
		carbon monoxide (CO) greater than or equal to 10 ppm, and ready to set a date to quit smoking	followed by placebo for 6 weeks Brief smoking cessation behavioural support at up to 15 visits during 12-week treatment, with shorter sessions at weeks 16, 20, and 24	cessation behavioural support at up to 15 visits during 12-week treatment, with shorter sessions)		
Tavakoli-Ardakai 2023 RCT N=47 Follow-up time: 6 months	Setting: inpatient psychiatric ward Location: Iran Funding: not reported	Adults, motivated to quit, psychiatric disorder	Cytisinicline, from 9mg/day reducing to 1.5mg/day, 25 days Medical/psychological care and counselling during treatment period	NRT gum 2mg, 8 weeks, maximum 24 gums/day for 6 weeks, decreasing daily until week 8 Medical/psychological care and counselling during treatment period	Abstinence 6 months (self-report) Abstinence at longest follow-up (self-report) Adverse events	High risk of bias (high risk for blinding, unclear allocation concealment, high attrition)

Abbreviations:

RCT: Randomised controlled trial

See appendix D for full evidence tables

1.1.6 Summary of effectiveness evidence

Cytisinicline vs placebo for smoking cessation

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	interpretation of effect
Smoking abstinence for longest follow-up (6+ months)	**RR 1.82** (1.18 to 2.81)	4755 (5 RCTs)[1,2,3,4,5]	⊕⊕⊕◯ Moderate	The data favours cytisinicline
Smoking abstinence at 6 months (or 24-weeks)	**RR 2.18** (1.13 to 4.19)	4055 (5 RCTs)[1,2,3,5,6]	⊕⊕◯◯ Low	The data favours cytisinicline
Smoking abstinence at 6 months (or 24-weeks): Rigotti 12-week treatment duration cytisinicline arm	**RR 4.40** (2.47 to 7.85)	541 (1 RCT)[6]	⊕⊕◯◯ Low	The data favours cytisinicline
Smoking abstinence at more than 1 month but less than 6 months from study baseline	**RR 1.79** (1.23 to 2.60)	4529 (5 RCTs)[2,3,4,5,6]	⊕◯◯◯ Very low	The data favours cytisinicline
Smoking abstinence at more than 1 month but less than 6 months from study baseline: Rigotti 12-week cytisinicline arm	**RR 4.65** (2.92 to 7.41)	541 (1 RCT)[6]	⊕⊕◯◯ Low	The data favours cytisinicline
Subgroup analysis: Smoking abstinence: Heavy smokers (>20 cigarettes per day) at more than 1 month but less than 6 months from study baseline: Rigotti 12-week cytisinicline arm	**RR 3.93** (2.32 to 6.66)	354 (1 RCT)[6]	⊕⊕◯◯ Low	The data favours cytisinicline
Serious adverse events	**RR 1.28** (0.90 to 1.82)	3553 (3 RCTs)[1,3,6]	⊕⊕⊕◯ Moderate	The data does not differentiate
Serious adverse events: Rigotti 12-week treatment duration cytisinicline arm	**RR 2.68** (0.72 to 9.98)	541 (1 RCT)[6]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events: all	**RR 1.13** (1.01 to 1.27)	3855 (5 RCTs)[1,2,3,5,6]	⊕⊕◯◯ Low	The data favours placebo

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	interpretation of effect
Adverse events: Rigotti 12-week treatment duration cytisinicline arm	**RR 1.11** (0.98 to 1.26)	541 (1 RCT)[6]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events, insomnia	**RR 1.83** (1.12 to 2.98)	3144 (3 RCTs)[3,5,6]	⊕⊕◯◯ Low	The data favours placebo
Adverse events, insomnia: Rigotti 12-week treatment duration cytisinicline arm	**RR 2.01** (1.05 to 3.82)	541 (1 RCT)[6]	⊕◯◯◯ Very low	The data favours placebo
Adverse events, abnormal dreams	**RR 2.26** (1.16 to 4.41)	3012 (2 RCTs)[3,6]	⊕⊕◯◯ Low	The data favours placebo
Adverse events, abnormal dreams: Rigotti 12-week treatment duration cytisinicline arm	**RR 2.63** (1.19 to 5.84)	541 (1 RCT)[6]	⊕⊕◯◯ Low	The data favours placebo
Adverse events, headache	**RR 0.95** (0.61 to 1.47)	4055 (5 RCTs)[1,2,3,5,6]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events, headache: Rigotti 12-week treatment duration cytisinicline arm	**RR 0.96** (0.54 to 1.70)	541 (1 RCT)[6]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events, nausea	**RR 1.08** (0.71 to 1.64)	4055 (5 RCTs)[1,2,3,5,6]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events, nausea: Rigotti 12-week treatment duration cytisinicline arm	**RR 0.75** (0.39 to 1.44)	541 (1 RCT)[6]	⊕◯◯◯ Very low	The data does not differentiate
Health related QoL: WHOQOL-BREF-THAI, change from baseline to 24-weeks	**MD 0.18 higher** (0.06 lower to 0.42 higher)	132 (1 RCT)[5]	⊕◯◯◯ Very low	The data does not differentiate

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	interpretation of effect
Health related QoL: WHOQOL-BREF-THAI, change from baseline to 48-weeks	**MD 0.03 higher** (0.24 lower to 0.3 higher)	132 (1 RCT)[5]	⊕◯◯◯ Very low	The data does not differentiate
Health related QoL: EQ-5D-5L, change from baseline to 24-weeks	**MD 2.82 higher** (3.83 lower to 9.47 higher)	132 (1 RCT)[5]	⊕◯◯◯ Very low	The data does not differentiate
Health related QoL: EQ-5D-5L, change from baseline to 48-weeks	**MD 2.00 higher** (2.27 lower to 6.27 higher)	132 (1 RCT)[5]	⊕◯◯◯ Very low	The data does not differentiate

References

1.West 2011.

2.Vinnikov 2008.

3.Dogar 2020.

4.Schaffenberg 1971.

5.Phusahat 2022.

6.Rigotti 2023.

Cytisinicline vs no medication for smoking cessation

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect Comments
Smoking abstinence for longest follow-up at 6 months (or 24-weeks)	**RR 4.42** (3.04 to 6.34)	869 (1 RCT)[1]	⊕⊕◯◯ Low	The data favours cytisinicline
Serious adverse events	**RR 0.97** (0.63 to 1.51)	869 (1 RCT)[1]	⊕◯◯◯ Very low	The data does not differentiate

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect Comments
Adverse events: all	**RR 1.25** (1.05 to 1.49)	869 (1 RCT)[1]	⊕⊕◯◯ Low	The data favours no medication

References

1.Pastorino 2022 – population were all heavy smokers

Cytisinicline vs varenicline for smoking cessation

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect Comments
Smoking abstinence for longest follow-up (6+ months)	**RR 0.92** (0.67 to 1.28)	2508 (3 RCTs)[1,2,3]	⊕◯◯◯ Very low	The data does not differentiate
Smoking abstinence at 6 months (or 24 weeks)	**RR 0.95** (0.65 to 1.40)	2508 (3 RCTs)[1,2,3]	⊕◯◯◯ Very low	The data does not differentiate
Smoking abstinence at more than 1 month but less than 6 months from study baseline	**RR 1.01** (0.80 to 1.28)	2508 (3 RCTs)[1,2,3]	⊕◯◯◯ Very low	The data does not differentiate
Serious adverse events	**RR 0.67** (0.46 to 0.96)	2508 (3 RCTs)[1,2,3]	⊕◯◯◯ Very low	The data favours cytisinicline
Adverse events: all	**RR 0.84** (0.70 to 1.00)	2508 (3 RCTs)[1,2,3]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events: Nausea	**RR 0.41** (0.33 to 0.50)	2017 (2 RCTs)[1,2]	⊕⊕◯◯ Low	The data favours cytisinicline
Adverse events: Abnormal dreams	**RR 0.59** (0.23 to 1.49)	2081 (2 RCTs)[1,2]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events: Insomnia	**RR 0.79** (0.44 to 1.39)	2017 (2 RCTs)[1,2]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events: Headache	**RR 1.04** (0.80 to 1.35)	2017 (2 RCTs)[1,2]	⊕◯◯◯ Very low	The data does not differentiate
Adverse events: Depression	**RR 3.04** (0.12 to 74.47)	679 (1 RCT)[1]	⊕⊕◯◯ Low	The data does not differentiate

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect Comments
Adverse events: Suicidal ideation	**RR 0.33** (0.01 to 8.02)	2017 (2 RCTs)[1,2]	⨁⨁◯◯ Low	The data does not differentiate
Smoking abstinence: People with mental health conditions (6+ months)	**RR 0.83** (0.40 to 1.69)	246 (1 RCT)[2]	⨁⨁⨁◯ Moderate	The data does not differentiate

References

1.Walker 2021.

2.Courtney 2021.

3.Oreskovic 2023.

Cytisinicline vs Nicotine Replacement Therapy (NRT) for smoking cessation

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect Comments
Smoking abstinence at 6 months (or 24 weeks)	**RR 1.43** (1.13 to 1.80)	1310 (1 RCT)[1]	⨁⨁⨁◯ Moderate	Identified a significant effect for cytisinicline compared to NRT for smoking cessation (6 months).
Smoking abstinence at more than 1 month but less than 6 months from study baseline	**RR 1.41** (1.17 to 1.70)	1310 (1 RCT)[1]	⨁⨁⨁◯ Moderate	Identified a significant effect for cytisinicline compared to NRT for smoking cessation (1 to 6 months).
Serious adverse events	**RR 1.15** (0.76 to 1.75)	1310 (1 RCT)[1]	⨁◯◯◯ Very low	Identified no significant effect for cytisinicline compared to NRT for serious adverse effects.
Adverse events: Nausea	**RR 15.00** (3.60 to 62.51)	1310 (1 RCT)[1]	⨁⨁◯◯ Low	Identified a significant effect for cytisinicline compared to NRT for nausea.

References

1.Walker 2014.

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to all review questions in this guideline update. See the literature search strategy in Appendix B .

4 economic studies were identified which were applicable to this review question. (see economic study selection flow chart in Appendix G).

Of those, 2 health economic studies with relevant comparators were included in the review:

- One compared cytisine (cytisinicline) with varenicline (Leaviss 2014 et al.)
- One comparing cytisine (cytisinicline) with several other smoking cessation interventions (Anraad 2018 et al.)

These are summarised in the health economic evidence profiles below and the health economic evidence tables in Appendix H.

1.1.7.2 Excluded studies

Two studies were excluded. Details of the study excluded at full text, along with reasons for exclusion, are given in Appendix J.

1.1.8 Summary of included economic evidence

Table 3: Cytisine (cytisinicline) vs varenicline

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Leaviss 2014	Directly applicable	Potentially serious limitations[a]	• Markov model (BENESCO) with transition probabilities based on a NMA of 23 RCTs (10,610 people) • Cost-utility analysis • Population: People who smoke in England and Wales aged 18 or over who are motivated to quit smoking • Comparators: 1. Cytisine 100 1.5 mg tablets 2. Varenicline: 2 weeks of tapered treatment plus 20 weeks at full dose • Time horizon: Lifetime	2-1: saves £251[b]	2-1: 0.03 QALYs	Cytisine dominates varenicline (cheaper and most effective)	A PSA was conducted. At any threshold of willingness to pay, up to £100,000 per QALY gained, cytisine was the most cost-effective intervention in over 90% of the simulations. Several one-way sensitivity analyses were conducted. In all, except one, cytisine dominated varenicline. The only exception occurred when the relative efficacies of varenicline and cytisine were altered.

Abbreviations: BENESCO= Benefits of Smoking Cessation on Outcomes; NMA = Network meta-analysis; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life years; RCT= randomised controlled trial;

(a) The clinical effectiveness is based on a NMA and contradicts the results of the clinical review based on head-to-head trials. The model did not include an underlying quitting rate. Some inputs and probabilities were taken from the HTA on varenicline and it's unclear whether this still represents the best source. The cost of cytisine was unknown and the estimated price of £16.79 is much lower than the current estimation of £115

(b) 2010/2011 UK pounds

Table 4: Cytisine (cytisinicline) vs current practice vs brief physician advice vs group-based behavioural therapy vs SMS test-messaging support vs a combination of these

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Anraad 2018	Directly applicable	Potentially serious limitations[a]	• Markov model (EQUIPTMOD) with transition probabilities estimated through a clinical evidence review) • Cost-utility analysis • Population: People who smoke in England aged 16 or over who are motivated to quit smoking • Comparators: 1. Current practice 2. Increase reach of brief physician advice 3. Increase reach of specialist group-based behavioural therapy 4. Increase reach of SMS test-messaging support 5. Pharmacotherapy with cytisine 6. Combined change: intervention 2, 3, 4 and 5 together • Time horizon: Lifetime	2-1: £0[b] 3-2: saves £1[b] 4-3 £1[b] 5-4: saves £9[b] 6-5: saves £1[b]	2-1: 0.0001 QALYs 3-2: 0.0001 QALYs 4-3: -0.0001 QALYs 5-4: +0.0013 QALYs 6-5: +0.0003 QALYs	• Cytisine dominates 1, 2, 3 and 4 • Combined change intervention dominated cytisine	No PSA was conducted. A one-way sensitivity analysis was performed to assess the treatment effect of cytisine. The results indicated that cytisine was no longer cost-effective in England when the lower bound of the lower bound of the 95% confidence interval of its risk ratio was applied.

Abbreviations: EQUIPT = European study on quantifying utility of investment in protection from tobacco; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life year
(a) No PSA conducted. The cost of cytisine was assumed to be £17.63 (not licensed) while the current estimation amounts to £115
(b) 2015/2016 UK pounds

1.1.9 Economic model

No original health economic model was developed for this update.

1.1.10 Unit costs

Table 5 Unit costs

Resource	Quantity	Total cost	Source
Cytisine (cytisinicline)	25 days course – 100 tablets	£115[(1)]	Lipanovic 2023, Drug Tariff
Varenicline	12 weeks course	£230	NICE surveillance report
Bupropion	7 weeks course	£134	NICE surveillance report

[1]Available from January 2024. This price was set up to recoup a substantial expense in getting MHRA approvals and setting up the distribution, the drug itself is extremely cheap to produce and there is the expectation that the price will come down substantially.

1.1.11 Committee discussion and interpretation of the evidence

1.1.11.1 Key outcomes

The committee agreed that in line with the previous review on stopping smoking interventions smoking abstinence at 6 months is the key outcome. Additional important outcomes are abstinence at longest follow-up (defined as at least 6 months from study baseline) and at between 1 month and 6 were the primary outcomes when considering the effectiveness of cytisinicline as a means of smoking cessation. When considering abstinence, the definition of abstinence reported in each study (for example prolonged or continuous over point prevalence), and where available biochemically validated over self-reported abstinence were favoured as these were considered to represent the most reliable measures of smoking cessation. The committee highlighted that understanding the impact of cytisinicline on adverse events, serious adverse events and health-related quality of life (HRQoL) compared to placebo and other smoking cessation pharmacotherapies (nicotine replacement therapy [single-mode or multi-mode]; bupropion, varenicline, electronic cigarettes)

were also important outcomes when considering the effectiveness of cytisinicline.

1.1.11.2 Quality of the evidence

The committee noted that the Livingstone-Banks et al. (2023) Cochrane review provided a robust foundation for evaluating cytisinicline's effectiveness. The committee had confidence in the review's findings due to its rigorous methodology, comprehensive search strategy (up to April 2022), and thorough risk of bias assessments. The emphasis on biochemically validated abstinence over self-reported abstinence where available, aligned well with their priorities for assessing effectiveness. The committee agreed on the appropriateness of incorporating four new randomised controlled trials published since April 2022 to ensure the most current evidence was considered.

The committee agreed that the quality of the evidence for smoking abstinence, adverse events and serious adverse events across all comparisons and outcomes ranged from moderate to very low due high risk of bias (some studies did not adequately blind participants and/or investigators with one paper having an open-label design potentially influencing self-reported smoking cessation outcomes; other studies demonstrated a unclear risk of bias for random sequence generation, allocation concealment, incomplete outcome data), imprecision (some studies and meta-analysis of studies produced wide confidence intervals indicating imprecise estimates of effect; some studies had too few participants to confidently detect meaningful differences between treatments); indirectness (some meta-analyses had more than 33.3% of papers that were based populations that may not be representative of the UK smoking population - for instance, some studies were conducted in populations with much higher smoking prevalence rates than the UK, some had samples that were predominantly male or of white ethnicity which does not reflect the diversity of UK smokers, and some were conducted in healthcare settings that may differ from UK smoking cessation services) inconsistency (meta-analysis demonstrated moderate and

substantial unexplained heterogeneity). The committee noted that the cytisinicline regimen in some trials differed from the regimen used in the UK. They noted that the behavioural support intervention differed across trials, and this had the potential to impact the effectiveness of smoking cessation pharmacotherapies.

The committee highlighted the limited evidence regarding the effectiveness of cytisinicline in various population subgroups. There was some limited evidence available from two studies in people with mental health conditions - one comparing cytisinicline with varenicline found no significant difference between treatments and another comparing cytisinicline with NRT in psychiatric inpatients. Evidence was lacking for other important subgroups including those with cardiovascular disease, COPD, diabetes, and those from deprived areas. The committee noted that while these studies in people with mental health conditions were valuable, more research would be needed to fully understand cytisinicline's effectiveness in this population. As the current NICE guideline (NG209: Tobacco: preventing uptake, promoting quitting and treating dependence) already has two key research recommendations focused on 'Stop-smoking interventions for under-served groups' and 'Support for people with mental health conditions to stop smoking', the committee agreed that these covered the key gaps in the evidence. The committee highlighted that understanding more about the optimal cytisinicline treatment duration and adherence to regimens would be informative as well as understanding how cytisinicline is implemented in various healthcare settings and its impact on existing smoking cessation services given the complexity in the cytisinicline treatment regimen. The committee discussed the need for more trials comparing cytisinicline with other smoking cessation treatments, and trials considering the effectiveness of cytisinicline in combination with other smoking cessation aids or behavioural interventions. They concluded that more evidence regarding the effectiveness and safety of cytisinicline in various population subgroups, particularly those with health inequalities were key. The committee noted that while the evidence base for cytisinicline demonstrates effectiveness for smoking cessation, the volume and maturity of

evidence is not yet equivalent to that available for long-established treatments like varenicline, NRT, or bupropion.

1.1.11.3 Benefits and harms

The committee discussed the evidence for cytisinicline's effectiveness and safety compared to placebo, no medication, varenicline, and nicotine replacement therapy (NRT).

For smoking abstinence outcomes, they noted that cytisinicline demonstrated effectiveness compared to placebo, with a statistically significant effect at all measured time points. When compared with varenicline, cytisinicline showed similar effectiveness, with no significant differences in abstinence rates. Limited evidence comparing cytisinicline with NRT suggested potential benefits of cytisinicline, though the committee noted this was based on fewer studies.

The committee noted that cytisinicline was associated with more adverse events than placebo overall and specifically for insomnia and abnormal dreams. The committee discussed that differentiating between medication side effects and nicotine withdrawal symptoms can be challenging when evaluating adverse events in smoking cessation trials. When compared with varenicline, cytisinicline showed a similar overall adverse event profile, though with lower rates of nausea.

The committee agreed that the evidence showed cytisinicline to be an effective option for smoking cessation. They emphasised that having an additional treatment option would benefit people trying to stop smoking. As with all smoking cessation treatments, they noted that any treatment decision would be discussed with the individual, considering their preferences and circumstances.

The committee discussed potential barriers to the implementation of cytisinicline in practice. These included the complexity of the dosing regimen which could affect adherence, the need to integrate the treatment into existing

smoking cessation pathways, and how healthcare providers would manage prescribing and monitoring. The committee noted that the shorter duration of cytisinicline treatment (25 days) compared to varenicline (typically 12 weeks) could be advantageous for some patients, while the more complex dosing schedule might be challenging for others. The committee noted that in some areas cytisinicline is already being prescribed. The committee reflected that patient choice is at the centre of treatment decision making and that the differences in and suitability of treatment options would be part of these discussions.

1.1.11.4 Cost effectiveness and resource use

Two health economic analyses were identified in the literature review. One study was a UK NIHR health technology assessment and compared cytisinicline with varenicline. The study was published in 2014 when no head-to-head trials comparing cytisinicline with varenicline were available. Therefore, the authors conducted a network meta-analysis (NMA) of 23 studies (10,610 patients) which found clinical benefits of cytisinicline over varenicline. The committee acknowledged that this is in contrast with the clinical review that found no clinically or statistically significant difference. The latter is based on head-to-head trials and, therefore, may be more reliable. The NIHR HTA found cytisinicline dominant (cheaper and more effective), however the price assumed in the base case is considerably lower than the current estimated price, £115, which was set to recover the costs of the recent MHRA application. Nevertheless, the current price remains below the £250 threshold, above which cytisinicline would no longer be considered cost-effective according to the authors' estimates.

The second study looked at various interventions to help people smoking in the UK, including physician advice, group-based behavioural therapy, SMS test-messaging support and pharmacotherapy with cytisinicline compared with current practice and a combination of all. Similarly to the first study, the analysis assumed a price for cytisinicline that is considerably lower than the

current estimated price, and therefore, it was deemed as having potentially serious limitations.

The unit cost of cytisinicline was presented to the committee alongside the cost of other drugs commonly used for smoke cessation. It was noted that, although cytisinicline is relatively inexpensive to produce, the company set a price of £115 for a pack of 100 tablets, sufficient for a full treatment course, to recover the expenses of getting the MHRA approval and set up the distribution. Although this price is around 6-7 times higher than the one assumed in the two economic evaluations, the expectation is that this will go down in future, as more companies enter the market. The committee observed that cytisinicline remained the least expensive option compared to varenicline and bupropion, primarily due to its shorter treatment course.

The clinical review showed that cytisinicline was superior to NRT and placebo and non-inferior to varenicline. This is in line with the evidence used for the economic models although the NMA found cytisinicline superior to varenicline. For this reason, cytisinicline was included among the pharmacological tools to help people stop smoking. It was acknowledged that, due to the high costs and severe consequences of smoking-related diseases, most interventions that are clinically effective in smoking cessation, would generally be cost-effective as well. Given cytisinicline's relatively low cost and well-established efficacy, it is highly probable that the drug is a cost-effective intervention for smoking cessation. Therefore, this recommendation will provide the NHS with a cost-effective tool to facilitate smoking cessation, potentially leading to significant savings in healthcare expenditure and improved health outcomes.

1.1.11.5 Other factors the committee took into account

The committee noted that that in line with the BNF, cytisinicline should not be used in those who are pregnant, under 18 or over 65. They included this information in the existing guideline recommendations for those who are pregnant and breast feeding, and those under 18. An additional recommendation was added for those who are over 65.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.12.2, 1.12.4, 1.12.5, 1.12.8, 1.12.10, and 1.20.11.

1.1.13 References

1.1.13.1 Effectiveness evidence

Included studies

Livingstone-Banks, Jonathan, Fanshawe, Thomas R, Thomas, Kyla H et al. (2023) Nicotine receptor partial agonists for smoking cessation. The Cochrane database of systematic reviews 5: cd006103

Oreskovic, Tin, Percac-Lima, Sanja, Ashburner, Jeffrey M et al. (2023) Cytisine Versus Varenicline for Smoking Cessation in a Primary Care Setting: A Randomized Non-inferiority Trial. Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco 25(9): 1547-1555

Phusahat, Pum, Dilokthornsakul, Piyameth, Boonsawat, Watchara et al. (2022) Efficacy and Safety of Cytisine in Combination with a Community Pharmacists' Counselling for Smoking Cessation in Thailand: A Randomized Double-Blinded Placebo-Controlled Trial. International journal of environmental research and public health 19(20)

Rigotti, Nancy A, Benowitz, Neal L, Prochaska, Judith et al. (2023) Cytisinicline for Smoking Cessation: A Randomized Clinical Trial. JAMA 330(2): 152-160

Tavakoli-Ardakani, Maria, Gholamzadeh Sani, Zeinab, Beyraghi, Narges et al. (2023) Comparison between cytisine and Nicotine Replacement Therapy in smoking cessation among inpatient psychiatric patients. Journal of addictive diseases: 1-8

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Cessation: A Randomized Clinical Trial. JAMA. 2021 Jul 6;326(1):56-64. doi: 10.1001/jama.2021.7621. PMID: 34228066; PMCID: PMC8261608.

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Scharfenberg G, Benndorf S, Kempe G. Cytisin (Tabex) als medikamentöse Raucherentwöhnungshilfe [Cytisine (Tabex) as a pharmaceutical aid in stopping smoking]. Dtsch Gesundheitsw. 1971 Mar 4;26(10):463-5. German. PMID: 4930772.

Vinnikov D, Brimkulov N, Burjubaeva A. A Double-Blind, Randomised, Placebo-Controlled Trial of Cytisine for Smoking Cessation in Medium-Dependent Workers. Journal of Smoking Cessation. 2008;3(1):57-62. doi:10.1375/jsc.3.1.57

Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V, Parag V, Bassett B, Bullen C. Cytisine versus nicotine for smoking cessation. N Engl J Med. 2014 Dec 18;371(25):2353-62. doi: 10.1056/NEJMoa1407764. PMID: 25517706.

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West R, Zatonski W, Cedzynska M, Lewandowska D, Pazik J, Aveyard P, Stapleton J. Placebo-controlled trial of cytisine for smoking cessation. N Engl J Med. 2011 Sep 29;365(13):1193-200. doi: 10.1056/NEJMoa1102035. PMID: 21991893.

1.1.13.2 Economic evidence

Anraad C, Cheung KL, Hiligsmann M, Coyle K, Coyle D, Owen L, West R, de Vries H, Evers SM, Pokhrel S. Assessment of cost-effective changes to the current and potential provision of smoking cessation services: an analysis based on the EQUIPTMOD. Addiction. 2018 Jun;113 Suppl 1(Suppl Suppl 1):96-105.

Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens JW, Strong M, Cantrell A. 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 May;18(33):1-120.

Appendices

Appendix A Review protocol

Review protocol for the partial update of the tobacco Suite: The effectiveness of cytisinicline as an intervention to aid smoking cessation

Field	Content
Review question	What is the effectiveness of the nicotine receptor partial agonist cytisinicline as a means of smoking cessation?
Type of review question	Intervention
Objective	Cytisinicline is a plant-based alkaloid that acts as a partial agonist of nicotinic acetylcholine receptors. This review aims to assess the efficacy of cytisinicline for smoking cessation.
Condition or domain being studied	Smoking cessation
Population	Inclusion: • Adults who smoke tobacco and want to stop smoking Exclusion: • People who do not smoke • Pregnant and breastfeeding women • People aged 17 and under • People who want to stop using smokeless tobacco but not smoking

Interventions	• Cytisinicline • Cytisinicline in combination with behavioural support

Comparators	• Placebo
	• No medication
	• Other smoking cessation pharmacotherapies with or without behavioural support:
	  ○ Nicotine replacement therapy (single-mode or multi-mode)
	  ○ Bupropion
	  ○ Varenicline
	  ○ Electronic cigarettes
	• These pharmacotherapies may be used in combination with each other

Types of study to be included	We will include: • Systematic reviews of RCTs • Randomised controlled trials (RCTs) • Cluster-randomised controlled trials (cRCTs)
Other exclusion criteria	1. Studies where the proportion of ineligible participants (e.g., 17 years or younger) is more than 20% of the total study population will be excluded. 2. For studies including both eligible and ineligible participants: • If results are reported separately for the eligible group (adults 18 years and older), we will include the study and use only the data for the eligible participants. 3. Studies that focus on 'Heat not burn' tobacco products – these are products that heat tobacco leaves to release nicotine and other chemical and are distinct from electronic cigarettes which heat a liquid containing nicotine and other ingredients, but do not contain tobacco leaves
Context	Cytisinicline 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 cytisinicline for smoking cessation. This review is being conducted as part of an update to the NICE guideline on "Tobacco: preventing uptake, promoting quitting and treating

	dependence" (NG209), on the inclusion of cytisinicline as a medicinally licensed product to be used as a stop-smoking intervention.
Outcomes	Primary outcomes (critical outcomes): • Smoking abstinence at 6 months. • Smoking abstinence at longest follow-up, at least 6 months from study baseline • Smoking abstinence at more than 1 month but less than 6 months from study baseline. • Adverse events • Health related QoL For the abstinence outcomes, we will use the strictest definition of abstinence reported in each study (e.g. prolonged or continuous over point prevalence), and where available, we will favour biochemically validated over self-reported abstinence.
Searches	We will search for new studies added to bibliographic databases from April 2022 to the present day. April 2022 has been chosen as the start date as this is the date of the last searches carried out for Cochrane review by Livingstone Banks and colleagues (2023). **Sources:** The following databases will be searched: • Cochrane Central Register of Controlled trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos (for systematic reviews only) • Medline ALL • PsycInfo **Search filters, limits and classifiers:** Database functionality will be used, where available, to exclude: • Animal studies • Papers not published in the English language. • Conference abstracts • Trial registry records We will use the version of the Cochrane randomised controlled trial (RCT) classifier (Thomas et al, 2021), built into EPPI Reviewer 5, to

	exclude non-RCTs from the search results. References indexed as RCTs at source and those with no abstract will be assumed to be potential RCTs. These references will go straight to sifting without being run through the RCT classifier. Epistemonikos and the Cochrane Database of Systematic Reviews will be used as the sole sources to identify systematic reviews. **Supplementary search techniques:** Reference lists for all included studies will be checked for additional, relevant trials. **Quality assurance:** The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final evidence review document.
Data extraction (selection and coding)	**Approach to using the Livingstone-Banks et al (2023) Cochrane review** We will review and extract summary data and GRADE assessments and analyses from the Livingstone-Banks et al (2023) Cochrane review that meet the inclusion criteria for this review question. These findings will be considered alongside the data identified in the updated search. We will review the included papers in Livingstone-Banks et al (2023) Cochrane review that contribute data to address the review question under investigation (effectiveness of cytisinicline as a means of smoking cessation) for the following outcomes of interest: • Smoking abstinence at 6 months. • Smoking abstinence at more than 1 month but less than 6 months from study baseline. As the above outcomes were outside of the protocol for the Livingston-Banks et al (2023) Cochrane review we will conduct data extraction for these two outcomes using a standardised form (see Developing NICE guidelines: the manual section 6) and consider this data along with data identified as

	part of the '**New searches'** undertaken for this guideline. **New searches** All references identified by the 'new searches' and from other sources will be uploaded into EPPI reviewer and de-duplicated. Two reviewers will independently screen 10% of the abstracts, with disagreements resolved through discussion or, if necessary, by a third independent reviewer. The full text of potentially eligible studies will be assessed against the inclusion criteria. Disagreements will be resolved through discussion or, if needed, by consulting a third independent reviewer. For new SR of RCTs, RCTs and cRCTs identified, we will conduct full data extraction using a standardised form. A standardised form will be used to extract data from included studies (see Developing NICE guidelines: the manual section 6). The findings of the 'new searches' will be considered alongside the findings of the Livingstone-Banks et al (2023) Cochrane review as outlined in 'Approach to using the Livingstone-Banks et al (2023) Cochrane review'.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For systematic reviews including the Livingstone-Banks 2023 review, the ROBIS (Risk of Bias in Systematic Reviews) checklist will be used. We will use the risk of bias assessments from the Livingstone-Banks 2023 Cochrane review for studies (RCTs) included in that review. For any newly identified RCTs, we will conduct risk of bias assessment using the Cochrane RoB 2 tool. For randomised controlled trials (RCTs), the Cochrane risk of bias (RoB) 2 tool will be used. For cluster-randomised control trials (cRCTs) the Cochrane risk of bias (RoB) 2 for cluster-randomised trials will be used.

	We will present the results of the risk of bias assessment in summary tables and consider them in the interpretation of review findings.
Strategy for data synthesis	Data from the Livingstone-Banks et al (2023) review will be presented to the committee and will not undergo any further analysis. RoB and GRADE undertaken by the authors of that paper will be used to assess certainty of evidence. For any additional papers identified from the search, the individual studies will be considered as to whether they meet the inclusion criteria for the Livingstone-Banks et al (2023) review and a decision made on whether they will be added to the analysis or presented as additional findings. 1. Analysis for smoking abstinence at more than 1 month but less than 6 Months and for smoking abstinence at 6 months: • We will review all studies included in the Livingstone-Banks et al (2023) Cochrane review to identify those reporting smoking abstinence at more than 1 month but less than 6 months and at 6 months from baseline. • Data from these studies will be extracted and combined with any new studies reporting this outcome from the 'new searches'. • A new meta-analysis will be conducted for this outcome using the following approach: o Mantel-Haenszel fixed-effect model o For dichotomous outcomes a calculation of pooled risk ratios (RRs) with 95% confidence intervals (CIs) will be calculated o Heterogeneity assessment using the I^2 statistic o GRADE assessment of certainty of evidence • If substantial heterogeneity is found (I^2 ≥40%), we will explore potential causes through subgroup or sensitivity analyses as described above. • Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I^2 ≥50%,

	when random effects models will be used instead. 2. If new analyses are necessary for any of the outcomes outlined: • Meta-analyses will use a Mantel-Haenszel fixed-effect model • Pooled risk ratios (RRs) with 95% confidence intervals (CIs) will be calculated for dichotomous outcomes • Pooled mean difference with 95% CIs (using the inverse variance method) will be calculated for continuous outcomes when the same scale is used to measure an outcome across different studies. If studies present data measuring the same outcome using different numerical scales these outcomes will be converted to the same scale before meta-analysis is conducted. • Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I^2 ≥50%, when random effects models will be used instead. • Heterogeneity will be assessed using the I^2 statistic: o 0% to 39%: may not be important o 40% to 60%: may represent moderate heterogeneity o 60%: may represent substantial heterogeneity o ≥80%: data may be too heterogeneous to pool • For GRADE assessments of inconsistency: o No serious inconsistency: I^2 <40% o Serious inconsistency: I^2 40-60% o Very serious inconsistency: I^2 >60% • For I^2 ≥40%, we will explore potential causes through subgroup or sensitivity analyses. • For I^2 ≥80%, we will carefully consider whether to pool data or present a narrative synthesis. • All analyses will be conducted using RevMan Web.

Analysis of sub-groups	If sufficient data are available, we will consider subgroup analyses for: 1. People with mental health conditions 2. People with cardiovascular disease 3. People with COPD 4. People with diabetes 5. Heavy smokers (>20 cigarettes per day) 6. Those with previous quit attempts Feasibility of these analyses depends on: • Number of new studies identified • Level of detail reported on participant characteristics Sensitivity analyses: • Remove studies at high risk of bias • Remove studies comparing against no medication in pooled analyses • Treat population subgroups as subgroups of main analyses, using I^2 to test for differences
Health inequalities	While no specific items have been included in this review protocol to identify evidence related to health inequalities, the guideline committee will consider health inequalities and the issues raised in NICE's health inequality impact assessment (EHIA) when interpreting the evidence and making recommendations. The EHIA highlights the following trends regarding smoking behaviour and where the evidence identified allows these groups (which includes groups with protected characteristics and inclusion health and vulnerable populations), socioeconomic deprivation and geographical variation will be considered in the guideline's development. The EHIA highlights that the prevalence of smoking is greater in younger adults (16-34 year olds) than older adults (60+); that adults with serious mental health conditions smoke more than the general population and that a greater proportion of adults identifying as lesbian, gay or bisexual smoke compared to their heterosexual counterparts. The EHIA outlines that individuals on the lowest income levels have a higher rate of smoking compared to those on the highest incomes and that those in routine and manual occupations smoke more than those in managerial and professional occupations occupation. The EHIA highlighted regional trends in UK smoking behaviour with people from more deprived areas more likely to smoke and less likely to quit.

	The EHIA outlines that prisoners and the gypsy and travelling population had a higher prevalence of smoking than the general population.
Contact information	Tobacco_cytisinicline@nice.org.uk This email address is specific to the cytisinicline review and allows stakeholders and other interested parties to contact the team responsible for this guideline update.
Protocol amendments	A protocol amendment was made and this is outlined in the evidence review in section 1.1.3.1 'Protocol deviations'.

Appendix B Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. Searches for the review of effectiveness were run on the 28th August 2024. Searches for the cost effectiveness review were run on the 2nd September 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below and translations for other databases were quality assured (QA) by another SIS to ensure their accuracy. These procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The 2023 Cochrane review on nicotine receptor partial agonists for smoking cessation (Livingstone-Banks J et al) was used as the source of evidence for the effectiveness review up to April 2022. This was the date of the searches carried out for the Cochrane review. NICE's searches cover the period after the Cochrane searches and focus solely on cytisinicline rather than a wider range of nicotine receptor partial agonists.

Livingstone-Banks J et al (2023) Cochrane review on Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews*. Issue 6, CD006103.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Conference abstracts and posters
- References from trials registries
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of April 2022 to the present day was a was applied for the effectiveness review question, per the review protocol. This decision was taken in order to allow the effectiveness review searches to cover studies reported in the period not covered by the existing Cochrane review (Livingstone-Banks et al, 2023).

Where a specific search end date was reported for a source in the Cochrane review this was used as the start date for NICE's searches. Where a new source was used, we searched from the 1st April 2022.

For the cost effectiveness review, searches were limited to publications from 2009 onwards.

Search filters and classifiers

Effectiveness searches

References with abstracts from Medline, Embase and PsycInfo were classified using a version of the Cochrane RCT classifier (Thomas et al, 2021) if they were not indexed as randomised controlled trials (RCTs) at source. The version of the Cochrane classifier used is built into EPPI Reviewer v5. References with a low probability or being genuine RCTs were automatically excluded.

Systematic review searching was limited to two sources: Epistemonikos and the Cochrane Database of Systematic Reviews (CDSR). Epistemonikos is a database which aggregates systematic reviews. This approach was adopted due to the high sensitivity and specificity of the methods used to populate Epistemonikos (Rada et al., 2020), compared to the use of standard Boolean search filters in general medical literature databases (see: Lee et al, 2012, for example).

Lee E et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

Rada G et al. (2020) Epistemonikos: a comprehensive database of systematic reviews for health decision-making. *BMC Medical Research Methodology,* 20, 286.

Thomas J, McDonald S, Noel-Storr A et al. (2021) Machine learning reduced workload with minimal risk of missing studies: development and evaluation of a randomized controlled trial classifier for Cochrane Reviews. *Journal of Clinical Epidemiology*. 133, 140-51.

Cost effectiveness searches

The sensitive versions of the NICE cost utility study filters were used in MEDLINE and Embase, along with additional terms to identify other types of economic evaluation.

> Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Medline ALL	28th August 2024	Ovid	1946 to August 27, 2024	87
Embase	28th August 2024	Ovid	1974 to 2024 August 27	137
PsycInfo	28th August 2024	Ovid	1806 to August 2024 Week 4	50
Cochrane Database of Systematic Reviews (CDSR)	28th August 2024	Wiley	Issue 8 of 12, August 2024	3
CENTRAL	28th August 2024	Wiley	Issue 7 of 12, July 2024	20
Epistemonikos	28th August 2024	Native website	Not applicable	8

Search strategy history

Database name: Medline ALL

Searches
1 cytisin*.af. (1033) 2 cytizin*.af. (1)

Searches	
3	cytisiniclin*.af. (11)
4	cytiziniclin*.af. (0)
5	"6039-sopharma*".af. (0)
6	6039sopharma*.af. (0)
7	baptitoxin*.af. (0)
8	belnifrem*.af. (0)
9	belnifrelm*.af. (0)
10	cytiton*.af. (8)
11	desmoxan*.af. (1)
12	glavrinxa*.af. (0)
13	laburnine*.af. (3)
14	"NSC-407282*".af. (0)
15	NSC407282*.af. (0)
16	sophorin*.af. (4)
17	tabex*.af. (23)
18	tsitizin*.af. (8)
19	ulexin*.af. (4)
20	cravv*.af. (0)
21	or/1-20 (1051)
22	limit 21 to ed=20220404-20240828 (81)
23	limit 21 to dt=20220404-20240828 (99)
24	22 or 23 (105)
25	animals/ (7495960)
26	exp Animals, Laboratory/ (970688)
27	exp Animal Experimentation/ (10544)
28	exp Models, Animal/ (659304)
29	exp Rodentia/ (3637006)
30	(rat or rats or mouse or mice or rodent*).ti. (1504936)
31	or/25-30 (7622933)
32	31 not humans/ (5336829)
33	24 not 32 (91)
34	limit 33 to english language (87)
35	limit 34 to abstracts (78)
36	34 not 35 (9)
37	exp Randomized Controlled Trial/ (621511)
38	37 and 34 (10)
39	36 or 38 (19)
40	34 not 39 (68)

Searches
Line 34 should be seen as the last line of the search. Subsequent lines appear only for the purposes of selecting which references to run through the RCT classifier in EPPI Reviewer v5.

Database name: Embase

Searches
1 cytisinicline/ (40)
2 cytisin*.af. (1639)
3 cytizin*.af. (3)
4 cytisiniclin*.af. (50)
5 cytiziniclin*.af. (0)
6 "6039-sopharma*".af. (0)
7 6039sopharma*.af. (0)
8 baptitoxin*.af. (1)
9 belnifrem*.af. (0)
10 belnifrelm*.af. (0)
11 cytiton*.af. (2)
12 desmoxan*.af. (5)
13 glavrinxa*.af. (0)
14 laburnine*.af. (6)
15 "NSC-407282*".af. (0)
16 NSC407282*.af. (0)
17 sophorin*.af. (9)
18 tabex*.af. (67)
19 tsitizin*.af. (3)
20 ulexin*.af. (4)
21 cravv*.af. (0)
22 or/1-21 (1658)
23 limit 22 to dc=20220327-20240828 (194)
24 animal/ (1677089)
25 nonhuman/ (7848730)
26 exp Animal Experiment/ (3236245)
27 exp Experimental Animal/ (867017)
28 animal model/ (1828789)
29 exp Rodent/ (4196751)
30 (rat or rats or mouse or mice or rodent*).ti. (1688516)
31 or/24-30 (10409450)

Searches	
32	31 not human/ (7410712)
33	23 not 32 (143)
34	limit 33 to english language (137)
35	limit 34 to abstracts (114)
36	34 not 35 (23)
37	exp randomized controlled trial/ (843164)
38	34 and 37 (19)
39	36 or 38 (41)
40	34 not 39 (96)

Line 34 should be seen as the last line of the search. Subsequent lines appear only for the purposes of selecting references to run through the RCT classifier in EPPI Reviewer v5.

Database name: PsycInfo

Searches	
1	cytisin*.af. (627)
2	cytizin*.af. (0)
3	cytisiniclin*.af. (5)
4	cytiziniclin*.af. (0)
5	"6039-sopharma*".af. (0)
6	6039sopharma*.af. (0)
7	baptitoxin*.af. (0)
8	belnifrem*.af. (0)
9	belnifrelm*.af. (0)
10	cytiton*.af. (2)
11	desmoxan*.af. (0)
12	glavrinxa*.af. (0)
13	laburnine*.af. (0)
14	"NSC-407282*".af. (0)
15	NSC407282*.af. (0)
16	sophorin*.af. (0)
17	tabex*.af. (27)
18	tsitizin*.af. (0)
19	ulexin*.af. (0)
20	cravv*.af. (0)
21	or/1-20 (631)
22	limit 21 to up=20220403-20240828 (53)

Searches
23 animal.po. (448893)
24 (rat or rats or mouse or mice).ti. (128504)
25 or/23-24 (453672)
26 25 not (female or human or inpatient or male or outpatient or transgender).po. (213462)
27 22 not 26 (53)
28 limit 27 to english language (50)
29 limit 28 to abstracts (50)
30 28 not 29 (0)
31 exp randomized controlled trials/ (1651)
32 28 and 31 (0)
33 30 or 32 (0)
34 28 not 33 (50)

Database name: Cochrane Database of Systematic Reviews and CENTRAL

Searches
#1 cytisin*:ti,ab,kw
#2 cytizin*:ti,ab,kw
#3 cytisiniclin*:ti,ab,kw
#4 cytiziniclin*:ti,ab,kw
#5 (6039 NEXT sopharma*):ti,ab,kw
#6 6039sopharma*:ti,ab,kw
#7 baptitoxin*:ti,ab,kw
#8 belnifrem*:ti,ab,kw
#9 belnifrelm*:ti,ab,kw
#10 cytiton*:ti,ab,kw
#11 desmoxan*:ti,ab,kw
#12 glavrinxa*:ti,ab,kw
#13 laburnine*:ti,ab,kw
#14 (NSC NEXT 407282*):ti,ab,kw
#15 NSC407282*:ti,ab,kw
#16 sophorin*:ti,ab,kw
#17 tabex*:ti,ab,kw
#18 tsitizin*:ti,ab,kw
#19 ulexin*:ti,ab,kw

Searches
#20 cravv*:ti,ab,kw #21 {or #1-#20} #22 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 527901 #23 "conference":pt #24 #21 NOT (#22 OR #23) *On-screen limits used for dates.* *CDSR - limited to items published from 1st April 2022* *CENTRAL - limited to items added to database from 1st April 2022*

Database name: Epistemonikos

Searches
Title and abstract search for… cytisin* OR cytizin* OR cytisiniclin* OR cytiziniclin* OR (6039 AND sopharma*) OR (6039-sopharma*) OR 6039sopharma* OR baptitoxin* OR belnifrem* OR belnifrelm* OR cytiton* OR desmoxan* OR glavrinxa* OR laburnine* OR (nsc AND 407282*) OR (nsc-407282*) OR nsc407282* OR sophorin* OR tabex* OR tsitizin* OR ulexin* OR cravv* *… systematic review filter and date-added-to-database limit applied on screen (from 1st April 2022 on)* *Full search string, as run:* (title:(cytisin* OR cytizin* OR cytisiniclin* OR cytiziniclin* OR (6039 AND sopharma*) OR (6039-sopharma*) OR 6039sopharma* OR baptitoxin* OR belnifrem* OR belnifrelm* OR cytiton* OR desmoxan* OR glavrinxa* OR laburnine* OR (nsc AND 407282*) OR (nsc-407282*) OR nsc407282* OR sophorin* OR tabex* OR tsitizin* OR ulexin* OR cravv*) OR abstract:(cytisin* OR cytizin* OR cytisiniclin* OR cytiziniclin* OR (6039 AND sopharma*) OR (6039-sopharma*) OR 6039sopharma* OR baptitoxin* OR belnifrem* OR belnifrelm* OR cytiton* OR desmoxan* OR glavrinxa* OR laburnine* OR (nsc AND 407282*) OR (nsc-407282*) OR nsc407282* OR sophorin* OR tabex* OR tsitizin* OR ulexin* OR cravv*))

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Medline ALL	2nd September 2024	Ovid	1946 to August 29, 2024	19
Embase	2nd September 2024	Ovid	1974 to 2024 August 30	55
INAHTA International HTA Database	2nd September 2024	Native website	Not applicable	2

Search strategy history

Database name: Medline ALL

Searches	
1	cytisin*.af. (1033)
2	cytizin*.af. (1)
3	cytisiniclin*.af. (11)
4	cytiziniclin*.af. (0)
5	"6039-sopharma*".af. (0)
6	6039sopharma*.af. (0)
7	baptitoxin*.af. (0)
8	belnifrem*.af. (0)
9	belnifrelm*.af. (0)
10	cytiton*.af. (8)
11	desmoxan*.af. (1)
12	glavrinxa*.af. (0)
13	laburnine*.af. (3)
14	"NSC-407282*".af. (0)
15	NSC407282*.af. (0)
16	sophorin*.af. (4)
17	tabex*.af. (23)
18	tsitizin*.af. (8)
19	ulexin*.af. (4)

Searches
20 cravv*.af. (0)
21 or/1-20 (1051)
22 animals/ (7497291)
23 exp Animals, Laboratory/ (970851)
24 exp Animal Experimentation/ (10543)
25 exp Models, Animal/ (659490)
26 exp Rodentia/ (3637611)
27 (rat or rats or mouse or mice or rodent*).ti. (1505044)
28 or/22-27 (7624273)
29 28 not humans/ (5337441)
30 21 not 29 (530)
31 limit 30 to (english language and yr="2009 -Current") (294)
32 Economics/ (27539)
33 Value of life/ (5829)
34 exp "Costs and Cost Analysis"/ (272759)
35 exp Economics, Hospital/ (25953)
36 exp Economics, Medical/ (14444)
37 Economics, Nursing/ (4013)
38 Economics, Pharmaceutical/ (3146)
39 exp "Fees and Charges"/ (31501)
40 exp Budgets/ (14249)
41 budget*.ti,ab. (38013)
42 cost*.ti. (151990)
43 (economic* or pharmaco?economic*).ti. (64961)
44 (pharmaco?economic* adj (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).ab. (1183)
45 (price* or pricing*).ti,ab. (57399)
46 (cost* adj2 (minimi* or unit* or estimat* or variable* or consequence*)).ab. (32899)
47 (CMA or CEA or CUA or CEA or CBA).ti,ab. (46777)
48 (financ* or fee or fees).ti,ab. (174159)
49 (value adj2 (money or monetary)).ti,ab. (3238)
50 Cost-Benefit Analysis/ (95545)
51 Quality-Adjusted Life Years/ (16766)
52 Markov Chains/ (16397)
53 exp Models, Economic/ (16489)
54 cost*.ti. (151990)
55 (cost* adj2 utilit*).tw. (8242)
56 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (298607)

Searches
57 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (50823)
58 (qualit* adj2 adjust* adj2 life*).tw. (19139)
59 QALY*.tw. (15535)
60 (incremental* adj2 cost*).tw. (18642)
61 ICER.tw. (6637)
62 utilities.tw. (10016)
63 markov*.tw. (33837)
64 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (57017)
65 ((utility or effective*) adj2 analys*).tw. (26859)
66 (willing* adj2 pay*).tw. (10773)
67 (EQ5D* or EQ-5D*).tw. (14856)
68 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4343)
69 (european* adj2 quality adj3 ("5" or five)).tw. (790)
70 or/32-69 (968492)
71 31 and 70 (19)

Database name: Embase

Searches
1 cytisinicline/ (42)
2 cytisin*.af. (1641)
3 cytizin*.af. (3)
4 cytisiniclin*.af. (52)
5 cytiziniclin*.af. (0)
6 "6039-sopharma*".af. (0)
7 6039sopharma*.af. (0)
8 baptitoxin*.af. (1)
9 belnifrem*.af. (0)
10 belnifrelm*.af. (0)
11 cytiton*.af. (2)
12 desmoxan*.af. (5)
13 glavrinxa*.af. (0)
14 laburnine*.af. (6)
15 "NSC-407282*".af. (0)
16 NSC407282*.af. (0)
17 sophorin*.af. (9)

Searches
18 tabex*.af. (67)
19 tsitizin*.af. (3)
20 ulexin*.af. (4)
21 cravv*.af. (0)
22 or/1-21 (1660)
23 animal/ (1677480)
24 nonhuman/ (7848849)
25 exp Animal Experiment/ (3236647)
26 exp Experimental Animal/ (867009)
27 animal model/ (1829080)
28 exp Rodent/ (4197245)
29 (rat or rats or mouse or mice or rodent*).ti. (1688553)
30 or/23-29 (10409889)
31 30 not human/ (7411191)
32 22 not 31 (882)
33 limit 32 to (english language and yr="2009 -Current") (520)
34 exp economic evaluation/ (373704)
35 Health economics/ (36746)
36 exp health care cost/ (357736)
37 exp Fee/ (45591)
38 exp Budget/ (35096)
39 Funding/ (82443)
40 budget*.ti,ab. (50147)
41 (economic* or pharmaco?economic*).ti. (80945)
42 (pharmaco?economic* adj (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).ab. (2365)
43 (price* or pricing*).ti,ab. (78200)
44 (cost* adj2 (minimi* or unit* or estimat* or variable* or consequence*)).ab. (51313)
45 (CMA or CEA or CUA or CEA or CBA).ti,ab. (68198)
46 (financ* or fee or fees).ti,ab. (248585)
47 (value adj2 (money or monetary)).ti,ab. (4362)
48 cost utility analysis/ (13164)
49 quality adjusted life year/ (38300)
50 cost*.ti. (204234)
51 (cost* adj2 utilit*).tw. (13582)
52 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (410925)
53 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (70987)

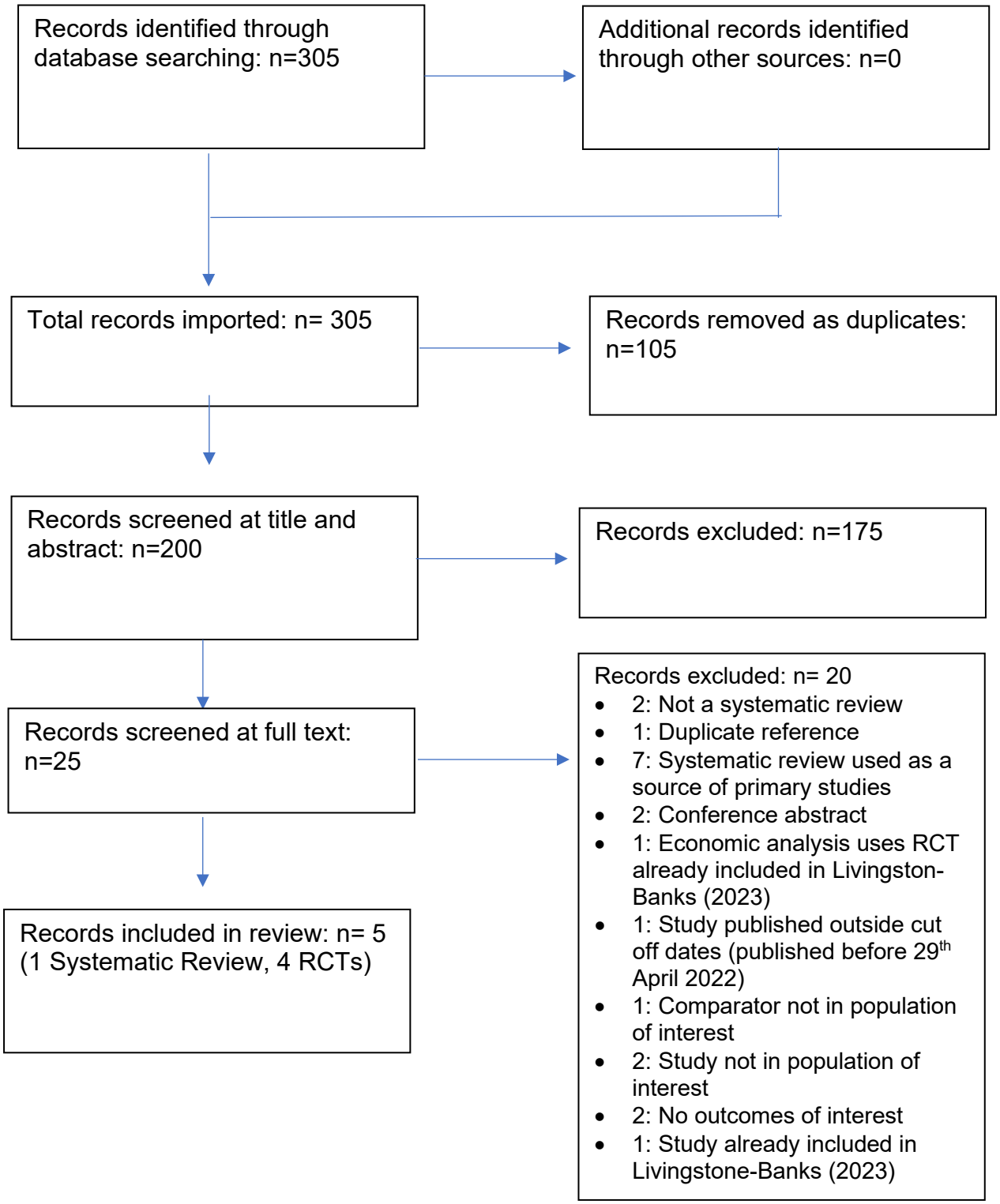
Searches
54 (qualit* adj2 adjust* adj2 life*).tw. (29253)
55 QALY*.tw. (28690)
56 (incremental* adj2 cost*).tw. (30621)
57 ICER.tw. (14134)
58 utilities.tw. (16009)
59 markov*.tw. (42648)
60 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (76742)
61 ((utility or effective*) adj2 analys*).tw. (40391)
62 (willing* adj2 pay*).tw. (16015)
63 (EQ5D* or EQ-5D*).tw. (28411)
64 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (5838)
65 (european* adj2 quality adj3 ("5" or five)).tw. (1094)
66 or/34-65 (1484498)
67 33 and 66 (55)

Database name: INAHTA International HTA Database

Searches
Searched all fields for… cytisin* OR cytizin* OR cytisiniclin* OR cytiziniclin* OR (6039-sopharma*) OR (6039 sopharma*) OR 6039sopharma* OR baptitoxin* OR belnifrem* OR belnifrelm* OR cytiton* OR desmoxan* OR glavrinxa* OR laburnine* OR (NSC-407282*) OR (NSC 407282*) OR NSC407282* OR sophorin* OR tabex* OR tsitizin* OR ulexin* OR cravv*

Appendix C Study selection - effectiveness evidence

This diagram shows the results of searching for new studies published after April 2022 (the cut-off date for the Livingstone-Banks et al. 2023 systematic review).



Appendix D Effectiveness evidence

Livingstone-Banks, 2023

Bibliographic Reference	Livingstone-Banks, Jonathan; Fanshawe, Thomas R; Thomas, Kyla H; Theodoulou, Annika; Hajizadeh, Anisa; Hartman, Lilian; Lindson, Nicola; Nicotine receptor partial agonists for smoking cessation.; The Cochrane database of systematic reviews; 2023; vol. 5; cd006103

Study characteristics

Study design	Systematic review
Study details	Dates searched Up to 29 April 2022 Databases searched The following databases were searched: 1. Cochrane Central Register of Controlled Trials (CENTRAL) 2. MEDLINE (via OVID) 3. Embase (via OVID) 4. PsycINFO (via OVID) Additionally, the review mentions that their search of the Cochrane Tobacco Addiction Group's Specialised Register also covered ongoing and unpublished trials included in: 1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov 2. World Health Organization (WHO) International Clinical Trials Registry Platform The authors also checked reference lists of included studies for potentially eligible trials. Sources of funding The authors specifically state: "This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure and Cochrane Programme Grant funding to the Cochrane Tobacco Addiction Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic

	Reviews Programme, NIHR, National Health Service, or the Department of Health and Social Care." No other sources of funding are mentioned in the text.
Inclusion criteria	Types of studies • Randomised controlled trials (RCTs) • Cluster-RCTs Other criteria • Minimum follow-up period of six months from baseline • Studies testing the effect of nicotine receptor partial agonists for smoking cessation (not focused on harm reduction) Settings Studies were conducted across multiple settings including: • Community pharmacy settings (Walker 2021) • Lung screening clinic (Pastorino 2022) • Tuberculosis treatment centres (Dogar 2020) • National quitline service (Walker 2014) • Mining company occupational health service (Vinnikov 2008) • Smoking cessation clinics (West 2011, Scharfenberg 1971)
Exclusion criteria	Types of studies • Quasi-randomised studies (where allocation sequence is not truly random) Types of participants • Non-adults (though "adult" is not specifically defined) • Smokeless tobacco users Types of interventions • Studies testing nicotine receptor partial agonists to help smokeless tobacco users quit • Studies testing nicotine receptor partial agonists as a relapse prevention intervention among people already abstinent from smoking tobacco • Studies focused on harm reduction rather than smoking cessation

	Types of outcome measures • Studies that did not report a minimum follow-up period of six months from baseline
Intervention(s)	Cytisinicline • Standard dose: 9 mg per day for 20 to 25 days • One study tested longer durations (40 and 84 days) Varenicline • Standard dose: 2 mg per day (1 mg twice a day) • Some studies tested lower doses (e.g., 1 mg per day) • Some studies tested longer durations (24 weeks, 52 weeks) • One study tested participant-regulated dosage (0.5 mg to 2.0 mg daily) Dianicline • Dose: 40 mg tablet twice a day for seven weeks Comparators • Placebo • No medication • Nicotine replacement therapy (NRT) - both monotherapy and combination • Bupropion • Electronic cigarettes • Different doses or regimens of the same drug

Outcomes	Primary outcomes
	
	• Abstinence from smoked tobacco at longest follow-up (at least six months from study baseline)
	  ○ Using the strictest definition of abstinence reported
	  ○ Preferring biochemically validated over self-reported abstinence
	• Number of participants who experienced the following adverse events:
	  ○ Nausea
	  ○ Insomnia
	  ○ Abnormal dreams
	  ○ Headache
	  ○ Depression
	  ○ Suicidal ideation
	• Number of participants who experienced serious adverse events (as defined by study authors)
	• Number of participants who experienced neuropsychiatric serious adverse events

	• Number of participants who experienced cardiac serious adverse events The review does not explicitly list secondary outcomes. All the outcomes mentioned are categorised as primary outcomes.
Number of studies included in the systematic review	According to the review, a total of 75 studies were included, involving 45,049 participants. Specifically: • 8 studies investigated cytisine use in just under 9,000 people • 68 studies investigated varenicline use in over 37,000 people • 1 study investigated dianicline use in 602 people
Studies from the systematic review that are relevant for use in the current review	Courtney 2021 Dogar 2020 Pastorino 2022 Schaffenberg 1971 Vinnikov 2008 Walker 2014 Walker 2021 West 2011
Studies from the systematic review that are not relevant for use in the current review	Other studies included in the review that were not assessed for cytisinicline: Anthenelli 2013, Ashare 2019, Aubin 2008, Baker 2016, Baker 2021, Benli 2017, Bohadana 2020, Bolliger 2011, Carson-Chahhoud 2020, Chen 2020, Chengappa 2014, Cinciripini 2013, Cinciripini 2018, Cox 2022, De Dios 2012, EAGLES 2016, Ebbert 2015, Ebbert 2016, Fouz-Roson 2017, Gonzales 2006, Gonzales 2014, Gray 2019, Heydari 2012, Hong 2015, Hurt 2018, Ikonomidis 2017, Ioakeimidis 2018, Johns 2017a, Johns 2017b, Jorenby 2006, King 2022, Le Mao 2020, Lerman 2015, Littlewood 2017, Mercie 2018, Nahvi 2014a, Nakamura 2007, NCT01162239, Niaura 2008, Nides 2006, O'Malley 2018, Oncken 2006, Qin 2021, Rennard 2012, Rigotti 2010, Rohsenow 2017, Rose 2013, Schnoll 2019, Stein 2013, Steinberg 2011, Steinberg 2018, Tashkin 2011, Tonstad 2011, Tsai 2007, Tsukahara 2010, Tuisku 2016, Tulloch 2016, Wang 2009, Westergaard 2015, Williams 2007, Williams 2012, Windle 2018, Wong 2012, Yang 2016, Zawertailo 2020, Zhang 2022, Zincir 2013.
Additional comments	• The comparison of cytisinicline vs placebo is based on 4 studies with a total of 4623 participants.

- The comparison of cytisinicline vs no medication is based on 1 study with 869 participants.
- Smoking abstinence outcomes used the strictest definition reported and favoured biochemically validated over self-reported where available.
- All smoking abstinence outcomes were measured at least 6 months from study baseline.
- Dosing regimens across all studies were generally consistent with the British National Formulary (BNF) recommendations for cytisinicline in adults aged 18-65 years. This involves a 25-day course with gradual dose reduction, starting at 9 mg per day and ending with 1.5-3 mg per day.
- Most studies followed a 25-day regimen, with some variations:
    - Some studies (e.g., West 2011, Walker 2014, 2021, Vinnikov 2008) provided detailed dosing schedules that closely matched BNF guidelines.
    - Others (e.g., Courtney 2021, Dogar 2020, Pastorino 2022, Scharfenberg 1971) aligned with the overall 25-day duration and starting doses but didn't provide specific daily dosing details.
    - One study (Pastorino 2022) also investigated extended treatment durations (40-day and 84-day regimens) beyond the standard 25-day course.
- The dosing information was extracted from the original papers cited in the Livingstone-Banks 2023 review, as it was not provided in detail in the systematic review itself.

Overall risk of bias assessments of studies included in the review:

Courtney 2021: Low risk of bias

Dogar 2020: Low risk of bias

Pastorino 2022: Unclear risk of bias for random sequence generation, allocation concealment, incomplete outcome data. High risk of bias for blinding.

Schaffenberg 1971: Unclear risk of bias assessment for all 5 domains.

Vinnikov 2008: Unclear risk of bias. The study population was mostly male workers in the mining industry, which may limit generalisability. Additionally, the authors note this as a limitation: "This was a limitation of our study, and we assume abstinence rates in the active group could be different if more women were

included in the group". In addition, there was unclear risk of bias with regards to incomplete outcome data.

Walker 2014: High risk of bias due to a lack of blinding

Walker 2021: High risk of bias due to the open-label nature of the study and a high rate of loss to follow-up

West 2011: Low risk of bias

Directness assessments:

The systematic review did not consistently assess directness for all included studies. However, it did provide some insights into potential issues with directness for a few studies. Dogar 2020, a cytisinicline versus placebo trial, was noted to have a highly motivated population that smoked fewer cigarettes per day compared to other cytisinicline trials. This may have contributed to higher placebo quit rates and potentially minimised the apparent benefit of pharmacotherapy, suggesting some indirectness in the study population. Walker 2014, which compared cytisinicline to nicotine replacement therapy (NRT), had a design where participants in the cytisinicline arm also received NRT vouchers after their initial cytisinicline course. The review authors noted this could potentially distort results, indicating some indirectness in the intervention. For Courtney 2021, Pastorino 2022, Schaffenberg 1971, Vinnikov 2008, Walker 2021, and West 2011, the review included these studies but did not explicitly comment on their directness. Overall, while the review did not systematically evaluate directness for each study, it did highlight potential directness issues in some cases that could impact the interpretation of results.

The decision to use fixed-effects meta-analyses throughout

The authors consistently used fixed-effects models (Mantel-Haenszel) for their meta-analyses involving cytisinicline, as stated in their methods section. While they did not provide an explicit rationale for choosing fixed-effects over random-effects models, they did outline a strategy for dealing with heterogeneity:

1. They planned to investigate moderate to substantial heterogeneity using subgroup analyses.
2. For considerable unexplained heterogeneity ($I^2 \geq 75\%$), they would evaluate whether it was appropriate to report a pooled result.
3. They conducted sensitivity analyses, removing high-risk-of-bias studies to see if this affected the overall result.

Subgroup analyses:

Upon review of the included studies, it was found that while some baseline characteristics relevant to potential subgroup analyses were collected, most studies did not conduct or report subgroup analyses for most of the populations of interest (cardiovascular disease, COPD, diabetes, or those with previous quit attempts).

However, subgroup data was available for people with mental health conditions (Courtney 2021) and heavy smokers (Rigotti 2023).

Dosing regimens compared to BNF recommendations:

The British National Formulary (BNF) recommends a specific dosing schedule for cytisinicline in adults aged 18-65 years. This schedule involves a gradual reduction in dosage over 25 days, starting with a maximum of 9 mg per day and ending with 1.5-3 mg per day.

When comparing the dosing regimens used in the reviewed studies to the BNF recommendations, we observe the following:

- Courtney 2021 used a 25-day course that appears to align with the BNF recommendations, starting with 1.5 mg capsules taken 6 times daily and gradually reducing over 25 days. However, specific details of the reduction schedule are not provided.
- Dogar 2020 and Pastorino 2022 both used identical 25-day regimens that match the BNF recommendations in terms of starting and ending doses (9 mg on day 0, gradually reduced to 1.5 mg by day 25). However, the specific daily dosing schedule is not detailed in the provided information.
- Pastorino 2022 also investigated extended treatment durations beyond the standard 25-day course, with a 40-day standard schedule and an 84-day prolonged schedule. These extended regimens go beyond the BNF recommendations.
- Scharfenberg 1971 was obtained but it is written in German so we cannot ascertain the dosing with certainty.
- West 2011 used a 25-day regimen that exactly matches the BNF recommendations, providing detailed dosing information that aligns with the guidelines.
- Walker 2014 and 2021 and Vinnikov 2008 all used dosing regimens that closely align with the BNF recommendations, following a 25-day schedule with gradual dose reduction.

In summary, all of the reviewed studies followed dosing regimens that are consistent with the BNF recommendations in terms of the 25-day duration and the principle of gradual dose reduction. Some studies (West, Walker, Vinnikov) provide detailed dosing information that matches the BNF guidelines exactly. Others (Courtney, Dogar, Pastorino) align with the overall 25-day duration and starting doses, but don't provide the specific daily dosing details. Pastorino et al.'s investigation of extended treatment durations represents a departure from the standard BNF recommendations, potentially exploring the effects of longer-term treatment.

The arms in each study were as follows:

Courtney 2021:

- Cytisinicline: 1.5 mg capsules taken 6 times daily initially then gradually reduced over a 25-day course (n=725)
- Varenicline: 0.5 mg tablets titrated to 1 mg twice daily for 84 days (12 weeks) (n=727)

Dogar 2020:

- Cytisinicline: 9 mg on day 0, gradually reduced to 1.5 mg by day 25, for a total of 25 days, plus behavioural support (n=1239)
- Placebo: matching placebo for 25 days, plus behavioural support (n=1233)

Pastorino 2022:

- Cytisinicline: 9 mg on day 0, gradually reduced to 1.5 mg by day 25, for a total of 25 days, plus behavioural support (n=470)
- Placebo: Matched placebo for 25 days, plus behavioural support (n=399)

Additionally, the cytisinicline arm was further randomised into:

- Standard schedule: 40 days treatment (n not provided)
- Prolonged schedule: 84 days treatment with reduced dosage after first 40 days (n not provided)

Scharfenberg 1971:

- Scharfenberg 1971 was obtained but it is written in German so we cannot ascertain the dosing with certainty.

Vinnikov 2008:

- Cytisinicline: Gradually reduced dosage over 25 days, starting with 6 tablets (1.5 mg each) per day for first 3 days, then 5 tablets per day for days 4-12, 4 tablets per day for days 13-16, 3 tablets per day for days 17-20, 2 tablets per day for days 21-22, and 1 tablet per day for days 23-25 (n=85)
- Placebo: Matched placebo following same dosing schedule as cytisinicline arm (n=86)

	Walker 2014: • Cytisinicline: 1.5 mg tablets, gradually reduced dosage over 25 days - days 1-3: 6 tablets per day, days 4-12: 5 tablets per day, days 13-16: 4 tablets per day, days 17-20: 3 tablets per day, days 21-22: 2 tablets per day, days 23-25: 1 tablet per day (n=655) • Nicotine replacement therapy: Nicotine patches (7 mg, 14 mg, or 21 mg) and gum (2 mg or 4 mg) or lozenges (1 mg or 2 mg) for 8 weeks (n=655) Walker 2021: • Cytisinicline: Gradually reduced dosage over 25 days - days 1-3: one 1.5 mg tablet every 2 hours (6 tablets/day), days 4-12: one tablet every 2.5 hours (5 tablets/day), days 13-16: one tablet every 3 hours (4 tablets/day), days 17-20: one tablet every 4-5 hours (3 tablets/day), days 21-25: one tablet every 6 hours (2 tablets/day). Maintenance dose of 2 tablets/day from day 26 to week 12. (n=337) • Varenicline: Standard 12-week regimen - days 1-3: 0.5 mg once daily, days 4-7: 0.5 mg twice daily, day 8-week 12: 1 mg twice daily (n=342) West 2011: • Cytisinicline: Gradually reduced dosage over 25 days - days 1-3: six 1.5 mg tablets per day (one tablet every 2 hours), days 4-12: five tablets per day, days 13-16: four tablets per day, days 17-20: three tablets per day, days 21-25: two tablets per day (n=370) • Placebo: Matching placebo tablets following same dosing schedule as cytisinicline arm (n=370)

Study arms

Cytisinicline (N = 2311)

Placebo (N = 2312)

No medication (N = 399)

Varenicline (N = 1064)

Nicotine Replacement Therapy (NRT) (N = 655)

Cytisinicline vs Placebo

Result	Arm 1 (Cytisinicline, N=2316)	Arm 2 (Placebo, N=2307)	Summary statistic
Smoking abstinence: Vs placebo, at least 6 months	476/2316	364/2307	RR 1.30 [1.15, 1.47]

Cytisinicline vs No medication

Result	Arm 1 (Cytisinicline, N=470)	Arm 2 (No medication, N=399)	Summary statistic
Smoking abstinence: Vs no medication, at least 6 months	151/470	29/399	RR 4.44 [3.06, 6.46]
Adverse events: Any, follow-up timepoint not specified	100/470	66/399	RR 1.25 [0.98, 1.60]

Cytisinicline vs Placebo or no medication

Result	Arm 1 (Cytisinicline, N=varies)	Arm 2 (Placebo or no medication, N=varies)	Summary statistic
Adverse events: Any, follow-up timepoint not specified	374/2067	282/1985	RR 1.22 [1.07, 1.39]
Serious adverse events: Any, follow-up timepoint not specified	105/1982	83/1799	RR 1.04 [0.78, 1.37]

Cytisinicline vs Varenicline

Result	Arm 1 (Cytisinicline, N=varies)	Arm 2 (Varenicline, N=varies)	Summary statistic
Smoking abstinence: Vs varenicline, at least 6 months	117/1067	140/1064	RR 0.83 [0.66, 1.05]
Serious adverse events: Vs varenicline, follow-up timepoint not specified	33/1012	49/1005	RR 0.67 [0.44, 1.03]
Adverse events: Nausea, follow-up timepoint is not specified	104/1012	252/1005	RR 0.41 (95% CI 0.33 to 0.50)

Adverse events: Abnormal dreams, follow-up timepoint is not specified	128/1012	209/1005	RR 0.60 (95% CI 0.50 to 0.73)
Adverse events: Insomnia, follow-up timepoint is not specified	150/1012	165/1005	RR 0.90 (95% CI 0.73 to 1.10)
Adverse events: Headache, follow-up timepoint is not specified	102/1012	99/1005	RR 1.02 (95% CI 0.79 to 1.33)
Adverse events: Depression, follow-up timepoint is not specified	1/337	0/342	RR 3.04 (95% CI 0.12 to 74.47)
Adverse events: Suicidal ideation, follow-up timepoint is not specified	0/1012	1/1005	RR 0.33 (95% CI 0.01 to 8.02)

Cytisinicline vs Nicotine Replacement Therapy (NRT)

Result	Arm 1 (Cytisinicline, N=655)	Arm 2 (NRT, N=655)	Summary statistic
Smoking abstinence: Vs NRT, at least 6 months	143/655	100/655	RR 1.43 [1.13, 1.80]
Serious adverse events, follow-up timepoint not specified	45/655	39/655	RR 1.15 [0.76, 1.75]
Adverse events: Nausea, follow-up timepoint is not specified	30/655	2/655	RR 15.00 [3.60, 62.51]

Abbreviations:
N - Number of participants
NRT - Nicotine Replacement Therapy
vs - versus

Data from the studies included in Livingstone-Banks 2023

Courtney 2021

Result	Arm 1: Cytisinicline (N=725)	Arm 2: Varenicline (N=727)
Smoking abstinence at 6 months (or 24 weeks) exactly	85/ (11.7%)	97/ (13.3%)

Smoking abstinence at more than 1 month but less than 6 months from the study baseline	111/ (15.3%)	131/ (18.0%)
Adverse events: Any adverse event	482 (71.4%)	510 (76.9%)
Adverse events: Serious adverse events	17 (2.5%)	32 (5.0%)
Adverse events: Nausea	79 (10.9%)	198 (27.2%)
Adverse events: Abnormal dreams	120 (16.6%)	185 (25.4%)
Adverse events: Insomnia	135 (18.6%)	137 (18.8%)
Adverse events: Headache	67 (9.2%)	59 (8.1%)
Adverse events: Suicidal ideation	0 (0%)	1 (0.14%)
Subgroup analysis		
Smoking abstinence: People with mental health conditions, 7-month follow-up	11/108 (10.2%)	17/138 (12.3%)

Dogar 2020

Result	**Arm 1 (Cytisinicline, N=1239)**	**Arm 2 (Placebo, N=1233)**
Smoking abstinence at 12 months	309 (24.9%)	275 (22.3%)
Smoking abstinence at 6 months (or 24 weeks) exactly	401 (32.4%)	366 (29.7%)
Smoking abstinence at more than 1 month but less than 6 months from the study baseline	685 (55.3%) at 12 weeks	643 (52.1%) at 12 weeks
Adverse events: Patients with one or more non-serious adverse events	98 (7.9%)	86 (7.0%)
Adverse events: Patients with one or more serious adverse events	53 (4.3%)	46 (3.7%)
Adverse events: Nausea	11 (0.9%)	8 (0.7%)
Adverse events: Abnormal dreams	5 (0.4%)	4 (0.3%)
Adverse events: Insomnia	13 (1.1%)	10 (0.9%)

Adverse events: Headache	8 (0.7%)	8 (0.7%)

Pastorino 2022

Result	Arm 1 (Cytisinicline, N=470)	Arm 2 (No medication, N=399)
Smoking abstinence: Continuous abstinence, 12 months	151 (32.1%)	29 (7.3%)
Adverse events: Any adverse event	196 (41.7%)	133 (33.3%)
Adverse events: Any psychiatric event	77 (16.4%)	53 (13.3%)
Adverse events: Any central nervous system event	62 (13.2%)	39 (9.8%)
Adverse events: Serious adverse events	39 (8.3%)	34 (8.5%)
Subgroup analyses		
Smoking abstinence: Heavy smokers (More than or equal to 30 pack-years), 12 months (all participants were heavy smokers)	151 (32.1%)	29 (7.3%)

Scharfenberg 1971

Result	Arm 1 (Cytisinicline, N=607)	Arm 2 (Placebo, N=607)
Smoking abstinence at more than 1 month but less than 6 months from the study baseline	395 (65.1%) at 4 weeks	246 (40.6%) at 4 weeks

Vinnikov 2008

Result	Arm 1 (Cytisinicline, N=85)	Arm 2 (Placebo, N=86)
Smoking abstinence at 6 months (or 24 weeks) exactly	9 (10.6%)	1 (1.2%)
Smoking abstinence at more than 1 month but less than 6 months from the study baseline	9 (10.6%)	5 (5.7%)
Adverse events: Number of people experiencing at least one adverse event	4 (4.7%)	4 (4.7%)

Adverse events: Nausea	2 (2.4%)	1 (1.2%)
Adverse events: Headache	1 (1.2%)	1 (1.2%)

Walker 2014

Result	Arm 1 (Cytisinicline, N=655)	Arm 2 (NRT, N=655)
Smoking abstinence at 6 months (or 24 weeks) exactly	143 (22%)	100 (15%)
Smoking abstinence at more than 1 month but less than 6 months from the study baseline	202 (31%) at 2 months	143 (22%) at 2 months
Adverse events: Any adverse event	204 (31%)	134 (20%)
Adverse events: Serious adverse events	45 (7%)	39 (6%)

Walker 2021

Result	Arm 1: Cytisinicline (N=337)	Arm 2: Varenicline (N=342)
Smoking abstinence: continuous abstinence, 12 months	43 (16.3%)	32 (12.4%)
Smoking abstinence at 6 months (24 weeks) exactly	41/ (12.1%)	27/ (7.9%)
Smoking abstinence at more than 1 month but less than 6 months from study baseline	124/ (36.7%)	102/ (29.7%)
Adverse events: Participants experiencing at least one adverse event	111 (32.9%)	138 (40.4%)
Adverse events: Serious adverse events	16 (4.7%)	17 (5.0%)
Adverse events: All	111 (32.9%)	138 (40.4%)
Adverse events: Nausea	25 (22.5%)	54 (39.1%)
Adverse events: Abnormal dreams	8 (7.2%)	24 (17.4%)
Adverse events: Insomnia	15 (13.5%)	28 (20.3%)

Adverse events: Headache	35 (31.5%)	40 (29.0%)
Adverse events: Depression	1 (0.15%)	0 (0%)
Adverse events: Suicidal ideation	0 (0%)	0 (0%)

West 2011

Result	**Arm 1: Cytisinicline (N=370)**	**Arm 2: Placebo (N=370)**
Smoking abstinence: Continuous abstinence, 12 months	31 (8.4%)	9 (2.4%)
Smoking abstinence at 6 months (or 24 weeks) exactly	37 (10.0%)	13 (3.5%)
Adverse events: Any adverse event	76 (20.5%)	59 (15.9%)
Adverse events: Any serious adverse event	4 (1.1%)	3 (0.8%)
Adverse events: Nausea	14 (3.8%)	10 (2.7%)
Adverse events: Headache	7 (1.9%)	8 (2.2%)

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study	Yes

Section	Question	Answer
	quality, outcomes measured)?	
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(The review demonstrates low concern regarding the specification of study eligibility criteria. The objectives and eligibility criteria were pre-defined, appropriate for the review question, and unambiguous. All restrictions in eligibility criteria, whether based on study characteristics or sources of information, were deemed appropriate.)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	Yes
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Yes
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low *(The review conducted a comprehensive search using a well-designed strategy across multiple databases, employed*

Section	Question	Answer
		additional methods to identify studies, and used a rigorous selection process involving multiple reviewers. The provided search strategy further confirms the thoroughness of the search methods. There are no major concerns in this domain.)
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(The review demonstrates rigorous methods for data collection and study appraisal. It used a standardised form for data extraction, involved multiple reviewers to minimise errors, collected comprehensive study characteristics and results, and employed a widely accepted tool for risk of bias assessment. The process for resolving disagreements was clearly described. There are no major concerns in this domain.)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes	Yes

Section	Question	Answer
	across included studies?	
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Yes
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(The review demonstrates a thorough and appropriate approach to synthesis. It included all relevant studies, used appropriate methods for meta-analysis, addressed heterogeneity, conducted sensitivity analyses, and considered the risk of bias in primary studies when interpreting results. The review also assessed publication bias where possible. There are no major concerns in this domain.)*
Overall study ratings	Overall risk of bias	Low *(The review demonstrates strong methodological rigor across all domains assessed. The eligibility criteria were clear and appropriate, the search strategy was comprehensive, data collection and study appraisal were thorough, and the synthesis was appropriate and considered potential biases. The interpretation of findings addressed all concerns, considered the relevance of studies to the research question, and presented a balanced view of the results. There are no major concerns that would raise the risk of bias in this review.)*
Overall study ratings	Applicability as a source of data	Fully applicable *(The Livingstone-Banks et al. (2023) Cochrane systematic review is fully applicable to this updated top-up review. It addresses the same core question regarding the effectiveness of cytisinicline for smoking cessation, focuses on the same population*

Section	Question	Answer
		of adult tobacco smokers, and includes the same interventions and comparators. The primary outcome of smoking abstinence at 6 months or longer aligns with our review's critical outcomes. The Cochrane review's inclusion of randomised controlled trials and cluster-randomised controlled trials matches our study design criteria. Its search date (up to April 2022) perfectly aligns with the start date for our new searches, ensuring a seamless update. The review's approach to data synthesis, including the use of Mantel-Haenszel fixed-effect models and assessment of heterogeneity, is consistent with our protocol. While the Cochrane review used the Cochrane Risk of Bias 1 tool, our updated review will employ the more recent Risk of Bias 2 tool, which may provide a more nuanced assessment of potential biases. Despite this difference and the inclusion of some additional outcomes and subgroup analyses in our review, the Cochrane review provides a robust and directly applicable foundation for our updated analysis.)

Oreskovic, 2023

Bibliographic Reference	Oreskovic, Tin; Percac-Lima, Sanja; Ashburner, Jeffrey M; Tiljak, Hrvoje; Rifel, Janez; Klemenc Ketis, Zalika; Oreskovic, Stjepan; Cytisine Versus Varenicline for Smoking Cessation in a Primary Care Setting: A Randomized Non-inferiority Trial.; Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco; 2023; vol. 25 (no. 9); 1547-1555

Study details

Trial registration number and/or trial name	Not provided
Study type	Randomised controlled trial (RCT)
Study location	Croatia and Slovenia
Study setting	Primary care practices. Data was recorded through in-person visits and phone calls with participants.
Study dates	14 July 2020 to 4 November 2022

Sources of funding	3-year project grant from GRAND (Global Research Awards for Nicotine Dependence), supported by Pfizer
Inclusion criteria	Adults aged 18 years or older Currently smoking at least one cigarette per day Indicated a desire to quit smoking Indicated interest in pharmacotherapy Had a primary care doctor at one of the participating practices
Exclusion criteria	Psychiatric disorders (depression, schizophrenia) Pregnant or breastfeeding Cognitive impairment Considered insufficiently collaborative by doctors History of frequent adverse reactions to multiple drugs Participating in another smoking cessation program
Intervention(s)	Cytisinicline for 25 days following standard dosage protocol, plus behavioural support from trained doctors and research assistants
Comparator	Varenicline for 12 weeks following standard dosage protocol, plus behavioural support from trained doctors and research assistants
Outcome measures	Smoking abstinence at 6 months Smoking abstinence at longest follow-up, at least 6 months from study baseline Smoking abstinence at more than 1 month but less than 6 months from study baseline Adverse events
Number of participants	Total number of participants: N = 377 • Cytisinicline: 186 (49.3%) • Varenicline: 191 (50.7%)
Duration of follow-up	24 weeks
Loss to follow-up	13.72% (48/377) by final 24-week call
Methods of analysis	Bayesian logistic regression models were used for the primary effectiveness and feasibility analyses. Secondary analyses included multivariable models adjusting for baseline characteristics

	and multilevel models accounting for clustering within practices. Negative binomial regression was used to analyse adverse events.
Additional comments	The COVID-19 pandemic significantly impacted the study, affecting recruitment and potentially influencing participants' smoking behaviours due to increased stress and lifestyle changes.

Study arms

Cytisinicline: 25-day supply, standard manufacturer's dosage protocol (N = 186)

Varenicline: 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks (N = 191)

Characteristics

Arm-level characteristics

Characteristic	Cytisinicline: 25-day supply, standard manufacturer's dosage protocol (N = 186)	Varenicline: 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks (N = 191)
% Female No of events	n = 109; % = 58.6	n = 109; % = 57.1
Age (years) Mean (SD)	48.7 (13)	49.2 (11.5)
Level of nicotine dependence (Fagerström test category): Low No of events	n = 21; % = 11.3	n = 31; % = 16.2
Level of nicotine dependence (Fagerström test category): Low to moderate No of events	n = 67; % = 36	n = 55; % = 28.8
Level of nicotine dependence	n = 84; % = 45.2	n = 88; % = 46.1

Characteristic	Cytisinicline: 25-day supply, standard manufacturer's dosage protocol (N = 186)	Varenicline: 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks (N = 191)
(Fagerström test category): Moderate No of events		
Level of nicotine dependence (Fagerström test category): High No of events	n = 13; % = 7	n = 16; % = 8.4
Level of nicotine dependence (Fagerström test category): Not available No of events	n = 1; % = 0.5	n = 1; % = 0.5
Number of cigarettes per day (number) Mean (SD)	18.6 (9.05)	18.9 (8.82)
Age when first started smoking (years) Mean (SD)	18.6 (3.71)	19 (4.81)

Cytisinicline vs Varenicline

Result	Arm 1 (Cytisinicline, N=186)	Arm 2 (Varenicline, N=191)
Smoking abstinence: Self-reported 7-day abstinence, 24 weeks	43 (23.12%)	62 (32.46%)
Smoking abstinence: Self-reported 7-day abstinence, 4 weeks	59 (31.72%)	62 (32.46%)
Adverse events: follow-up timepoint is not specified	93 (53.76%)	131 (72.78%)
Serious adverse events: follow-up timepoint is not specified	13 (7.51%)	21 (11.67%)

Critical appraisal – Cochrane risk of bias tool 1

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(The study states "A random number generator was used to allocate varenicline or cytisine treatment in a 1:1 ratio stratified by practice and based on the order of enrolment. The pre-specified random allocation was uploaded to REDCap (a data management tool)." This indicates an appropriate method was used to generate the random sequence.)*
Selection bias	Allocation concealment	Low risk of bias *(The use of REDCap for the pre-specified random allocation suggests allocation was likely concealed until participants were enrolled and assigned to interventions.)*
Performance bias	Blinding of participants and personnel	High risk of bias *(The study states "Because of differences in the duration and dosages of the treatments as well as the medications' different shapes, neither the participants nor the MDs and RAs could be blinded." The lack of blinding could potentially influence participants' behaviour and adherence.)*
Detection bias	Blinding of outcome assessment	High risk of bias *(The primary outcome of self-reported 7-day abstinence was not blinded. The lack of blinding of participants and personnel means outcome assessment was also not blinded, which could influence self-reported abstinence rates.)*
Attrition bias	Incomplete outcome data	Low risk of bias *(The study reports that only 13.72% of participants were lost to follow-up by the final 24-week call. Missing outcome data were handled appropriately in the analysis: "We considered participants lost to follow-up not to have reported 7-day abstinence after 24 weeks.")*
Reporting bias	Selective reporting	Low risk of bias *(The study reports on all pre-specified outcomes outlined in the methods. The statistical analysis plan was pre-specified and made available as supplementary material.)*
Other sources of bias	Any other sources of bias	Unclear risk of bias *(The study was funded by a grant program supported by Pfizer, who manufacture varenicline. While the authors state Pfizer was not involved in the design, conduct, analysis or reporting of the trial, the funding source introduces a potential conflict of interest. Additionally, the COVID-19 pandemic impacted recruitment and may have affected participants' smoking behaviours.)*

Section	Question	Answer
Overall risk of bias and directness	Overall risk of bias	High
Overall risk of bias and directness	Risk of bias variation across outcomes	This study measured smoking abstinence using self-reported 7-day abstinence, which as a subjective outcome could be influenced by the lack of blinding. The lack of biochemical verification makes this outcome particularly susceptible to detection and performance bias. For adverse events reporting, while also self-reported and potentially affected by lack of blinding, the impact may be different as these are more specific symptoms that participants would notice. The open-label design thus likely introduced varying levels of bias across these different outcome types.
Overall risk of bias and directness	Directness	Partially applicable *(The study by Oreskovic et al. (2023) is partially applicable to the UK NHS setting for the following reasons: Population: The study was conducted in Croatia and Slovenia, where smoking prevalence rates (36.9% and 22.3% respectively) are higher than in the UK (approximately 14.5% as of 2020). This difference in prevalence might indicate a population with different characteristics, motivations, or levels of tobacco dependence compared to UK smokers. However, the study's primary care setting is similar to how smoking cessation services are often delivered in the UK NHS. Healthcare system: While both Croatia and Slovenia have universal healthcare systems, there may be differences in how smoking cessation services are organised and delivered compared to the UK NHS. The study was conducted in primary care practices, which is similar to how many smoking cessation interventions are delivered in the UK. However, the UK also has specialised stop smoking services, which were not part of this study's setting. COVID-19 impact: The study was conducted during the COVID-19 pandemic, which affected recruitment and may have influenced smoking behaviours.)*

Phusahat, 2022

Bibliographic Reference	Phusahat, Pum; Dilokthornsakul, Piyameth; Boonsawat, Watchara; Zaeoue, Uraiwan; Hansuri, Nadthatida; Tawinkan, Nirachara; Theeranut, Ampornpan; Lertsinudom, Sunee; Efficacy and Safety of Cytisine in Combination with a Community Pharmacists' Counselling for Smoking Cessation in Thailand: A Randomized

Double-Blinded Placebo-Controlled Trial.; International journal of environmental research and public health; 2022; vol. 19 (no. 20)

Study details

Trial registration number and/or trial name	TCTR20180312001
Study type	Randomised controlled trial (RCT)
Study location	Thailand
Study setting	Community pharmacy at the Faculty of Pharmaceutical Sciences, Khon Kaen University. Trial data was recorded through participant visits and follow-ups.
Study dates	June 2018 to March 2021
Sources of funding	Government Pharmaceutical Organization, Thailand (grant No. 4/2561)
Inclusion criteria	Age 18-65 years old Smoked >10 cigarettes/day Willing to quit smoking at preparation level based on trans-theoretical model Could be contacted by phone
Exclusion criteria	Cardiac arrhythmia Cardiovascular disease Cancer Chronic renal disease (eGFR ≤ 30 mL/min/1.73 m2) Psychiatric disorders (depression, schizophrenia) Using other drugs like marijuana or amphetamines Pregnant or breastfeeding Being treated with other smoking cessation medications
Intervention(s)	• Cytisinicline tablets with tapering 25-day regimen plus five sessions of smoking cessation counselling by trained community pharmacists using the 5As model (ask, advise, assess, assist, arrange)

Comparator	• Matching placebo tablets plus five sessions of smoking cessation counselling by trained community pharmacists using the 5As model
Outcome measures	Smoking abstinence at longest follow-up, at least 6 months from study baseline Smoking abstinence at more than 1 month but less than 6 months from study baseline Adverse events Health-related quality of life
Number of participants	Total number of participants: N = 132 • Cytisinicline group: 67 (50.8%) • Placebo group: 65 (49.2%)
Duration of follow-up	48 weeks
Loss to follow-up	• Cytisinicline group: 38 (56.7%) • Placebo group: 34 (52.3%)
Methods of analysis	Intention-to-treat analysis was applied, assuming participants lost to follow-up had failed to quit smoking. Chi-square tests were used for dichotomous outcomes and t-tests for continuous outcomes. Risk ratios, mean differences and 95% confidence intervals were calculated. A subgroup analysis by Fagerström Test for Nicotine Dependence score was performed.
Additional comments	The authors highlighted several limitations of the study. Firstly, there was a high rate of loss to follow-up, with only about half of the participants completing the study as planned. This attrition could introduce bias, although the authors attempted to mitigate this by assuming that those lost to follow-up had failed to quit smoking. Secondly, despite efforts to standardise the smoking cessation counselling, there might have been variations among pharmacists, potentially affecting the smoking cessation rates. Thirdly, the study population was predominantly male (95.5%), limiting the generalisability of findings to female smokers. The study setting, a pharmacy within a university faculty, may not be representative of other pharmacy settings such as chain or private stand-alone pharmacies. This could affect the external validity of the results. Additionally, the authors noted that they were unable to perform serum cotinine tests to confirm smoking abstinence due to the community pharmacy setting, relying instead on exhaled carbon monoxide measurements. A strength of the study is its randomised, double-blind, placebo-controlled design, which helps to minimise bias. The use of both

self-reported abstinence and biochemical verification (exhaled CO) adds robustness to the outcome measures. The inclusion of health-related quality of life measures provides valuable additional information beyond smoking cessation rates.

However, the study's relatively small sample size (132 participants) may have limited its power to detect significant differences, particularly for the primary outcome at 48 weeks. The authors do not report a formal power calculation for the 48-week outcome, which would have been helpful to interpret the results.

The study provides data on the use of cytisinicline in a Thai population, which may differ from populations in previous studies. However, the lack of direct comparison with other established smoking cessation pharmacotherapies (e.g., varenicline or nicotine replacement therapy) limits the ability to contextualise the efficacy of cytisinicline within the broader landscape of smoking cessation treatments.

Overall, while this study adds to the evidence base for cytisinicline, the limitations in sample size, generalisability, and duration of follow-up suggest that the results should be interpreted cautiously. The trend towards improved short-term abstinence rates with cytisinicline is promising, but the lack of significant difference at 48 weeks highlights the need for larger, more diverse studies with longer follow-up periods.

Notes:

1. Follow-up time points: 12 weeks (more than 1 month but less than 6 months), 24 weeks (6 months), and 48 weeks (12 months, longest follow-up).
2. The study did not report data for the specified subgroups (people with mental health conditions, cardiovascular disease, COPD, diabetes, heavy smokers, or those with previous quit attempts).
3. All smoking abstinence outcomes were biochemically validated using exhaled carbon monoxide.
4. Quality of life measures are reported as changes from baseline, calculated using methods from the Cochrane Handbook section 6.5.2.8:

Statistical analysis for continuous outcomes (mean difference)

For continuous outcomes, mean differences (MDs) and 95% confidence intervals (CIs) were calculated between intervention and control groups. The MD for each outcome was obtained by subtracting the mean value in the control group from the mean value in the intervention group. The standard error (SE) of the MD was calculated using the formula:

	SE(MD) = √[(SD_intervention² / n_intervention) + (SD_control² / n_control)] where SD refers to the standard deviation of the group and n is the sample size. The 95% CIs were then computed as: 95% CI = MD ± 1.96 × SE(MD) For example, for the WHOQOL-BREF-THAI at 24 weeks, the mean difference was 0.18 (95% CI: -0.21 to 0.57). For the WHOQOL-BREF-THAI at 48 weeks, the mean difference was 0.03 (95% CI: -0.40 to 0.46). Similarly, for the EQ-5D-5L at 24 weeks, the mean difference was 2.82 (95% CI: -7.93 to 13.57), and for the EQ-5D-5L at 48 weeks, the mean difference was 2.00 (95% CI: -4.86 to 8.86).

Study arms

Cytisinicline tablets: 1.5 mg per tablet, 25-day regimen with tapering dosage (N = 67)

Placebo tablets (N = 65)

Characteristics

Arm-level characteristics

Characteristic	Cytisinicline tablets: 1.5 mg per tablet, 25-day regimen with tapering dosage (N = 67)	Placebo tablets (N = 65)
% Female No of events	n = 4; % = 5.97	n = 2; % = 3.08
Age Mean (SD)	43.8 (11.76)	42.46 (14.59)
Level of nicotine dependence (Fagerström score) Mean (SD) Fagerström Test for Nicotine Dependence scores: **0–2**: Very low dependence **3–4**: Low dependence **5**: Moderate dependence **6–7**: High dependence	5 (2.35)	4.25 (2.05)

Characteristic	Cytisinicline tablets: 1.5 mg per tablet, 25-day regimen with tapering dosage (N = 67)	Placebo tablets (N = 65)
8–10: Very high dependence		

Cytisinicline vs Placebo

Result	Arm 1 (Cytisinicline, N=67)	Arm 2 (Placebo, N=65)
Smoking abstinence: Continuous abstinence rate (CAR), 6 months (24 weeks)	11 (16.42%)	6 (9.23%)
Smoking abstinence: Continuous abstinence rate (CAR), longest follow-up (48 weeks)	10 (14.93%)	4 (6.15%)
Smoking abstinence: Continuous abstinence rate (CAR), more than 1 month but less than 6 months (12 weeks)	18 (26.87%)	7 (10.77%)
Adverse events: Total, follow-up timepoint is not specified	37 (55.22%)	26 (40.00%)
Adverse events: Nausea and vomiting, follow-up timepoint is not specified	0 (0%)	1 (1.54%)
Adverse events: Headache, follow-up timepoint is not specified	3 (4.48%)	0 (0%)
Adverse events: Insomnia, follow-up timepoint is not specified	8 (11.94%)	1 (1.54%)
Adverse events: Depression, follow-up timepoint is not specified	1 (1.49%)	2 (3.08%)
Health related QoL: WHOQOL-BREF-THAI, to 24 weeks, mean ± SD	3.68 ± 0.77	3.50 ± 0.64
Health related QoL: WHOQOL-BREF-THAI, to 48 weeks, mean ± SD	3.68 ± 0.77	3.65 ± 0.79
Health related QoL: EQ-5D-5L, to 24 weeks, mean ± SD	84.18 ± 23.38	81.36 ± 14.32
Health related QoL: EQ-5D-5L, to 48 weeks, mean ± SD	88.18 ± 11.68	86.18 ± 13.04

Abbreviations:
MD: Mean Difference
SD: Standard Deviation
QoL: Quality of Life
WHOQOL-BREF-THAI: World Health Organization Quality of Life-BREF-THAI

version
EQ-5D-5L: EuroQol 5-Dimension 5-Level

Critical appraisal – Cochrane risk of bias tool 1

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(The study used stratified randomisation with the Fagerström test for nicotine dependence as the stratifying factor. A lottery ticket method was used to randomly assign participants to receive either cytisinicline or placebo.)*
Selection bias	Allocation concealment	Unclear risk of bias *(The study states that "The procedures and randomization results were concealed and blinded to both providers and participants." However, details on how allocation was concealed are not provided.)*
Performance bias	Blinding of participants and personnel	Low risk of bias *(The study is described as double-blind. Participants received either cytisinicline tablets or matching placebo tablets. The manufacturer provided both active and placebo tablets, and both participants and care providers were blinded.)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(The primary outcome of continuous abstinence was biochemically verified using exhaled carbon monoxide levels. As the study was double-blind, outcome assessors were likely blinded to treatment allocation.)*
Attrition bias	Incomplete outcome data	High risk of bias *(There was a high rate of loss to follow-up, with only 29/67 (43.3%) participants in the cytisinicline group and 31/65 (47.7%) in the placebo group remaining at week 48. An intention-to-treat analysis was used, assuming those lost to follow-up had failed to quit smoking. However, the high attrition rate may still introduce bias.)*
Reporting bias	Selective reporting	Low risk of bias *(Low risk of bias. All pre-specified outcomes in the methods section appear to be reported in the results. The study protocol was registered (TCTR20180312001).)*
Other sources of bias	Any other sources of bias	Unclear risk of bias *(The study was funded by the Government Pharmaceutical Organization, which provided the cytisinicline and placebo tablets. While the authors state the manufacturer had no important role beyond providing medications, the potential for bias is unclear. Additionally, the study sample was 95%*

Section	Question	Answer
		male, which may limit generalisability to female smokers.)
Overall risk of bias and directness	Overall risk of bias	High
Overall risk of bias and directness	Risk of bias variation across outcomes	Risk of bias assessments varied by outcome type in this study. The primary outcome of smoking abstinence was biochemically verified using exhaled carbon monoxide, making it relatively objective and less susceptible to bias from the study's open-label design. However, the assessment of adverse events relied on participant self-reporting, which could be influenced by knowledge of treatment allocation. The quality-of-life outcomes (WHOQOL-BREF-THAI and EQ-5D-5L) were subjective patient-reported measures that could also be affected by lack of blinding. The high attrition rate (over 50%) likely impacts all outcomes but may particularly affect the longer-term assessments at 48 weeks compared to earlier timepoints.
Overall risk of bias and directness	Directness	Partially applicable *(This study has several aspects that are applicable to the UK NHS setting, but there are also some important differences to consider: Study population: The study was conducted in Thailand, which may have different cultural attitudes towards smoking and smoking cessation compared to the UK. Additionally, the study population was predominantly male (95%), which does not reflect the gender distribution of smokers in the UK. This limits the generalisability of the findings to female smokers in the UK NHS setting. Comparator: The placebo plus counselling comparator is relevant to the UK NHS setting, as it allows for the assessment of the additional benefit of cytisinicline over counselling alone. Outcomes: The primary outcome of continuous abstinence at 48 weeks, verified by exhaled carbon monoxide, is directly applicable to UK NHS smoking cessation services. The secondary outcomes, including point prevalence abstinence, quality of life measures, and adverse events, are also relevant to UK practice. Setting: The study was conducted in a community pharmacy setting, which is similar to one of the settings where smoking cessation services are provided in the UK NHS. However, the specific pharmacy was affiliated with a university, which may not be representative of all community pharmacies in the UK. In conclusion, while there are several aspects of this*

Section	Question	Answer
		study that are applicable to the UK NHS setting, the differences in population demographics mean that the results should be applied with caution. The partial applicability suggests that while the findings are relevant, they may need to be interpreted in the context of this difference when considering implementation in the UK NHS.)

Rigotti, 2023

Bibliographic Reference	Rigotti, Nancy A; Benowitz, Neal L; Prochaska, Judith; Leischow, Scott; Nides, Mitchell; Blumenstein, Brent; Clarke, Anthony; Cain, Daniel; Jacobs, Cindy; Cytisinicline for Smoking Cessation: A Randomized Clinical Trial.; JAMA; 2023; vol. 330 (no. 2); 152-160

Study details

Trial registration number and/or trial name	NCT04576949, ORCA-2 trial
Study type	Randomised controlled trial (RCT)
Study location	United States
Study setting	17 sites across the US, with the largest number in the Southeast. Trial data was recorded at in-person visits.
Study dates	October 2020 to December 2021
Sources of funding	Achieve Life Sciences
Inclusion criteria	Adults aged 18 years or older Currently smoked 10 or more cigarettes per day Had expired air carbon monoxide (CO) greater than or equal to 10 ppm Ready to set a date to quit smoking
Exclusion criteria	Used any noncigarette tobacco product in the 28 days before randomisation Used electronic cigarettes in the 28 days before randomisation

	Used smoking cessation medication in the 28 days before randomisation Used marijuana in the 28 days before randomisation Uncontrolled hypertension Hepatic or kidney impairment 3-month history of acute myocardial infarction, unstable angina, cerebrovascular incident, or hospitalisation for congestive heart failure Moderate to severe depression symptoms (Hospital Anxiety and Depression Scale score ≥11) Diagnosis of schizophrenia or bipolar disorder Current psychosis Suicidal ideation or suicide risk Positive urinary screen for illicit drugs
Intervention(s)	• Cytisinicline 3 mg taken orally 3 times daily for 12 weeks • Cytisinicline 3 mg taken orally 3 times daily for 6 weeks followed by placebo 3 times daily for 6 weeks Both intervention groups also received brief smoking cessation behavioural support provided by trained counsellors at each visit for up to 15 visits from randomisation through week 12. Shorter sessions were offered at weeks 16, 20, and 24.
Comparator	• Placebo taken orally 3 times daily for 12 weeks. The placebo group also received the same brief smoking cessation behavioural support as the intervention groups.
Outcome measures	Smoking abstinence at 6 months Smoking abstinence at longest follow-up, at least 6 months from study baseline Smoking abstinence at more than 1 month but less than 6 months from study baseline Adverse events
Number of participants	Total number of participants: N = 810 • Cytisinicline for 12 weeks: 270 (33.3%) • Cytisinicline for 6 weeks: 269 (33.2%) • Placebo: 271 (33.5%)

Duration of follow-up	24 weeks
Loss to follow-up	192 participants (23.7%) did not complete the 24-week follow-up
Methods of analysis	Analyses for the primary and secondary outcomes were based on exact analyses of 2 × 2 tables that compared randomised groups, stratified by clinical site. The Hochberg procedure was used to control for primary outcome multiplicity. Sensitivity analyses included assessments of effect modification related to subsets defined by baseline attributes using a logistic regression model. Longitudinal analyses used mixed model for repeated measures methodology with a constrained model when using pre-randomisation data.
Additional comments	The authors noted several limitations of this study: 1. The sample was predominantly White, limiting generalisability to other racial and ethnic groups. 2. The study excluded participants with serious mental illness, suicidal ideation, moderate to severe depression symptoms, recent unstable cardiovascular disease, and current marijuana or illicit drug use, which limits the applicability of findings to these populations. 3. While adverse events were assessed for 24 weeks, the trial was not large or long enough to detect uncommon adverse events. 4. The follow-up period was limited to 12 weeks after treatment ended, which doesn't allow for assessment of longer-term abstinence. 5. The intensity of behavioural support and attention to treatment dosing in this trial likely exceeds what can be provided in typical healthcare settings. The study has several strengths, including its large sample size, multisite design, and use of biochemical verification for smoking abstinence. The inclusion of both 6-week and 12-week cytisinicline treatment arms allows for comparison of different treatment durations. One potential weakness is the lack of an active comparator arm (e.g., varenicline or nicotine replacement therapy), which would have provided valuable information on the relative efficacy of cytisinicline compared to currently approved smoking cessation treatments. The study did not report on health-related quality of life outcomes, which could have provided additional insight into the broader impacts of the treatment. The authors mention that cytisinicline has been used for decades in Central and Eastern Europe, which provides some reassurance about its long-term safety. However, the novel dosing regimen used

	in this study (3 mg three times daily) differs from the traditional regimen, and long-term safety data for this specific dosing schedule may be limited. The study was funded by Achieve Life Sciences, the company developing cytisinicline, which could potentially introduce bias. However, the involvement of independent researchers and the use of a placebo-controlled design help to mitigate this concern. Notes: 1. The study excluded participants with a diagnosis of serious mental illness, suicidal ideation, moderate to severe depression symptoms, recent unstable cardiovascular disease, and current marijuana or illicit drug use. 2. Events were not calculated from percentage data; absolute numbers were provided in the paper. 3. Adverse event data was reported as percentages in the paper; absolute numbers were calculated based on the group sizes. 4. The study did not report health-related quality of life outcomes. The 6-week treatment arm of Rigotti 2023 has been added to the meta-analyses rather than the 12-week treatment arm because 6 weeks of cytisinicline is closer to the BNF recommendation than 12 weeks. Only 1 arm was added to the meta-analyses to prevent double-counting of the control arm.

Study arms

Cytisinicline 3 mg taken orally 3 times daily for 12 weeks (N = 270)

Cytisinicline 3 mg taken orally 3 times daily for 6 weeks (N = 269)

Placebo for 12 weeks (N = 271)

Characteristics

Arm-level characteristics

Characteristic	Cytisinicline 3 mg taken orally 3 times daily for 12 weeks (N = 270)	Cytisinicline 3 mg taken orally 3 times daily for 6 weeks (N = 269)	Placebo for 12 weeks (N = 271)
% Female (number) No of events	n = 141	n = 149; % = 55.4	n = 152; % = 56.1
Mean age (SD) (years)	52.9 (11.5)	52.3 (11.7)	52.2 (11.3)

Characteristic	Cytisinicline 3 mg taken orally 3 times daily for 12 weeks (N = 270)	Cytisinicline 3 mg taken orally 3 times daily for 6 weeks (N = 269)	Placebo for 12 weeks (N = 271)
Mean (SD)			
Heavy smokers (greater than 20 cigarettes per day) No of events	n = 106; % = 39.3	n = 107; % = 39.8	n = 110; % = 40.6
Ethnicity: white No of events	n = 234; % = 86.7	n = 226; % = 84	n = 235; % = 86.7
Level of nicotine dependence (Fagerström score) Mean (SD) Fagerström Test for Nicotine Dependence scores: **0–2**: Very low dependence **3–4**: Low dependence **5**: Moderate dependence **6–7**: High dependence **8–10**: Very high dependence	5.6 (2)	5.6 (2)	5.7 (2.1)

Cytisinicline vs Placebo

Result	Arm 1 (Cytisinicline for 12 weeks, N=270)	Arm 2 (Cytisinicline for 6 weeks, N=269)	Arm 3 (Placebo, N=271)
Smoking abstinence: Biochemically verified continuous abstinence, 6 months	57 (21.1%)	37 (13.8%)	13 (4.8%)

Smoking abstinence: Biochemically verified continuous abstinence, 3 months	88 (32.6%)	68 (25.3%)	19 (7.0%)
Adverse events: Any treatment-emergent adverse event, follow-up timepoint is not specified	184 (68%)	172 (64%)	166 (61.5%)
Adverse events: Any serious adverse event, follow-up timepoint is not specified	8 (3%)	10 (4%)	3 (1.1%)
Adverse events: Insomnia, follow-up timepoint is not specified	26 (10%)	23 (9%)	13 (5%)
Adverse events: Abnormal dreams, follow-up timepoint is not specified	21 (8%)	22 (8%)	8 (3%)
Adverse events: Headache, follow-up timepoint is not specified	21 (8%)	18 (7%)	22 (8%)
Adverse events: Nausea, follow-up timepoint is not specified	15 (6%)	16 (6%)	20 (7%)

Abbreviations:
QoL: Quality of Life

Relevant subgroup analysis

Result	**Arm 1 (Cytisinicline for 12 weeks, N=177)**	**Arm 3 (Placebo, N=177)**
Smoking abstinence: Heavy smokers (Greater than 20 cigarettes per day), 9 to 12 weeks	59 (33%)	15 (9%)

Critical appraisal – Cochrane risk of bias tool 1

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(The study used a "predetermined central computer-generated randomization sequence" to assign participants in a 1:1:1 ratio stratified by study site.)*
Selection bias	Allocation concealment	Low risk of bias *(The randomisation sequence was centrally generated and predetermined, which suggests allocation was likely concealed from investigators enrolling participants.)*
Performance bias	Blinding of participants and personnel	Low risk of bias *(The study is described as "double-blind" and used "identical-appearing tablets containing 3 mg of cytisinicline or placebo". This suggests participants and study personnel were likely adequately blinded.)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(The primary outcomes were biochemically verified continuous smoking abstinence, which is an objective measure unlikely to be influenced by lack of blinding. The study also states it was double-blind, suggesting outcome assessors were likely blinded.)*
Attrition bias	Incomplete outcome data	Low risk of bias *(The study used an intention-to-treat analysis, including all randomised participants in the primary efficacy analyses. Missing data were handled conservatively by classifying participants with missing outcome data as smoking. Attrition rates were similar across groups (16.7% cytisinicline 12 weeks, 26% cytisinicline 6 weeks, 28.4% placebo).)*
Reporting bias	Selective reporting	Low risk of bias *(The reported outcomes match those specified in the trial protocol. All expected outcomes appear to have been reported.)*
Other sources of bias	Any other sources of bias	Low risk of bias *(The study appears to be free of other sources of bias. Baseline characteristics were well-balanced between groups. The study was industry-funded but had involvement from independent academic researchers in design, analysis and reporting.)*
Overall risk of bias and directness	Overall risk of bias	Low
Overall risk of bias and directness	Risk of bias variation across outcomes	Risk of bias varied by outcome type. The primary outcome of smoking abstinence was biochemically verified using expired carbon monoxide at week 12, providing an objective measure less susceptible to

Section	Question	Answer
		bias. While abstinence at week 24 relied on self-reporting and could be influenced by lack of blinding. Adverse events were systematically collected through standardized assessments at study visits, but their self-reported nature means they could be affected by participants' knowledge of treatment assignment. Patient-reported outcomes like cigarettes smoked per day and nicotine withdrawal symptoms were subjective measures more susceptible to bias from the open-label design.
Overall risk of bias and directness	Directness	Partially applicable *(The study has limited direct applicability to the UK NHS setting for several key reasons:* 1. *The cytisinicline dosing regimen used (3 mg three times daily for 6 or 12 weeks) differs substantially from the BNF-recommended tapering schedule over 25 days, limiting applicability to current UK practice. The behavioural support provided was more intensive than typically available in NHS services (15 visits over 12 weeks).* 2. *The study excluded several important patient groups (those with serious mental illness, unstable cardiovascular disease, current drug use) commonly seen in NHS smoking cessation services.* 3. *The US healthcare setting and systems differ from the UK NHS context.* *While the study provides valuable evidence on efficacy and safety, these differences suggest results should be interpreted cautiously when considering NHS implementation.)*

Tavakoli-Ardakani, 2023

Bibliographic Reference	Tavakoli-Ardakani, Maria; Gholamzadeh Sani, Zeinab; Beyraghi, Narges; Najarimoghadam, Shadi; Kheradmand, Ali; Comparison between cytisine and Nicotine Replacement Therapy in smoking cessation among inpatient psychiatric patients.; Journal of addictive diseases; 2023; 1-8

Study details

Trial registration number	Not provided

and/or trial name	
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Hospital (psychiatric inpatient ward). Trial data was recorded by researchers in the hospital during patients' daily hospitalisation.
Study dates	March 2020 to June 2021
Sources of funding	Not provided
Inclusion criteria	Adults aged 18 years or older Daily smokers Motivated to quit smoking Diagnosed with psychiatric disorder
Exclusion criteria	Pregnant or breastfeeding Participating in another smoking cessation program Systolic blood pressure >150 mmHg Diastolic blood pressure >100 mmHg Cardiovascular incidents in past 2 weeks
Intervention(s)	Cytisinicline tablets taken according to manufacturer's instructions over 25 days, starting at 9 mg/day and reducing to 1.5 mg/day. Patients also received medical/psychological care and counselling.
Comparator	Nicotine gum 2 mg used for 8 weeks based on number of cigarettes smoked daily. Maximum 24 gums per day for 6 weeks, then decreasing daily consumption until week 8. Patients also received medical/psychological care and counselling.
Outcome measures	Smoking abstinence at 6 months Smoking abstinence at longest follow-up, at least 6 months from study baseline Smoking abstinence at more than 1 month but less than 6 months from study baseline Adverse events
Number of participants	Total number of participants: N = 47 • Cytisinicline arm: 17 (36.2%) • NRT arm: 30 (63.8%)

Duration of follow-up	6 months
Loss to follow-up	13 patients left the study (reasons not fully specified)
Methods of analysis	Chi-Square test, independent t-test, and Mann-Whitney U test were used for statistical analysis. Within-group and between-group analyses were conducted to compare smoking cessation rates and number of cigarettes smoked.
Additional comments	The authors acknowledged several limitations of the study. The small sample size, particularly in the cytisinicline group, was a significant constraint. The limited number of female participants also restricts the generalisability of the findings. The researchers faced difficulties in procuring cytisinicline, which may have affected the study's implementation. A notable weakness is the lack of blinding in the study design. The open-label nature of the trial introduces potential bias, as both patients and providers were aware of the treatment allocation. This could have influenced patient reporting and provider assessments. The study did not account for differences in use disorder severity among participants, which could have significantly impacted the results. The authors noted that the quantity of cigarettes smoked is not necessarily indicative of the severity of tobacco use disorder, as defined in DSM-V. The follow-up period of six months is relatively short for assessing long-term smoking cessation outcomes. A longer follow-up period would have provided more robust data on the sustained effectiveness of the interventions. The study lacks a placebo control group, which limits the ability to distinguish between treatment effects and potential placebo effects. Additionally, the unequal group sizes (30 in NRT vs 17 in cytisinicline) may have affected the statistical power of the comparisons. The authors did not provide information on the sources of funding for the study, which is an important consideration when evaluating potential conflicts of interest or bias. The reporting of adverse events could have been more comprehensive. While the study mentioned some side effects, a more structured approach to collecting and reporting adverse events would have been beneficial.

Study arms

Cytisinicline: 9 mg/day reducing to 1.5 mg/day over 25 days (N = 17)

Nicotine replacement therapy (NRT): Nicotine gum 2 mg for 8 weeks (N = 30)

Characteristics

Arm-level characteristics

Characteristic	Cytisinicline: 9 mg/day reducing to 1.5 mg/day over 25 days (N = 17)	Nicotine replacement therapy (NRT): Nicotine gum 2 mg for 8 weeks (N = 30)
% Female No of events	n = 2; % = 11.8	n = 4; % = 13.3
Age (years) Mean (SD)	41.17 (10.78)	38.33 (10.46)
Participants with mental health conditions No of events	n = 17; % = 100	n = 30; % = 100

Cytisinicline vs Nicotine replacement therapy (NRT)

Result	Arm 1 (Cytisinicline, N=17)	Arm 2 (NRT, N=30)
Smoking abstinence: At longest follow-up, 6 months	3 (17.64%)	2 (6.66%)
Adverse events: follow-up timepoint not specified	2 (13.33%)	7 (23.33%)
Serious adverse events, follow-up timepoint not specified	0 (0%)	0 (0%)
Nausea, follow-up timepoint not specified	0 (0%)	1 (3.33%)
Insomnia, follow-up timepoint not specified	0 (0%)	3 (10%)

The study focused on inpatient psychiatric patients, so all results can be considered under the subgroup “People with mental health conditions”.

Critical appraisal – Cochrane risk of bias tool 1

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias
Selection bias	Allocation concealment	Unclear risk of bias *(No information is provided about how the allocation sequence was concealed from the researchers enrolling participants. It is unclear*

Section	Question	Answer
		whether appropriate steps were taken to prevent foreknowledge of group assignments.)
Performance bias	Blinding of participants and personnel	High risk of bias *(The study is described as an "open-label randomized trial". This indicates that participants and personnel were not blinded to treatment allocation, which could have influenced their behaviour and responses.)*
Detection bias	Blinding of outcome assessment	High risk of bias *(There is no mention of blinding of outcome assessors. Given the open-label nature of the trial, it is likely that outcome assessors were aware of treatment assignments, which could have influenced their assessments.)*
Attrition bias	Incomplete outcome data	High risk of bias *(There was substantial attrition, with only 7 out of 30 participants remaining in the NRT group and 6 out of 17 in the cytisinicline group at 6 months. The reasons for dropout are not fully explained. This high and imbalanced attrition could have biased the results.)*
Reporting bias	Selective reporting	Unclear risk of bias *(No study protocol is referenced, so it is not possible to compare the reported outcomes with those that were pre-specified. While several outcomes are reported, without a protocol it is unclear if all planned outcomes were included.)*
Other sources of bias	Any other sources of bias	High risk of bias *(There are several concerns that may have introduced bias: The sample size is small, particularly in the cytisinicline group. There is a notable imbalance in group sizes (30 vs 17). The study duration of 25 days for cytisinicline treatment versus 8 weeks for NRT introduces a potential confound. The study was conducted in a single centre, which may limit generalisability.)*
Overall risk of bias and directness	Overall risk of bias	High
Overall risk of bias and directness	Risk of bias variation across outcomes	Risk of bias varied by outcome type. The main outcome of smoking abstinence relied on self-reporting without biochemical verification, making it particularly susceptible to bias given the study's open-label design. Similarly, adverse events were self-reported and could be influenced by participants' knowledge of treatment assignment. The high attrition rate (28% dropout) likely affects all outcomes but may particularly impact longer-term outcomes at 6 months compared to earlier

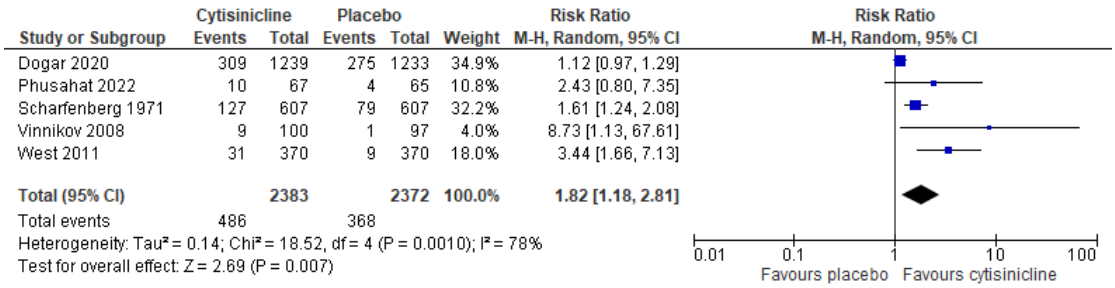
Section	Question	Answer
		timepoints. The inpatient psychiatric setting also means that adherence to medication was directly observed, potentially reducing performance bias for treatment implementation compared to self-administered outcomes.
Overall risk of bias and directness	Directness	Partially applicable *(This study has limited direct applicability to the UK NHS setting for several key reasons:* 1. *While psychiatric inpatients are treated in the NHS, this single-centre Iranian study's small sample size and specific healthcare context may not fully represent UK practice.* 2. *The inpatient psychiatric setting, while relevant, differs from the majority of UK smoking cessation services which occur in community settings.* 3. *The Iranian healthcare system differs from the UK NHS in terms of resources and standard practices for smoking cessation support.* *These differences suggest the results should be interpreted cautiously when considering implications for UK practice.)*

Appendix E Forest plots

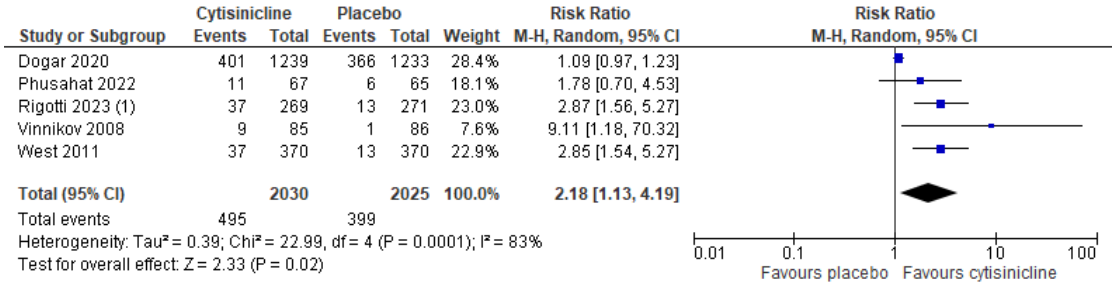
Forest plots are presented only for analyses including two or more studies. This approach is taken because a key function of forest plots is to visually represent the relative weights of different studies in a meta-analysis. In single-study analyses, there is no weighting to display, as the single study accounts for 100% of the effect. Therefore, for outcomes with only one study, results are reported in the GRADE tables.

Cytisinicline vs placebo for smoking cessation

Plot 1: Smoking abstinence for longest follow-up (6+ months)

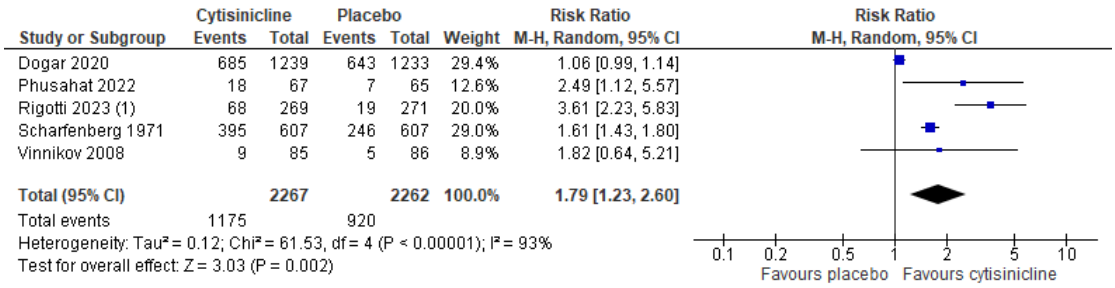


Plot 2: Smoking abstinence at 6 months (or 24 weeks)



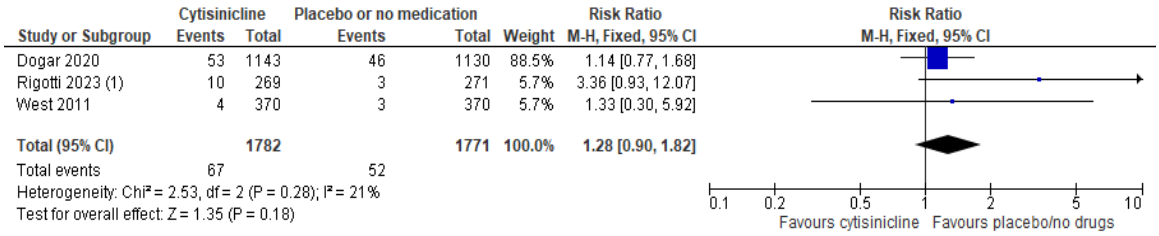
Footnotes
(1) 6-week cytisinicline arm

Plot 3: Smoking abstinence at more than 1 month but less than 6 months



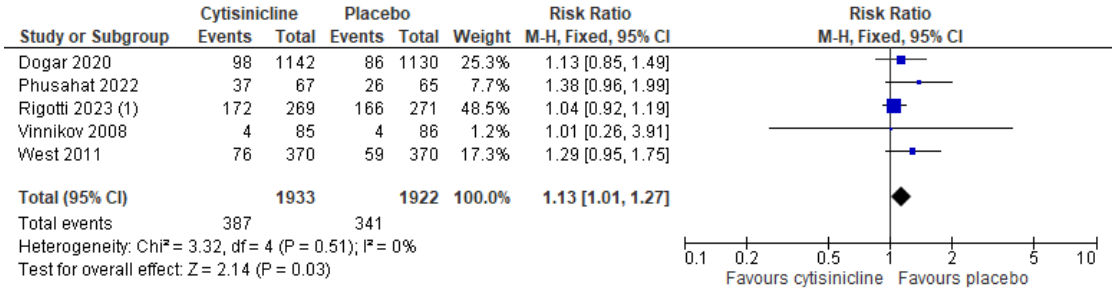
Footnotes
(1) 6-week cytisinicline arm

Plot 4: Serious adverse events



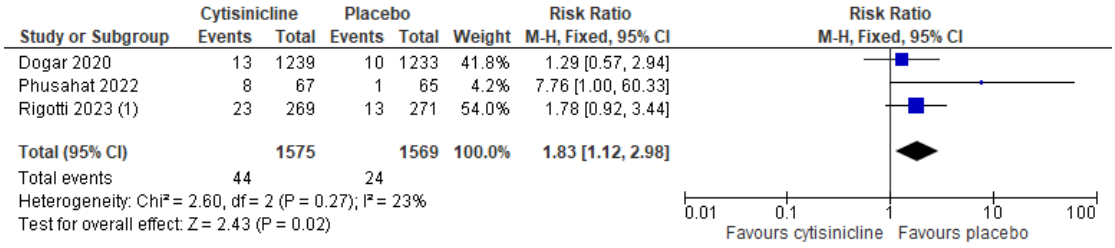
Footnotes
(1) 6-week cytisinicline arm

Plot 5: Adverse events



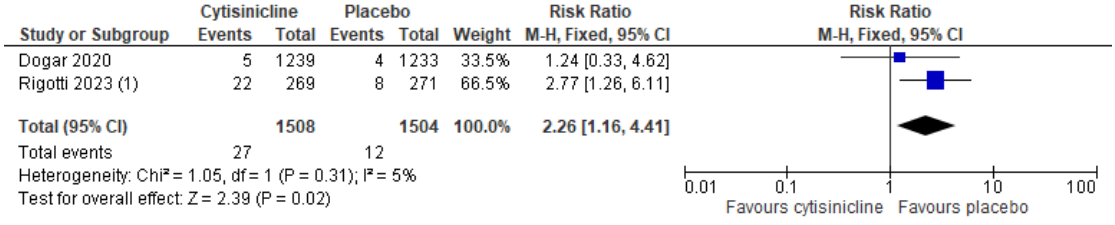
Footnotes
(1) 6-week cytisinicline arm

Plot 6: Adverse events, insomnia



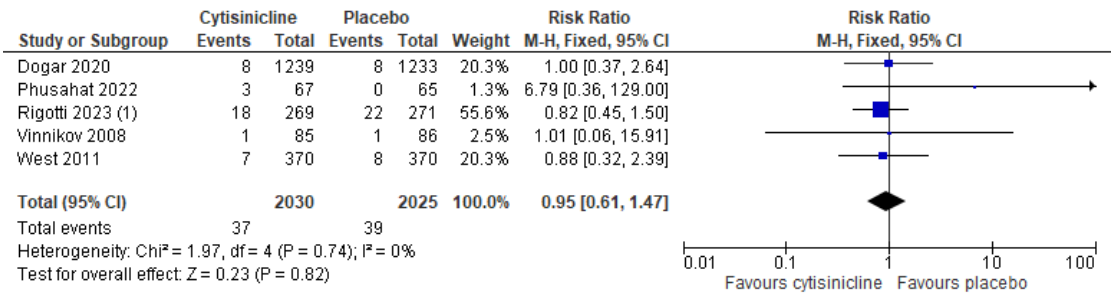
Footnotes
(1) 6-week cytisinicline arm

Plot 7: Adverse events, abnormal dreams



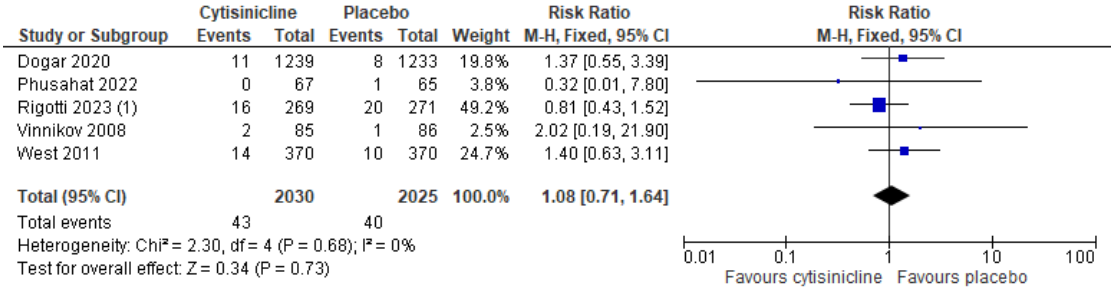
Footnotes
(1) 6-week cytisinicline arm

Plot 8: Adverse events, headache



Footnotes
(1) 6-week cytisinicline arm

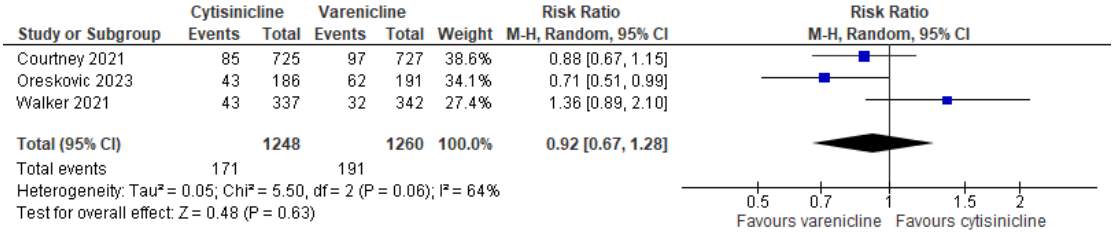
Plot 9: Adverse events, nausea



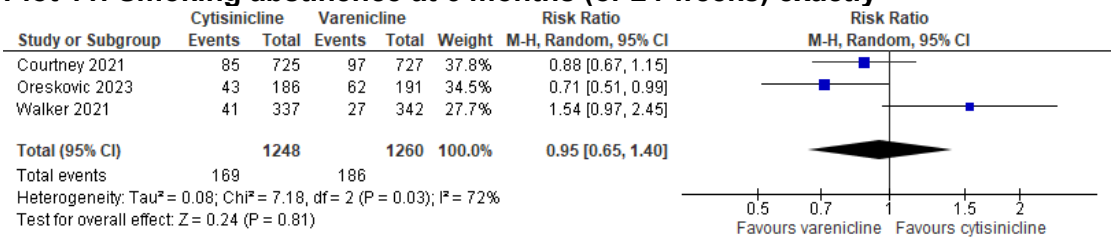
Footnotes
(1) 6-week cytisinicline arm

Cytisinicline vs varenicline for smoking cessation

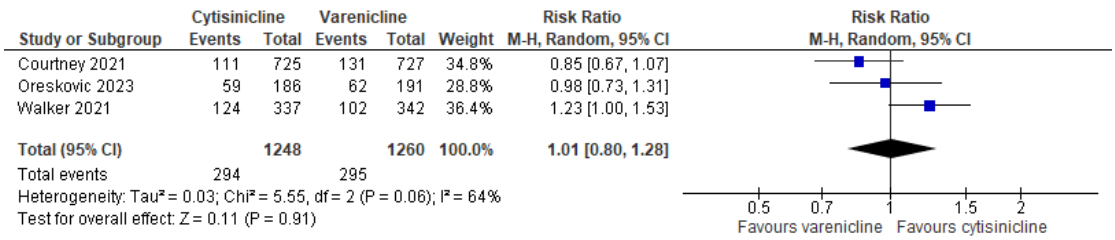
Plot 10: Smoking abstinence for longest follow-up (6+ months)



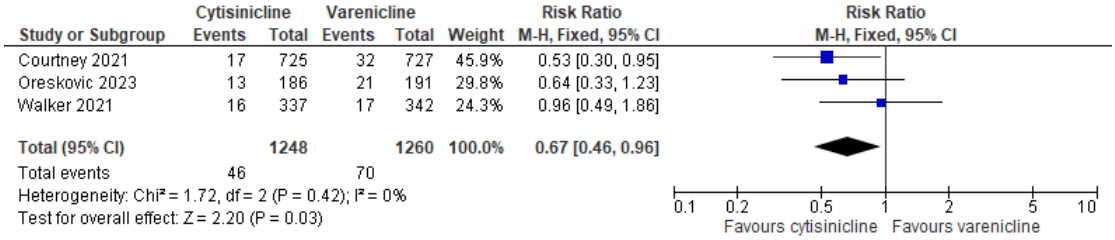
Plot 11: Smoking abstinence at 6 months (or 24 weeks) exactly



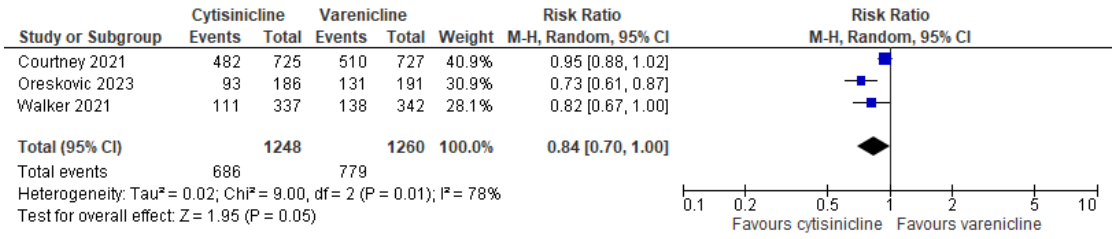
Plot 12: Smoking abstinence at more than 1 month but less than 6 months from study baseline



Plot 13: Serious adverse events

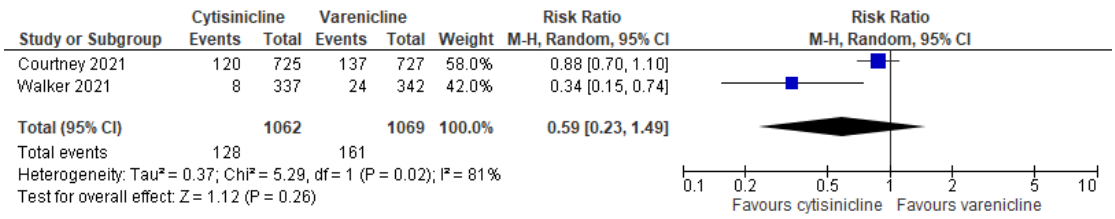


Plot 14: Adverse events

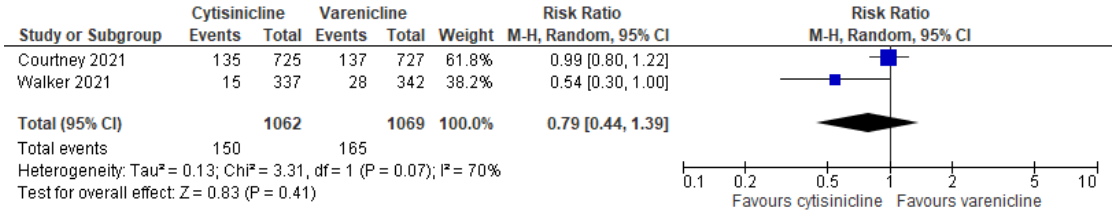


Plot 15: Adverse events: nausea

Plot 16: Adverse events: abnormal dreams

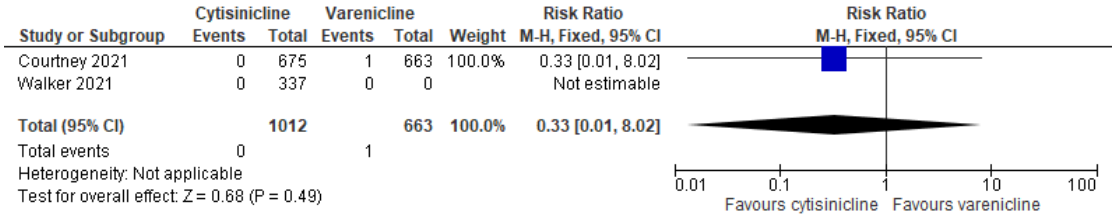


Plot 17: Adverse events: Insomnia



Plot 19: Adverse events: Headache

Plot 20: Adverse events: Suicidal ideation



Appendix F GRADE tables

Cytisinicline vs placebo for smoking cessation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Smoking abstinence for longest follow-up (6+ months)												
5	randomised trials[1,2,3,4,5]	not serious	serious[a]	not serious	not serious	none	486/2383 (20.4%)	368/2372 (15.5%)	**RR 1.82** (1.18 to 2.81)	**127 more per 1,000** (from 28 more to 281 more)	⨁⨁⨁◯ Moderate	CRITICAL
Smoking abstinence at 6 months (or 24 weeks)												
5	randomised trials[1,2,3,5,6]	not serious	very serious[b]	not serious	not serious	none	495/2030 (24.4%)	399/2025 (19.7%)	**RR 2.18** (1.13 to 4.19)	**233 more per 1,000** (from 26 more to 629 more)	⨁⨁◯◯ Low	CRITICAL
Smoking abstinence at 6 months (or 24 weeks): Rigotti 12-week treatment duration cytisinicline arm												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[6]	serious[c]	not serious	serious[d]	not serious	none	57/270 (21.1%)	13/271 (4.8%)	**RR 4.40** (2.47 to 7.85)	**163 more per 1,000** (from 71 more to 329 more)	⨁⨁◯◯ Low	CRITICAL
Smoking abstinence at more than 1 month but less than 6 months from study baseline												
5	randomised trials[2,3,4,5,6,e]	not serious	very serious[b]	serious[d]	not serious	none	1175/2267 (51.8%)	920/2262 (40.7%)	**RR 1.79** (1.23 to 2.60)	**321 more per 1,000** (from 94 more to 651 more)	⨁◯◯◯ Very low	CRITICAL
Smoking abstinence at more than 1 month but less than 6 months from study baseline: Rigotti 12-week cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	not serious	none	88/270 (32.6%)	19/271 (7.0%)	**RR 4.65** (2.92 to 7.41)	**256 more per 1,000** (from 135 more to 449 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Subgroup analysis: Smoking abstinence: Heavy smokers (>20 cigarettes per day) at more than 1 month but less than 6 months from study baseline: Rigotti 12-week cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	not serious	none	59/177 (33.3%)	15/177 (8.5%)	**RR 3.93** (2.32 to 6.66)	**248 more per 1,000** (from 112 more to 480 more)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events												
3	randomised trials[1,3,6,e]	not serious	not serious	not serious	serious[f]	none	67/1782 (3.8%)	52/1771 (2.9%)	**RR 1.28** (0.90 to 1.82)	**8 more per 1,000** (from 3 fewer to 24 more)	⊕⊕⊕◯ Moderate	CRITICAL
Serious adverse events: Rigotti 12-week treatment duration cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	very serious[g]	none	8/270 (3.0%)	3/271 (1.1%)	**RR 2.68** (0.72 to 9.98)	**19 more per 1,000** (from 3 fewer to 99 more)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events: all												
5	randomised trials[1,2,3,5,6,e]	not serious	not serious	serious[d]	serious[f]	none	387/1933 (20.0%)	341/1922 (17.7%)	**RR 1.13** (1.01 to 1.27)	**23 more per 1,000** (from 2 more to 48 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events: Rigotti 12-week treatment duration cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	serious[f]	none	184/270 (68.1%)	166/271 (61.3%)	**RR 1.11** (0.98 to 1.26)	**67 more per 1,000** (from 12 fewer to 159 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events, insomnia												
3	randomised trials[3,5,6,e]	not serious	not serious	serious[d]	serious[f]	none	44/1575 (2.8%)	24/1569 (1.5%)	**RR 1.83** (1.12 to 2.98)	**13 more per 1,000** (from 2 more to 30 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events, insomnia: Rigotti 12-week treatment duration cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	serious[f]	none	26/270 (9.6%)	13/271 (4.8%)	**RR 2.01** (1.05 to 3.82)	**48 more per 1,000** (from 2 more to 135 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events, abnormal dreams												
2	randomised trials[3,6,e]	not serious	not serious	serious[d]	serious[f]	none	27/1508 (1.8%)	12/1504 (0.8%)	**RR 2.26** (1.16 to 4.41)	**10 more per 1,000** (from 1 more to 27 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events, abnormal dreams: Rigotti 12-week treatment duration cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	not serious	none	21/270 (7.8%)	8/271 (3.0%)	**RR 2.63** (1.19 to 5.84)	**48 more per 1,000** (from 6 more to 143 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events, headache												
5	randomised trials[1,2,3,5,6,e]	serious[c]	not serious	serious[d]	very serious[h]	none	37/2030 (1.8%)	39/2025 (1.9%)	**RR 0.95** (0.61 to 1.47)	**1 fewer per 1,000** (from 8 fewer to 9 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events, headache: Rigotti 12-week treatment duration cytisinicline arm												
1	randomised trials[6]	serious[c]	not serious	serious[d]	very serious[h]	none	21/270 (7.8%)	22/271 (8.1%)	**RR 0.96** (0.54 to 1.70)	**3 fewer per 1,000** (from 37 fewer to 57 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events, nausea												
5	randomised trials[1,2,3,5,6,e]	not serious	not serious	serious[d]	very serious[h]	none	43/2030 (2.1%)	40/2025 (2.0%)	**RR 1.08** (0.71 to 1.64)	**2 more per 1,000** (from 6 fewer to 13 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events, nausea: Rigotti 12-week treatment duration cytisinicline arm												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[6]	serious[c]	not serious	serious[d]	very serious[h]	none	15/270 (5.6%)	20/271 (7.4%)	**RR 0.75** (0.39 to 1.44)	**18 fewer per 1,000** (from 45 fewer to 32 more)	⊕◯◯◯ Very low	CRITICAL

Health related QoL: WHOQOL-BREF-THAI, change from baseline to 24 weeks

1	randomised trials[5]	serious[c]	not serious	serious[d]	very serious[i]	none	67	65	-	MD **0.18 higher** (0.06 lower to 0.42 higher)	⊕◯◯◯ Very low	CRITICAL

Health related QoL: WHOQOL-BREF-THAI, change from baseline to 48 weeks

1	randomised trials[5]	serious[c]	not serious	serious[d]	serious[i]	none	67	65	-	MD **0.03 higher** (0.24 lower to 0.3 higher)	⊕◯◯◯ Very low	CRITICAL

Health related QoL: EQ-5D-5L, change from baseline to 24 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[5]	serious[c]	not serious	serious[d]	very serious[k]	none	67	65	-	MD **2.82 higher** (3.83 lower to 9.47 higher)	⨁◯◯◯ Very low	CRITICAL

Health related QoL: EQ-5D-5L, change from baseline to 48 weeks

1	randomised trials[5]	serious[c]	not serious	serious[d]	serious[i]	none	67	65	-	MD **2 higher** (2.27 lower to 6.27 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded one level for inconsistency due to substantial heterogeneity (I^2 = 78%). Downgraded once rather than twice as point estimates from all individual studies consistently suggested benefit from cytisinicline despite variations in effect magnitude.

b. Very serious inconsistency: Substantial unexplained heterogeneity in effect estimates across studies (I^2 > 75%)

c. Serious risk of bias: More than 33.3% of the evidence comes from studies with moderate or high risk of bias.

d. Serious indirectness: Greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies.

e. The 6-week treatment arm of Rigotti 2023 has been added to this meta-analysis rather than the 12-week treatment arm because 6 weeks of cytisinicline is closer to the BNF recommendation than 12 weeks. Only 1 arm was added to prevent double-counting of the control arm.

f. Serious imprecision: The 95% CI crosses the established minimal important difference of RR=1.25; for adverse events and other outcomes without established MIDs, imprecision was assessed based on optimal information size (fewer than 300 events) and/or 95% CI including potential for both meaningful benefit and harm.

g. Very serious imprecision: The 95% CI crosses the established minimal important difference of RR = 1.25; very few events (fewer than 100 total) and very wide confidence intervals that include potential for both substantial benefit and harm.

h. Very serious imprecision: The 95% CI crosses both the established minimal important difference (default MIDs 0.80, 1.25) and very few events (fewer than 100 total) and/or very wide confidence intervals that include potential for both substantial benefit and harm.

i. Serious imprecision: The sample size is small (n=132).

j. Very serious imprecision: The 95% confidence interval (-0.06 to 0.42) crosses zero and the MID threshold at the upper end (0.32). Sample size is small (n=132).

k. Very serious imprecision: The 95% confidence interval (-3.83 to 9.47) crosses zero and the MID threshold at the upper end (7.16). Sample size is small (n=132).

References

1.West 2011.

2.Vinnikov 2008.

3.Dogar 2020.

4.Schaffenberg 1971.

5.Phusahat 2022.

6.Rigotti 2023.

Cytisinicline vs no medication for smoking cessation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	no medication	Relative (95% CI)	Absolute (95% CI)		
Smoking abstinence at 6 months (or 24 weeks)												
1[b]	randomised trials[1]	very serious[a]	not serious	not serious	not serious	none	151/470 (32.1%)	29/399 (7.3%)	**RR 4.42** (3.04 to 6.34)[c]	**249 more per 1,000** (from 148 more to 388 more)	⊕⊕◯◯ Low	CRITICAL
Serious adverse events												
1[b]	randomised trials[1]	very serious[a]	not serious	not serious	very serious[d]	none	39/470 (8.3%)	34/399 (8.5%)	**RR 0.97** (0.63 to 1.51)	**3 fewer per 1,000** (from 32 fewer to 43 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events: all												
1[b]	randomised trials[1]	very serious[a]	not serious	not serious	not serious	none	196/470 (41.7%)	133/399 (33.3%)	**RR 1.25** (1.05 to 1.49)	**83 more per 1,000** (from 17 more to 163 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Very serious risk of bias: Majority of evidence comes from studies with major limitations across several key domains.

b. Serious imprecision: The optimal information size was not met (fewer than 300 events) and/or the 95% CI includes potential for both meaningful benefit and harm.

c. The relative risk (RR) presented in this analysis differs slightly from that reported in Livingstone-Banks 2023 (RR 4.44, 95% CI 3.06 to 6.46). This difference arises from the analytical approach taken with the Pastorino 2022 study.

d. Very serious imprecision: The 95% CI crosses the established minimal important difference for adverse events and other outcomes without established MIDs (default MIDs 0.80, 1.25) and very few events (fewer than 100 total).

References

1.Pastorino 2022.

Cytisinicline vs varenicline for smoking cessation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	varenicline	Relative (95% CI)	Absolute (95% CI)		
Smoking abstinence for longest follow-up (6+ months)												
3	randomised trials[1,2,3]	very serious[a]	serious[b]	serious[c]	serious[d]	none	171/1248 (13.7%)	191/1260 (15.2%)	**RR 0.92** (0.67 to 1.28)	**12 fewer per 1,000** (from 50 fewer to 42 more)	⊕◯◯◯ Very low	CRITICAL
Smoking abstinence at 6 months (or 24 weeks)												
3	randomised trials[1,2,3]	very serious[a]	serious[b]	serious[c]	serious[d]	none	169/1248 (13.5%)	186/1260 (14.8%)	**RR 0.95** (0.65 to 1.40)	**7 fewer per 1,000** (from 52 fewer to 59 more)	⊕◯◯◯ Very low	CRITICAL
Smoking abstinence at more than 1 month but less than 6 months from study baseline												
3	randomised trials[1,2,3]	very serious[a]	serious[b]	serious[c]	serious[d]	none	294/1248 (23.6%)	295/1260 (23.4%)	**RR 1.01** (0.80 to 1.28)	**2 more per 1,000** (from 47 fewer to 66 more)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	varenicline	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events												
3	randomised trials[1,2,3]	very serious[a]	not serious	serious[c]	serious[g]	none	46/1248 (3.7%)	70/1260 (5.6%)	**RR 0.67** (0.46 to 0.96)	**18 fewer per 1,000** (from 30 fewer to 2 fewer)	⊕◯◯◯ Very low	CRITICAL
Adverse events: all												
3	randomised trials[1,2,3]	very serious[a]	very serious[e]	serious[c]	serious[g]	none	686/1248 (55.0%)	779/1260 (61.8%)	**RR 0.84** (0.70 to 1.00)	**99 fewer per 1,000** (from 185 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Adverse events: Nausea												
2	randomised trials[1,2]	very serious[a]	not serious	not serious	not serious	none	104/1012 (10.3%)	252/1005 (25.1%)	**RR 0.41** (0.33 to 0.50)	**148 fewer per 1,000** (from 168 fewer to 125 fewer)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	varenicline	Relative (95% CI)	Absolute (95% CI)		
Adverse events: Abnormal dreams												
2	randomised trials[1,2]	very serious[a]	serious[b]	not serious	very serious[f]	none	128/1012 (12.6%)	161/1069 (15.1%)	**RR 0.59** (0.23 to 1.49)	**62 fewer per 1,000** (from 116 fewer to 74 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events: Insomnia												
2	randomised trials[1,2]	very serious[a]	serious[b]	not serious	very serious[f]	none	150/1012 (14.8%)	165/1005 (16.4%)	**RR 0.79** (0.44 to 1.39)	**34 fewer per 1,000** (from 92 fewer to 64 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events: Headache												
2	randomised trials[1,2]	very serious[a]	not serious	not serious	serious[g]	none	102/1012 (10.1%)	99/1005 (9.9%)	**RR 1.04** (0.80 to 1.35)	**4 more per 1,000** (from 20 fewer to 34 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events: Depression												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	varenicline	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[1]	not serious	not serious	not serious	very serious[f]	none	1/337 (0.3%)	0/342 (0.0%)	**RR 3.04** (0.12 to 74.47)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Adverse events: Suicidal ideation												
2	randomised trials[1,2]	not serious	not serious	not serious	very serious[f]	none	0/1012 (0.0%)	1/1005 (0.1%)	**RR 0.33** (0.01 to 8.02)	**1 fewer per 1,000** (from 1 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL
Smoking abstinence: People with mental health conditions (6+ months)												
1	randomised trials[2]	not serious	not serious	not serious	serious[d]	none	11/108 (10.2%)	17/138 (12.3%)	**RR 0.83** (0.40 to 1.69)	**21 fewer per 1,000** (from 74 fewer to 85 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Very serious risk of bias: Majority of evidence comes from studies with major limitations across several key domains.

b. Serious inconsistency: Moderate heterogeneity in effect estimates across studies that cannot be fully explained (I^2 40-75%)

c. Serious indirectness: Some evidence comes from studies with indirect comparisons or populations, or there's a mix of direct and indirect evidence

d. Serious imprecision: The 95% CI crosses the established minimal important difference (line of no effect)

e. Very serious inconsistency: Substantial unexplained heterogeneity in effect estimates across studies (I^2 > 75%)

f. Very serious imprecision: The 95% CI crosses both the established minimal important difference (default MIDs 0.80, 1.25), very few events (fewer than 100 total) and/or very wide confidence intervals

g. Serious imprecision: The 95% CI crosses one of the established minimal important difference (MID) (0.80, 1.25)

References

1.Walker 2021.

2.Courtney 2021.

3.Oreskovic 2023.

Cytisinicline vs Nicotine Replacement Therapy (NRT) for smoking cessation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	Nicotine Replacement Therapy (NRT)	Relative (95% CI)	Absolute (95% CI)		
Smoking abstinence at 6 months (or 24 weeks)												
1	randomised trials[1]	serious[a]	not serious	not serious	not serious	none	143/655 (21.8%)	100/655 (15.3%)	**RR 1.43** (1.13 to 1.80)	**66 more per 1,000** (from 20 more to 122 more)	⊕⊕⊕◯ Moderate	CRITICAL
Smoking abstinence at more than 1 month but less than 6 months from study baseline												
1	randomised trials[1]	serious[a]	not serious	not serious	not serious	none	202/655 (30.8%)	143/655 (21.8%)	**RR 1.41** (1.17 to 1.70)	**90 more per 1,000** (from 37 more to 153 more)	⊕⊕⊕◯ Moderate	CRITICAL
Serious adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cytisinicline	Nicotine Replacement Therapy (NRT)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials[1]	serious[a]	not serious	not serious	very serious[b]	none	45/655 (6.9%)	39/655 (6.0%)	**RR 1.15** (0.76 to 1.75)	**9 more per 1,000** (from 14 fewer to 45 more)	⊕◯◯◯ Very low	CRITICAL

Adverse events: Nausea

1	randomised trials[1]	serious[a]	not serious	not serious	serious[c]	none	30/655 (4.6%)	2/655 (0.3%)	**RR 15.00** (3.60 to 62.51)	**43 more per 1,000** (from 8 more to 188 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Serious risk of bias: Open-label design of the study (Walker 2014). The lack of blinding for participants, personnel, and outcome assessment may influence the self-reported smoking cessation outcomes. Additionally, there was no biochemical verification of abstinence.

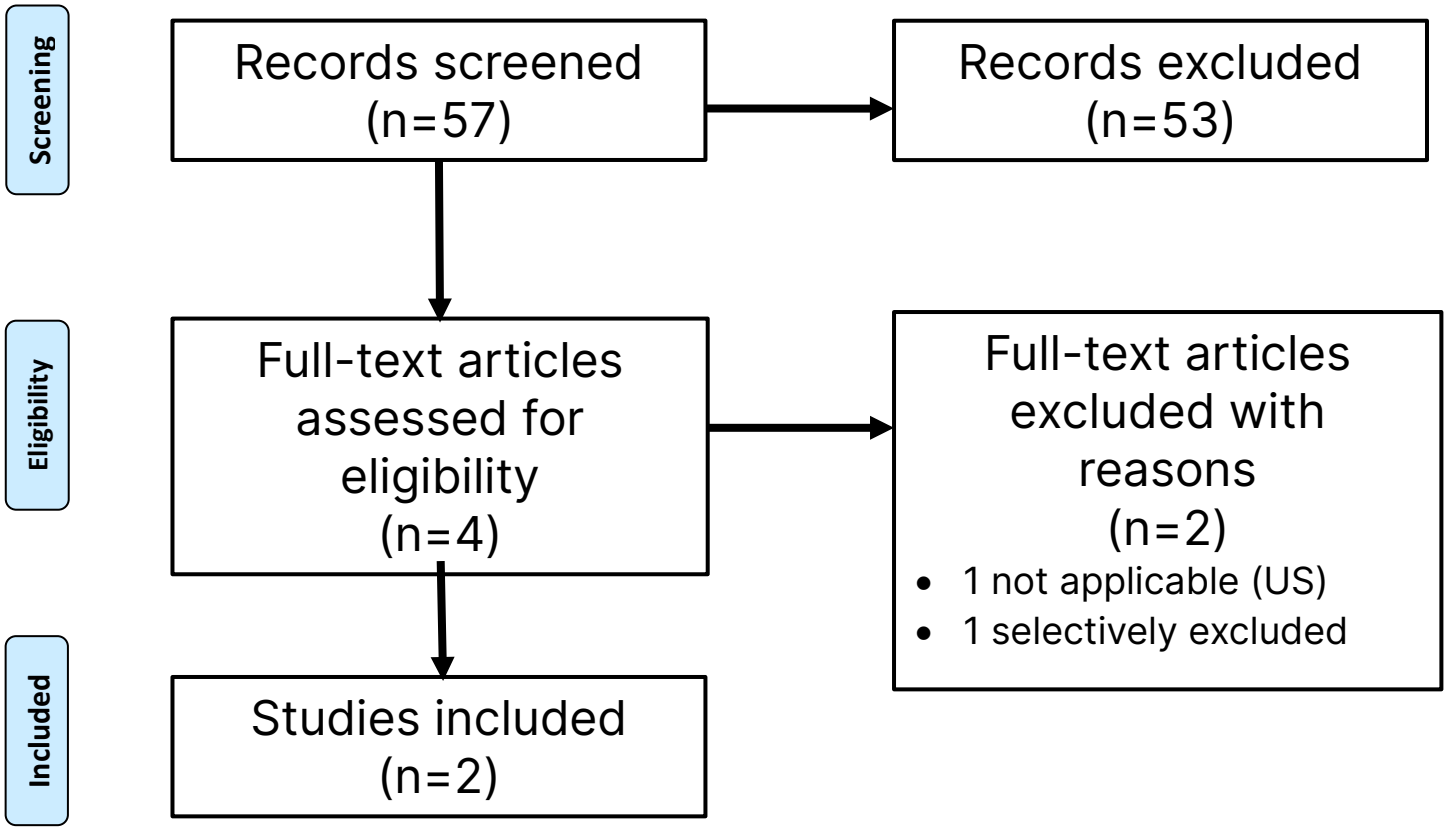
b. Very serious imprecision: The 95% CI crosses both the established minimal important difference (default MIDs 0.80, 1.25), very few events (fewer than 100 total).

c. The confidence interval is wide and there are very few events (fewer than 100 total).

References

1.Walker 2014.

Appendix G Economic evidence study selection



Appendix H Economic evidence tables

Table 6 Leaviss 2014: Cytisine (cytisinicline) vs varenicline

Study	**Leaviss 2014**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Markov model (BENESCO) **Approach to analysis:** A network meta-analysis including	**Population:** People who smoke in England and Wales aged 18 or over who are motivated to quit smoking **Cohort settings:** Start age: NR Male: NR	**Total costs (mean per patient):** Intervention 1: £4,973 Intervention 2: £5,225 Incremental (2−1): -£251 **Currency & cost year:**	**Total QALYs (mean per patient):** Intervention 1: 14.38 Intervention 2: 14.35 Incremental (2-1): 0.03	Cytisine dominates varenicline – it is cheaper and more effective **Analysis of uncertainty:** Uncertainty surrounding model parameters were investigated with a probabilistic sensitivity analysis. At any threshold of willingness to pay, up to £100,000 per QALY gained, cytisine was the most cost-

23 RCTs and 10,610 patients was conducted to estimate the probability of cessation at 1 year between the two interventions. A widely used model, BENESCO, was utilised to calculate long-term cost-effectiveness **Perspective:** UK NHS **Time horizon:** Lifetime	**Intervention 1:** Cytisine 100 1.5-mg tablets **Intervention 2:** Varenicline: starter pack (2 weeks) of tapered treatment plus 20 weeks at full dose	2010/2011 UK sterling pounds **Cost components Incorporated:** Cost of the interventions and of the diseases: COPD, CHD, asthma, stroke and lung cancer		effective intervention in over 90% of the simulations. Several one-way sensitivity analyses were conducted. In all, except ones, cytisine dominated varenicline. The only exception occurred when the relative efficacies of varenicline and cytisine were altered.

Discounting: 3.5%				

Data sources

Health outcomes: Smoking cessation at 1 year from a network meta-analysis (NMA) of 23 studies (10,610 patients) **Quality-of-life weights:** EQ-5D utility values from the Health Survey for England (HSE). Disease=specific utility values were calculated using utility multipliers provided in the Varenicline HTA (Pfizer) **Cost sources:** Published literature was used to estimate the cost of the various diseases in the UK. The cost of varenicline was estimated using the BNF. The cost of cytisine was unknown and assumed to be equal to the cost of Tabex available online (£16.79).

Comments

Source of funding: The National Institute for Health Research Health Technology Assessment programme. **Limitations:** The clinical effectiveness was estimated using an NMA, which found clinical benefits of cytisinicline, contrary to the findings of the clinical review. This latter is based on head-to-head trials which are considered more reliable. The analysis assumes no underlying relapse of quitting rates, meaning that people who could not stop smoke in the first year, were assumed to smoke for the rest of their life. This could overestimate the cost-effectiveness of the most effective intervention, cytisine. The framework of a classic Markov model did not allow to incorporate both an underlying quite rate and transition probabilities that vary with time. Transition probabilities and some parameters inputs were taken from the HTA on varenicline and it is unclear whether this represented the best source. Finally, the cost of cytisine was undetermined as the manufacturers did not provide any information. The authors assumed that the cost of a standard course would be £16,79. This is much lower than the current

estimation of £115 reported in the surveillance report. This is still lower than the current cost of varenicline, estimated to be £230 for a full course, and remains under the £250 threshold identified by the authors as the point beyond which cytisine would no longer be considered cost-effective. **Other:**
Overall applicability:[a] Directly applicable **Overall quality:**[b] With potentially serious limitations

Abbreviations: BENESCO= Benefits of Smoking Cessation on Outcomes; BNF = British National Formulary; COPD = Chronic obstructive pulmonary disease; CHD = coronary heart disease; EQ-5D = EuroQol-5 Dimension; HTA = Health technology assessment; NMA = Network meta-analysis; NR = Not reported; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life years; RCT= randomised controlled trial;

a) Directly applicable / Partially applicable / Not applicable

b) Minor limitations / Potentially serious limitations / Very serious limitations

Table 7 Anraad 2018: Cytisine vs brief physician advice vs current practice vs group-based behavioural therapy vs SMS test-messaging support vs a combination of these

Study	**Anraad 2018**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis	**Population:** People who smoke in England aged 16 or	**Total costs (mean per patient):**	**Total QALYs (mean per patient):**	**Incremental cost-effectiveness analysis table:**

Study design: Markov model (EQUIPTMOD) **Approach to analysis:** EQUIPTMOD, a Markov-based state transition economic model was used to estimate the cost-effectiveness of several smoking cessation services in the UK and the Netherlands. Treatment effectiveness was	over who are motivated to quit smoking **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Current practice: current provision and reach of services **Intervention 2:** Increase reach of brief physician advice **Intervention 3:**	Intervention 1: £11,717 Intervention 2: £11,717 Intervention 3: £11,716 Intervention 4: £11,717 Intervention 5: £11,708 Intervention 6: £11,707 **Currency & cost year:**	Intervention 1: 14.7909 Intervention 2: 14.7910 Intervention 3: 14.7911 Intervention 4: 14.7910 Intervention 5: 14.7923 Intervention 6: 14.7926	1 is dominated by all 4 is dominated by 3, 5 and 6 2 is dominated by 3, 5 and 6 3 is dominated by 5 and 6 5 is dominated by 6 6 dominates all **Analysis of uncertainty:** No probabilistic sensitivity analysis was conducted. A one-way sensitivity analysis was performed to assess the treatment effect of cytisine. The results indicated that cytisine was no longer cost-effective in England when the lower bound of its risk

based on best-evidence review **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** 3.5%	Increase reach of specialist group-based behavioural therapy **Intervention 4:** Increase reach of SMS test-messaging support **Intervention 5:** Pharmacotherapy with cytisine **Intervention 6:** Combined change: intervention 2, 3, 4 and 5 together	2015/2016 UK sterling pounds **Cost components Incorporated:** Cost of the interventions and of the diseases: COPD, CHD, stroke and lung cancer		ratio confidence interval was applied.

Data sources
Health outcomes: The effect sizes, i.e. the ratio of the proportion of smoker exposed to the intervention who are estimated to achieve 12 months of smoking abstinence compared to those who did not receive the intervention, were estimated from a systematic review **Quality-of-life weights:** EQ-5D utility values estimated using UK preferences **Cost sources:** Published literature and systematic review used to estimate the cost of the various diseases in the UK. The cost of varenicline was estimated using the BNF. The cost of cytisine was unknown and assumed to be equal to the cost to £17.63 for a full course
Comments
Source of funding: The EQUIPT project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 602 270(EQUIPT). **Limitations:** No probabilistic analysis was conducted despite the authors acknowledged high uncertainty caused by the wide confidence interval of the treatment effect of cytisine. The cost of cytisine in the UK was unknown as the medicine was not licensed yet. A cost of £17.63 was assumed for a full treatment cost. This is considerably lower than the current estimation of £115 reported in the surveillance report, although this cost is expected to come down eventually as more suppliers enter the market.
Overall applicability:[(c)] Directly applicable **Overall quality:**[(d)] With potentially serious limitations

Abbreviations: BNF = British National Formulary; COPD = Chronic obstructive pulmonary disease; CHD = coronary heart disease; EQ-5D = EuroQol-5 Dimension; EQUIPT = European study on quantifying utility of investment in protection from tobacco; NR = Not reported; QALY= quality-adjusted life years

a) Directly applicable / Partially applicable / Not applicable
b) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I Health economic model

No health economic model was developed for this update.

Appendix J Excluded studies

Effectiveness

Studies excluded from the effectiveness review

Study	Reason for exclusion
Anonymous (2024) Cytisine for smoking cessation. Drug and therapeutics bulletin 62(5): 71-76	Review article but not a systematic review
Bars, M.P. (2023) Cytisinicline for Smoking Cessation in Adult Smokers. US Respiratory and Pulmonary Diseases 8(1): 33-36	Systematic review used as source of primary studies
De Santi, O, Orellana, M, Di Niro, CA et al. (2023) Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: A systematic review and meta-analysis. Addiction (Abingdon, England) 119(4)	Systematic review used as source of primary studies
Foulds, Jonathan; Allen, Sophia I; Yingst, Jessica (2023) Cytisinicline to Speed Smoking Cessation in the United States. JAMA 330(2): 129-130	Review article but not a systematic review
Freibott, C., Biondi, B., Rao, S.R. et al. (2024) Is Abstinence From Alcohol and Smoking Associated With Better Mood Among People With HIV?. Drug and Alcohol	Study does not focus on the population of interest *This study is excluded primarily because it does not focus on the population of interest*

Study	Reason for exclusion
Dependence 260(supplement): 110847	*(adults who smoke tobacco and want to quit), but rather on people with HIV who use alcohol and smoke. The intervention and comparators do not align with the PICO criteria, as the study compares different active treatments without a placebo or no-treatment control. Additionally, the primary outcomes are mood-related (anxiety and depression scores) rather than smoking abstinence at 6 months or longer. While abstinence is measured, it is not the main focus of the study. The presence of significant comorbidities (HIV, alcohol use) in the study population further distances it from the target population specified in the inclusion criteria.*
Gossa, W. (2023) Nicotine Receptor Partial Agonists for Smoking Cessation. American Family Physician 108(3): 235a-235b	Conference abstract
Jacobs, Cindy, Fonseca, Marlene, Rigotti, Nancy A et al. (2023) A Phase I, Double-blind, Randomized, Placebo-controlled, Single Dose-escalation Study to Evaluate the Tolerability, and Safety of Cytisinicline in Adult Smokers. Nicotine & tobacco research : official journal of the Society for Research	No outcomes of interest *This study is excluded from the review because it does not measure any of the primary outcomes specified in our PICO criteria. As a Phase I dose-escalation study, it focuses on evaluating the tolerability, safety, and pharmacokinetics of cytisinicline in single ascending doses. The study does not assess smoking abstinence*

Study	Reason for exclusion
on Nicotine and Tobacco 25(4): 814-820	*at 6 months, at longest follow-up, or at any time point between 1 and 6 months from baseline. Additionally, while adverse events are reported, they are not evaluated in the context of a smoking cessation attempt. The study also does not measure health-related quality of life. The primary endpoints of this study (maximum tolerated dose, pharmacokinetic parameters) do not align with the outcomes of interest for evaluating the efficacy of cytisinicline as a smoking cessation aid.*
King, David (2023) Cytisinicline increased smoking abstinence at 6 and 12 wk. Annals of internal medicine 176(10): jc119	Duplicate reference *This is a report on an already included study: Rigotti 2023*
Li, Jinshuo, Parrott, Steve, Keding, Ada et al. (2022) Cost-utility of cytisine for smoking cessation over and above behavioural support in people with newly diagnosed pulmonary tuberculosis: an economic evaluation of a multicentre randomised controlled trial. BMJ open 12(8): e049644	The economic analysis uses RCTs already included in Livingstone-Banks 2023 *The Li et al. paper used data from two RCTs: EAGLES 2016 (Anthenelli 2016) ASCEND-ASIA (Carson-Chahhoud 2020). Both of these RCTs are included in the reference list: EAGLES 2016 is listed under "EAGLES 2016" with Anthenelli RM as the first author. Carson-Chahhoud 2020 is listed under that name.*
Mdege, Noreen D, Shah, Sarwat, Dogar, Omara et al. (2024)	Systematic review used as source of primary studies

Study	Reason for exclusion
Interventions for tobacco use cessation in people living with HIV. The Cochrane database of systematic reviews 8: cd011120	
Meng, Y, Xiang, S, Qu, L et al. (2024) The efficacy and acceptability of pharmacological monotherapies and e-cigarette on smoking cessation: a systemic review and network meta-analysis. Frontiers in public health 12: 1361186	Systematic review used as source of primary studies
Nides, Mitchell, Rigotti, Nancy A, Benowitz, Neal et al. (2021) A multicenter, double-blind, randomized, placebo-controlled Phase 2b trial of cytisinicline in adult smokers (the ORCA-1 trial). Nicotine & Tobacco Research 23(10): 1656-1663	Study was published before 29 April 2022 *Study was published on 12 April 2021*
Ofori, Sandra, Lu, Clara, Olasupo, Omotola O et al. (2023) Cytisine for smoking cessation: A systematic review and meta-analysis. Drug and alcohol dependence 251: 110936	Systematic review used as source of primary studies
Pastorino, Ugo, Ladisa, Vito, Trussardo, Sara et al. (2022) Cytisine Therapy Improved Smoking Cessation in the Randomized	Study already included in Livingstone-Banks 2023

Study	Reason for exclusion
Screening and Multiple Intervention on Lung Epidemics Lung Cancer Screening Trial. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 17(11): 1276-1286	*This study has already been included in Livingstone-Banks 2023 despite having a publication date of 28 July 2022 (after the 29 April 2022 cut-off).*
Puljevic, C., Stjepanovic, D., Meciar, I. et al. (2024) Systematic review and meta-analyses of cytisine to support tobacco cessation. Addiction (Abingdon, England)	Systematic review used as source of primary studies
Rigotti, Nancy A, Benowitz, Neal L, Prochaska, Judith J et al. (2024) Cytisinicline for Vaping Cessation in Adults Using Nicotine E-Cigarettes: The ORCA-V1 Randomized Clinical Trial. JAMA internal medicine 184(8): 922-930	Study does not focus on the population of interest *This study focuses on e-cigarette cessation rather than tobacco smoking cessation. The population and the primary aim of the intervention do not match the PICO criteria, which specifically focus on adults who smoke tobacco and want to stop smoking. This study instead looks at adults who use e-cigarettes and want to stop vaping, which is a different population and goal.*
Rungruanghiranya, Suthat, Tulatamakit, Sirapat, Chittawatanarat, Kaweesak et al. (2024) Efficacy and safety of cytisine versus nortriptyline for smoking	Comparator in study does not match that specified in protocol

Study	Reason for exclusion
cessation: A multicentre, randomized, double-blinded and placebo-controlled trial. Respirology (Carlton, Vic.)	*Nortriptyline is not a 'placebo' and is not a comparator that is considered in our protocol.*
Tindle, H.A., Cheng, D.M., Gnatienko, N. et al. (2023) EFFECT OF NICOTINE RECEPTOR AGONISTS ON INFLAMMATION AND RISK OF CHD AND DEATH IN HIV. Topics in Antiviral Medicine 31(2): 261	Conference abstract
Tindle, Hilary A, Freiberg, Matthew S, Cheng, Debbie M et al. (2022) Effectiveness of Varenicline and Cytisine for Alcohol Use Reduction Among People With HIV and Substance Use: A Randomized Clinical Trial. JAMA network open 5(8): e2225129	There are two key reasons for exclusion: 1) Primary Focus: The primary outcome of this study is alcohol consumption (number of heavy drinking days), not smoking cessation. While smoking abstinence is a secondary outcome, the study's main goal is not aligned with the PICO's focus on smoking cessation. 2) Specialised Population: The study specifically targets individuals with HIV who engage in risky drinking. This specialised population may not be representative of the general adult smoking population that the PICO aims to study.
Xing, X., Shang, X., Deng, X. et al. (2023) Efficacy and safety of pharmacological intervention for smoking cessation in smokers with	Systematic review used as source of primary studies

Study	Reason for exclusion
diseases: A systematic review and network meta-analysis. Journal of Evidence-Based Medicine 16(4): 520-533	

Economic

Study	Reason for exclusion
West et al. 2015	Selectively excluded due to the inclusion of a more applicable cost-utility analysis.
Stapleton et al. 2012	Excluded because not applicable: US perspective