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Nicotine receptor partial agonists for smoking cessation (Review)

Livingstone-Banks J, Fanshawe TR, Thomas KH, Theodoulou A, Hajizadeh A, Hartman L, Lindson N

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Nicotine receptor partial agonists for smoking cessation (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	14
OBJECTIVES	14
METHODS	14
RESULTS	16
Figure 1.	17
Figure 2.	20
Figure 3.	22
DISCUSSION	28
Figure 4.	30
Figure 5.	31
AUTHORS' CONCLUSIONS	32
ACKNOWLEDGEMENTS	33
REFERENCES	34
CHARACTERISTICS OF STUDIES	56
DATA AND ANALYSES	161
Analysis 1.1. Comparison 1: Cytisine vs placebo or no medication, Outcome 1: Abstinence at longest follow-up	162
Analysis 1.2. Comparison 1: Cytisine vs placebo or no medication, Outcome 2: Adverse events	162
Analysis 1.3. Comparison 1: Cytisine vs placebo or no medication, Outcome 3: Serious adverse events	163
Analysis 2.1. Comparison 2: Cytisine: longer vs shorter duration, Outcome 1: Abstinence at longest follow-up	163
Analysis 3.1. Comparison 3: Cytisine vs varenicline, Outcome 1: Abstinence at longest follow-up	164
Analysis 3.2. Comparison 3: Cytisine vs varenicline, Outcome 2: Nausea	164
Analysis 3.3. Comparison 3: Cytisine vs varenicline, Outcome 3: Abnormal dreams	165
Analysis 3.4. Comparison 3: Cytisine vs varenicline, Outcome 4: Insomnia	165
Analysis 3.5. Comparison 3: Cytisine vs varenicline, Outcome 5: Headache	165
Analysis 3.6. Comparison 3: Cytisine vs varenicline, Outcome 6: Depression	166
Analysis 3.7. Comparison 3: Cytisine vs varenicline, Outcome 7: Suicidal ideation	166
Analysis 3.8. Comparison 3: Cytisine vs varenicline, Outcome 8: SAEs	166
Analysis 4.1. Comparison 4: Cytisine vs NRT, Outcome 1: Abstinence at longest follow-up	167
Analysis 4.2. Comparison 4: Cytisine vs NRT, Outcome 2: Nausea	167
Analysis 4.3. Comparison 4: Cytisine vs NRT, Outcome 3: SAEs	167
Analysis 5.1. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 1: Abstinence at longest follow-up	169
Analysis 5.2. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 2: Nausea	171
Analysis 5.3. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 3: Insomnia	172
Analysis 5.4. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 4: Abnormal dreams	173
Analysis 5.5. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 5: Headache	174
Analysis 5.6. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 6: Depression	175
Analysis 5.7. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 7: Suicidal ideation	176
Analysis 5.8. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 8: SAEs	177
Analysis 5.9. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 9: Neuropsychiatric SAEs (not deaths)	178
Analysis 5.10. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 10: Cardiac SAEs, including deaths	179
Analysis 6.1. Comparison 6: Varenicline: variations in usage, Outcome 1: Low-dose varenicline vs placebo	180
Analysis 6.2. Comparison 6: Varenicline: variations in usage, Outcome 2: Higher-dose varenicline versus lower-dose varenicline	181
Analysis 6.3. Comparison 6: Varenicline: variations in usage, Outcome 3: Longer vs standard duration varenicline	181
Analysis 6.4. Comparison 6: Varenicline: variations in usage, Outcome 4: 6 week vs 1 week preloading	182
Analysis 7.1. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 1: Cardiovascular disease	183

Analysis 7.2. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 2: COPD	183
Analysis 7.3. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 3: Asthma	183
Analysis 7.4. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 4: Schizophrenia/ bipolar/psychiatric disorder	184
Analysis 7.5. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 5: Depression	184
Analysis 7.6. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 6: Substance use disorder/ methadone-maintained at 24 weeks	184
Analysis 7.7. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 7: Alcohol- dependence	185
Analysis 7.8. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 8: HIV	185
Analysis 8.1. Comparison 8: Varenicline in specific settings/subgroups, Outcome 1: Hospital inpatients/perioperative patients	186
Analysis 8.2. Comparison 8: Varenicline in specific settings/subgroups, Outcome 2: Smokers with a previous quit attempt on varenicline	186
Analysis 8.3. Comparison 8: Varenicline in specific settings/subgroups, Outcome 3: Light or heavy smokers	186
Analysis 9.1. Comparison 9: Varenicline vs bupropion, Outcome 1: Abstinence at longest follow-up	187
Analysis 9.2. Comparison 9: Varenicline vs bupropion, Outcome 2: Nausea	188
Analysis 9.3. Comparison 9: Varenicline vs bupropion, Outcome 3: Insomnia	188
Analysis 9.4. Comparison 9: Varenicline vs bupropion, Outcome 4: Abnormal dreams	188
Analysis 9.5. Comparison 9: Varenicline vs bupropion, Outcome 5: Headache	189
Analysis 9.6. Comparison 9: Varenicline vs bupropion, Outcome 6: Depression	189
Analysis 9.7. Comparison 9: Varenicline vs bupropion, Outcome 7: Suicidal ideation	189
Analysis 9.8. Comparison 9: Varenicline vs bupropion, Outcome 8: SAEs	190
Analysis 9.9. Comparison 9: Varenicline vs bupropion, Outcome 9: Neuropsychiatric SAEs (not deaths)	190
Analysis 9.10. Comparison 9: Varenicline vs bupropion, Outcome 10: Cardiac SAEs, including deaths	190
Analysis 10.1. Comparison 10: Varenicline vs NRT monotherapy, Outcome 1: Abstinence at longest follow-up	191
Analysis 10.2. Comparison 10: Varenicline vs NRT monotherapy, Outcome 2: Nausea	192
Analysis 10.3. Comparison 10: Varenicline vs NRT monotherapy, Outcome 3: Insomnia	192
Analysis 10.4. Comparison 10: Varenicline vs NRT monotherapy, Outcome 4: Abnormal dreams	192
Analysis 10.5. Comparison 10: Varenicline vs NRT monotherapy, Outcome 5: Headache	193
Analysis 10.6. Comparison 10: Varenicline vs NRT monotherapy, Outcome 6: Depression	193
Analysis 10.7. Comparison 10: Varenicline vs NRT monotherapy, Outcome 7: Suicidal ideation	193
Analysis 10.8. Comparison 10: Varenicline vs NRT monotherapy, Outcome 8: SAEs	194
Analysis 10.9. Comparison 10: Varenicline vs NRT monotherapy, Outcome 9: Neuropsychiatric SAEs (not deaths)	194
Analysis 10.10. Comparison 10: Varenicline vs NRT monotherapy, Outcome 10: Cardiac SAEs, including deaths	194
Analysis 11.1. Comparison 11: Varenicline vs combination NRT, Outcome 1: Abstinence at longest follow-up	195
Analysis 11.2. Comparison 11: Varenicline vs combination NRT, Outcome 2: Nausea	195
Analysis 11.3. Comparison 11: Varenicline vs combination NRT, Outcome 3: Insomnia	196
Analysis 11.4. Comparison 11: Varenicline vs combination NRT, Outcome 4: Abnormal dreams	196
Analysis 11.5. Comparison 11: Varenicline vs combination NRT, Outcome 5: Headache	196
Analysis 11.6. Comparison 11: Varenicline vs combination NRT, Outcome 6: Depression	197
Analysis 11.7. Comparison 11: Varenicline vs combination NRT, Outcome 7: Suicidal ideation	197
Analysis 11.8. Comparison 11: Varenicline vs combination NRT, Outcome 8: SAEs	197
Analysis 11.9. Comparison 11: Varenicline vs combination NRT, Outcome 9: Neuropsychiatric SAEs (not deaths)	198
Analysis 11.10. Comparison 11: Varenicline vs combination NRT, Outcome 10: Cardiac SAEs, including deaths	198
Analysis 12.1. Comparison 12: Varenicline vs e-cigarettes, Outcome 1: Abstinence at longest follow-up	199
Analysis 12.2. Comparison 12: Varenicline vs e-cigarettes, Outcome 2: Nausea	199
Analysis 12.3. Comparison 12: Varenicline vs e-cigarettes, Outcome 3: SAEs	199
Analysis 12.4. Comparison 12: Varenicline vs e-cigarettes, Outcome 4: Neuropsychiatric SAEs (not deaths)	199
Analysis 12.5. Comparison 12: Varenicline vs e-cigarettes, Outcome 5: Cardiac SAEs, including deaths	200
Analysis 13.1. Comparison 13: Dianicline vs placebo, Outcome 1: Abstinence at longest follow-up	200
Analysis 13.2. Comparison 13: Dianicline vs placebo, Outcome 2: Nausea	201
Analysis 13.3. Comparison 13: Dianicline vs placebo, Outcome 3: Headache	201
Analysis 13.4. Comparison 13: Dianicline vs placebo, Outcome 4: Depression	201

Analysis 13.5. Comparison 13: Dianicline vs placebo, Outcome 5: Serious adverse events	201
Analysis 13.6. Comparison 13: Dianicline vs placebo, Outcome 6: Cardiac SAEs, including deaths	202
APPENDICES	202
WHAT'S NEW	204
HISTORY	204
CONTRIBUTIONS OF AUTHORS	205
DECLARATIONS OF INTEREST	205
SOURCES OF SUPPORT	205
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	206
INDEX TERMS	206

[Intervention Review]

Nicotine receptor partial agonists for smoking cessation

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ABSTRACT

Background

Nicotine receptor partial agonists may help people to stop smoking by a combination of maintaining moderate levels of dopamine to counteract withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist). This is an update of a Cochrane Review first published in 2007.

Objectives

To assess the effectiveness of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group's Specialised Register in April 2022 for trials, using relevant terms in the title or abstract, or as keywords. The register is compiled from searches of CENTRAL, MEDLINE, Embase, and PsycINFO.

Selection criteria

We included randomised controlled trials that compared the treatment drug with placebo, another smoking cessation drug, e-cigarettes, or no medication. We excluded trials that did not report a minimum follow-up period of six months from baseline.

Data collection and analysis

We followed standard Cochrane methods. Our main outcome was abstinence from smoking at longest follow-up using the most rigorous definition of abstinence, preferring biochemically validated rates where reported. We pooled risk ratios (RRs), using the Mantel-Haenszel fixed-effect model. We also reported the number of people reporting serious adverse events (SAEs).

Main results

We included 75 trials of 45,049 people; 45 were new for this update. We rated 22 at low risk of bias, 18 at high risk, and 35 at unclear risk.

We found moderate-certainty evidence (limited by heterogeneity) that cytisine helps more people to quit smoking than placebo (RR 1.30, 95% confidence interval (CI) 1.15 to 1.47; $I^2 = 83%$; 4 studies, 4623 participants), and no evidence of a difference in the number reporting SAEs (RR 1.04, 95% CI 0.78 to 1.37; $I^2 = 0%$; 3 studies, 3781 participants; low-certainty evidence). SAE evidence was limited by imprecision. We found no data on neuropsychiatric or cardiac SAEs.

Nicotine receptor partial agonists for smoking cessation (Review)

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We found high-certainty evidence that varenicline helps more people to quit than placebo (RR 2.32, 95% CI 2.15 to 2.51; $I^2 = 60\%$, 41 studies, 17,395 participants), and moderate-certainty evidence that people taking varenicline are more likely to report SAEs than those not taking it (RR 1.23, 95% CI 1.01 to 1.48; $I^2 = 0\%$; 26 studies, 14,356 participants). While point estimates suggested increased risk of cardiac SAEs (RR 1.20, 95% CI 0.79 to 1.84; $I^2 = 0\%$; 18 studies, 7151 participants; low-certainty evidence), and decreased risk of neuropsychiatric SAEs (RR 0.89, 95% CI 0.61 to 1.29; $I^2 = 0\%$; 22 studies, 7846 participants; low-certainty evidence), in both cases evidence was limited by imprecision, and confidence intervals were compatible with both benefit and harm.

Pooled results from studies that randomised people to receive cytisine or varenicline showed that more people in the varenicline arm quit smoking (RR 0.83, 95% CI 0.66 to 1.05; $I^2 = 0\%$; 2 studies, 2131 participants; moderate-certainty evidence) and reported SAEs (RR 0.67, 95% CI 0.44 to 1.03; $I^2 = 45\%$; 2 studies, 2017 participants; low-certainty evidence). However, the evidence was limited by imprecision, and confidence intervals incorporated the potential for benefit from either cytisine or varenicline. We found no data on neuropsychiatric or cardiac SAEs.

We found high-certainty evidence that varenicline helps more people to quit than bupropion (RR 1.36, 95% CI 1.25 to 1.49; $I^2 = 0\%$; 9 studies, 7560 participants), and no clear evidence of difference in rates of SAEs (RR 0.89, 95% CI 0.61 to 1.31; $I^2 = 0\%$; 5 studies, 5317 participants), neuropsychiatric SAEs (RR 1.05, 95% CI 0.16 to 7.04; $I^2 = 10\%$; 2 studies, 866 participants), or cardiac SAEs (RR 3.17, 95% CI 0.33 to 30.18; $I^2 = 0\%$; 2 studies, 866 participants). Evidence of harms was of low certainty, limited by imprecision.

We found high-certainty evidence that varenicline helps more people to quit than a single form of nicotine replacement therapy (NRT) (RR 1.25, 95% CI 1.14 to 1.37; $I^2 = 28\%$; 11 studies, 7572 participants), and low-certainty evidence, limited by imprecision, of fewer reported SAEs (RR 0.70, 95% CI 0.50 to 0.99; $I^2 = 24\%$; 6 studies, 6535 participants). We found no data on neuropsychiatric or cardiac SAEs.

We found no clear evidence of a difference in quit rates between varenicline and dual-form NRT (RR 1.02, 95% CI 0.87 to 1.20; $I^2 = 0\%$; 5 studies, 2344 participants; low-certainty evidence, downgraded because of imprecision). While pooled point estimates suggested increased risk of SAEs (RR 2.15, 95% CI 0.49 to 9.46; $I^2 = 0\%$; 4 studies, 1852 participants) and neuropsychiatric SAEs (RR 4.69, 95% CI 0.23 to 96.50; I^2 not estimable as events only in 1 study; 2 studies, 764 participants), and reduced risk of cardiac SAEs (RR 0.32, 95% CI 0.01 to 7.88; I^2 not estimable as events only in 1 study; 2 studies, 819 participants), in all three cases evidence was of low certainty and confidence intervals were very wide, encompassing both substantial harm and benefit.

Authors' conclusions

Cytisine and varenicline both help more people to quit smoking than placebo or no medication. Varenicline is more effective at helping people to quit smoking than bupropion, or a single form of NRT, and may be as or more effective than dual-form NRT. People taking varenicline are probably more likely to experience SAEs than those not taking it, and while there may be increased risk of cardiac SAEs and decreased risk of neuropsychiatric SAEs, evidence was compatible with both benefit and harm. Cytisine may lead to fewer people reporting SAEs than varenicline. Based on studies that directly compared cytisine and varenicline, there may be a benefit from varenicline for quitting smoking, however further evidence could strengthen this finding or demonstrate a benefit from cytisine.

Future trials should test the effectiveness and safety of cytisine compared with varenicline and other pharmacotherapies, and should also test variations in dose and duration. There is limited benefit to be gained from more trials testing the effect of standard-dose varenicline compared with placebo for smoking cessation. Further trials on varenicline should test variations in dose and duration, and compare varenicline with e-cigarettes for smoking cessation.

PLAIN LANGUAGE SUMMARY

Can medications like varenicline and cytisine (nicotine receptor partial agonists) help people to stop smoking and do they cause unwanted effects?

Key messages

- Varenicline can help people to stop smoking for at least 6 months. Evidence shows it works better than bupropion and using only one type of nicotine replacement therapy (e.g. only patches). Quit rates might be similar to using more than one type of nicotine replacement therapy at the same time (e.g. patches and gum together).
- Cytisine can help people to stop smoking for at least 6 months. It may work as well as varenicline, but future evidence may show that while it helps, it is not quite as helpful as varenicline.
- Future studies should test the effectiveness and safety of cytisine compared with varenicline and other stop-smoking medications, and should also investigate giving cytisine or varenicline at different doses and for different lengths of time.

What are 'nicotine receptor partial agonists'?

Smoking tobacco is extremely bad for people's health. For people who smoke, quitting is the best thing they can do to improve their health. Many people find it difficult to quit smoking. Nicotine receptor partial agonists (NRPAs) are a type of medication used to help people to

[Nicotine receptor partial agonists for smoking cessation \(Review\)](#)

stop smoking. They help to reduce the withdrawal symptoms people experience when they stop smoking, like cravings and unpleasant mood changes. They also reduce the pleasure people usually experience when they smoke. The most widely-available treatment in this drug type is varenicline. Cytisine is another, similar medication. They may cause unwanted effects such as feeling sick (nausea) and other stomach problems, difficulties sleeping, abnormal dreams, and headache. They may also lead to potentially serious unwanted effects, such as suicidal thoughts, heart problems and raised blood pressure.

What did we want to find out?

We wanted to find out if using NRPA can help people to quit smoking, and if they cause unwanted effects. We wanted to know:

- how many people stopped smoking for at least 6 months; and
- how many people had unwanted effects.

What did we do?

We searched for studies that investigated NRPA used to help people quit smoking. People in the studies had to be chosen at random to receive an NRPA, or another NRPA, placebo (medication like the NRPA but with no active ingredients) or no treatment. They had to be adult tobacco smokers who wanted to stop smoking.

What did we find?

We found 75 studies that compared NRPA with:

- placebo or no medicine;
- nicotine replacement therapy, such as patches or gum;
- bupropion (another medicine to help people stop smoking);
- another NRPA;
- e-cigarettes.

The USA hosted the most studies (28 studies). Other studies took place in a range of countries across the world, some in several countries.

Main results

People are more likely to stop smoking for at least six months using varenicline than using placebo (41 studies, 17,395 people), bupropion (9 studies, 7560 people), or just one type of nicotine replacement therapy, like patches alone (11 studies, 7572 people). They may be just as likely to quit as people using two or more kinds of nicotine replacement therapy, like patches and gum together (5 studies, 2344 people).

Cytisine probably helps more people to stop smoking than placebo (4 studies, 4623 people) and based on studies that compared cytisine with varenicline (2 studies, 2131 people), there may be a benefit from varenicline for quitting smoking, however further evidence could strengthen this finding or show a benefit from cytisine.

For every 100 people using varenicline to stop smoking, 21 to 25 might successfully stop, compared with only 18 of 100 people using bupropion, 18 of 100 people using a single form of nicotine-replacement therapy, and 20 of 100 using two or more kinds of nicotine-replacement therapy. For every 100 people using cytisine to stop smoking, 18 to 23 might successfully stop.

The most common unwanted effect of varenicline is nausea, but this is mostly at mild or moderate levels and usually clears over time. People taking varenicline likely have an increased chance of a more serious unwanted effect that could result in going to hospital, however these are still rare (2.7% to 4% of people on varenicline, compared with 2.7% of people without) and may include many that are unrelated to varenicline. People taking cytisine may also have a slightly increased chance of serious unwanted effects compared with people not taking it, but this may be less likely compared with varenicline.

What are the limitations of the evidence?

The evidence for some of our results is very reliable. We're very confident that varenicline helps people to quit smoking better than many alternatives. We're less sure of some other results because fewer or smaller studies provided evidence.

Several results suggest one treatment is better or less harmful than another, but the opposite could still be true.

How up to date is the evidence?

The evidence is up to date to 29 April 2022.

Nicotine receptor partial agonists for smoking cessation (Review)

SUMMARY OF FINDINGS

Summary of findings 1. Varenicline versus placebo or no medication for smoking cessation

Varenicline versus placebo or no medication for smoking cessation

Patient or population: people who smoke tobacco

Setting: smoking cessation clinics, hospitals, universities and other research centres

Intervention: varenicline

Comparison: placebo or no medication

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medication	Corresponding risk with varenicline				
Smoking abstinence at longest follow-up (6+ months) (varenicline vs placebo)	99 per 1000	230 per 1000 (213 to 249)	RR 2.32 (2.15 to 2.51)	17,395 (41 studies)	⊕⊕⊕⊕ ^a High	
SAEs (varenicline vs placebo or no medication)	27 per 1000	33 per 1000 (27 to 40)	RR 1.23 (1.01 to 1.48)	14,356 (26 studies)	⊕⊕⊕⊖ ^b Moderate	
Neuropsychiatric SAEs (varenicline vs placebo or no medication)	11 per 1000	10 per 1000 (7 to 14)	RR 0.89 (0.61 to 1.29)	7846 (22 studies)	⊕⊕⊖⊖ ^c Low	
Cardiac SAEs (varenicline vs placebo or no medication)	11 per 1000	13 per 1000 (8 to 20)	RR 1.20 (0.79 to 1.84)	7151 (18 studies)	⊕⊕⊖⊖ ^c Low	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aModerate heterogeneity detected, however all but three studies showed positive effect of varenicline, so we did not downgrade on this basis.

^bDowngraded one level because of imprecision: CI incorporates no clinical difference as well as clinically significant harm.

^cDowngraded two levels because of imprecision: CI incorporates clinically significant benefit and clinically significant harm.

Summary of findings 2. Cytisine versus placebo or no medication for smoking cessation

Cytisine versus placebo or no medication for smoking cessation

Patient or population: people who smoke tobacco

Setting: smoking cessation clinics, hospitals, universities and other research centres

Intervention: cytisine

Comparison: placebo or no medication

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medication	Corresponding risk with cytisine				
Smoking abstinence at longest follow-up (6+ months) (cytisine vs placebo)	158 per 1000	205 per 1000 (181 to 232)	RR 1.30 (1.15 to 1.47)	4623 (4 studies)	⊕⊕⊕ ^a Moderate	
SAEs (cytisine vs placebo or no medication)	46 per 1000	48 per 1000 (36 to 63)	RR 1.04 (0.78 to 1.37)	3781 (3 studies)	⊕⊕⊕ ^b Low	
Neuropsychiatric SAEs (cytisine vs placebo or no medication)	No data	No data	No data	No data	No data	
Cardiac SAEs (cytisine vs placebo or no medication)	No data	No data	No data	No data	No data	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded one level because of heterogeneity: $I^2 = 83\%$.

^bDowngraded two levels because of imprecision: CI incorporates clinically significant benefit and clinically significant harm.

Summary of findings 3. Cytisine versus varenicline for smoking cessation

Cytisine versus varenicline for smoking cessation

Patient or population: people who smoke tobacco

Setting: community, community pharmacy, participants' homes

Intervention: cytisine

Comparison: varenicline

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with varenicline	Corresponding risk with cytisine				
Smoking abstinence at longest follow-up (6+ months)	132 per 1000	109 per 1000 (87 to 138)	RR 0.83 (0.66 to 1.05)	2131 (2 studies)	⊕⊕⊕ ^a Moderate	
SAEs	49 per 1000	33 per 1000 (21 to 50)	RR 0.67 (0.44 to 1.03)	2017 (2 studies)	⊕⊕○○ ^b Low	

Neuropsychiatric SAEs	No data	No data	No data	No data	No data
Cardiac SAEs	No data	No data	No data	No data	No data

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded one level because of imprecision: CI incorporates no difference as well as clinically significant harm.

^bDowngraded two level because of imprecision: CI incorporates no difference as well as clinically significant benefit, and number of events in analysis very low (n = 82).

Summary of findings 4. Cytisine versus nicotine replacement therapy for smoking cessation

Cytisine versus nicotine replacement therapy for smoking cessation

Patient or population: people who smoke tobacco

Setting: participants' homes (participants were callers to a national Quitline)

Intervention: cytisine

Comparison: nicotine replacement therapy (NRT)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NRT	Corresponding risk with cytisine				

Smoking abstinence at longest follow-up (6+ months)	153 per 1000	218 per 1000 (173 to 275)	RR 1.43 (1.13 to 1.80)	1310 (1 study)	⊕⊕⊕⊕ ^{a,b} Low
SAEs	60 per 1000	68 per 1000 (45 to 104)	RR 1.15 (0.76 to 1.75)	1310 (1 study)	⊕⊕⊕⊕ ^{a,c} Very low
Neuropsychiatric SAEs	No data	No data	No data	No data	No data
Cardiac SAEs	No data	No data	No data	No data	No data

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **NRT:** nicotine replacement therapy; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded one level because of risk of bias: sole study at high risk.

^bDowngraded one level because of imprecision: fewer than 300 events in the analysis.

^cDowngraded two levels because of imprecision: CI incorporates clinically significant benefit and clinically significant harm.

Summary of findings 5. Varenicline versus bupropion for smoking cessation

Varenicline versus bupropion for smoking cessation

Patient or population: people who smoke tobacco

Setting: smoking cessation clinics, hospitals, universities and other research centres

Intervention: varenicline
Comparison: bupropion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with bupropion	Corresponding risk with varenicline				
Smoking abstinence at longest follow-up (6+ months)	177 per 1000	241 per 1000 (222 to 264)	RR 1.36 (1.25 to 1.49)	7560 (9 studies)	⊕⊕⊕⊕ High	
SAEs	20 per 1000	18 per 1000 (12 to 27)	RR 0.89 (0.61 to 1.31)	5317 (5 studies)	⊕⊕⊕⊕ ^a Low	
Neuropsychiatric SAEs	2 per 1000	2 per 1000 (0 to 16)	RR 1.05 (0.16 to 7.04)	866 (2 studies)	⊕⊕⊕⊕ ^a Low	
Cardiac SAEs	0 per 1000	0 per 1000 (0 to 0)	RR 3.17 (0.33 to 30.18)	866 (2 studies)	⊕⊕⊕⊕ ^a Low	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels because of imprecision: CI incorporates clinically significant benefit and clinically significant harm.

Summary of findings 6. Varenicline versus nicotine replacement therapy monotherapy for smoking cessation

Varenicline versus nicotine replacement therapy (NRT) monotherapy for smoking cessation

Patient or population: people who smoke tobacco

Setting: smoking cessation clinics, hospitals, universities and other research centres

Intervention: varenicline

Comparison: nicotine replacement therapy (NRT) monotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NRT monotherapy	Corresponding risk with varenicline				
Smoking abstinence at longest follow-up (6+ months)	180 per 1000	225 per 1000 (205 to 247)	RR 1.25 (1.14 to 1.37)	7572 (11 studies)	⊕⊕⊕⊕ High	
SAEs	9 per 1000	6 per 1000 (5 to 9)	RR 0.70 (0.50 to 0.99)	6535 (6 studies)	⊕⊕⊕⊕ ^a Low	No events in two studies
Neuropsychiatric SAEs	Not estimable (no events in analysis)	Not estimable (no events in analysis)	Not estimable (no events in analysis)	137 (1 study)		
Cardiac SAEs	Not estimable (no events in analysis)	Not estimable (no events in analysis)	Not estimable (no events in analysis)	137 (1 study)		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **NRT:** nicotine replacement therapy; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels because of imprecision: fewer than 150 events in the analysis.

Summary of findings 7. Varenicline versus combination nicotine replacement therapy for smoking cessation

Varenicline versus combination nicotine replacement therapy for smoking cessation

Patient or population: people who smoke tobacco

Setting: smoking cessation clinics, hospitals, universities and other research centres

Intervention: varenicline

Comparison: combination nicotine replacement therapy (NRT)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with combination NRT	Corresponding risk with varenicline				
Smoking abstinence at longest follow-up (6+ months)	195 per 1000	199 per 1000 (170 to 234)	RR 1.02 (0.87 to 1.20)	2344 (5 studies)	⊕⊕⊕⊕ ^a Low	
SAEs	2 per 1000	5 per 1000 (1 to 20)	RR 2.15 (0.49 to 9.46)	1852 (4 studies)	⊕⊕⊕⊕ ^b Low	
Neuropsychiatric SAEs	0 per 1000	0 per 1000 (0 to 0)	RR 4.69 (0.23 to 96.50)	764 (2 studies)	⊕⊕⊕⊕ ^b Low	Only one study reported any events
Cardiac SAEs	2 per 1000	1 per 1000 (0 to 19)	RR 0.32 (0.01 to 7.88)	819 (2 studies)	⊕⊕⊕⊕ ^b Low	Only one study reported any events

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **NRT:** nicotine replacement therapy; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels because of imprecision: confidence intervals include the potential for clinically significant benefit from either intervention.

^bDowngraded two levels because of imprecision: CI incorporates clinically significant benefit and clinically significant harm.

Summary of findings 8. Varenicline versus e-cigarettes for smoking cessation

Varenicline versus e-cigarettes for smoking cessation

Patient or population: people who continued to smoke tobacco following acute coronary syndrome

Setting: hospital

Intervention: varenicline

Comparison: e-cigarettes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with e-cigarettes	Corresponding risk with varenicline				
Smoking abstinence at longest follow-up (6+ months)	148 per 1000	481 per 1000 (179 to 1000)	RR 3.25 (1.21 to 8.71)	54 (1 study)	⊕⊕⊕⊕ ^{a,b} Very low	
SAEs	Not estimable (no events in analysis)	Not estimable (no events in analysis)	Not estimable (no events in analysis)	54 (1 study)		
Neuropsychiatric SAEs	Not estimable	Not estimable	Not estimable	54 (1 study)		

	(no events in analysis)	(no events in analysis)	(no events in analysis)	
Cardiac SAEs	Not estimable (no events in analysis)	Not estimable (no events in analysis)	Not estimable (no events in analysis)	54 (1 study)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: confidence interval; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels because of imprecision: fewer than 150 events in the analysis.

^bDowngraded one level because of risk of bias: sole study at high risk.

BACKGROUND

Description of the condition

Smoking is the main preventable cause of morbidity and premature death worldwide, killing more than 8 million people each year (WHO 2022). It is also a leading cause of health inequalities (ASH 2019). Quitting tobacco smoking significantly reduces risk of tobacco-related disease and death (USDHHS 2020). There are a range of interventions available to help people quit smoking, including different kinds of behavioural and pharmacological support, but even with the most effective interventions, long-term quit rates remain relatively low (Livingstone-Banks 2022a; Rigotti 2022).

Description of the intervention and how it might work

Nicotine receptor partial agonists are a family of drugs that aim to mitigate the addictiveness of tobacco by binding to the $\alpha 4\beta 2$ nicotinic acetylcholine receptor (the receptor that mediates nicotine dependence through released dopamine). When bound to the receptor, a partial agonist prompts the receptor to release dopamine in the way nicotine would, and prevents nicotine from tobacco from binding to the receptor. This reduces nicotine withdrawal symptoms and reduces the rewarding effects of tobacco. There are two main nicotine receptor partial agonists: varenicline and cytisine. A third drug, dicianiline, was developed but unfavourable results led to its withdrawal from further development (Kirchhoff 2009).

Varenicline was developed by Pfizer Inc in 1997 (Coe 2005), and was approved as a prescription-only aid to smoking cessation in 2006 by the American Food and Drug Administration under the trade name Chantix, and by the European Medicines Evaluation Agency under the trade name Champix. In July 2007 it was approved by the National Institute for Health and Clinical Excellence (NICE) for prescribing by the UK National Health Service (ASH 2006; NICE 2007). In 2021, the World Health Organization added varenicline to its Essential Medicines List (WHO 2021). Post-marketing surveillance raised subsequent concerns about possible links between varenicline and major health risks, including suicidal ideation and behaviour, depression, and serious adverse cardiovascular events (FDA 2008), which led to an FDA warning label in 2009. This warning was removed in 2016 after a large trial found no evidence to support the concerns (EAGLES 2016). In 2021, Pfizer announced a recall of varenicline because it exceeded acceptable intake limits of a nitrosamine impurity, called N-nitroso-varenicline. While this is believed to only be temporary, it has led to shortages at the time of writing.

Cytisine was developed in Bulgaria in the 1960s, and is less widely available than varenicline (Foulds 2004; Tutka 2005; Tutka 2006). Its original manufacturer, Sopharma Pharmaceuticals, developed their phytoproduct from the plant *Cytisus Laburnum* L. (Golden Rain). Although cytisine is not licensed and available for use as a smoking cessation aid across most countries outside Eastern Europe, it works by the same mechanism as varenicline and it is available for substantially less cost (Tutka 2019; Gotti 2021). An important difference between the treatments is that standard treatment with cytisine lasts 25 days, compared with 12 weeks for varenicline.

Why it is important to do this review

The scale of the impact on health from tobacco worldwide makes it imperative that we continue to develop our understanding of smoking cessation interventions. While the effectiveness of varenicline for smoking cessation is well established, substantial questions remain about different doses and durations of treatment, and what impact they have on how effective varenicline is at helping people to quit smoking.

Varenicline is a front-line smoking cessation medication in many countries, and its current shortage poses a substantial challenge for tobacco control strategies around the world. Learning more about how effective and safe cytisine is for smoking cessation may inform decisions about whether to licence it in countries that have historically relied on varenicline.

This is an update of a Cochrane Review first published in 2007, and most recently updated in 2016. The previous update found high-certainty evidence of a benefit from varenicline, but only included a limited number of studies testing cytisine for smoking cessation (Cahill 2016). New evidence comparing cytisine with placebo and with varenicline warranted an update of this review.

OBJECTIVES

To assess the effectiveness of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and cluster-RCTs. We did not include quasi-randomised studies, in which the allocation sequence is not truly random, for example, studies where participant date of birth determines participant allocation.

Types of participants

We included studies that recruited adult tobacco smokers. Studies testing nicotine receptor partial agonists to help smokeless tobacco users to quit, or as a relapse prevention intervention among people who are already abstinent from smoking tobacco, are covered in separate Cochrane Reviews (Ebbert 2011a; Livingstone-Banks 2019; Livingstone-Banks 2022b).

Types of interventions

Selective nicotine receptor partial agonists, including cytisine, dicianiline and varenicline (or any other in this class of drug as they reach Phase 3 trial stage), compared with placebo, no medication, or another smoking cessation pharmacotherapy (including nicotine replacement therapy, bupropion, electronic cigarettes, and other nicotine receptor partial agonists). We also included studies that compared different doses and regimes of eligible treatments. Lobeline is covered in an earlier Cochrane Review (Stead 2003). We only included studies that tested the effect of nicotine receptor partial agonists for smoking cessation and not studies focused on harm reduction, which is covered in a separate Cochrane Review (Lindson-Hawley 2016).

Types of outcome measures

Primary outcomes

- Abstinence from smoked tobacco at longest follow-up, at least six months from study baseline. We used the strictest definition of abstinence reported in each study (e.g. prolonged or continuous over point prevalence), and where available, we favoured biochemically validated over self-reported abstinence. We only included studies that measured abstinence from tobacco smoking at six months or longer from baseline.
- Number of participants who experienced the following adverse events: nausea, insomnia, abnormal dreams, headache, depression, and suicidal ideation
- Number of participants who experienced serious adverse events as defined by the authors of included studies
- Number of participants who experienced neuropsychiatric serious adverse events
- Number of participants who experienced cardiac serious adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Tobacco Addiction Group's Specialised Register for studies, using relevant terms (e.g. 'cytisine' or 'Tabex' or 'dianicline' or 'varenicline' or 'nicotine receptor partial agonist') in the title or abstract, or as keywords. This Register has been developed from electronic searching of the Cochrane Central Register of Controlled trials (CENTRAL), MEDLINE, Embase, and PsycINFO, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. The most recent search of the Register was on 29 April 2022, and included reports of trials indexed in CENTRAL, 2022, Issue 3; MEDLINE (via OVID) to update 20220405; Embase (via OVID) to week 202214; PsycINFO (via OVID) to update 20220404, all from inception. See the [Cochrane Tobacco Addiction Group Website](#) for details of the search strategies for these databases. The search strategy for this specific review is listed in [Appendix 1](#). We did not place any limits on our searches (e.g. by language, year of publication, or publication format).

Searching other resources

Our search of the Cochrane Tobacco Addiction Group Specialised Register also covered ongoing and unpublished trials included in the following databases, as these are indexed in CENTRAL.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov, searched via CENTRAL); and
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch, searched via CENTRAL).

We also checked the reference lists of included studies for potentially eligible trials.

Data collection and analysis

Selection of studies

For this update we screened the search results in two stages using the software [Covidence](#). Two review authors (of JL-B, AT,

AH and NL) independently screened the title and abstract of each study found in our searches. We then reviewed the full text of all potentially eligible reports in duplicate. At each stage, we resolved any disagreement through discussion and if needed by referring to a third review author. We noted the reasons for study exclusion at full-text stage for our PRISMA diagram illustrating the flow of studies ([Liberati 2009](#)).

Data extraction and management

Two review authors (of JL-B, AT, AH, LH, TRF, and KT) independently extracted the following information about each included study in duplicate, using a prepiloted data extraction form. We resolved disagreement through discussion and if needed by referring to a third review author.

- Country and setting (e.g. primary care, community, hospital outpatient/inpatient)
- Method of recruiting participants
- Definition of smoker used
- Methods of randomisation and allocation, and blinding of study personnel, participants and assessors
- Demographic characteristics of participants (e.g. average age, sex, average cigarettes per day)
- Intervention and control description (dose, provider, duration, number of visits, etc.)
- Outcomes including definition of abstinence used, and biochemical validation of cessation
- Proportion of participants with follow-up data
- Any adverse events
- Declarations of interest and sources of study funding

Assessment of risk of bias in included studies

We assessed each included study using Cochrane's RoB 1 tool for the following domains of risk ([Higgins 2011](#)).

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and study personnel and blinding/objectivity of outcome assessment (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other potential risks of bias. For this domain, we assessed and reported any forms of bias present in studies that did not fall under one of the above domains. Where no relevant form of other potential bias was found, we left this field blank.

Two review authors (of JL-B, AT, AH, LH, TRF, and KT) independently judged each study as at low, unclear, or high risk of bias for each domain, justifying judgements using information from the study report. We resolved disagreements in judgements through discussion and by referral to a third review author where needed.

Measures of treatment effect

We present estimates of effects for individual studies using risk ratios (RRs), calculated as ((number of events in intervention condition/intervention denominator)/(number of events in control condition/control denominator)), with a 95% confidence interval (CI). An RR greater than one indicates a higher rate of outcome

(either smoking abstinence or adverse events) in the intervention group than in the control group.

Unit of analysis issues

As cluster-randomised trials are eligible for inclusion in this review, there is the potential for unit of analysis issues. Where required, we adjusted for clustering using an intraclass correlation, either from the study in question or from a similar study. Where studies compared more than one eligible intervention arm with a non-intervention control, we either pooled intervention arms together (assuming they did not differ in pharmacotherapy given) or added them separately to the meta-analysis and split the control group data evenly between them, to avoid double-counting any participants in the analysis.

Dealing with missing data

We conducted our analyses on an intention-to-treat basis, including all participants in the study arms to which they were randomised, regardless of whether they received the intervention. We counted participants lost to follow-up as continuing smoking, which is standard in the field (West 2005). Where study reports lacked the information needed for our analyses, we tried to contact study authors to ask for this information. Attempts to contact study authors are recorded in the [Characteristics of included studies](#) tables.

Assessment of heterogeneity

To investigate heterogeneity, we used the I^2 statistic, given by the formula $[(Q - df)/Q] \times 100\%$, where Q is the χ^2 statistic and df is its degrees of freedom (Higgins 2003). This describes the percentage of variability in effect estimates that is due to heterogeneity rather than to sampling error (chance). We interpreted the I^2 result using the following overlapping bands (Deeks 2022):

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Where we found moderate to substantial heterogeneity, we investigated further using subgroup analyses based on study characteristics decided upon through review author consensus. In the event of considerable unexplained statistical heterogeneity (i.e. $I^2 = 75\%$ or over), we evaluated whether it was still appropriate to report a pooled result (Deeks 2022).

Assessment of reporting biases

For the two smoking cessation comparisons with 10 or more studies, we assessed the risk of reporting bias using a funnel plot. Regardless of the number of studies included, we considered the possibility of reporting bias in our discussion.

Data synthesis

We conducted a narrative summary of the included studies and, where more than one study reported an outcome comparing an eligible intervention with placebo, no medication, another eligible intervention, or the same intervention delivered with a different

dose or regime, we conducted meta-analyses to pool data from sufficiently similar studies using a Mantel-Haenszel fixed-effect model to calculate pooled RRs with 95% CIs.

Subgroup analysis and investigation of heterogeneity

Where studies compared an intervention pharmacotherapy with either placebo or no medication and there was substantial heterogeneity, we considered subgrouping analyses based on comparator and using the I^2 statistic to test for difference between subgroups and decide whether to report an overall pooling or by subgroup only.

Sensitivity analysis

We conducted sensitivity analyses testing the effect of removing studies we judged to be at high risk of bias to see if those studies affected the overall result. In analyses where we pooled studies that compared an intervention with either placebo or no medication but did not subgroup, we conducted sensitivity analyses testing removing studies comparing against no medication. In our comparison of varenicline versus placebo we also conducted a further ad hoc sensitivity analysis to explore the high level of heterogeneity, removing studies that used an extended treatment course of 24 or 52 weeks rather than the 12 weeks of the other studies.

Because we were primarily interested in whether there is evidence that varenicline works differently for disease-specific populations and people in specific subgroups and healthcare settings, we conducted sensitivity analyses, treating studies in these populations and settings as subgroups of the main analyses and using the I^2 statistic to test for subgroup differences.

Summary of findings and assessment of the certainty of the evidence

Following standard Cochrane methods, we produced summary of findings tables for smoking abstinence at longest follow-up and all of our serious adverse events outcomes for each comparison of varenicline or cytisine with placebo or another pharmacotherapy (Schünemann 2022). Two review authors (JLB, NL) assessed the certainty of the evidence using the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias (Schünemann 2013).

RESULTS

Description of studies

Results of the search

Our literature searches for this update found 810 studies (from 885 records). After we removed duplicates, 682 studies remained for title and abstract screening. We ruled out 544 studies at this stage, leaving 138 studies for full-text screening. From this, we identified 45 new included studies and 20 new ongoing studies, combined with studies from previous updates of this review, this resulted in a total of 75 included studies of 45,049 people and 28 ongoing studies. See [Figure 1](#) for PRISMA diagram detailing study flow (Liberati 2009). For this update, we contacted authors of four studies and received additional results data.

Figure 1. Study flow diagram of searches for 2022 update

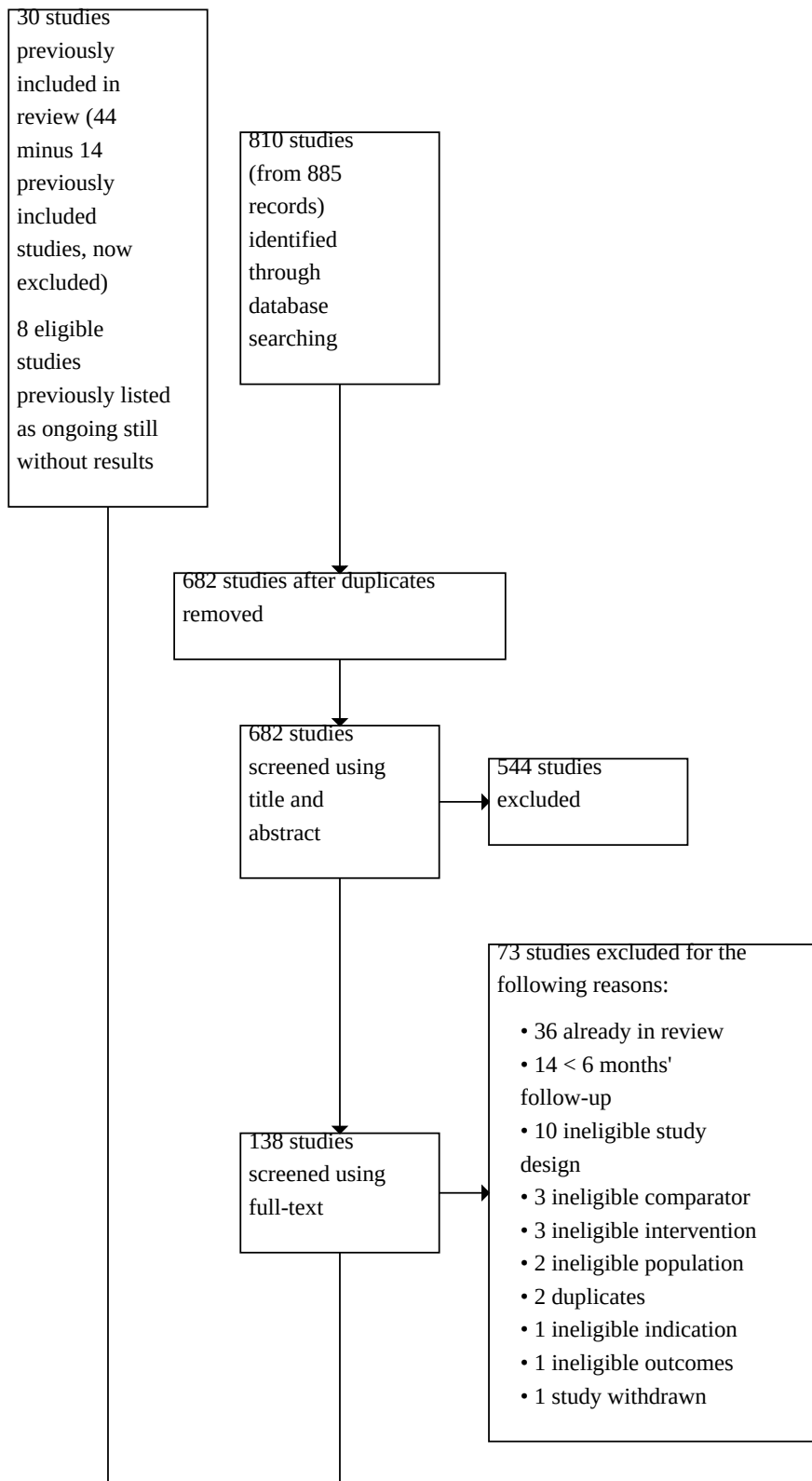
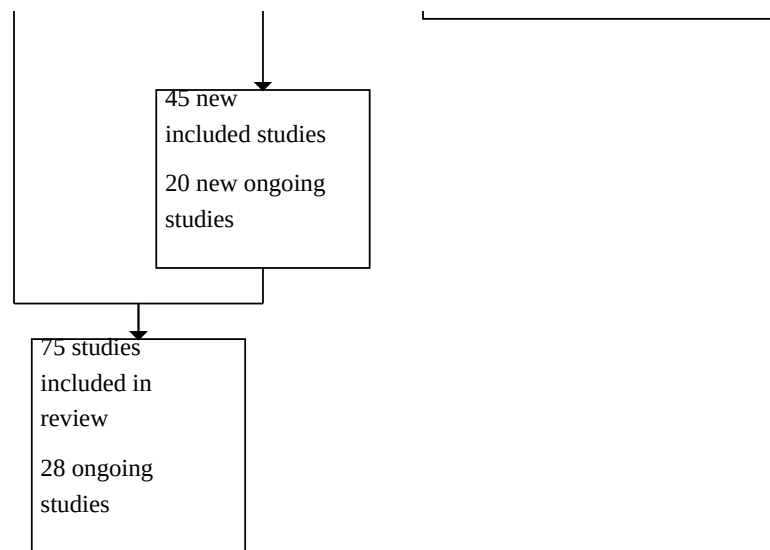


Figure 1. (Continued)



For this update, we excluded 14 previously included studies because they focused on relapse prevention (these studies are covered in a separate review; [Livingstone-Banks 2019](#)), or had previously been included for data on harms but did not fully meet our inclusion criteria.

Included studies

Full details of the included studies are given in the [Characteristics of included studies](#) tables.

Cytisine

Eight studies in just under 9000 people investigated cytisine as a smoking cessation drug. Four studies compared cytisine with placebo, two with varenicline, one with nicotine replacement therapy (NRT), and one with no medication. [Pastorino 2022](#) also compared longer with shorter duration cytisine. Studies tested cytisine at a dose of 9 mg per day for 20 to 25 days, except for [Pastorino 2022](#), which gave cytisine for 40 and 84 days in different arms.

Studies were conducted in Australia, Bangladesh and Pakistan, Italy, East Germany, Kyrgyzstan, New Zealand, and Poland. Two studies took place in smoking cessation clinics, and two in the community. [Walker 2014](#) recruited people who contacted a national smoking quitline. [Vinnikov 2008](#) was set in a Kyrgyz mining company, and [Dogar 2020](#) took place in tuberculosis treatment centres. [Pastorino 2022](#) recruited heavy smokers participating in a lung-screening trial.

Varenicline

Sixty-eight studies of over 37,000 people tested varenicline for smoking cessation. This excludes two studies that compared varenicline with cytisine, which are described above.

Setting

Twenty-eight studies were conducted in the USA, four in Canada, three in China, three in Japan, two in France, two in Greece, two in

India, two in Turkey, one in Australia, one in Iran, one in Denmark, one in Finland, one in Israel, and one in Spain. Fifteen studies took place internationally, in between two and 15 countries. The studies were conducted in smoking cessation clinics, hospitals, universities and other research centres.

Participants

Participants in the majority of trials were adult smokers, willing to make a quit attempt. Several trials were conducted in clinical subgroups, including hospital inpatients ([Carson-Chahhoud 2020](#); [Hong 2015](#); [Le Mao 2020](#); [Steinberg 2011](#); [Windle 2018](#); [Wong 2012](#)), and disease-specific patient groups: cardiovascular disease ([Rigotti 2010](#); [Windle 2018](#)); chronic obstructive pulmonary disease ([Hong 2015](#); [Le Mao 2020](#); [Tashkin 2011](#); [Yang 2016](#)); HIV ([Ashare 2019](#); [Mercie 2018](#)); asthma ([Westergaard 2015](#)); substance use disorder ([Nahvi 2014a](#); [Stein 2013](#)); alcohol dependence ([Hurt 2018](#); [O'Malley 2018](#); [Zawertailo 2020](#)); depression ([Anthenelli 2013](#); [Cinciripini 2018](#)); and bipolar/schizophrenia, schizoaffective disorder ([Chengappa 2014](#); [Williams 2012](#)). [EAGLES 2016](#) enrolled two cohorts of adult smokers with and without histories of psychiatric disorders, including primary affective disorders (70%), anxiety disorders (19%), psychotic disorders (9.5%) and personality disorders (0.6%). [Gonzales 2014](#) recruited people who had previously used varenicline in an unsuccessful quit attempt. [De Dios 2012](#) and [Ebbert 2016](#) tested varenicline in light smokers.

Interventions

Forty-seven trials used the standard 12-week regimen of varenicline, routinely titrating the first week up to the recommended daily dose of 1 mg twice a day. [Nakamura 2007](#), [Nides 2006](#) and [Oncken 2006](#) tested 1 mg per day, and [Niaura 2008](#) allowed participants to regulate their own dosage throughout the treatment phase. [Ebbert 2015](#) and [Stein 2013](#) tested a 24-week regimen, and [Williams 2007](#) tested 52 weeks.

Comparators

Forty-five studies compared varenicline with placebo and five with no medication. Of the 14 studies that compared varenicline with NRT, 12 randomised participants to receive single-form NRT and five to a combination of two or more forms of NRT (3 studies tested varenicline against both NRT monotherapy and combination NRT). Ten studies compared varenicline with bupropion.

Seven studies compared standard varenicline with either a lower dose (4 studies) or a longer duration (3 studies).

Outcomes

All studies measured smoking cessation at least six months after study baseline. Follow-up lengths ranged from six months to two years. Many studies biochemically validated abstinence using either exhaled carbon monoxide, or salivary or urinary cotinine.

Thirty-eight studies measured adverse events, including nausea, insomnia, abnormal dreams, headache, depression, and suicidal ideation. Twenty-eight measured serious adverse events, neuropsychiatric serious adverse events and cardiac serious adverse events.

Dianicline

One trial investigated dianicline. It was set in 22 sites across six European countries (Tonstad 2011). Dianicline was administered as a 40 mg tablet twice a day for seven weeks, with brief counselling at each contact. Final follow-up of the participants was at 26 weeks, with self-reported abstinence verified by expired carbon monoxide and by plasma cotinine samples.

Study funding

Of the trials included in this review, 35 received funds from pharmaceutical companies with interests in the treatment being tested, 13 received free study medications, and four trials without pharmaceutical support had authors who had received funds for other work. Fifteen studies reported no conflicts, and two did not report study funding or author declarations of interests. This is significant because a recent analysis found that authors of opinion pieces on varenicline who reported financial ties to the pharmaceutical industry (as a conflict of interest or funding source) were more likely to minimise the cardiovascular and psychiatric risk of varenicline compared to those without conflicts of interest or industry funding (odds ratio 4.00, 95% CI 1.32 to 12.16 for cardiovascular risk; odds ratio 8.51, 95% CI 3.79 to 19.11 for psychiatric risk; Fabbri 2022).

Excluded studies

We list 95 potentially eligible but ultimately excluded studies, along with reasons for exclusion, in the [Characteristics of excluded](#)

[studies](#) tables. Common reasons for exclusion were following up with participants for less than six months, not randomising participants, testing an eligible intervention for an ineligible purpose (smoking reduction or alcohol dependence), or testing another intervention as an adjunct to an eligible one.

For this update we excluded 14 studies that were included in the previous version of the review. [Evins 2014](#), [Tonstad 2006](#), [Tønnesen 2013](#), and [NCT00828113](#) recruited already abstinent participants and tested varenicline for relapse prevention, a topic covered in a different Cochrane Review ([Livingstone-Banks 2019](#)). We excluded [Hajek 2015](#) because follow-up was under six months. [Brandon 2011](#), [Ebbert 2011b](#), [Faessel 2009](#), [Fagerström 2010](#), [Garza 2011](#), [Hughes 2011](#), [McClure 2013](#), [Meszaros 2013](#) and [Mitchell 2012](#) were previously included for data on harms only but did not meet all of our prespecified inclusion criteria.

We did not find sufficient information to include or exclude two studies. These are listed in [Characteristics of studies awaiting classification](#).

Ongoing studies

We found 28 eligible ongoing studies, some with multiple relevant comparisons. Studies that tested varenicline compared it with placebo (11 studies), no medication (two studies), bupropion (one study), NRT (seven studies), e-cigarettes (one study), and different doses or regimes of varenicline (six studies). Studies that tested cytisine compared it with placebo (two studies), varenicline (two studies), NRT (one study), and e-cigarettes (one study).

Studies were set in various populations and setting, including HIV (three studies), hospital and perioperative patients (three studies), cardiovascular disease (three studies), substance abuse (two studies), mental health (two studies), and single studies in lung cancer, diabetes, chronic obstructive pulmonary disease, adolescents, and e-cigarette users who smoke.

Further details of the ongoing studies are given in the [Characteristics of ongoing studies](#) tables.

Risk of bias in included studies

Overall, we judged 22 studies to be at low risk of bias (low risk of bias across all domains), 18 at high risk of bias (high risk of bias in at least one domain), and the remaining 35 at unclear risk of bias. Our judgements on the risks of bias of all the included studies are summarised in [Figure 2](#) and [Figure 3](#), and reasons for the judgements are detailed in the [Characteristics of included studies](#) tables.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
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	?	+	+	+	+	
Courtney 2021	+	+	+	+	+	
Cox 2022	+	+	+	+	+	
De Dios 2012	?	?	?	+	?	
Dogar 2020	+	+	+	+	+	
EAGLES 2016	+	+	+	+	+	
Ebbert 2015	+	+	+	+	+	
Ebbert 2016	+	+	+	-	?	

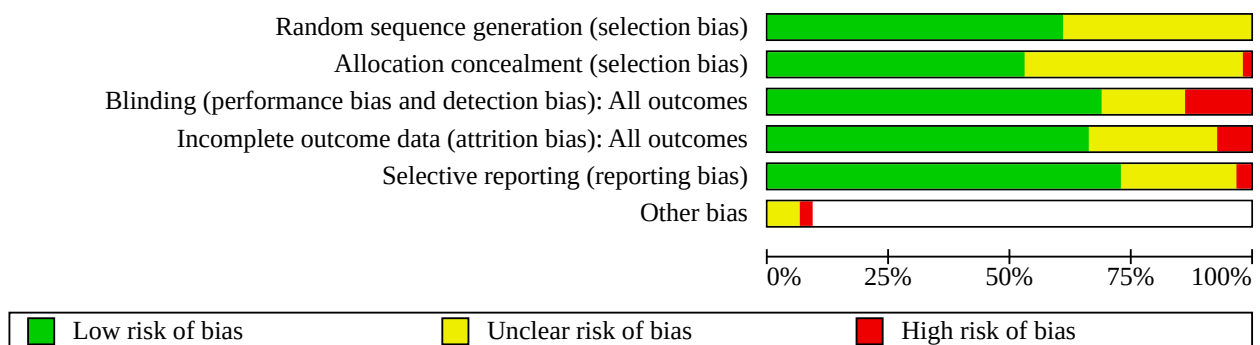
Figure 2. (Continued)

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	?	?	+	+	+	
Pastorino 2022	?	?	-	?	+	
Qin 2021	+	+	+	+	+	
Rennard 2012	+	+	+	+	+	
Rigotti 2010	+	+	+	+	+	
Rohsenow 2017	+	+	+	+	+	
Rose 2013	?	?	?	+	+	?
Scharfenberg 1971	?	?	?	?	?	
Schnoll 2019	?	+	+	+	+	
Stein 2013	?	?	+	+	+	
Steinberg 2011	+	+	+	?	+	
Steinberg 2018	+	?	+	+	+	

Figure 2. (Continued)

Steinberg 2011	+	+	+	?	+	
Steinberg 2018	+	?	+	+	+	
Tashkin 2011	?	?	?	?	?	
Tonstad 2011	+	+	+	+	+	
Tsai 2007	+	+	+	?	?	
Tsukahara 2010	?	?	+	?	+	
Tuisku 2016	+	?	+	+	-	
Tulloch 2016	+	+	+	+	+	
Vinnikov 2008	+	+	+	?	+	
Walker 2014	+	+	-	+	+	?
Walker 2021	+	+	+	-	+	
Wang 2009	?	?	?	?	+	
West 2011	+	+	+	+	+	
Westergaard 2015	?	?	?	?	?	
Williams 2007	?	?	?	+	+	
Williams 2012	?	?	+	?	+	
Windle 2018	+	?	+	+	+	
Wong 2012	+	+	+	+	+	
Yang 2016	?	?	-	?	?	
Zawertailo 2020	+	+	+	+	+	
Zhang 2022	+	+	+	+	?	
Zincir 2013	?	?	-	?	?	-

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

We separately assessed allocation bias resulting from randomisation sequence generation and from allocation concealment. We judged 29 studies to be at unclear risk of

allocation bias as a result of insufficient information about randomisation sequence generation. The remaining studies were judged at low risk, with none deemed to be at high risk.

We judged one study to be at high risk of allocation bias as a result of inadequate concealment of randomisation because that study's participant allocation was unblinded. We judged 34 studies to be at unclear risk because there was insufficient information to make a judgement. We judged the remaining studies to be at low risk.

Blinding

We judged 10 studies to be at high risk of performance or detection bias because they were open-label studies without blinding of participant allocation. We judged 13 studies to be at unclear risk because there was insufficient information to make a judgement. The remaining studies were deemed at low risk.

Incomplete outcome data

We judged five studies to be at high risk of attrition bias, four because of either high levels of attrition or highly differential attrition rates between study arms, and one that did not provide a baseline number of participants, and reported only those followed up at 12 months as a denominator (Benli 2017). We judged 20 studies to be at unclear risk because of insufficient reporting of follow-up rates for us to make a judgement. The remaining studies were deemed at low risk.

Selective reporting

We judged two studies to be at high risk of reporting bias. In Nakamura 2007, continuous abstinence rates for all participants were reported, but demographics, withdrawal and craving measures, and point-prevalence abstinence were reported for the nicotine-dependent subset of participants only. The trial registry entry for Tuisku 2016 planned a 12-month follow-up, which was not reported in their results paper. However, it is possible that this may be reported in a subsequent paper. We judged 18 studies to be at unclear risk because there was insufficient information to make a judgement; typically because no protocol or trial registry entry was available. We judged the remaining studies to be at low risk.

Other potential sources of bias

We judged two studies to be at high risk of bias for other reasons. For Ioakeimidis 2018, we found only an abstract and poster, which reported different quit rates in the e-cigarette arm. Zincir 2013 reported that no participants experienced adverse events, which is unlikely given standard definitions of adverse events.

We judged five studies to be at unclear risk of bias from other sources. In Rose 2013, there was a minor unexplained reporting disparity, with different denominators given for the varenicline arm. Walker 2014 supplied cytisine for free, while NRT users had to pay a nominal charge (NZD 3 for an 8-week course of each NRT item). Le Mao 2020 reported that their small sample size was because of premature interruption of pharmaceutical funding. Cinciripini 2013 began comparing nortriptyline with bupropion, but after three months nortriptyline was changed to varenicline. In Chengappa 2014, four participants in each arm received bupropion for depression. Three out of 15 varenicline quitters and one out of three placebo quitters were on long-term bupropion.

Effects of interventions

See: [Summary of findings 1 Varenicline versus placebo or no medication for smoking cessation](#); [Summary of findings 2 Cytisine versus placebo or no medication for smoking cessation](#); [Summary](#)

[of findings 3 Cytisine versus varenicline for smoking cessation](#); [Summary of findings 4 Cytisine versus nicotine replacement therapy for smoking cessation](#); [Summary of findings 5 Varenicline versus bupropion for smoking cessation](#); [Summary of findings 6 Varenicline versus nicotine replacement therapy monotherapy for smoking cessation](#); [Summary of findings 7 Varenicline versus combination nicotine replacement therapy for smoking cessation](#); [Summary of findings 8 Varenicline versus e-cigarettes for smoking cessation](#)

See summary of findings tables ([Summary of findings 1](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#); [Summary of findings 6](#); [Summary of findings 7](#); [Summary of findings 8](#)).

Cytisine versus placebo or no medication

Smoking cessation

We pooled five studies that compared cytisine to either placebo or no medication, subgrouping by comparator type (placebo versus no medication). We found evidence of a substantial subgroup difference ($I^2 = 97.3\%$; [Analysis 1.1](#)) and so present the subgroup effects separately here. Four studies, including 4623 participants, compared standard dose cytisine (9 mg per day) with placebo. More people successfully quit smoking in the cytisine arm (RR 1.30, 95% CI 1.15 to 1.47; moderate-certainty evidence; [Analysis 1.1.1](#)), but there was a high level of heterogeneity ($I^2 = 83\%$). We present the pooled estimate despite this heterogeneity as all point estimates suggested a benefit from cytisine. [Pastorino 2022](#) compared standard-dose cytisine with no medication. This three-arm trial tested different durations of cytisine (40 days and 84 days), so we split the control arm. More people randomised to receive cytisine successfully quit than in the no-medication arm (RR 4.44, 95% CI 3.06 to 6.46; $I^2 = 0\%$; 869 participants; [Analysis 1.1.2](#)).

We were unable to conduct our planned sensitivity analysis removing studies at high risk of bias because we judged all studies comparing with placebo to be at low or unclear risk and the sole study comparing with no medication to be at high risk.

Adverse events

None of the studies in this comparison measured our prespecified adverse events outcomes, so we pooled all non-serious adverse events. Results from four studies of 4052 participants showed that more people randomised to receive cytisine reported experiencing non-serious adverse events than those randomised to receive placebo or no medication (RR 1.22, 95% CI 1.07 to 1.39; $I^2 = 0\%$; [Analysis 1.2](#)). However, a sensitivity analysis removing one study comparing cytisine with no medication resulted in a confidence interval that crossed the null (RR 1.19, 95% CI 0.97 to 1.46; $I^2 = 0\%$; 3 studies, 3183 participants).

Serious adverse events

Results from three studies of 3781 participants comparing cytisine with placebo or no medication showed no evidence of difference in the number who experienced serious adverse events (RR 1.04, 95% CI 0.78 to 1.37; $I^2 = 0\%$; low-certainty evidence; [Analysis 1.3](#)). A sensitivity analysis removing one study comparing cytisine with no medication did not affect the interpretation of this result (RR 1.15, 95% CI 0.79 to 1.67; $I^2 = 0\%$; 2 studies, 3012 participants). None of

the studies measured neuropsychiatric or cardiac serious adverse events.

Cytisine: variations in usage

Pastorino 2022 compared 40 days and 84 days of cytisine, and found that more people successfully quit on the longer treatment, although confidence intervals did cross the null, indicating the potential for no difference in the effects (RR 1.28, 95% CI 0.98 to 1.67; 480 participants; Analysis 2.1).

Cytisine versus varenicline

Smoking cessation

Two studies including 2131 people compared standard-dose cytisine (9 mg per day) with standard-dose varenicline (2 mg per day). The point estimate showed more people quitting in the varenicline arm, but confidence intervals indicate imprecision and incorporate the potential for no difference or slight benefit from cytisine (RR 0.83, 95% CI 0.66 to 1.05; $I^2 = 0\%$; moderate-certainty evidence; point estimate favours varenicline; Analysis 3.1).

Adverse events

Two studies of 2017 participants found that people randomised to receive cytisine were less likely to report experiencing nausea (RR 0.41, 95% CI 0.33 to 0.50; $I^2 = 0\%$; Analysis 3.2) and abnormal dreams (RR 0.60, 95% CI 0.50 to 0.73; $I^2 = 58\%$; Analysis 3.3) than those in the varenicline arm.

The same two studies of 2017 participants, found no evidence of clear differences between the cytisine and varenicline arms in the number of people experiencing insomnia (RR 0.90, 95% CI 0.73 to 1.10; $I^2 = 68\%$; Analysis 3.4), headaches (RR 1.02, 95% CI 0.79 to 1.33; $I^2 = 0\%$; Analysis 3.5), and suicidal ideation (RR 0.33, 95% CI 0.01 to 8.02; I^2 not estimable as events only in 1 study; Analysis 3.7). However, in all cases confidence intervals indicated imprecision, and the potential for more adverse events when using either treatment.

One study of 679 participants did not find evidence of a clear difference between cytisine and varenicline arms in the number of people experiencing depression (RR 3.04, 95% CI 0.12 to 74.47; Analysis 3.6); however, this result should also be treated with caution because of substantial imprecision.

Serious adverse events

Two studies of 2017 participants compared the number of people in cytisine and varenicline arms reporting experiencing serious adverse events. The point estimate showed that fewer people in the cytisine arm reported serious adverse events (RR 0.67, 95% CI 0.44 to 1.03; $I^2 = 45\%$; low-certainty evidence; point estimate favours cytisine; Analysis 3.8), but confidence intervals did incorporate the potential for no difference. Neither study measured neuropsychiatric or cardiac serious adverse events.

Cytisine versus nicotine replacement therapy

Smoking cessation

Walker 2014 provided participants with cytisine, compared with an eight-week course of NRT, supplied in the form of vouchers that required redemption by participants. Participants in the cytisine arm also received vouchers for NRT to use after their initial 25-day

course of cytisine, and study authors reported that at week one 26 participants were using NRT obtained through the vouchers; only 19 participants used NRT and cytisine concomitantly. This study found that more people in the cytisine arm successfully quit than in the NRT arm (RR 1.43, 95% CI 1.13 to 1.80; 1310 participants; low-certainty evidence; Analysis 4.1).

Adverse events

Nausea was the only one of our adverse event outcomes measured. Walker 2014 reported that, compared with people randomised to receive NRT, those in the cytisine arm were more likely to report experiencing nausea (RR 15.00, 95% CI 3.60 to 62.51; 1310 participants; Analysis 4.2).

Serious adverse events

Walker 2014 did not find evidence of a difference in the rate of serious adverse events between those randomised to receive cytisine or NRT (RR 1.15, 95% CI 0.76 to 1.75; 1310 participants; very low-certainty evidence; Analysis 4.3). Walker 2014 did not measure neuropsychiatric or cardiac serious adverse events.

Varenicline versus placebo or no medication

Smoking cessation

We pooled studies that compared varenicline to either placebo or no medication, subgrouping by comparator type (placebo or no medication). We found evidence of a substantial subgroup difference ($I^2 = 95.8\%$; Analysis 5.1) and so present the subgroup effects separately here. Forty-six studies compared standard-dose varenicline (2 mg per day) with either placebo or no medication. Our meta-analysis found that more people successfully quit smoking when randomised to receive varenicline compared with placebo (RR 2.32, 95% CI 2.15 to 2.51; $I^2 = 60\%$, 41 studies, 17,395 participants; high-certainty evidence; Analysis 5.1.1) or with no medication (RR 1.57, 95% CI 1.37 to 1.80; $I^2 = 95\%$; 5 studies, 1050 participants; Analysis 5.1.2). Despite the substantial heterogeneity in the latter subgroup we present the pooled estimate as all the individual study point estimates suggested a benefit of varenicline.

A sensitivity analysis removing studies at high risk of bias did not reduce the heterogeneity found in the varenicline versus placebo analysis or the interpretation of the effect. However, removing three studies that used an extended treatment course of 24 or 52 weeks rather than the 12 weeks of the other studies, resulted in a minor impact, reducing the I^2 statistic to 53%. We were unable to conduct a sensitivity analysis removing high risk of bias studies for the varenicline versus no medication analysis, as we judged all studies to be at high risk.

King 2022 tested varenicline combined with NRT patch against NRT patch with a varenicline placebo. We did not include this study in our analysis, but it showed no clear evidence of a difference in quit rates as a result of adding varenicline (RR 0.94, 95% CI 0.51 to 1.72; 122 participants). However, confidence intervals incorporated the possibilities of both an increased and a decreased quit rate, as well as no difference.

Adverse events

Studies comparing varenicline with placebo or no medication found that people randomised to receive varenicline were more likely to report experiencing nausea (RR 2.61, 95% CI 2.44 to 2.80;

Nicotine receptor partial agonists for smoking cessation (Review)

$I^2 = 79\%$; 36 studies, 17,080 participants; [Analysis 5.2](#)), insomnia (RR 1.37, 95% CI 1.27 to 1.47; $I^2 = 29\%$; 35 studies, 16,803 participants; [Analysis 5.3](#)), abnormal dreams (RR 1.82, 95% CI 1.67 to 1.97; $I^2 = 70\%$; 32 studies, 16,211 participants; [Analysis 5.4](#)), and headaches (RR 1.11, 95% CI 1.03 to 1.19; $I^2 = 30\%$; 31 studies, 16,326 participants; [Analysis 5.5](#)). Statistical heterogeneity was substantial in our analyses for nausea and abnormal dreams, but we decided to present the pooled estimate because the point estimates of individuals studies were almost entirely in the same direction.

Studies comparing varenicline with placebo or no medication did not find clear evidence of difference in the numbers of participants who reported experiencing depression (RR 1.05, 95% CI 0.91 to 1.20; $I^2 = 0\%$; 32 studies, 15,922 participants; [Analysis 5.6](#)), and found fewer people reporting suicidal ideation in the varenicline arm (RR 0.69, 95% CI 0.44 to 1.08; $I^2 = 0\%$; 22 studies, 12,343 participants; [Analysis 5.7](#)). However, confidence intervals indicated imprecision, and included the potential for harm as well as no difference.

We conducted sensitivity analyses removing studies comparing varenicline with no medication rather than placebo, but this had no substantial impact on heterogeneity or results.

Serious adverse event

Serious adverse events

Twenty-six studies of 14,356 participants found that more people randomised to receive varenicline reported experiencing serious adverse events than those randomised to receive placebo or no medication (RR 1.23, 95% CI 1.01 to 1.48; $I^2 = 0\%$; moderate-certainty evidence; [Analysis 5.8](#)). Absolute rates for serious adverse events were 3.3% and 2.7% in varenicline and control arms respectively. [King 2022](#) tested varenicline combined with NRT patch against NRT patch with a varenicline placebo. We did not include this study in our analysis, but it reported two participants with serious adverse events in the varenicline arm and none in the NRT-alone arm. A sensitivity analysis removing one study comparing varenicline with no medication had no substantial impact on this result.

Neuropsychiatric serious adverse events

The point estimate from pooling 22 studies of 7846 people showed that fewer people reported experiencing neuropsychiatric serious adverse events in the varenicline arm compared with placebo or no medication (RR 0.89, 95% CI 0.61 to 1.29; $I^2 = 0\%$; low-certainty evidence; [Analysis 5.9](#)). However confidence intervals demonstrated imprecision, also encompassing the possibility of more neuropsychiatric serious adverse events in the varenicline arm. A sensitivity analysis removing one study comparing varenicline with no medication had no substantial impact on this result.

Cardiac serious adverse events

The point estimate from pooling 18 studies of 7151 people showed that more people reported experiencing cardiac serious adverse events in the varenicline arm compared with placebo or no medication (RR 1.20, 95% CI 0.79 to 1.84; $I^2 = 0\%$; low-certainty evidence; [Analysis 5.10](#)). However confidence intervals demonstrated imprecision, also encompassing the possibility of no difference or fewer serious adverse events in the varenicline arm. A

sensitivity analysis removing one study comparing varenicline with no medication had no substantial impact on this result.

Varenicline: variations in usage

Low-dose varenicline versus placebo

Four studies tested varenicline at doses lower than standard (under 2 mg per day). Three studies tested 1 mg per day compared with placebo and still found that more people quit in the varenicline arm (RR 1.87, 95% CI 1.35 to 2.60; 906 participants; [Analysis 6.1.1](#)). There was substantial heterogeneity ($I^2 = 71\%$), however in all cases point estimates favoured varenicline.

[Niaura 2008](#) allowed participants to choose their own dose of varenicline, ranging between 0.5 mg and 2.0 mg daily, and found more people in the varenicline arm quit than in the placebo arm (RR 2.92, 95% CI 1.57 to 5.41; 320 participants; [Analysis 6.1.2](#)).

Higher-dose varenicline versus lower-dose varenicline

Four studies compared varenicline at 2 mg per day with 1 mg per day and did not provide clear evidence of a difference in how many people quit (RR 1.12, 95% CI 0.97 to 1.30; 1563 participants; $I^2 = 44\%$; [Analysis 6.2.1](#)); however confidence intervals encompassed potential benefit and a slight disadvantage of the higher dose. [Nides 2006](#) also compared other dosages and also did not find clear evidence of a difference in quit rates among participants randomised to receive 2 mg compared with 0.3 mg per day (RR 1.84 95% CI 0.89 to 3.84; 253 participants; [Analysis 6.2.2](#)) or 1 mg compared with 0.3 mg per day (RR 0.71, 95% CI 0.28 to 1.81; 254 participants; [Analysis 6.2.3](#)). However, in both cases confidence intervals were wide and may indicate benefit and harm of higher doses.

Longer-duration varenicline versus standard-duration varenicline

Three studies tested extended durations of varenicline compared with standard duration of varenicline (12 weeks). We found no clear evidence of a difference as a result of extending varenicline treatment to 24 weeks (RR 0.97, 95% CI 0.77 to 1.23; $I^2 = 17\%$; 2 studies, 1458 participants; [Analysis 6.3.1](#)) or 52 weeks (RR 1.30, 95% CI 0.70 to 2.43; 1 study; 107 participants; [Analysis 6.3.2](#)). However, the confidence intervals indicate imprecision and uncertainty in the point estimates.

Six weeks versus one week of varenicline preloading

[Bohadana 2020](#) tested varenicline with a preloading period of six weeks before quit date against the standard one week of preloading and found that more people in the six-week preloading arm quit than in the one-week arm (RR 5.60, 95% CI 2.24 to 14.02; 242 participants).

Varenicline in specific patient groups

Studies testing varenicline against placebo or no medication in specific patient populations did not find any clear evidence of varenicline working differently in these groups than in the general population.

Analyses found more people successfully quitting in the varenicline arm than in control in studies of people with cardiovascular disease (RR 1.88, 95% CI 1.44 to 2.47; $I^2 = 81\%$; 2 studies, 1006 participants; [Analysis 7.1](#)); schizophrenia, bipolar disorder,

or another psychiatric disorder (RR 2.26, 95% CI 1.78 to 2.86; $I^2 = 0\%$; 3 studies, 2245 participants; [Analysis 7.4](#)); depression (RR 2.17, 95% CI 1.45 to 3.24; $I^2 = 0\%$; 2 studies, 745 participants; [Analysis 7.5](#)); HIV (RR 1.96, 95% CI 1.06 to 3.63; $I^2 = 0\%$; 2 studies, 427 participants; [Analysis 7.8](#)); and chronic obstructive pulmonary disease (RR 1.47, 95% CI 1.28 to 1.69; $I^2 = 94\%$; 4 studies of 860 participants; [Analysis 7.2](#)).

Treating these trials as a subgroup of the main analysis ([Analysis 5.1](#)), testing for subgroup differences showed no evidence that varenicline works differently from in the general population: cardiovascular disease, $P = 0.24$, $I^2 = 26.2\%$; psychiatric disorders, $P = 0.40$, $I^2 = 0\%$; depression, $P = 0.92$, $I^2 = 0\%$; HIV, $P = 0.69$, $I^2 = 0\%$. Testing the COPD result for subgroup difference initially showed evidence that varenicline may work differently, with lower effectiveness, in this population ($P < 0.00001$, $I^2 = 96.8\%$), however this difference disappeared when we performed a sensitivity analysis removing studies comparing varenicline with no medication rather than placebo ($P = 1.00$, $I^2 = 0\%$).

Analyses presented inconclusive evidence for three patient populations: asthma (RR 1.25, 95% CI 0.38 to 4.14; 1 study; 52 participants; [Analysis 7.3](#)), substance use disorder (RR 3.72, 95% CI 0.50 to 27.59; $I^2 = 0\%$; 2 studies, 294 participants; [Analysis 7.6](#)), and alcohol dependence (RR 3.01, 95% CI 0.92 to 9.92; $I^2 = 54\%$; 3 studies, 195 participants; [Analysis 7.7](#)). However, point estimates all favoured varenicline, and wide confidence intervals were likely the result of very low numbers of events. Treating the trials as a subgroup of the main analysis ([Analysis 5.1](#)) and testing for subgroup differences showed no evidence that varenicline works differently in these populations (asthma: $P = 0.76$, $I^2 = 0.4\%$; substance use disorder: $P = 0.61$, $I^2 = 0\%$; alcohol dependence: $P = 0.70$, $I^2 = 0.4\%$).

Varenicline in specific settings or subgroups

Six studies of 1324 participants tested varenicline against placebo or no medication among hospital inpatients and perioperative patients and found that more people successfully quit in the varenicline arm (RR 1.27, 95% CI 1.12 to 1.43; $I^2 = 58\%$; [Analysis 8.1](#)). Treating these trials as a subgroup of the main analysis ([Analysis 5.1](#)), which includes studies conducted in both clinical and community settings such as cessation clinics and university campuses, and testing for subgroup differences did show evidence of subgroup difference, with lower effectiveness ($P < 0.00001$; $I^2 = 98.6\%$). Heterogeneity remained when we performed a sensitivity analysis removing studies comparing varenicline with no medication rather than placebo ($P < 0.00001$; $I^2 = 96\%$).

[Gonzales 2014](#) tested varenicline against placebo among people who had previously used varenicline for two weeks or more, at least three months prior to admission to the study, and had not successfully quit but were motivated to try again. This single study found that more people successfully quit in the varenicline arm (RR 6.15, 95% CI 2.98 to 12.70; 494 participants; [Analysis 8.2](#)).

Two studies of 114 participants tested varenicline against placebo among light smokers and found that more people successfully quit in the varenicline arm (RR 4.16, 95% CI 1.58 to 10.97; $I^2 = 0\%$; [Analysis 8.3](#)). Treating these trials as a subgroup of the main analysis ([Analysis 5.1](#)) and testing for subgroup differences showed

no evidence that varenicline works differently in this population ($P = 0.20$, $I^2 = 39.3\%$).

Varenicline versus bupropion

Smoking cessation

Nine studies of 7560 participants compared varenicline with bupropion and found that more people quit smoking when using varenicline (RR 1.36, 95% CI 1.25 to 1.49; $I^2 = 0\%$; high-certainty evidence; [Analysis 9.1](#)).

[Johns 2017b](#) randomised 300 participants to receive varenicline, bupropion, or both. They did not provide any useable results data but reported that more people quit in the combined varenicline and bupropion arm compared with the bupropion- or varenicline-alone arms. However, only an abstract was available for this study, and without further information, this result should be treated with caution.

Adverse events

Studies comparing varenicline with bupropion found that people randomised to receive varenicline were more likely to report experiencing nausea (RR 2.46, 95% CI 2.20 to 2.75; $I^2 = 0\%$; 4 studies, 5808 participants; [Analysis 9.2](#)), abnormal dreams (RR 1.56, 95% CI 1.39 to 1.76; $I^2 = 0\%$; 4 studies, 5808 participants; [Analysis 9.4](#)), and headache (RR 1.24, 95% CI 1.06 to 1.45; $I^2 = 13\%$; 3 studies, 4888 participants; [Analysis 9.5](#)). However, people randomised to receive varenicline were less likely to report experiencing insomnia (RR 0.84, 95% CI 0.75 to 0.93; $I^2 = 75\%$; 6 studies, 6789 participants; [Analysis 9.3](#)).

Two studies of 4210 people did not find evidence a difference between those randomised to receive varenicline or bupropion in reported rates of depression (RR 0.90, 95% CI 0.35 to 2.35; $I^2 = 0\%$; [Analysis 9.6](#)) or suicidal ideation (RR 1.99, 95% CI 0.18 to 21.93; I^2 not estimable as events only in 1 study; [Analysis 9.7](#)).

Serious adverse events

Serious adverse events

Five studies of 5317 people did not find evidence of a clear difference in the number of people reporting experiencing serious adverse events (RR 0.89, 95% CI 0.61 to 1.31; $I^2 = 0\%$; low-certainty evidence; [Analysis 9.8](#)).

Neuropsychiatric serious adverse events

Two studies of 866 people did not find evidence of a clear difference in the number of people reporting experiencing neuropsychiatric serious adverse events (RR 1.05, 95% CI 0.16 to 7.04; $I^2 = 10\%$; low-certainty evidence; [Analysis 9.9](#)), though confidence intervals were very wide.

Cardiac serious adverse events

Two studies of 866 people did not find evidence of a clear difference in the number of people reporting experiencing cardiac serious adverse events (RR 3.17, 95% CI 0.33 to 30.18; $I^2 = 0\%$; low-certainty evidence; [Analysis 9.10](#)), though confidence intervals were very wide.

Nicotine receptor partial agonists for smoking cessation (Review)

Varenicline versus nicotine replacement therapy (NRT) monotherapy

Smoking cessation

Eleven studies of 7572 participants compared varenicline with NRT monotherapy and found that more people quit smoking in the varenicline arm (RR 1.25, 95% CI 1.14 to 1.37; $I^2 = 28\%$; high-certainty evidence; [Analysis 10.1](#)).

Adverse events

Studies comparing varenicline with NRT monotherapy found that people randomised to receive varenicline were more likely to report experiencing nausea (RR 2.69, 95% CI 2.41 to 3.01; $I^2 = 59\%$; 6 studies, 6500 participants; [Analysis 10.2](#)) and headache (RR 1.14, 95% CI 1.01 to 1.28; $I^2 = 69\%$; 4 studies, 6287 participants; [Analysis 10.5](#)). However, they did not find evidence of a clear difference in the number of people reporting experiencing insomnia (RR 1.08, 95% CI 0.96 to 1.21; $I^2 = 42\%$; 5 studies, 6319 participants; [Analysis 10.3](#)), abnormal dreams (RR 0.93, 95% CI 0.83 to 1.05; $I^2 = 67\%$; 4 studies, 5803 participants; [Analysis 10.4](#)), or depression (RR 0.94, 95% CI 0.76 to 1.16; $I^2 = 0\%$; 3 studies, 5541 participants; [Analysis 10.6](#)). The pooled point estimate from two studies found a higher rate of suicidal ideation among participants in the varenicline arm (RR 5.00, 95% CI 0.87 to 28.77; $I^2 = 0\%$; 2 studies, 4876 participants; [Analysis 10.7](#)), but confidence intervals were very wide and incorporated the potential for no difference or reduced harm. Statistical heterogeneity was substantial in several analyses, but we decided to present the pooled estimate because the point estimates of individual studies were almost entirely in the same direction in each analysis.

Serious adverse events

Serious adverse events

Six studies of 6535 people comparing varenicline with NRT monotherapy found that people randomised to receive varenicline were less likely to report experiencing serious adverse events (RR 0.70, 95% CI 0.50 to 0.99; $I^2 = 24\%$; low-certainty evidence; [Analysis 10.8](#)).

Neuropsychiatric serious adverse events

Only one study measured neuropsychiatric serious adverse events, and reported no events in either arm ([Rohsenow 2017](#); 137 participants).

Cardiac serious adverse events

Only one study measured cardiac serious adverse events, and reported no events in either arm ([Rohsenow 2017](#); 137 participants).

Varenicline versus combination NRT

Smoking cessation

Five studies of 2344 participants compared varenicline with combination NRT and did not detect evidence of a clear difference in the number of people who quit smoking, although confidence intervals indicate imprecision, which reduces our certainty in the effect (RR 1.02, 95% CI 0.87 to 1.20; $I^2 = 0\%$; low-certainty evidence; [Analysis 11.1](#)).

Adverse events

Studies comparing varenicline with combination NRT found that people randomised to receive varenicline were more likely to report experiencing nausea (RR 1.76, 95% CI 1.45 to 2.15; $I^2 = 47\%$; 3 studies, 1609 participants; [Analysis 11.2](#)), insomnia (RR 1.40, 95% CI 1.15 to 1.70; $I^2 = 82\%$; 3 studies, 1609 participants; [Analysis 11.3](#)), and abnormal dreams (RR 1.59, 95% CI 1.22 to 2.08; 1 study; 549 participants; [Analysis 11.4](#)). However, they did not find evidence of a clear difference in the number of people reporting experiencing headache (RR 0.98, 95% CI 0.78 to 1.23; $I^2 = 0\%$; 3 studies, 1609 participants; [Analysis 11.5](#)), depression (RR 1.08, 95% CI 0.83 to 1.40; $I^2 = 82\%$; 3 studies, 1609 participants; [Analysis 11.6](#)), or suicidal ideation (RR 0.94, 95% CI 0.06 to 14.79; I^2 not estimable as events only in 1 study; 2 studies, 764 participants; [Analysis 11.7](#)). Statistical heterogeneity was substantial in several analyses, but we decided to present the pooled estimate because the point estimates of individual studies were almost entirely in the same direction.

Serious adverse events

Serious adverse events

Pooled data from four studies of 1852 people showed more people in the varenicline arm reporting serious adverse events compared with combination NRT (RR 2.15, 95% CI 0.49 to 9.46; $I^2 = 0\%$; low-certainty evidence; [Analysis 11.8](#)). However, confidence intervals were very wide and included the potential for no difference or reduced risk.

Neuropsychiatric serious adverse events

Two studies of 764 people reported the number of people reporting neuropsychiatric serious adverse events. While the point estimate suggested participants receiving varenicline were more likely to report experiencing neuropsychiatric serious adverse events, confidence intervals were extremely wide, and incorporated both benefit and harm (RR 4.69, 95% CI 0.23 to 96.50; I^2 not estimable as events only in 1 study; low-certainty evidence; [Analysis 11.9](#)).

Cardiac serious adverse events

Two studies of 819 people reported the number of people reporting cardiac serious adverse events. While the point estimate suggested that participants receiving varenicline were less likely to report experiencing cardiac serious adverse events, confidence intervals were very wide, and incorporated both benefit and harm (RR 0.32, 95% CI 0.01 to 7.88; I^2 not estimable as events only in 1 study; low-certainty evidence; [Analysis 11.10](#)).

Varenicline versus e-cigarettes

Smoking cessation

One study of 54 participants compared varenicline with e-cigarettes and found that more people quit smoking in the varenicline arm (RR 3.25, 95% CI 1.21 to 8.71; very low-certainty evidence; [Analysis 12.1](#)).

Adverse events

The only one of our adverse event outcomes reported by this study was nausea. While the point estimate suggested that participants receiving varenicline were more likely to report experiencing nausea, confidence intervals were extremely wide,

and incorporated both benefit and harm (RR 3.00, 95% CI 0.33 to 27.06; [Analysis 12.2](#)).

Serious adverse events

While the study reported serious adverse events, neuropsychiatric serious adverse events, and cardiac serious adverse events as outcomes, they reported no events among study participants in either arm.

Dianicline versus placebo

Smoking cessation

[Tonstad 2011](#) (602 participants) compared dianicline with placebo and did not detect evidence of a clear difference in the number of people who quit smoking (RR 1.20, 95% CI 0.82 to 1.75; [Analysis 13.1](#)), however, results were imprecise and confidence intervals encompass the possibility of benefit and harm of dianicline.

Adverse events

[Tonstad 2011](#) reported that more people randomised to receive dianicline reported experiencing nausea (RR 2.83, 95% CI 1.88 to 4.27; 602 participants; [Analysis 13.2](#)) and depression (RR 8.05, 95% CI 1.01 to 63.99; 602 participants; [Analysis 13.4](#)) than those in the placebo arm. They did not detect a difference in the number of people reporting experiencing headaches (RR 1.23, 95% CI 0.82 to 1.85; 602 participants; [Analysis 13.3](#)). The study did not measure our other adverse event outcomes.

Serious adverse events

[Tonstad 2011](#) did not detect a difference in rates of serious adverse events (RR 1.01, 95% CI 0.20 to 4.95; 602 participants; [Analysis 13.5](#)) or cardiac serious adverse events (RR 1.01, 95% CI 0.06 to 16.02; 602 participants; [Analysis 13.6](#)) between participants in the dianicline and placebo study arms. However, in both instances confidence intervals were very wide and included the potential for both harm and benefit. The study did not measure neuropsychiatric serious adverse events.

DISCUSSION

Summary of main results

This review includes eight studies that investigated cytisine use in just under 9000 people, 68 studies that investigated varenicline use in over 37,000 people, and one study that investigated dianicline use in 602 people. Forty-five of these studies are new to this update.

We found moderate-certainty evidence that cytisine probably helps more people to quit smoking than placebo. While people randomised to receive cytisine were more likely to experience adverse events than those in the placebo arm, low-certainty evidence gave no clear indication of an increased risk of serious adverse events. We found no data on neuropsychiatric or cardiac serious adverse events.

Our analysis did not find definitive evidence of a difference in cessation rates between cytisine and varenicline. The point estimate favoured varenicline, but this moderate-certainty evidence is subject to imprecision and may change as more evidence becomes available. A component network meta-analysis that is currently underway may reveal a more certain result by also employing data from indirect comparisons ([Lindson 2022](#)).

Although the point estimates in the separate analyses comparing varenicline with placebo and cytisine with placebo did differ (with the varenicline analysis producing a higher risk ratio) the issue with this type of indirect comparison is it does not adjust for potential differences in baseline event rates. In our analysis, [Dogar 2020](#) was the largest study that compared cytisine with placebo. It recruited people diagnosed with pulmonary tuberculosis who, as part of the behavioural aspect of the intervention, were informed of the dangers of continued tobacco use in people with tuberculosis. This made for a highly motivated population, who also happened to smoke fewer cigarettes per day than in other cytisine trials. These two characteristics may have contributed to the higher placebo arm quit rates in the cytisine studies and minimised the benefit gained from pharmacotherapy. These factors may also explain why the results from [Dogar 2020](#) are less compelling than those of the other studies, and may also account for the statistical heterogeneity in the cytisine versus placebo analysis ($I^2 = 83%$).

Participants in the cytisine arm were less likely to experience nausea or abnormal dreams than those in the varenicline arm, and there was no evidence of a difference in rates of insomnia, headache, depression, or suicidal ideation. The same studies provided low-certainty evidence of fewer people experiencing serious adverse events in the cytisine arm compared with varenicline. However, in all cases, confidence intervals indicated imprecision, and the potential for more adverse events when using either treatment. We found no data on neuropsychiatric or cardiac serious adverse events.

Low-certainty evidence suggested that cytisine may help more people to quit than NRT monotherapy ([Walker 2014](#)). However, after the initial 25-day course, participants in the cytisine arm also received vouchers for NRT. This may distort the results as some participants in the cytisine arm may have in fact received two pharmacotherapies, but study authors reported that few participants in the cytisine arm used their NRT vouchers. Low-certainty evidence did not show a difference in the number of people reporting serious adverse events. We found no data on neuropsychiatric or cardiac serious adverse events.

Evidence on the effect of different lengths of cytisine treatment was sparse and inconclusive.

There is high-certainty evidence that varenicline increases the chances of successful smoking cessation by more than two-fold compared with placebo. Since the previous version of this review was published ([Cahill 2016](#)), this estimate has remained stable, despite the growing inclusion of pragmatic trials in real-world settings and those conducted in particular groups of smokers previously excluded from clinical trials, such as those in lower- and middle-income countries, and in disease-specific populations.

We also found high-certainty evidence that varenicline helped more people to quit than bupropion, or NRT monotherapy, with no clear evidence of difference between varenicline and bupropion in rates of serious adverse events, neuropsychiatric serious adverse events, or cardiac serious adverse events (all low-certainty evidence), and low-certainty evidence suggesting reduced risk of serious adverse events compared with NRT. We found no data comparing varenicline with NRT monotherapy for neuropsychiatric or cardiac serious adverse events.

Nicotine receptor partial agonists for smoking cessation (Review)

Low-certainty evidence did not show a difference in quit rates compared with combination NRT, and while low-certainty evidence suggested potentially increased risk of serious adverse events and neuropsychiatric serious adverse events, and reduced risk of cardiac serious adverse events, in all cases confidence intervals were very wide, encompassing both substantial harm and benefit.

One small study of 54 people provided very-low certainty evidence of more people quitting with varenicline than with e-cigarettes (Ioakeimidis 2018); however this study was at high risk of bias and imprecise due to few events, and while they reported serious adverse events, neuropsychiatric serious adverse events, and cardiac serious adverse events as outcomes, they reported no events among study participants in either arm. Studies that tested varenicline versus placebo in specific populations and settings did not demonstrate varenicline working differently than it does in the general population in disease-specific groups of patients (e.g. cardiovascular, chronic obstructive pulmonary disease, HIV, schizophrenia and psychiatric disorders, depression, alcohol dependence), or in specific subgroups or settings (e.g. hospital inpatients, light-smokers, smokers who failed to quit on varenicline previously).

Analyses found evidence of increased rates of adverse events such as nausea, insomnia, abnormal dreams, and headache among people randomised to receive varenicline compared with placebo. However, we found no clear evidence of increased rates of depression or suicidal ideation, although confidence intervals indicated imprecision, and the potential for more or fewer adverse events when using varenicline compared with control. Moderate-certainty serious adverse event data suggest there may be a 23% increased risk of such events among the varenicline groups

compared with the controls. However, serious adverse events were still rare (2.7% to 4% of people on varenicline, compared with 2.7% of people without) and this finding is based on simple counts across the trials of participants reporting one or more such events, thus not distinguishing between events attributed and those unrelated to treatment. We did not find evidence of an increased risk of neuropsychiatric serious adverse events, but pooled results did suggest a potential increased risk of cardiac serious adverse events, although again these results were subject to imprecision, and we deemed this evidence to be low certainty because of its compatibility with both increased and decreased risk of harm.

One trial compared dianicline with placebo for smoking cessation and the results were inconclusive (Tonstad 2011).

Overall completeness and applicability of evidence

We conducted systematic searches of multiple online databases, including clinical trials registries and followed Cochrane methods for screening. We therefore expect that any published trials we have missed will be through chance rather than systematic error. We were able to assess publication bias for two comparisons by constructing funnel plots: varenicline versus placebo (Figure 4), and varenicline versus NRT monotherapy (Figure 5). Figure 5 appears to show a small amount of asymmetry that may suggest a lack of smaller trials with negative findings. However, the number of studies is still very low with few smaller studies, and so we cannot treat this as definitive evidence of publication bias. These were the only cessation comparisons with enough studies to construct a funnel plot, so we were unable to assess publication bias for other comparisons. As such, we cannot ignore the possibility of publication bias for some comparisons in this review.

Figure 4. Funnel plot of comparison 6: varenicline (1.0 mg 2/d) vs placebo, outcome: 6.1 abstinence at longest follow-up

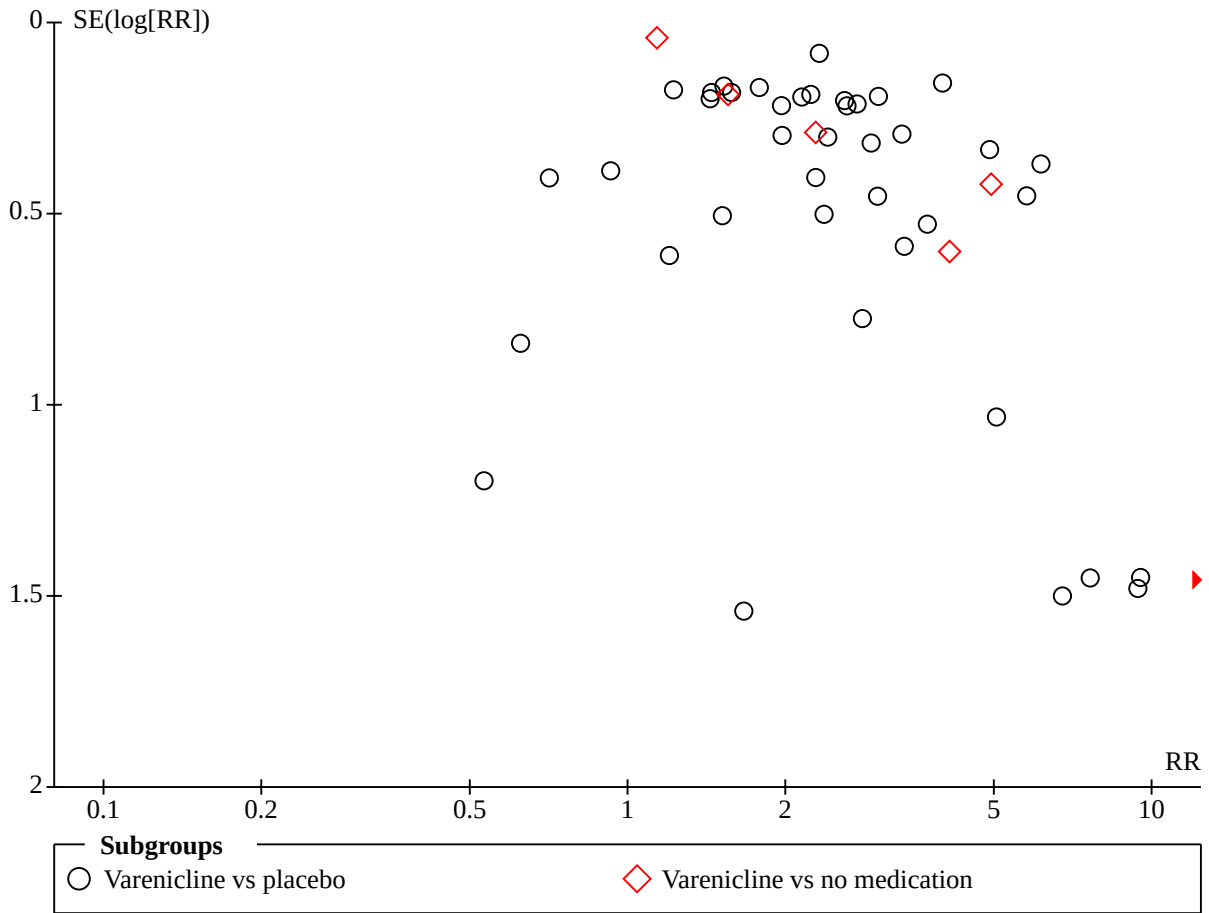
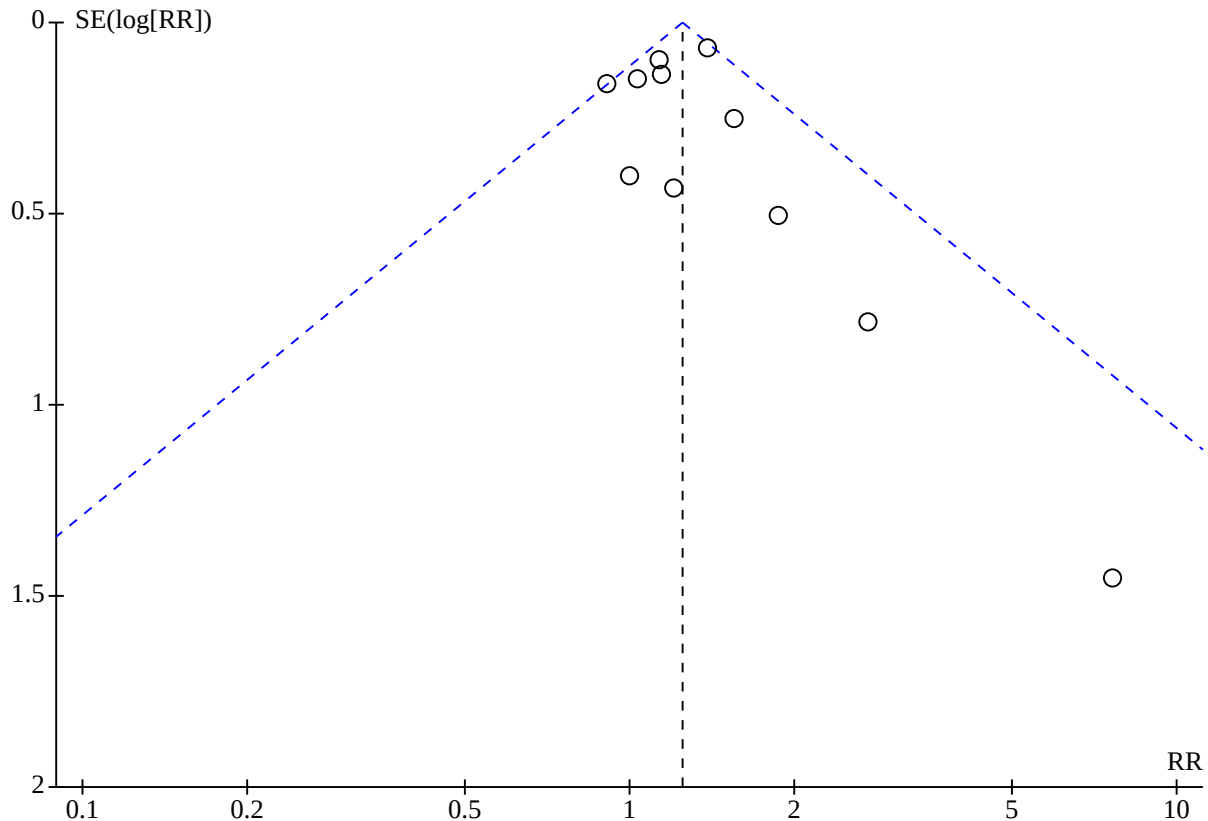


Figure 5. Funnel plot of comparison 13: varenicline vs nicotine replacement therapy monotherapy, outcome: 13.1 abstinence at longest follow-up



The benefits of varenicline for smoking cessation is now well established, with the point estimate remaining unchanged as more studies (including non-manufacturer- (Pfizer) funded trials) accumulate. Trials are now being conducted and reported in areas where the evidence is less comprehensive, such as testing cytisine (against placebo and varenicline), and testing varenicline in specific populations and settings, and in variations of treatment dose or duration.

Quality of the evidence

We judged the evidence comparing varenicline with placebo for smoking cessation to be of high certainty. While we detected moderate heterogeneity ($I^2 = 60\%$), all but three studies had a point estimate that favoured varenicline over placebo, so we did not downgrade on this basis. The effectiveness of varenicline for smoking cessation has remained constant through several updates of this review, and we think it is unlikely to change with further evidence. We judged the evidence on serious adverse events to be of moderate certainty, downgraded because of imprecision. For cardiac and neuropsychiatric serious adverse events, we downgraded evidence to low because of imprecision. Despite respectable numbers of studies and participants in each analysis, because of the rarity of these kinds of adverse events, there were very few events in the analyses, with some studies reporting no events at all.

We judged the evidence comparing cytisine with placebo to be of moderate certainty for smoking cessation and low certainty for serious adverse events, downgraded due to substantial unexplained heterogeneity and imprecision, respectively. We judged the evidence comparing cytisine with varenicline for smoking cessation and serious adverse events to be of moderate and low certainty, respectively, downgraded for imprecision in both cases.

We judged the evidence comparing varenicline with bupropion and NRT monotherapy for smoking cessation to be of high certainty, and with combination NRT to be of low certainty, limited by imprecision. Only one small study compared varenicline with e-cigarettes for smoking cessation, and we graded this evidence as of very low certainty because of imprecision and risk of bias.

Potential biases in the review process

We have followed standard Cochrane methodology, which endeavours to minimise biases in the review process, so we are confident that any errors in our data will be through chance rather than systematic error. However, it is impossible to rule out individual errors in the review process.

A potential limitation to our review is that for data on harms we relied on adverse events and serious adverse events as defined by papers reporting included studies. This does not take into account whether those events were genuinely attributable to the tested interventions. Further, we only considered the number of

participants reporting these events, which does not account for people who experienced more than one event.

Another potential limitation is that the majority of varenicline trials reported in this review received either funding or study medication from Pfizer Inc, the manufacturers of varenicline. Evidence from systematic reviews suggests that industry-funded trials, although conducted to a high standard, are more likely to have outcomes favourable to the product sponsor than studies with other sponsors (Etter 2007; Walsh 2011). However, we deem the provision of study medication less likely to amount to the kind of sponsorship that may bias results, and modern trials increasingly report funders and medication providers as having no involvement in trial conduct or decision making.

Agreements and disagreements with other studies or reviews

Reviews of controlled studies of cytisine have focused upon its potential as an established and affordable aid to smoking cessation (Etter 2006; Etter 2008; Tutka 2005; Tutka 2006; Tutka 2008). Many of the early cytisine studies excluded from this review are discussed and evaluated in Etter 2006, who concluded that cytisine may be effective for smoking cessation. A systematic review and network meta-analysis (Leaviss 2014), compared the benefits and cost-effectiveness of cytisine (2 trials: Vinnikov 2008; West 2011), with varenicline (21 trials). While the analysis found both treatments to be effective for smoking cessation, cytisine delivered more quality-adjusted life-years at a lower cost than varenicline. Cytisine was also associated with lower rates of headache and nausea than varenicline. Our analyses on harms, using direct evidence, found lower rates of nausea, but did not find evidence of difference in rates of headache. A recent review of cytisine found similar results to ours, though with a slightly higher point estimate for smoking cessation (Tutka 2019). This is likely because they had broader inclusion criteria than our review, and included studies with shorter follow-up periods.

A Cochrane overview and network meta-analysis of a number of pharmacological interventions for smoking cessation assessed 12 Cochrane Reviews published to November 2012 (Cahill 2013), and therefore drew on the previous version of this review. Comparisons between varenicline, bupropion and single-treatment NRT found varenicline to be superior to both treatments (OR 1.59, 95% credible interval 1.29 to 1.96 and OR 1.57, 95% credible interval 1.29 to 1.91, respectively). Varenicline demonstrated comparable benefits for smoking cessation to combination NRT (OR 1.06, 95% credible interval 0.75 to 1.48), but the number of NRT trials informing this comparison was low (9 trials). This review is currently being updated (Lindson 2022). A 2012 network meta-analysis (Mills 2012), comparing high-dose and combination NRT versus varenicline and versus bupropion across 146 RCTs, found varenicline (11 trials) to be superior to placebo and to bupropion at all time points, and similar in benefits for smoking cessation to standard and to high-dose NRT, in line with our findings. A more recent systematic review with network meta-analysis reported similar findings to ours, reporting a benefit from varenicline compared with placebo (OR 2.69, 95% CI 2.27 to 3.19), bupropion (OR 1.46, 95% CI 1.18 to 1.81), and standard-dose NRT (OR 1.32, 95% CI 1.05 to 1.65; Thomas 2020). However, they did not find evidence of increased rates of serious adverse events amongst those randomised to receive varenicline compared with placebo (OR 1.09, 95% CI 0.91 to 1.34), contrary to the increased risk we detected. This may be due to their choice of

a random-effects rather than fixed-effect model for their analysis. They did not find clear evidence of a difference in cardiac serious adverse events (OR 0.76, 95% CI 0.41 to 1.25) and neuropsychiatric serious adverse events (OR 0.96, 95% CI 0.76 to 1.21), which is in line with our findings.

An earlier systematic review and meta-analysis of 39 RCTs (10,761 participants) by the same team assessed the risk of neuropsychiatric adverse events among users of varenicline (Thomas 2015). In line with our findings, the authors found no clear evidence of an increased risk of suicide or attempted suicide (Peto odds ratio (OR) 1.67, 95% CI 0.33 to 8.57), suicidal ideation (Peto OR 0.58, 95% CI 0.28 to 1.20), depression (Peto OR 0.96, 95% CI 0.75 to 1.22) or death (Peto OR 1.05, 95% CI 0.47 to 2.38) associated with varenicline. Lee 2016 compared cardiovascular serious adverse event rates between people randomised to receive varenicline or placebo. They did not find evidence of increased risk of cardiovascular serious adverse events (RR 1.03, 95% CI 0.72 to 1.49) in 38 trials of 12,706 people. This result was consistent among cardiovascular (RR 1.04, 95% CI 0.57 to 1.89) and non-cardiovascular patients (RR 1.03, 95% CI 0.64 to 1.64).

AUTHORS' CONCLUSIONS

Implications for practice

- Cytisine is likely to help more people to quit smoking than placebo or no medication.
- Varenicline at standard dosage (1.0 mg twice a day) increased the chances of successful long-term smoking cessation by more than two-fold compared with placebo. We did not find evidence that varenicline is less effective in any of the specific populations we investigated.
- Varenicline is more effective at helping people to quit smoking than bupropion, or a single form of nicotine replacement therapy, and may be as effective as or more effective than dual-form nicotine replacement therapy.
- People taking varenicline are probably more likely to experience serious adverse events than those not taking it, and while there may be increased risk of cardiac serious adverse events and decreased risk of neuropsychiatric serious adverse events, evidence was compatible with both benefit and harm.
- Cytisine may lead to fewer people reporting serious adverse events than varenicline. There may be a benefit from varenicline for quitting smoking, however further evidence could strengthen this finding or demonstrate a benefit from cytisine.

Implications for research

- Future trials should test the effectiveness and safety of cytisine compared with varenicline and other pharmacotherapies, and should also test variations in dose and duration.
- There is limited benefit to be gained from more trials testing the effect of standard dose varenicline compared with placebo for smoking cessation.
- Further varenicline trials should test the effect of variations in dose and duration and preloading varenicline before quitting, and may be useful in specific populations and settings where there is a plausible rationale that the effect may differ.

Nicotine receptor partial agonists for smoking cessation (Review)

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The following people conducted the editorial process for the most recent update:

Sign-off Editor (final editorial decision): Lisa Bero, Cochrane Editorial Board,

- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Sam Hinsley, Cochrane Central Editorial Service

- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service

- Copy Editor (copy editing and production): Denise Mitchell, Cochrane Evidence Production and Methods Directorate

- Peer-reviewers (provided comments and recommended an editorial decision): Jennifer Hilgart, Cochrane Evidence Production and Methods Directorate (methods), Steve MacDonald, Cochrane Australia (search), Michael B. Steinberg, MD, MPH; Rutgers Center for Tobacco Studies and Robert Wood Johnson Medical School (clinical), Ryan J Courtney, UNSW Sydney, National Drug and Alcohol Research Centre (clinical), Timothy B. Baker Department of Medicine University of Wisconsin School of Medicine and Public Health (clinical).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Anthenelli 2013
Study characteristics

Methods	Country: USA (9 centres) and international (24 centres, across Bosnia & Herzegovina, Croatia, Germany, Hungary, Romania, Russian Federation, Spain) Setting: academic clinical trial centres and SC clinics Aim: to assess the efficacy and safety of 12 weeks of varenicline treatment or placebo for SC, with 40 weeks of non-treatment follow-up, in adults with current or past depression (MDD) Study design: double-blind placebo-controlled RCT Dates conducted: March 2010 - June 2012
Participants	525 adult smokers, aged 18-75, smoking at least 10 CPD, motivated to quit, diagnosed with unipolar MDD without psychotic features. 37% male, mean age 46, average CPD at baseline 22, mean FTND 5.9. Allocated to varenicline (256) or placebo (269) Exclusion criteria: current or past diagnosis of dementia, schizophrenia, schizoaffective disorder, or other psychotic disorder, bipolar I disorder, bipolar II disorder. People with antisocial, schizotypal, or any other personality disorder severe enough to compromise their ability to comply with the study requirements Current use of either bupropion or nortriptyline
Interventions	<ul style="list-style-type: none"> • Varenicline 1 mg x 2/day, titrated for first week • Placebo inactive tablets, same regimen All participants received manual-guided SC support, telephone support and one-to-one 10-min counselling by the same person where possible. Participants in both groups could reduce the dosage if they wished TQD was set for week 1 visit

Nicotine receptor partial agonists for smoking cessation (Review)

Anthenelli 2013 (Continued)

Treatment period was 12 weeks. Visits at screening, baseline, weekly for weeks 1-12, and then at weeks 13, 16, 24, 32, 40, 52 (or early termination); phone calls at weeks 14, 20, 28, 36, 44 and 48. Weekly pill counts to assess adherence

Safety data were reviewed regularly by an external independent data safety monitoring committee

Outcomes

Primary: CO-confirmed CAR for weeks 9-12

Secondary: CO-confirmed CAR for weeks 9-24, 9-52; 7-day PPA at weeks 12, 24, 52; AEs and SAEs
Verification: CO < 10 ppm

Notes

New for 2016 update

Study funding: "This study was funded by Pfizer. Dr. Anthenelli's writing of this manuscript was funded, in part, by a Department of Veterans Affairs Merit Review award (NEUA-003-08S) and by a National Institute on Alcohol Abuse and Alcoholism grant (AA019720). Dr. Morris was supported, in part, by grants from the University of California, San Francisco, Smoking Cessation Leadership Center, and Colorado Department of Public Health and Environment. Drs. Ramey, Tsilkos, Russ, and Yunis and Ms. Dubrava are employees of Pfizer. Editorial support was provided by Abegale Templar, PhD, of Engage Scientific and funded by Pfizer."

Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomly assigned to varenicline or placebo in a 1:1 ratio by using a computer generated, 4-block randomization scheme at each site."
Allocation concealment (selection bias)	Low risk	"Randomization was stratified by antidepressant medication use at baseline (any vs. none) and baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score (11 vs. 11) (32). Investigators obtained participant identification numbers and randomized study drug assignments by using a Web-based or telephone call-in computerized drug management system."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The study drug was supplied in blinded bottles by the sponsor to the study sites, where they were dispensed according to computerized instructions."
Incomplete outcome data (attrition bias) All outcomes	Low risk	68.4% of varenicline group completed study (lost 15.6% in treatment and 16% in follow-up); 66.6% of placebo group completed study (lost 21.9% in treatment and 11.5% in follow-up)
Selective reporting (reporting bias)	Low risk	Results reported for all outcomes pre-specified in NCT record.

Ashare 2019

Study characteristics

Methods

Country: USA

Setting: not explicitly reported, likely at home and in hospital

Aim: to evaluate the safety and efficacy of varenicline for SC among people living with HIV

Ashare 2019 (Continued)

Study design: parallel placebo-controlled phase 3 RCT

Dates conducted: October 2012-September 2018

Participants	179 adult smokers all with a confirmed HIV diagnosis, currently smoking and motivated to quit. All treated with antiretroviral therapy with HIV loads < 1000 copies/mL and CD4+ counts > 200 cells/mm ³ . 32% female, mean age 48.6, average CPD at baseline 11.5
Interventions	<ul style="list-style-type: none"> Varenicline 1 mg x 2/day Placebo inactive tablets, same regimen <p>All participants received 6 sessions over 9 weeks of interactive behavioural support in person or by telephone. Treatment period was 12 weeks.</p>
Outcomes	<p>Primary: 7-day PPA, CO-confirmed, at weeks 12 and 24</p> <p>Secondary: CA and time to relapse</p>
Notes	<p>New for 2022 update</p> <p>Funding source: "National Institute on Drug Abuse, Penn Center for AIDS Research, Penn Mental Health AIDS Research Center. Pfizer provided medication and placebo free of charge"</p> <p>Declaration of interests: "Dr. Schnoll has provided consultation to Pfizer, GlaxoSmithKline, and Curaleaf. Dr. Gross serves on a Pfizer Data and Safety Monitoring Board for a drug unrelated to smoking or HIV. Dr. Ashare has an investigator-initiated grant from Novo Nordisk for a drug unrelated to the current study."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomized 1:1 by a computer-generated protocol provided by the study statistician to the University of Pennsylvania's Investigational Drug Service (IDS)"
Allocation concealment (selection bias)	Low risk	Randomisation conducted separately by the University of Pennsylvania's Investigational Drug Service (IDS), and all other study personnel were blinded. Therefore, concealment was likely adequate.
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence was biochemically validated and "All participants and study personnel, aside from IDS [Investigational Drug Service], were blinded from treatment arm allocation throughout the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were similar between study arms.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry entry all reported in published results

Aubin 2008
Study characteristics

Methods	Country: Belgium, France, Netherlands, UK, USA Setting: 24 research centres
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Nicotine receptor partial agonists for smoking cessation (Review)

Aubin 2008 (Continued)

Aim: to compare the efficacy of varenicline with nicotine patch, both open-label
 Dates conducted: January 2005-June 2006
 Study design: open-label randomised trial

Participants	757 healthy adults, recruited from SC clinics or by local advertising, aged 18-75, weight > 45.5 kg, BMI 15-38, smoking ≥ 15 CPD. Varenicline arm 378, NRT arm 379. Mean age 42.9, 49.2% men, 93% white. Mean CPD 22.7. Previous use of nicotine patch 47.4%, previous use of bupropion 20%. Mean FTND 5.5. Exclusion criteria: standard pharmacotherapy trial criteria, + participants must not have been in a varenicline trial in previous year, or used NRT in previous 6 months
Interventions	<ul style="list-style-type: none"> Varenicline 1 mg x 2/day for 12 weeks, titrated 1st week Nicotine patch (21 mg weeks 2-6, 14 mg weeks 7-9, 7 mg weeks 10-11) <p>All participants received <i>Clearing the Air</i> booklet at baseline, and brief counselling (≤ 10 min) at each clinic visit or by phone. TQD was at week 1 visit. Weekly visits throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at weeks 13, 16, 24, 32, 40, 48 and 52, plus brief phone calls at weeks 14, 20, 28, 36 and 44</p>
Outcomes	<p>CO-confirmed CAR for last 4 weeks' treatment (varenicline weeks 9-12, NRT weeks 8-11) CO-confirmed CAR at weeks 9-24 and 9-52 (varenicline) and 8-24 and 8-52 (NRT) 7-day PPA at EoT and at weeks 24 and 52 Other outcomes: weight change, withdrawal symptoms (using MNWS and mCEQ), AEs Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 17.3% varenicline, 20.3% NRT. Losses to follow-up 17% in each group 65.7% of varenicline and 62.2% of NRT groups completed study</p>
Notes	<p>New for 2008 update</p> <p>Study funding: study funded by Pfizer</p> <p>Author declaration of interests: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a central computer-generated sequence"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"Using an open-label design". However, comparators were two active treatments, minimising risk of performance bias, and abstinence was biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing CO data were assumed to be < 10 ppm provided other conditions were met", i.e. no NRT other than prescribed patches. Missing = negative assumption reduced successes by 1 in each group
Selective reporting (reporting bias)	Low risk	All predicted outcomes fully reported

Baker 2016

Study characteristics

Methods	<p>Country: USA Setting: 2 University sites in Wisconsin (Madison, Milwaukee)</p> <p>Aim: to compare the efficacy of varenicline with nicotine patch, and with combination NRT (C-NRT) Dates conducted: May 2012-November 2015 Study design: open-label randomised trial (no placebo)</p>
Participants	<p>1086 healthy adults, recruited from participants in the ongoing Wisconsin Smokers Health Study or by media and community outreach, aged 17+, smoking ≥ 5 CPD, motivated to quit Varenicline arm 424, nicotine patch arm 241, combination NRT arm 421</p> <p>Mean age 48.1, 47.9% men, 67% white. Mean CPD 17. Mean FTND 4.8 Exclusion criteria: standard pharmacotherapy trial criteria, CO < 4 ppm, no suicide attempts in previous 5 years, or current suicidal ideation, diagnosis or treatment of psychoses in previous 10 years</p>
Interventions	<ul style="list-style-type: none"> • Varenicline 1 mg x 2/day for 12 weeks, titrated 1st week • Nicotine patch: 11+ CPD on 21 mg weeks 1-8, 14 mg weeks 9-10, 7 mg weeks 11-12; 5-10 CPD on 14 mg weeks 1-10, 7 mg weeks 11-12 • Nicotine patch as above, plus nicotine lozenge (2 mg or 4 mg), at least 5 times a day for 12 weeks <p>All participants received counselling (20 min at visits 1, 2 and 3, and 10 min by phone and at visits 4, 5) at 1 week pre-TQD and at TQD, weeks 1, 4, 12 post-TQD, plus phone call at week 8 In follow-up phase, participants were contacted at weeks 26 and 52 by phone</p>
Outcomes	<p>All comparisons were based on varenicline and C-NRT versus patch (reference arm), and on varenicline versus C-NRT</p> <p>CO-confirmed PPA at week 26 CO-confirmed PA from day 7 post-TQD to day 181</p> <p>CO-confirmed PPA at weeks 4, 12, 52 Other outcomes: adherence, withdrawals, AEs Validation was by expired CO ≤ 9 ppm and ≤ 5 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Withdrawal rates were 8.3% varenicline, 6.2% nicotine patch, 3.1% C-NRT</p>
Notes	<p>The trial was funded by grant 5R01HL109031 from National Heart, Lung, and Blood Institute, and by grant K05CA139871 from the National Cancer Institute</p> <p>New for 2016 update</p> <p>Author declaration of interests: "All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stein reports receipt of data and safety monitoring board honoraria from Lilly and Abbott. No other disclosures were reported."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-based randomisation"
Allocation concealment (selection bias)	High risk	"Treatment assignment was unblinded" (open-label)
Blinding (performance bias and detection bias)	High risk	"Treatment assignment was unblinded" (open-label)

Baker 2016 (Continued)

All outcomes		"The follow-up telephone assessments were intended to be blinded, but a database search by interviewers could have revealed treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of attrition, ITT analysis used
Selective reporting (reporting bias)	Low risk	All predicted outcomes reported, protocol available

Baker 2021
Study characteristics

Methods	Country: USA Setting: 2 research clinics in Wisconsin Aim: to compare combinations of varenicline plus the nicotine or placebo patch vs combinations used for either 12 weeks (standard duration) or 24 weeks (extended duration) Study design: double-blind, 2 × 2 factorial RCT
Participants	1251 adult smokers, smoking at least ≥ 5 CPD and motivated to quit. 54% female, mean age 49.1, average CPD at baseline 16
Interventions	<ul style="list-style-type: none"> Varenicline monotherapy for 12 weeks. 1 mg x 2/day, titrated for first week Varenicline 1 mg x 2/day for 12 weeks, titrated for first week. Plus nicotine patch 14 mg/day for 12 weeks Varenicline monotherapy for 24 weeks. 1 mg x 2/day, titrated for first week Varenicline 1 mg x 2/day for 24 weeks, titrated for first week. Plus nicotine patch 14 mg/day for 24 weeks <p>All participants received a total of 1.5 h (6 x 15 min over 10 weeks) of interactive behavioural support, either as face-to-face consultations or via telephone.</p> <p>Treatment period was either 12 or 24 weeks</p>
Outcomes	Primary outcome: CO-confirmed self-reported 7-day PPA at 52 weeks Secondary outcome: prolonged CO-confirmed self-reported abstinence - from day 7-week 52 after TQD) Verification: CO ≤ 5 ppm
Notes	New for 2022 update. Study funding: "Pfizer supplied the study with free active and placebo varenicline as per an investigator-initiated research agreement. This research was supported by grant 5R01HL109031 from the National Heart, Lung, and Blood Institute and grant K05CA139871 from the National Cancer Institute (both awarded to the University of Wisconsin Center for Tobacco Research and Intervention)." Author declaration of interests: "Dr Baker reported receiving personal fees from the National Cancer Institute for editing a monograph and grants from the National Cancer Institute. Dr Bolt reported receiving grants from the National Institutes of Health. Dr Fiore reported receiving personal fees from the National Cancer Institute. No other disclosures were reported."

Risk of bias
Nicotine receptor partial agonists for smoking cessation (Review)

Baker 2021 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of software (SASProcPlanversion9.4) to generate randomisation schedule. Quote: "Participants were randomized to 1 of 2 levels of the 2 experimental factors (medication type and medication duration) via a database that used stratified permuted block randomization."
Allocation concealment (selection bias)	Unclear risk	Allocation process not reported (how interventions (active or placebo pills and patches) were put into the letters and sent to participants)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and study personnel blinded to allocation. Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up < 50% overall, loss similar across treatment arms, missing observations were assumed to reflect current smoking
Selective reporting (reporting bias)	Low risk	Outcomes pre-specified in trial registry all reported in results paper

Benli 2017
Study characteristics

Methods	Study design: RCT Country: Turkey Setting: SC clinic Recruitment method: participants applied to the SC clinic directly by calling the Turkish Ministry of Health's 'stop smoking' helpline and making an appointment.
Participants	An unspecified number of participants were randomised. 405 participants were analysed. 17.5% female; average age 35.2; average age 35.2; average CPD 23; mean FTND 6.3
Interventions	<ul style="list-style-type: none"> Bupropion. Provided for 3 months Varenicline. Provided for 3 months Common components: behavioural therapy support with a biopsychosocial approach
Outcomes	SC: 7-day PPA at 12 months. Validated by a CO level \leq 5 ppm
Notes	Funding source: no funding Author conflicts of interest: the authors declare that they have no competing interests Unclear from study reporting if study is a genuine trial or a follow-up of treatment in a clinic. However, treatment was randomly allocated, so we have treated this study as a trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who were to receive the medication were randomly determined by the medication support center in order to provide a constant distri-

Nicotine receptor partial agonists for smoking cessation (Review)

Benli 2017 (Continued)

		<p>but ion rate of varenicline and bupropion and so that physicians would not be aware of the medication distribution.”</p> <p>Comment: no further detail is provided.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: “Patients who were to receive the medication were randomly determined by the medication support center in order to provide a constant distribution rate of varenicline and bupropion and so that physicians would not be aware of the medication distribution.”</p> <p>Comment: no further detail is provided.</p>
Blinding (performance bias and detection bias) All outcomes	Unclear risk	<p>Quote: “Patients who were to receive the medication were randomly determined by the medication support center in order to provide a constant distribution rate of varenicline and bupropion and so that physicians would not be aware of the medication distribution”</p> <p>Comment: some attempt appears to have been made to blind physicians to group assignment, however no further detail is given, so it is unclear whether participants and outcome assessors were blinded.</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	Only those followed up at 12 months are included in analysis
Selective reporting (reporting bias)	Unclear risk	No protocol found

Bohadana 2020
Study characteristics

Methods	<p>Country: Israel</p> <p>Setting: Pulmonary Institute of Shaare Zedek Medical Center (SZMC), Jerusalem, Israel, in participants' home</p> <p>Aim: to assess whether varenicline preloading for 6 weeks prior to the TQD reduced pre-quit smoke intake and enhanced 6-month abstinence outcomes compared with the standard 1-week preloading.</p> <p>Study design: parallel placebo-controlled RCT</p>
Participants	242 daily smokers, smoking ≥ 10 CPD, and had smoked for ≥ 5 pack years, and were motivated to quit. 27% female, mean age 48, average CPD at baseline 25
Interventions	<ul style="list-style-type: none"> 1 week of varenicline preload: 5 mg of varenicline once daily for 3 days and 0.5 mg twice daily for 4 days (week 1), followed by varenicline 1 mg twice daily for 5 additional weeks 6 weeks of varenicline preload: matched placebo tablets for 5 weeks, followed by a 1-week titration of varenicline as in group 1 <p>TQD was 6 weeks post-initiation of treatment.</p>
Outcomes	<p>Primary: 24-week biochemically verified CAR from weeks 6–30</p> <p>Secondary: 23-week CAR from 1-week post-TQD (week 7) to week 30; 7-day PPA at week 30</p> <p>Biochemically validated: expired CO ≤ 5 ppm and urine cotinine equivalent concentration ≤ 1 mg/mL</p>
Notes	New for 2022 update

Nicotine receptor partial agonists for smoking cessation (Review)

Bohadana 2020 (Continued)

Study funding: "2013 Global Research Award for Nicotine Dependence (GRAND) supported by Pfizer, Inc. (#WI182915)"

Author declaration of interests: "None"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was accomplished by extracting a systematic sample via a pre-prepared list of alternate allocations"
Allocation concealment (selection bias)	Unclear risk	"These procedures were performed by the randomisation monitor (VP) in a secure room where the study medication, provided free of charge by Pfizer Inc., NY, was stored in identically packaged, blinded bottles containing varenicline or placebo. Participants were referred to the secure room where they were randomly allocated (in a 1:1 ratio) to the experimental group."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind during preloading phase (open-label afterwards as both groups were receiving identical treatments).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition similar in both groups, overall < 50%
Selective reporting (reporting bias)	Low risk	Outcomes reported as in clinical trials record

Bolliger 2011
Study characteristics

Methods	Countries: Brazil, Colombia, Costa Rica, Egypt, Jordan, Lebanon, Mexico, Saudi Arabia, South Africa, United Arab Emirates, Venezuela Setting: 42 research centres (51.2% Latin America, 30.6% Africa, 18.2% Middle East) Aim: to test the efficacy and tolerability of varenicline in regions not previously exposed to SC RCTs of varenicline Dates conducted: April 2008-August 2009 Study design: double-blind placebo-controlled RCT
Participants	593 adults, recruited from SC clinics, aged 18-75, weight > 45.5 kg, BMI 15-38, smoking ≥ 10 CPD, motivated to quit. Randomised to varenicline 394 (390 got medication), or placebo 199 (198 got medication). Mean age 43.5, 63.6% men, mean CPD 23.8, mean FTND 6.0. 55% had no prior quit attempt Exclusion criteria: standard pharmacotherapy trial criteria, + participants must not have used NRT, bupropion, clonidine or nortriptyline in previous 6 months
Interventions	<ul style="list-style-type: none"> Varenicline 1 mg x 2/day, titrated during week 1 Placebo inactive tablets, same regimen Treatment period was 12 weeks. All participants received <i>You can quit smoking</i> self-help booklet (available in English, Spanish, Portuguese and Arabic) at baseline, and brief counselling (≤ 10 min) at each clinic or telephone contact. TQD set for week 1. Clinic visits at weeks 2, 3, 4, 6, 8, 10 and 12 throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at weeks 13, 16, 20 and 24, plus brief phone calls at weeks 14, 18 and 22

Nicotine receptor partial agonists for smoking cessation (Review)

Bolliger 2011 (Continued)

Outcomes Primary outcome: CO-validated CAR at 9-12 weeks
 Secondary outcomes: CO-validated CAR at 9-24 weeks; 7-day PPA at weeks 12 and 24
 Other outcomes: AEs, clinically significant changes in vital signs, SAEs
 Abstinence was assessed using the Nicotine-Use Inventory (NUI); validation was by expired CO \leq 10 ppm
 Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis). [4 (V) 1 (P) who did not receive allocated intervention re-included in denominators in this analysis.] Attrition in treatment phase was 11.2% (V) and 20.6% (P); in follow-up phase 2.5% (V) and 0.5% (P)

Notes New for 2012 update

The study was funded and managed by Pfizer Inc

Author declaration of interests: "(1) the institutions of Drs. Bolliger, Issa, Posadas-Valay, and Safwat received financial support from Pfizer for the clinical trial; (2) Drs. Bolliger, Issa, Posadas-Valay, and Safwat received no financial support from Pfizer for the submitted work; (3) Drs. Bolliger, Issa, Posadas-Valay, and Safwat have specified relationships with Pfizer that might have an interest in the submitted work in the previous 3 years, including investigator payments, consulting honoraria, and grants; (4) their spouses, partners, and children have no financial relationships that may be relevant to the submitted work; and (5) Drs. Bolliger, Issa, Posadas-Valay, and Safwat have no nonfinancial interests that may be relevant to the submitted work. Drs. Bolliger, Issa, Posadas-Valay, and Safwat did not receive financial support with respect to the writing or development of the manuscript. Dr. Abreu, Mr. Correia, Dr. Park, and Mr. Chopra are employees of, and stockholders in, Pfizer."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a block randomization within each site, eligible participants were randomly assigned in a 2:1 ratio to receive varenicline or placebo"
Allocation concealment (selection bias)	Low risk	"a web-based or telephone call-in drug management system directed by the sponsor"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All of the study personnel and participants were blinded to treatment assignment until the end of the nontreatment follow-up phase"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and attrition fully reported
Selective reporting (reporting bias)	Low risk	All predicted and expected outcomes reported

Carson-Chahhoud 2020

Study characteristics

Methods Country: Australia
 Setting: respiratory, cardiology, neurology, vascular and general medicine wards of 3 Adelaide (South Australia) hospitals
 Aim: to evaluate efficacy and safety of varenicline + quitline counselling vs quitline counselling alone in people admitted with smoking-related acute illnesses
 Study design: phase II/III open-label single-blind RCT
 Dates conducted: August 2008-December 2011

Carson-Chahhoud 2020 (Continued)

Study name: Smoking Termination Opportunity for inPatients (STOP)

Participants	<p>392 adult smokers, aged 18-75, smoking 10 CPD+, willing to quit, admitted with acute smoking-related illnesses; randomised to varenicline + counselling (196) or counselling alone (196)</p> <p>Mean age 53, 32% women, 96% white, mean CPD 25, mean FTND 5.6</p> <p>Exclusion criteria: standard pharmacotherapy criteria, acute or pre-existing psychiatric illness, history of psychosis or suicidal ideation, use of varenicline in past 12 months</p>
Interventions	<ul style="list-style-type: none"> Varenicline 1.0 mg x 2/d for 12 weeks, including week 1 at titrated dose (described as standard MIMS dosing schedule), + counselling Counselling only <p>Both groups received Quit SA 5A behavioural counselling, i.e. maximum of 8 calls over 3 months. Also booklet <i>Quit because you can</i>, + stickers and fridge magnets. Participants had to set a TQD within first 2 weeks</p> <p>Contacts were attempted with all participants at days 3 and 5, weeks 1, 2, 3, 4, 12 (EoT). Additional contacts at weeks 26 and 52</p>
Outcomes	<p>Primary outcome: self-reported CAR (< 5 cigarettes in total) (2 weeks-12 months)</p> <p>Secondary outcomes: CAR at 4, 12 and 26 weeks. 7-day PPA each week for first 4 weeks; craving; reduced hospital bed utilisation; reduction in healthcare costs</p> <p>CO validation ≤ 10 ppm used only in "a random sub-set of subjects"</p>
Notes	<p>Partially funded by the Department of Respiratory Medicine, Queen Elizabeth Hospital, Adelaide, SA</p> <p>New for 2012 update (study ID was Smith 2012; changed for 2015 update)</p> <p>Author declaration of interests: "The authors have read the journal's policy and have the following potential competing interests: KVCC was paid an honorarium and provided with economy airfares and accommodation by Pfizer Australia to present at the 2019 Smoking Exchange Summit in New South Wales where she spoke about 'culturalspecific issues in smoking cessation' and as an invited panellist in a plenary session about 'a national approach to smoking cessation'. In 2017 she received an honorarium and provided with economy airfares and accommodation to speak about 12-month results of the STOP trial at the annual Pfizer Australia conference in New South Wales, Hunter Valley. This does not alter our adherence to PLOS ONE policies on sharing data and materials. There are no patents, products in development or marketed products associated with this research to declare."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A pre-defined, central, computer-generated randomization sequence was used to assign subjects in a 1:1 ratio to either 12 weeks of treatment with varenicline plus Quitline-counseling or 12 weeks of Quitline-counseling alone."
Allocation concealment (selection bias)	Low risk	"using opaque, sealed envelopes with consecutive numbers"
Blinding (performance bias and detection bias) All outcomes	High risk	<p>Open-label design. Attempt at single-blinding (statistical investigator). "Participants and investigators were not blinded to treatment assignment".</p> <p>"Randomization and allocation concealment were performed by respiratory staff independent of the study". Biochemical validation of abstinence conducted in a random subset of participants via exhaled CO levels ≤ 10 ppm</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Missing data from questionnaire (e.g., a question missed when administering follow-up) were randomly imputed via a computer programme"

Nicotine receptor partial agonists for smoking cessation (Review)

Carson-Chahhoud 2020 (Continued)

84% varenicline completed the study at 52 weeks, vs 82% in the placebo group

Selective reporting (reporting bias)

Unclear risk

Results unavailable for some secondary outcomes prespecified in NCT record, however results may still be forthcoming in future publications

Chen 2020
Study characteristics

Methods	Country: USA Aim: to compare the efficacies of cNRT and varenicline with one another and with placebo, as a function of the rs16969968 genotype Dates: May 2015-August 2019 Study design: genotype-stratified randomised, double-blind, placebo-controlled clinical trial
Participants	822 current smokers, smoking > 5 CPD, with exhaled CO ≥ 8 ppm. 54.6% female, mean age 46.5, baseline average CPD 17.6
Interventions	<ul style="list-style-type: none"> • Placebo • cNRT (nicotine patch 21 mg/day + nicotine lozenge 2 or 4 mg/day) • Varenicline 2 x 1 mg/day Randomisation was stratified by rs16969968 genotype in blocks of 6 patients (2 per treatment per block)
Outcomes	Primary: 7-day PPA at week 12 Secondary: 7-day PPA with CO verification at 6 months; 7-day PPA at 1 year by self-report; AEs, and adherence Abstinence was defined as no self-reported smoking for at least 7 days before the assessment with biochemical verification (CO < 8 ppm) for those self-reporting abstinence.
Notes	New for 2022 update Funding by National Institute on Drug Abuse, Siteman Cancer Center and NCI Cancer Center Support Grant. Pfizer supplied the study medication free of charge. Author declaration of interests: "L.-S.C. received free supply of study medication (varenicline and placebo) for this research project via an investigator-initiated research agreement (IIR) from Pfizer. This free Pfizer product constitutes the support for this study. Pfizer supports the Principal Investigator to exercise the academic freedom and encourages publication of study results whether or not they are favorable for the Pfizer Product. R.M.C. or a member of his family owns stock in Pfizer Inc. L.J.B. is listed as an inventor on Issued US Patent 8,080,371 "Markers for Addiction" covering the use of certain single nucleotide polymorphisms in determining the diagnosis, prognosis, and treatment of addiction, and served as a consultant for the pharmaceutical company Pfizer Inc. (New York City, NY) in 2008. The spouse of N.L.S. is also listed as an inventor on Issued US Patent 8,080,371 "Markers for Addiction." All other authors declared no competing interests for this work."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"SAS Version 9 statistical software will be used to generate the random assignment table stratified by CHRNA5 genotype rs16969968" From protocol

Nicotine receptor partial agonists for smoking cessation (Review)

Chen 2020 (Continued)

Allocation concealment (selection bias)	Low risk	"The group assignment and genotype will be coded to ensure that the double blind is maintained, and the interface will prevent staff from having access to the participant's assignment and genotype until after the baseline and post treatment assessments have been completed."
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled and matched contact between groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 50% and similar between arms
Selective reporting (reporting bias)	Low risk	Results for all prespecified outcomes reported

Chengappa 2014
Study characteristics

Methods	<p>Country: Pittsburgh, USA Setting: 2 outpatient clinics, Western Psychiatric Institute and Clinic; and Dubois Medical Regional Center, Pennsylvania</p> <p>Aim: to assess the efficacy and safety of varenicline to assist in SC among patients with bipolar disorder who were euthymic and motivated to quit smoking Study design: double-blind placebo-controlled RCT</p> <p>Dates conducted: February 2010-March 2013</p>
Participants	<p>60 outpatient smokers with DSM-IV-diagnosed bipolar disorder, aged 18-65, stable state or on medication, willing to quit in the next 30 days, 10+ CPD; randomised to varenicline (31) or placebo (29)</p> <p>Mean age 46, 69% women, 66% white, mean CPD 18.1, mean FTND 6.2</p> <p>Exclusions: bupropion use (for SC); usual pharmacological criteria</p>
Interventions	<ul style="list-style-type: none"> Varenicline 1 mg x 2/day, titrated for first week Placebo inactive tablets, same regimen <p>All participants received 15-min SC counselling at each visit. CO tested and pill counts at each visit. Participants in both groups could reduce the dosage if they wished. TQD was set for week 2 onwards (i.e. full dosage reached) Treatment period was 12 weeks. Weekly pill counts to assess adherence</p> <p>Safety data were reviewed blind monthly by an external independent data safety and monitoring board (DSMB)</p>
Outcomes	<p>Primary: 7-day PPA, CO-verified, at 12 weeks</p> <p>Secondary outcomes: 7-day PPA at 24 weeks; CA at 12, 24 weeks</p> <p>Validation: CO < 10 ppm</p>
Notes	<p>New for 2016 update</p> <p>Study funding: "The National Institute of Mental Health (NIMH) of the NIH, under award R21MH087928 (Dr Chengappa), provided the main funding for this study. Pfizer provided drug/placebo and an inves-</p>

Nicotine receptor partial agonists for smoking cessation (Review)

Chengappa 2014 (Continued)

tigator-initiated grant, WS-515343 (Dr Chengappa). These monies channeled through the University of Pittsburgh were used to offset costs of study procedures, participant payments, and a percentage of the time and effort of research staff and faculty salaries."

Author declaration of interests: "Dr Turkin has served on the speaker's bureau of Forest, Sunovion, and Otsuka; and owns shares of Pfizer stock. Dr George has received investigator-initiated and contract research support from Pfizer, served as a consultant to Novartis, and received honoraria from National Institutes of Health (NIH) and American College of Neuropsychopharmacology. Drs Chengappa, Perkins, Brar, and Levine, and Mss Schlicht and Hetrick and have no financial disclosures with regards to this study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated, other than "stratified by gender"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"The treatment assignment was blinded to participating subjects, raters, investigators and statisticians"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	24 participants in each group completed treatment phase, and 24 (77%) and 20 (69%) completed full study in varenicline and placebo groups respectively Data were analysed using ITT with LOCF
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry all reported
Other bias	Unclear risk	8 participants (4 in each arm) were on bupropion for depression; 3/15 varenicline quitters and 1/3 placebo quitters were on long-term bupropion

Cinciripini 2013
Study characteristics

Methods	Country: Houston, TX, USA Setting: University of Texas MD Anderson Cancer Center Aim: to assess the relative efficacy of varenicline and bupropion SR plus intensive counselling on SC and emotional functioning Study design: double-blind placebo-controlled RCT Dates conducted: August 2006-October 2007
Participants	294 volunteer smokers, aged 18-65, 5+ CPD, fluent in English, no uncontrolled chronic illness, baseline CO > 6 ppm. Mean age 44, 39% women, 66% white, mean CPD 20, mean FTND 4.5, mean baseline CO 24.5 ppm. Allocated to varenicline (86), bupropion (102) or placebo (106) Exclusions: usual pharma exclusions, current or history of psychotic disorder, moderate or high risk of suicidality, contra-indications to varenicline or bupropion
Interventions	<ul style="list-style-type: none"> Varenicline: 12-week course (1 mg x 2/day) + non-active bupropion course (placebo) Bupropion: 12-week course (150 mg x 2/day) + non-active varenicline course (placebo)

Nicotine receptor partial agonists for smoking cessation (Review)

Cinciripini 2013 (Continued)

- Placebo: 12-week course (placebo pill x 2/day)

Blinded study physician could adjust dosages to reduce side effects if required throughout study

All participants got intensive counselling, i.e. 6 x in-person 30-min individual counselling sessions and 4 x 15-min phone calls during treatment phase, based on MI techniques. During follow-up, each participant got a 15-min in-person visit at 3 months and 6 months, and a 15-min phone call at 4 months

Outcomes	Primary: PA at EoT Secondary: PA at 3 months post-quit, 6 months post-quit; CA at 3 months post-quit, 6 months post-quit; 7-day PPA at EoT, 3 months post-quit, 6 months post-quit Validation: CO < 10 ppm. Self-reported abstainers were asked to send a salivary cotinine sample (< 15 ng/mL) by post
Notes	New for 2016 update Funding: NIDA grant DA017073, NCI grant P50CA70907; varenicline supplied by Pfizer Author declaration of interests: "Dr Cinciripini served on the scientific advisory board of Pfizer, conducted educational talks sponsored by Pfizer on SC (2006-2008), and has received grant support from Pfizer."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Adaptive randomization (minimization) was used to stratify the groups for sex, race/ethnicity, history of depression, and baseline smoking rate."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence was biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to treatment and follow-up reported, and key variables with significant differences (FTND, years of education) identified between those who stayed in and those who left. ITT analysis conducted. By 6 months, 21/86 for varenicline (24.4%), 29/102 for bupropion (28.4%) and 30/106 for placebo (28.3%) had been lost to follow-up
Selective reporting (reporting bias)	Low risk	Abstinence outcomes reported as prespecified in trial registry record
Other bias	Unclear risk	Study began as nortriptyline vs bupropion; 3 months later, 19 people had been recruited to bupropion and 18 to placebo; nortriptyline was replaced as the target treatment by varenicline. The nortriptyline phase group (cohort 1) had 19 days of medication and 3 counselling sessions before TQD, whereas varenicline phase group (cohort 2) had 12 days of medication and 2 counselling sessions before TQD. No differences were found between the 2 cohorts, nor between overall findings and cohort 2 findings. Study authors therefore combined both groups into a single study cohort for analysis.

Cinciripini 2018
Study characteristics

Methods	<p>Country: USA</p> <p>Setting: hospital-based outpatient clinic</p> <p>Aim: to determine if varenicline and bupropion combination treatment would result in higher abstinence rates than varenicline alone</p> <p>Study design: double-blind, parallel-group RCT</p>
Participants	<p>386 adult smokers who were "moderately dependent", and motivated to quit. 41.56% female, mean age 48.97, baseline average CPD 19.66</p>
Interventions	<ul style="list-style-type: none"> Varenicline 2 x 1 mg/day (titrated for first week) plus placebo Varenicline 2 x 1 mg/day (titrated for first week) plus bupropion 2 x 150 mg/day (titrated for first 3 days) Placebo <p>Participants were randomised in a 3:1 ratio of active treatment:placebo</p> <p>All smokers received 13 x 15-min in-person individual behavioral SC support, and 2 brief supportive telephone calls.</p>
Outcomes	<p>Primary: PA at the 12-month follow-up as a function of treatment, specifically between the 2 active treatment groups</p> <p>Secondary: PA at EoT and the 6-month follow-up; all other abstinence definitions; nicotine withdrawal, affect; smoking reinforcement/satisfaction; sleep problems</p> <p>Self-reported abstinence was validated by exhaled CO < 4 ppm</p>
Notes	<p>New for 2022 update</p> <p>Study funding: "United States National Institutes of Health (NIH) grant R01DA024709 (PI Cinciripini) and by The University of Texas MD Anderson's Cancer Center Support Grant CA016672, funded by the National Cancer Institute (NCI)."</p> <p>Author declaration of interests: "Dr. Cinciripini served on the scientific advisory board of Pfizer Pharmaceuticals, conducted educational talks sponsored by Pfizer on SC (2006–2008), and has received grant support and medication support from Pfizer. Dr. Karam-Hage participated in two multi-site Pfizer-funded trials and received varenicline from Pfizer to conduct 4 NIH funded trials. Pfizer (New York, NY) provided the active and matching placebo varenicline capsules. All other authors declare that they have no conflicts of interest."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Group assignment was generated with an algorithm developed and managed by study data managers, whose role was limited to data quality and integrity management.
Allocation concealment (selection bias)	Low risk	Allocation method not reported but likely low risk of selection bias "Participants were enrolled onto the trial by study staff [...] Participants, medical and research staff who interacted with participants, and the study investigators were blinded to group assignment"
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo controlled. "Participants, medical and research staff who interacted with participants, and the study investigators were blinded to group assignment". Cessation was biochemically validated

Nicotine receptor partial agonists for smoking cessation (Review)

Cinciripini 2018 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete loss to follow-up = 28%, similar loss to follow-up across groups (36%, 29%, 23%)
Selective reporting (reporting bias)	Low risk	Outcomes on Clinicaltrials.gov record are reported

Courtney 2021
Study characteristics

Methods	Country: Australia Setting: in the community Aim: to determine if cytisine is non-inferior to varenicline regarding SC Study design: non-inferiority, outcome-blinded, open-label RCT
Participants	1452 adult smokers, motivated to quit. 51% female, mean age 43, baseline average CPD 18. Recruited via advertisements and SC telephone line
Interventions	<ul style="list-style-type: none"> • Cytisine 1.5 mg 6 times daily initially, then gradually reduced over the 25-day course • Varenicline 0.5 mg tablets titrated to 1 mg twice daily <p>No placebo control group. All participants received up to 6 telephone calls providing interactive behavioural support.</p>
Outcomes	Primary: 6-month CA verified using a CO breath test at 7-month follow-up Secondary: self-reported 3- and 6-month CA; 7-day PPA at 4 weeks after baseline and at 4-month and 7-month follow-up; cigarette consumption at each follow-up
Notes	New for 2022 update Funding by Australian National Health and Medical Research Council, and the Australian government (under the Substance Misuse Prevention and Service Improvements Fund). Author declaration of interests: "Dr McRobbie reported receiving honoraria from Pfizer for speaking at smoking cessation meetings and attending advisory board meetings. Drs McRobbie and Walker reported previously receiving cytisine from Sopharma for the conduct of a noninferiority trial of cytisine vs nicotine replacement therapy. Dr Tutka reported serving as consultant to Aflofarm, which is a manufacturer of cytisine. Dr Mendelsohn reported receiving funding from Pfizer Australia, GlaxoSmithKline, and Johnson & Johnson Pacific for teaching, consulting, serving on an advisory board, and conference expenses. Dr Kwan reported receiving speaking fees from Pfizer. Dr Walker reported receiving cytisine from Achieve Life Sciences for the conduct of a noninferiority trial of cytisine (Tabex) vs varenicline; receiving investigator-initiated grants and smoking cessation medication (varenicline) and matching placebo from Pfizer for the conduct of a relapse prevention trial in patients with chronic obstructive pulmonary disease who smoke; and serving as a consultant for and receiving honoraria and travel support for speaking at research meetings from Achieve Life Sciences and Pfizer (manufacturers of smoking cessation medications). Dr Gartner reported receiving grants from the Australian Research Council, Metro South Health Service, Central Queensland Hospital and Health Service, Arthritis Australia, and the HIV Foundation Queensland. Dr Ferguson reported previously serving as a consultant to Pfizer and GlaxoSmithKline Consumer Healthcare on matters relating to smoking cessation and harm minimization; having been a member of a scientific advisory board for Johnson & Johnson; receiving researcher-initiated project grant funding from Pfizer (through the Grand initiative); and having provided consulting services to JUUL Labs Inc while working as a consultant for Pinney Associates. Dr Zwar reported receiving honoraria from Pfizer and GlaxoSmithKline for advice on smoking cessation educa-

Nicotine receptor partial agonists for smoking cessation (Review)

Courtney 2021 (Continued)

tion programs and for conference expenses. Dr West reported serving as a consultant to Pfizer, which manufactures varenicline, and receiving grants from Pfizer. Dr Farrell reported receiving unrestricted research funding from Mundipharma, Seqirus, and Indivior. No other disclosures were reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A data management system (UNICOM Intelligence) located at the social research center was used to assign a unique randomization number to study participants using a pregenerated randomization list embedded in the system"
Allocation concealment (selection bias)	Low risk	"A data management system (UNICOM Intelligence) located at the social research center was used to assign a unique randomization number to study participants using a pregenerated randomization list embedded in the system. Only an independent statistician located at the social research center had access to the pregenerated randomization list. After the baseline computer-assisted telephone interview, the datamanagement system was used to randomly assign each participant to 1 of the treatment groups in a 1:1 ratio (Figure 1)." The permuted block randomization used unequal block sizes of 12 and 16.
Blinding (performance bias and detection bias) All outcomes	Low risk	Open-label study; however, both groups received active SC treatment. Abstinence was biochemically validated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were < 50% and similar between arms.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes from protocol reported in results paper

Cox 2022
Study characteristics

Methods	Study design: RCT Country: USA Recruitment method: through media and physician referral Double-blind parallel-group RCT
Participants	500 adult African Americans who smoked 5+ CPD, motivated to quit. Baseline average CPD: 12.5. Average age 52. 87% female
Interventions	<ul style="list-style-type: none"> Varenicline (standard dose) vs placebo All participants received culturally relevant individualised counselling over 16 weeks
Outcomes	7-day PPA at 6 months biochemically validated by saliva cotinine 15 ng/mL
Notes	Study funding: "This work was funded by the National Institute on Drug Abuse (R01DA035796; Cox). Pfizer Global Pharmaceuticals and Pfizer Global Medical Grants provided study medication. Analytical chemistry was supported in part by P30 DA 012393 from the National Institute on Drug Abuse and S10 RR 026437 from the National Center for Research Resources (Benowitz). Dr Tyndale is supported by the

Nicotine receptor partial agonists for smoking cessation (Review)

Cox 2022 (Continued)

Canada Research Chairs Program (Canada Research Chair in Pharmacogenomics). Dr Ahluwalia is supported by P20GM130414, a National Institutes of Health–funded Centers of Biomedical Research Excellence. [...] The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.”

Author declaration of interests: “Dr Nollen reported receiving grants from the National Institutes of Health during the conduct of the study and nonfinancial support from Pfizer, which has provided study medication for this and other studies, outside the submitted work. Dr Mayo reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Faseru reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Ellerbeck reported receiving grants from the National Institute on Drug Abuse during the conduct of the study. Dr Tyndale reported consulting for Quinn Emanuel Urquhart & Sullivan and Ethimos and receiving grant support from the National Institutes of Health and Canadian Institutes of Health Research during the conduct of the study for work on other projects. Dr Benowitz reported receiving personal fees from Pfizer for serving on an advisory committee and Achieve Life Sciences for serving on a data and safety monitoring board and being a paid expert witness in litigation against tobacco companies outside the submitted work. Dr Ahluwalia reported receiving personal fees from Respira Technologies as a consultant and equity owner outside the submitted work. No other disclosures were reported”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"participants were assigned to receive varenicline or placebo in a 3:2 ratio via computergenerated individual random assignment to allow more participants to receive active treatment and concurrently strengthen evaluation of medication adverse events (Figure 1). Randomization was stratified by smoking level (≤ 10 or >10 cigarettes/d) and sex. A block size of 10 was used to generate the randomization schema."
Allocation concealment (selection bias)	Low risk	"The university pharmacy bottled study medication, per randomization code, labelled with participant ID numbers to ensure that study staff, investigators, and participants were blinded to treatment assignment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinance was biochemically validated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates similar between study arms
Selective reporting (reporting bias)	Low risk	Outcomes pre-specified in NCT record are reported in results paper

De Dios 2012
Study characteristics

Methods	Country: Rhode Island and Massachusetts, USA Setting: Butler Hospital, RI Aim: to assess the relative efficacy of varenicline and NRT on SC in Latino light smokers (< 10 CPD) Study design: feasibility double-blind placebo-controlled 3-arm RCT Dates conducted: April 2010-July 2010
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Nicotine receptor partial agonists for smoking cessation (Review)

De Dios 2012 (Continued)

Participants	<p>32 Latino volunteer light smokers (≤ 10 CPD), aged 18+, willing to set a quit date. Mean age 42, 53.1% women, mean CPD 7.6, mean FTND 2.9. Allocated to varenicline (10), NRT (11), placebo (11)</p> <p>Exclusions: usual pharmacological conditions, on NRT or smokeless tobacco, history of suicide attempts, chronic or acute psychiatric disorder, employed as a pilot, driver or heavy machinery operator</p>
Interventions	<ul style="list-style-type: none"> • Varenicline 12-week treatment course, titrated 1st week • NRT 24-h patch: 12 weeks: 4 weeks @ 14 mg, 8 weeks @ 7 mg • Varenicline-placebo, i.e. identical tablet, same regimen <p>All participants received a 30-min face-to-face "culturally informed" SC behavioural intervention, + a non-tailored self-help brochure, all available in both English and Spanish. All participants were compensated for attendance, and could receive travel vouchers if necessary</p>
Outcomes	<p>Primary: 7-day PPA at 6 months</p> <p>Secondary: 7-day PPA at weeks 1, 2, 1 month, 2 months, 3 months, 4 months; adherence</p> <p>Validation: CO < 5 ppm; salivary cotinine (not for the NRT group) > 10 mg/mL</p> <p>AEs not reported in detail, although study reports that "There was no pattern that suggested a higher side-effect profile for those in the varenicline group"</p>
Notes	<p>New for 2016 update</p> <p>Funding: NCI grant R01CA0129226-S1 (De Dios); NIDA grant K24-DA000512 (Stein); NIDA grant R01-DA1234, NCI grant K07-CA95623 (Stanton)</p> <p>Author declaration of interests: "The authors of this article do not have any conflicts of interest to declare."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	<p>"Study personnel and participants in the two-pill groups (varenicline and varenicline-placebo) were blinded to treatment condition. The research pharmacy maintained the study blind."</p> <p>NRT group could not be blinded to treatment; outcome assessment blinding not reported</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were fully reported; per protocol and ITT analyses conducted
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Dogar 2020
Study characteristics

Methods	<p>Country: Bangladesh and Pakistan</p> <p>Setting: 32 tuberculosis treatment centres, and at home</p> <p>Aim: to assess the effectiveness and safety of cytosine as a SC aid in patients with tuberculosis</p> <p>Study design: randomised, double-blind, placebo-controlled trial</p>
Participants	2472 adult daily smokers with pulmonary tuberculosis diagnosed in the previous 4 weeks, and motivated to quit smoking. 24.1% female, mean age 42.5, average CPD at baseline 11
Interventions	<ul style="list-style-type: none"> • Cytosine (9 mg on day 0, gradually reduced to 1.5 mg by day 25) • Placebo <p>Randomisation was 1:1 across trial arms. All participants received interactive in-person behavioural support, which included a 5-min session on the day of enrolment, and a 10-min session on the quit date.</p>
Outcomes	<p>Primary: CA at 6 months, defined as self-report (of not having used > 5 cigarettes, bidis, a water pipe, or smokeless tobacco products since the quit date)</p> <p>Abstinence was confirmed biochemically by a breath CO < 10 ppm.</p> <p>Secondary: CA at 12 months; PPA at weeks 5 and 12, and 6 and 12 months; early lapses; clinical tuberculosis score; chest X-ray grade, sputum smear microscopy; adherence to tuberculosis treatment; tuberculosis treatment outcome; Mood and Physical Symptoms Scale score; Strength of Urges To Smoke scores; time to first use of tobacco product of the day</p>
Notes	<p>New for 2022 update</p> <p>Funding by European Union Horizon 2020 research and innovation programme. Aflofarm provided the study drug cytosine at no cost.</p> <p>Author declaration of interests: "Dogar 2020: DK reports an unrestricted grant from Pfizer in 2009 for an investigator initiated trial on the effectiveness of practice nurse counselling and varenicline for SC in primary care (Dutch Trial Register NTR3067). EK reports participation in clinical studies by Pfizer, and has received grants from Pfizer, before and during the conduct of the study. KS reports a research grant from Pfizer to study the effects of varenicline on waterpipe SC. All other authors declare no competing interests."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation plus stratification; Randomisation lists were pregenerated by the trial statistician at York Trials Unit (University of York).
Allocation concealment (selection bias)	Low risk	"Randomisation lists were pregenerated by the trial statistician at York Trials Unit (University of York) and held securely at the offices of the study partners (ARK Foundation [Dhaka, Bangladesh] and The Initiative [Islamabad, Pakistan]) for sequential allocation by masked trial coordinating staff."
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence was biochemically validated and investigators, clinicians, and patients were masked to treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Attrition rates were very low and similar between study arms.

Nicotine receptor partial agonists for smoking cessation (Review)

Dogar 2020 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Pre-specified outcomes are reported.
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EAGLES 2016
Study characteristics

Methods	<p>Countries: Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Denmark, Finland, Germany, Mexico, New Zealand, Russian Federation, Slovakia, South Africa, Spain, USA</p> <p>Setting: multiple research centres</p> <p>Aim: to evaluate the efficacy of varenicline, bupropion SR, nicotine patch and placebo for SC, and to assess how far this is moderated by the presence of psychiatric disorders</p> <p>Dates conducted: November 2011-January 2015</p> <p>Study design: phase 4 triple-dummy, double-blind placebo-controlled parallel-group RCT</p> <p>Study name: EAGLES (Evaluating Global Events in a Global Smoking Cessation Study)</p>
Participants	<p>Treatment-seeking adult smokers, aged 18-75, smoking at least 10 CPD, with exhaled CO > 10 ppm at screening. Participants in the psychiatric disorder cohort had to have a current or lifetime stable psychiatric diagnosis, confirmed by Structured Clinical Interview for DSM-IV disorders, i.e. no acute exacerbation in the previous 6 months, no changes to treatment for 3 months, not imminently likely to change treatment, and not at risk of self-harm. Allocation for the psychiatric cohort was balanced across 4 diagnostic group disorders, i.e. mood, anxiety, psychotic, personality</p> <p>44% men, mean age 46, mean CPD 20.7, mean FTND 5.8</p> <p>Exclusions: past or current diagnosis of schizophreniform or delusional disorders, all delirium, dementia, and other cognitive disorders, and all substance-induced disorders (other than nicotine)</p> <p>In the psychiatric disorders group, 70% had primary affective disorders, 19% anxiety disorders, 9.5% psychotic disorders, 0.6% personality disorders, and at least 1/3 were taking psychotropic medications</p> <p>Participants were grouped by the presence (4116) or absence (4028) of a history of psychiatric disorders</p> <p>Psychiatric disorders: varenicline 1032; bupropion 1033, NRT patch 1025, placebo 1026</p> <p>No psychiatric disorders: varenicline 1005; bupropion 1001, NRT patch 1013, placebo 1009</p> <p>Safety analyses were conducted in cohorts of 4074 (psychiatric) and 3984 (non-psychiatric)</p>
Interventions	<ul style="list-style-type: none"> Varenicline, 1 mg x 2/day (1 week titrated, then 11 weeks full dose) Bupropion SR, 150 mg x 2/day (titrated for 3 days, then full dose for 11 weeks) Nicotine patch, 21 mg x 7 weeks, 14 mg x 2 weeks, 7 mg x 2 weeks (11 weeks) Triple-dummy placebo for each arm of the trial (12 weeks) <p>All participants received counselling (up to 10 min) at all contacts, and were encouraged to complete all visits even if treatment was discontinued</p> <p>Participants were monitored at weeks 1-6, 8, 12, 13, 16, 20, 24; contacts were up to 15 face-to-face visits and 11 telephone visits</p>

EAGLES 2016 (Continued)

Outcomes	<p>At least 1 SAE of anxiety depression, feeling abnormal, or hostility, and/or moderate or severe AE of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic paranoia, psychosis, suicidal ideation/behaviour/completed</p> <p>4-week abstinence confirmed by CO < 10 ppm at weeks 9-12, and 15-week abstinence at weeks 9-24</p> <p>In the non-psychiatric cohort, 78.9% completed treatment, and 78.4% completed the study</p> <p>In the psychiatric cohort, 74.2% completed treatment, and 77.8% completed the study</p>
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Notes	<p>Trial was funded by Pfizer and GlaxoSmithKline</p> <p>Author declaration of interests: "RMA reports receiving grants from Pfizer and Alkermes, and providing consulting and advisory board services to Pfizer, Arena Pharmaceuticals, and Cerecor. RMA's writing of this manuscript was supported, in part, by National Institute on Alcohol Abuse and Alcoholism grant numbers U01 AA013641 and R01 AA019720; National Institute on Drug Abuse/Veterans Affairs Cooperative Studies numbers 1031 and 1032; and Veterans Affairs Merit Award number NEUA-003-08S. NLB reports providing consulting and advisory board services to Pfizer and GlaxoSmithKline, and having been a paid expert witness in litigation against tobacco companies. RW reports receiving grants from Pfizer, Johnson & Johnson, and GlaxoSmithKline, and receiving personal fees for advisory board services from Pfizer and GlaxoSmithKline. RW's salary is funded by Cancer Research UK. AEE reports receiving grants from Pfizer and Forum Pharmaceuticals, and receiving personal fees for advisory board services from Pfizer and Reckitt Benckiser. AEE's writing of the manuscript was supported by a National Institute on Drug Abuse Career Award in Patient-Oriented Research, number K24 DA030443. LSA, TM, DL, and CR are employees and stockholders of Pfizer. JA is an employee of GlaxoSmithKline and stockholder of that company. AK is a PAREXEL employee working on behalf of GlaxoSmithKline. The opinions expressed in this Article are the authors' own, and do not necessarily reflect the views of their employers."</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomisation schedule ... using a block size of 8 (1:1:1:1 ratio) for each of the 20 diagnosis by region combinations"
Allocation concealment (selection bias)	Low risk	"Investigators obtained participant identification numbers via a web-based or telephone call-in drug management system"
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>"Study product kit codes did not allow deciphering of randomised treatment or block size. As such, participants, investigators, and research personnel were masked to treatment assignment"</p> <p>"The triple dummy design feature required participants to take study medication as masked tablets dispensed in separate varenicline and bupropion pill bottles each with matching placebo along with either applying active or placebo patches on a daily basis"</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	All losses fully accounted for; ITT analysis conducted throughout
Selective reporting (reporting bias)	Low risk	All protocol-reported outcomes were addressed.

Ebbert 2015

Study characteristics

Nicotine receptor partial agonists for smoking cessation (Review)

Ebbert 2015 (Continued)

Methods	<p>Country: 65 centres in 10 countries: USA (14), Australia (4), Canada (6), Czech Republic (7), Egypt (3), Germany (7), Japan (6), Mexico (4), Taiwan (7), UK (7)</p> <p>Setting: clinics, hospitals, academic research centres</p> <p>Aim: to determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction</p> <p>Study design: double-blind placebo-controlled multinational RCT</p> <p>Study name: Reduce to Quit</p> <p>Dates conducted: July 2011-July 2013</p>
Participants	<p>1510 adult smokers, unwilling to quit abruptly (within the next month), aged 18+, smoking mean 10+ CPD, interested in trying to quit within 3 months. Mean age 44.5, 43.7% women, mean CPD 20.7, mean FTND 5.5. Allocated to varenicline (760) or placebo (750)</p> <p>Exclusions: suicidal behaviour in previous 2 years or history of suicide attempts; major depression, anxiety; diagnosis of psychosis, panic disorder, post-traumatic stress disorder, schizophrenia</p>
Interventions	<ul style="list-style-type: none"> Varenicline 24 weeks, titrated 1st week (12 weeks to quit + 12 weeks post-quit) Placebo 24 weeks, titrated 1st week (12 weeks to quit + 12 weeks post-quit) <p>All participants asked to reduce their smoking rate by 50% by week 4, by 75%+ by week 8, and 100% by week 12. Individual 10-min counselling at each visit (18 face-to-face and 10 phone calls), + a copy of <i>Clearing the air: quit smoking today</i></p>
Outcomes	<p>Primary: CAR at weeks 15-24</p> <p>Secondary: CAR at weeks 21-24, 15-52, 21-52; 7-day PPA at weeks 24, 52</p> <p>Validation: CO < 10 ppm</p>
Notes	<p>New for 2016 update</p> <p>Funding: Pfizer</p> <p>Author declaration of interests: "The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ebbert reports receiving grants from JHP Pharmaceuticals, Orexigen, Pfizer, and the National Institutes of Health; and receiving personal fees from GlaxoSmithKline during the conduct of the study. Dr Hughes reports receiving personal fees from Alere/Free and Clear, Cicatelli, DLA Piper, Dorffermeyer, Embera, Equinox, GlaxoSmithKline, Healthwise, Nicoventures, Pfizer, Pro Ed, Publicis, Selecta, and nonfinancial support from Swedish Match. Dr West reports receiving grants, personal fees, and nonfinancial support from Pfizer, GlaxoSmithKline, and Johnson & Johnson. His salary is funded by a Centre grant from Cancer Research UK. Dr Rennard reports being an advisory board member for A2B Bio, Almirall, Dalichi Sankyo, Novartis, Nycomed, and Pfizer; consulting for Almirall, APT Pharma/Britnall, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Decision Resource, Dunn Group, Easton Associates, Gerson, GlaxoSmithKline, MedImmune, Novartis, Pearl, Roche, Takeda, and Theravance; receiving lecture fees from CME Incite, Forest, Novis, PriMed, and Takeda; receiving grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Johnson & Johnson, Novartis, and Otsuka. Drs Russ, McRae, Yu, Dutro, Park, and Ms Treadow are employees and stockholders of Pfizer."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized to receive varenicline or placebo for 24 weeks of treatment in a 1:1 ratio using a computer generated block randomization schedule within site"

Nicotine receptor partial agonists for smoking cessation (Review)

Ebbert 2015 (Continued)

Allocation concealment (selection bias)	Low risk	"Investigators obtained participant identification numbers and treatment group assignments through a web-based or telephone call-in drug management system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants, investigators, and research personnel were blinded to randomization until after the database was locked"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported. ITT analyses conducted for efficacy (760 varenicline, 750 placebo), and treated denominators for safety outcomes (751 varenicline, 742 placebo)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry reported in results paper

Ebbert 2016
Study characteristics

Methods	Country: USA Setting: community Aim: to evaluate the efficacy of varenicline for smoking abstinence among light smokers Study design: placebo-controlled RCT
Participants	93 participants, all light smokers (defined as 5-10 CPD), and motivated to quit. 60% female, mean age 37, baseline mean CPD 7.7
Interventions	<ul style="list-style-type: none"> Varenicline 2 x 1 mg/day Placebo All participants received in-person interactive behavioural support, consisting of 6 x 10-min sessions
Outcomes	Primary: 7-day PPA rate at week 12. Biochemically verified with exhaled CO < 8 ppm Secondary: PA
Notes	Funding and medication provided by Pfizer Author declaration of interests: "JOE reports grants from Pfizer during the conduct of the study and grants from Takeda, the US Department of Defense, and the NIH outside the submitted work. RTH reports grants from Pfizer during the conduct of the study and grants from the NIH outside the submitted work. JTH reports grant from Pfizer during the conduct of the study. ITC and DRS declare no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated randomization sequence assigned participants in a 1:1 ratio to treatment conditions"
Allocation concealment (selection bias)	Low risk	"Pharmacy personnel dispensed study medication into containers labeled according to study identification numbers. Study participants, investigators, and pharmacy staff were blinded to treatment assignment."

Nicotine receptor partial agonists for smoking cessation (Review)

Ebbert 2016 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	"Study participants, investigators, and pharmacy staff were blinded to treatment assignment." Abstinence biochemically validated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study attrition rates were high and varied significantly between study arms: " Study completion rates were 62% (28/45) in the varenicline group and 42% (20/48) in the placebo group."
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in methods are reported in results. However, trial protocol or registry entry unavailable

Fouz-Roson 2017
Study characteristics

Methods	Country: Spain Setting: Stop-Smoking Clinic Aim: to test for differences between standard 1- and 0.5-mg doses of varenicline in smoking abstinence, adherence and side effects Study design: open-label randomised parallel-group controlled trial with 1-year follow-up
Participants	484 adult smokers aged between 20-80. 40% female, mean age 50.67 years and a smoking history of 37.5 pack-years. 60.5% had already made at least one attempt to quit previously. Exclusion criteria were: advanced neoplastic disease, advanced chronic kidney disease, pregnancy, breastfeeding or inclusion in a fertility programme
Interventions	<ul style="list-style-type: none"> Lower-dose varenicline: 0.5 mg/12 h for 8 weeks (titrated for the first week) Higher-dose varenicline 1 mg/12 h for 8 weeks (titrated for the first week) All participants received 6 sessions of interactive behavioural support, as face-to-face cognitive behavioural therapy sessions. Participants also had access to telephone support as needed.
Outcomes	Primary: continuous self-reported abstinence during 1 year, verified biochemically with exhaled CO < 6 ppm Secondary: adherence and side effects
Notes	New for 2022 update Funding research grant awarded by the Fundación Neumosur, within the 'Asociación de Neumología y Cirugía Torácica del SUR', partial funding by Grifols Author declaration of interests: "All the authors are grateful for the research grant awarded by the Fundación Neumosur within the 'Asociación de Neumología y Cirugía Torácica del SUR', as well as the funding made available to the Respiratory Unit of the Virgen Macarena University Hospital by Grifols. Research Ethics Committee Registry. C.P.- C.I. 2217 (promotor code and internal code)."

Risk of bias

Bias	Authors' judgement	Support for judgement
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Fouz-Roson 2017 (Continued)

Random sequence generation (selection bias)	Low risk	"Randomization was conducted by a statistician from our hospital, who generated a list of study group assignments for 460 patients, using computer-generated blocks of 10, with MAS software version 2.1".
Allocation concealment (selection bias)	Unclear risk	Concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Study open label, but abstinence was biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were very low in both study arms.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry entry found

Gonzales 2006
Study characteristics

Methods	Country: USA Setting: 19 research centres Aim: to test the efficacy and safety of varenicline for SC Dates conducted: June 2003-April 2005 Study design: double-blind placebo-controlled parallel-group RCT
Participants	1025 healthy adult volunteers, recruited through media advertising. Allocated to varenicline (352), bupropion (329) or placebo (344). 54% men, 79% white, mean age 42.4, mean CPD 21, mean FTND score 5.3. No significant differences between groups at baseline Exclusion criteria: standard pharmacotherapy trial criteria, + use of tobacco products other than cigarettes; use of NRT, clonidine, nortriptyline within last month; BMI < 15 or > 38 or weight < 45.5 kg; any prior use of bupropion or varenicline
Interventions	<ul style="list-style-type: none"> • Varenicline 1 mg x 2/day • Bupropion 150 mg x 2/day • Placebo inactive tablets, same regimen <p>Treatment period was 12 weeks. All participants received <i>Clearing the Air</i> self-help booklet at baseline, and brief counselling (≤ 10 min) at each clinic visit. Weekly visits throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at weeks 13, 24, 36, 44 and 52, plus brief phone calls at weeks 16, 20, 28, 32, 40 and 48</p>
Outcomes	Primary outcome: CO-validated CAR at 9-12 weeks Secondary outcomes: CO-validated CAR at 9-24 weeks and 9-52 weeks; 7-day PPA at weeks 12, 24 and 52 Other outcomes: weight change, withdrawal symptoms (using MNWS, QSU-brief and mCEQ), AEs Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 31.5%, losses to follow-up 16% of treatment completers
Notes	This trial had the same aims and study design as Jorenby 2006

Nicotine receptor partial agonists for smoking cessation (Review)

Gonzales 2006 (Continued)

Study funding: "This study was supported by Pfizer Inc, which provided funding, study drug and placebo, and monitoring"

Author declaration of interests: "Dr Gonzales reports having received research contracts from Pfizer, SanofiAventis, GlaxoSmithKline, and Nabi Biopharmaceuticals; consulting fees and honoraria from Pfizer, SanofiAventis, and GlaxoSmithKline; and owning 5 shares of Pfizer stock. Dr Rennard reports having had or currently having a number of relationships with companies who provide product and/or services relevant to outpatient management of chronic obstructive pulmonary disease. These relationships include serving as a consultant for Adams, Almirall, Altana, Array Biopharma, AstraZeneca, Aventis, Biolipox, Centocor, Dey, Critical Therapeutics, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Ono Pharma, Otsuka, RJ Reynolds, Roche, Sankyo, Schering-Plough, Scios, and Wyeth; advising regarding clinical trials for Altana, AstraZeneca, Aventis, Centocor, GlaxoSmithKline, Novartis, Pfizer, and Philip Morris; and speaking at continuing medical education programs and performing funded research both at basic and clinical levels for Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis. Dr Nides reports having received research grants, consulting fees, and honoraria from Pfizer, SanofiAventis, and GlaxoSmithKline. Dr Oncken reports having received research grants, consulting fees, and honoraria from Pfizer; receiving, at no cost, nicotine replacement and placebo products from GlaxoSmithKline for SC studies; and receiving honoraria from Pri-Med. Drs Azoulay, Watsky, Gong, Williams, and Reeves and Mr Billing report owning Pfizer stock or having stock options in Pfizer"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"predefined ... computer-generated randomization sequence", 1:1:1, using block size of 6, stratified by centre
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants and investigators were blinded to drug treatment assignments[, and] ... were not encouraged to guess their treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Considered abstinent if, at next non-missed visit, they reported no smoking... Missing CO but otherwise OK considered abstinent, except at end of study, where all criteria had to be present
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Gonzales 2014
Study characteristics

Methods	Country: 37 centres in 8 countries: USA (8), Australia (4), Belgium (4), Canada (4), Czech Republic (4), France (3), Germany (5), UK (5) Setting: clinics, hospitals, academic research centres Aim: to evaluate the efficacy and safety of retreatment with varenicline in smokers who had taken varenicline for ≥ 2 weeks in a previous SC attempt Study design: double-blind placebo-controlled multinational RCT Dates conducted: December 2010-November 2012
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Gonzales 2014 (Continued)

Participants	498 adult smokers (varenicline 251, placebo 247) with previous use of 2+ weeks of varenicline at least 3 months prior to screening, aged 18+, CPD 10+, motivated to quit. Mean age 47.5, 50.4% women, 93% white, mean CPD 20.5, mean FTND 5.5
Interventions	<ul style="list-style-type: none"> Varenicline 12 weeks, titrated in 1st week, 1 mg x 2/day Placebo, identical regimen <p>Brief (< 10 min) counselling at each contact. TQD set for week 1 visit. Clinic visits at weeks 1, 2, 3, 4, 6, 8, 9, 10, 11, 12; 13, 16, 24, 32, 40, 48, 52. Brief phone calls at weeks 5, 7, 14, 20, 36, 44. Dosage could be halved if intolerable</p>
Outcomes	<p>Primary: CAR at weeks 9-12, 9-52</p> <p>Secondary: CAR at weeks 9-24; 7-day PPA at weeks 12, 24, 52</p> <p>Validation: CO < 10 ppm</p>
Notes	<p>New for 2016 update</p> <p>Funding: Pfizer</p> <p>Author declaration of interests: "D.G. reports grants, and nonfinancial and other support from Pfizer during the conduct of the study; and grants, stock ownership, and nonfinancial and other support from Pfizer, grants from Nabi Biopharmaceuticals, and personal fees and nonfinancial support from GlaxoSmithKline outside the submitted work. P.H. reports grants from Queen Mary University of London during the conduct of the study and grants and personal fees from Pfizer, McNeil, GlaxoSmithKline, and Novartis outside the submitted work. L.P. reports grants from Pfizer outside the submitted work. K.N. reports funding and nonfinancial support from Pfizer during the conduct of the study and personal fees from Pfizer (Belgium) outside the submitted work, for serving as an advisory board member and for lectures. L.-J.T, T.D.M., and J.T. are employees of Pfizer."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomly assigned to receive either varenicline or placebo at a 1:1 ratio for 12 weeks of drug treatment using computer-generated block randomization within each site"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported. ITT analyses conducted
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry reported in results paper

Gray 2019

Study characteristics

Nicotine receptor partial agonists for smoking cessation (Review)

Gray 2019 (Continued)

Methods	Country: USA Setting: university outpatient clinic Aim: to evaluate whether varenicline, when added to brief cessation counselling, is efficacious and safe for SC in adolescents Study design: parallel double-blind placebo-controlled RCT
Participants	157 treatment-seeking adolescent current smokers, aged 14-21, and motivated to quit. 40% female, mean age 19.4, baseline average CPD 11.3. Participants must have smoked daily for at least 6 months and had at least one failed attempt at quitting. Exclusion criteria: history of mood or psychotic disorder, suicidality, homicidality, or significant hostility or aggression; substance dependence other than nicotine, unstable medical disorder, pregnancy, breastfeeding, or use of medications with SC efficacy; known hypersensitivity to varenicline
Interventions	<ul style="list-style-type: none"> Varenicline 2 x 1 mg/day Placebo Participants were randomised in a 1:1 ratio. All participants received in-person interactive behavioural support weekly for 12 weeks.
Outcomes	Primary: 7-day abstinence at the end of the 12 weeks of treatment. Confirmed with urine-cotinine level Secondary: weekly abstinence throughout active treatment; abstinence at post-treatment follow-up visits; time to first 7-day abstinence
Notes	New for 2022 update. Study authors provided additional results data upon request Funding by grants from then NIH, and varenicline and placebo were supplied at no cost by Pfizer. Author declaration of interests: "Dr Gray reported consulting for Pfizer, Inc, and receiving grant support from the National Institutes of Health (NIH). Mr Baker reported receiving grant support from the NIH. Dr McClure reported receiving grant support from the NIH. Dr Tomko reported receiving grant support from the NIH during the conduct of the study and outside the submitted work. Dr Squeglia reported receiving grant support from the NIH. Dr Saladin reported receiving grant support from the NIH. Dr Carpenter reported consulting for Pfizer, Inc, during the conduct of the study. No other disclosures were reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated randomised, but randomisation method not specified
Allocation concealment (selection bias)	Unclear risk	Concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial described as double blinded and equivalent face to face contact identical between study arms. Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were similar between study arms
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported

Nicotine receptor partial agonists for smoking cessation (Review)

Heydari 2012

Study characteristics

Methods	<p>Country: Tehran, Iran Setting: SC clinics in the Tobacco Prevention and Control Research Centre, Shahid Beheshti University of Medical Sciences</p> <p>Aim: to evaluate the effectiveness of varenicline in the Iranian community of tobacco quitters and compare it with other treatment methods Study design: 3-arm randomised parallel clinical study</p> <p>Dates conducted: 2009-2010 Analysis: 91 participants per group were required</p>
Participants	272 treatment-seeking participants: brief advice (91), NRT (92), varenicline (89). 41.2% women, mean age 42.5 years, mean FTND 5.5
Interventions	<ul style="list-style-type: none"> Control group: no pharmacotherapy NRT: 8 weeks of 15 mg NRT patches 8 weeks of 1 mg x 2/day varenicline (titrated 1st week) <p>All participants were managed by the same physician. All received brief (5 min) education and counselling at 4 x weekly sessions. TQD was day 14</p>
Outcomes	Abstinence at 6 months and 12 months, in person or by phone, verified by expired CO (cut-off value not given)
Notes	<p>Funding: Masih Daneshvari Hospital Research Institute, Tehran</p> <p>New for 2016 update</p> <p>Author declaration of interests: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Smokers who attended the clinic for help in quitting were divided randomly"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label; blinding of outcome assessors not reported, but abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition: "Participants entered the study of their own accord and none left the study"
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry reported in results paper

Hong 2015
Study characteristics

Methods	Country: China Setting: hospital Study design: parallel RCT
Participants	300 COPD inpatients/perioperative patients, all smokers. 3% female, mean age 58
Interventions	<ul style="list-style-type: none"> • 5As (Ask, Advise, Assess, Assist, and Arrange) • 5As + varenicline All participants received interactive behavioural support, either in person or on the telephone
Outcomes	Self-reported CA at 24 weeks
Notes	Study funding: not reported Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated randomised but methods not reported
Allocation concealment (selection bias)	Unclear risk	Concealment not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study reported no participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Hurt 2018
Study characteristics

Methods	Country: USA Study design: phase II/III randomised quadruple-blind placebo-controlled trial Study period: July 2011-April 2013
Participants	33 adult alcohol-dependent smokers
Interventions	Varenicline 1 mg 2 x day for 12 weeks vs placebo
Outcomes	PA at 12 weeks (EoT), and at 6 months

Nicotine receptor partial agonists for smoking cessation (Review)

Hurt 2018 (Continued)

Abstinence self-reported and biochemically validated by exhaled CO

Notes

 Study results posted on www.clinicaltrials.gov May 2014

Study funding: "This current study was supported by grant R21 DA30645 to Dr Richard D. Hurt and Pfizer IIR to Dr J. Taylor Hays"

Author declaration of interests: "R.T.H. reports research grants from Pfizer and the NIH. J.T.H. reports research grants from Pfizer. J.O.E. reports grants from Pfizer during the conduct of the study and grants from Takeda, the U.S. Department of Defense and the NIH outside the submitted work. R.D.H. reports a research grant from the NIH. All other others have nothing to disclose"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomized" but method not reported
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"Pharmacy personnel dispensed study medication into containers labeled with study identification numbers. Study participants, investigators, and pharmacy staff were blinded to treatment assignment." Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rates: 4/16 varenicline group (1 withdrawal, 3 lost), 12/17 placebo group (7 withdrawals, 5 lost)
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes from NCT record all reported in results paper

Ikonomidis 2017
Study characteristics

Methods	Country: Greece Setting: hospital SC clinic Study design: parallel RCT Recruitment method: approached everyone attending SC clinic
Participants	188 adults who smoke and were motivated to quit. Average age 50. 45% female. Baseline CPD 30
Interventions	<ul style="list-style-type: none"> Nicotine patch + nicotine gum (12 weeks) Varenicline (12 weeks) No behavioural support
Outcomes	SC at 52 weeks, verified by CO < 10 ppm
Notes	Study funding: "The study was funded by a grant from the Hellenic Cardiac Society"

Nicotine receptor partial agonists for smoking cessation (Review)

Ikonomidis 2017 (Continued)

Author declaration of interests: "The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"One hundred eighty-eight current smokers were randomized to varenicline or nicotine replacement treatment (NRT) for a 3-month period" No further information provided
Allocation concealment (selection bias)	Unclear risk	"One hundred eighty-eight current smokers were randomized to varenicline or nicotine replacement treatment (NRT) for a 3-month period" No further information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Both groups received active treatments and SC was biochemically validated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates unclear
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

Ioakeimidis 2018
Study characteristics

Methods	Country: Greece Setting: hospital Aim: to compare the SC efficacy and safety of e-cigarettes vs varenicline among patients who continue to smoke after acute coronary syndrome Study design: parallel RCT
Participants	54 smokers, smoking ≥ 10 CPD and expressing motivation to quit. All had previous acute coronary syndrome (mean time interval between acute coronary syndrome and study entry 6 ± 2.7 months) Baseline average CPD 12
Interventions	<ul style="list-style-type: none"> Varenicline (dose not reported) E-cigarette (12 mg/mL nicotine) All participants received "low intensity" interactive behavioural support.
Outcomes	Primary: PPA, defined by self-report of complete abstinence in the 7 days before the 24-week clinic visit. Abstinence was not biochemically verified.
Notes	New for 2022 update Study funding: not reported Author declaration of interests: not reported

Nicotine receptor partial agonists for smoking cessation (Review)

Ioakeimidis 2018 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on randomisation methods
Allocation concealment (selection bias)	Unclear risk	No information provided on randomisation methods
Blinding (performance bias and detection bias) All outcomes	Low risk	2 effective treatments provided and equal amounts of contact between arms
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Abstract/poster only so not able to judge
Other bias	High risk	Abstract and poster only. 2 different figures presented for quit rate in e-cigarettes arm (no difference in those presented in varenicline arm) between abstract and poster. Poster percentage aligns with figure, so using that (16.5%) as opposed to abstract figure (32.5%). Contacted study authors but no reply. Calculated n quit based on percentages but unclear what denominators were; e-cigarettes calculates back to whole number for e-cigarettes but not for varenicline

Johns 2017a

Study characteristics

Methods	<p>Study design: RCT</p> <p>Country: India</p> <p>Setting: not reported</p> <p>Recruitment method: not reported</p>
Participants	200 people who smoked with one of the following: previous lung disease, a family history of lung cancer, past cancer treatment, lowered immunity, previous smoking-related cancers, exposure to certain chemicals and radon gas
Interventions	<ul style="list-style-type: none"> • Counselling alone • Counselling for 3 weeks + varenicline (1 mg twice/day) for 6 weeks • Counselling for 6 weeks + varenicline (1 mg twice/day) for 6 weeks
Outcomes	PPA at 52 weeks, verified by exhaled CO < 10 ppm
Notes	<p>Study funding: not reported</p> <p>Author declaration of interests: not reported</p> <p>Abstract only</p>

Nicotine receptor partial agonists for smoking cessation (Review)

Johns 2017a (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates not reported
Selective reporting (reporting bias)	Unclear risk	Both continuous and PPA collected but only point prevalence reported (abstract only)

Johns 2017b
Study characteristics

Methods	Study design: RCT Country: India Setting and recruitment method not specified
Participants	300 participants randomised
Interventions	<ul style="list-style-type: none"> Bupropion, 150 mg twice daily for 12 weeks Varenicline, 1 mg twice daily for 12 weeks Bupropion and varenicline, taken according to schedules above
Outcomes	<ul style="list-style-type: none"> SC: CA at 6 months. Validated by CO AEs: period of measurement not detailed
Notes	Funding source: none specified Author conflicts of interest: none specified Abstract only. Insufficient data to add to MA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States trial was randomised, no further detail given
Allocation concealment (selection bias)	Unclear risk	No relevant information given

Nicotine receptor partial agonists for smoking cessation (Review)

Johns 2017b (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	States only that the study was "double-blind", no further detail given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Jorenby 2006
Study characteristics

Methods	Country: USA Setting: 14 research centres Aim: to test the efficacy and safety of varenicline for SC Dates conducted: June 2003-March 2005 Study design: double-blind placebo-controlled RCT
Participants	1027 healthy adult volunteers. Allocated to varenicline (344), bupropion (342) or placebo (341). 58% men, 84% white, mean age 43.3, mean CPD 22, mean FTND score 5.3. No significant differences between groups at baseline Exclusion criteria: standard pharmacotherapy trial criteria, + use of tobacco products other than cigarettes; use of NRT, clonidine, nortriptyline within last month; BMI < 15 or > 38 or weight < 45.5 kg; any prior use of bupropion or varenicline
Interventions	<ul style="list-style-type: none"> • Varenicline 1 mg x 2/day • Bupropion 150 mg x 2/day • Placebo inactive tablets, same regimen <p>Treatment period was 12 weeks. All participants received brief counselling (≤ 10 min) at each clinic visit Weekly visits throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at weeks 13, 24, 36, 44 and 52, plus brief phone calls at weeks 16, 20, 28, 32, 40 and 48</p>
Outcomes	Primary outcome: CO-validated CAR at 9-12 weeks Secondary outcomes: CO-validated CAR at 9-24 weeks and 9-52 weeks; 7-day PPA at weeks 12, 24 and 52 Other outcomes: weight change, withdrawal symptoms (using MNWS, QSU-brief and mCEQ), AEs Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 29.3%, losses to follow-up 8% of treatment completers
Notes	<p>This trial had the same aims and study design as Gonzales 2006.</p> <p>Study funding: "The data reported in this article were derived from a clinical trial sponsored by Pfizer Inc, which provided funding, study drug and placebo, and monitoring."</p> <p>Author declaration of interests: "Dr Jorenby reported receiving research support from Pfizer, Nabi Biopharmaceutical, Sanofi-Aventis and consulting fees from Nabi Biopharmaceutical. Dr Hays reported receiving a research grant from Pfizer. Dr Rigotti reported receiving research grant funding and consulting fees from GlaxoSmithKline, which markets smoking cessation medications, and Pfizer and Sanofi-</p>

Jorenby 2006 (Continued)

Aventis, which are developing smoking cessation medications. Dr Rigotti also reported receiving consulting fees from Merck, which is developing smoking cessation medications."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated list"
Allocation concealment (selection bias)	Low risk	"completed centrally ... and sites used an electronic system to assign participants to treatment"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"in a double-blind manner"
Incomplete outcome data (attrition bias) All outcomes	Low risk	CA for missed visits: if self-reported abstinent at next visit, assumed abstinent, except at week 52 visit when all criteria had to be met
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

King 2022
Study characteristics

Methods	Country: USA Setting: 2 outpatient clinics Aim: to determine whether combined treatment with varenicline tartrate and nicotine patch improves CA from cigarette smoking among smokers who drink heavily Study design: double-blind, placebo-controlled, superiority RCT
Participants	122 current smokers participants, all alcohol-dependent. Eligible participants smoked between 5 and 30 CPD and drank heavily (> 14 drinks per week for men or > 7 drinks per week for women and ≥ 1 heavy drinking day (defined as > 5 drinks per occasion for men or > 4 drinks per occasion for women) per month for the past year) and were motivated to quit. 45.1% female, mean age 44, baseline average CPD 11.8
Interventions	<ul style="list-style-type: none"> Nicotine patch + varenicline 2 x 1 mg/day Nicotine patch + placebo Intervention duration was 12 weeks. Participants were randomised in a 1:1 ratio. All participants received 2x interactive behavioural support sessions 2 weeks apart.
Outcomes	Primary: self-reported cigarette CA through weeks 9-12. Abstinence was biochemically confirmed at the week 12 study visit with exhaled CO < 10 ppm. Secondary: frequency of weekly drinking and weekly heavy drinking during the study period
Notes	New for 2022 update

King 2022 (Continued)

Funding by grant P30 CA14599 from the University of Chicago Medicine Comprehensive Cancer Center, Global Research Award for Nicotine Dependence from Pfizer, Women's Board of the University of Chicago Cancer Research Foundation.

Author declaration of interests: "Dr King reported receiving grants from Pfizer during the conduct of the study and personal fees from the Respiratory Health Association outside the submitted work. Dr de Wit reported being on the board of directors of PharmAla Biotech; being a scientific advisor to Awakn Life Sciences, Gilgamesh Pharmaceuticals, and Schedule I Therapeutics; and receiving research support from the Beckley Foundation outside the submitted work. Dr Grant reported receiving grants from Biohaven Pharmaceuticals, Otsuka Pharmaceutical Company, and Promentis Pharmaceuticals outside the submitted work. No other disclosures were reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A 1:1 randomization list was generated by the data manager using a random number generator..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled, matched behavioural support and biochemically validated cessation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates low and similar between study arms
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported either in published results paper or on trial registry website

Le Mao 2020
Study characteristics

Methods	Country: France Setting: hospital, home Aim: to demonstrate that, in smoker patients hospitalised for COPD exacerbation, early initiation of varenicline for 12 weeks, combined with an intensive counselling, is associated with a higher CA rate as compared to intensive counselling alone Study design: multicentre, prospective, double-blind, randomised trial
Participants	81 smokers hospitalised for COPD exacerbation. Participants must have been hospitalised for at least 24 h, and smoked ≥ 10 CPD during the last year, and were motivated to quit smoking. 39.5% female, mean age 56.8, baseline average CPD 23.1 Exclusion criteria: patients who used concomitant treatment for SC, past history of severe depression requiring therapy drugs within 5 years or/with ≥ 2 episodes of severe depression requiring medication, attempted suicide
Interventions	<ul style="list-style-type: none"> • Placebo • Varenicline 2 x 1mg/day (titrated for the first week)

Nicotine receptor partial agonists for smoking cessation (Review)

Le Mao 2020 (Continued)

Participants were randomised on a 1:1 ratio. All participants received interactive behavioural support in person (weeks 1, 4, 8, 12, 26, 52) and on the telephone (weeks 2, 18, 34, 42).

Outcomes

Primary: CA rate at week 52, defined by the rate of participants who presented the all following criteria: SC for weeks 8-12, exhaled CO level ≤ 10 ppm at each clinic visit. < 6 cigarettes to weeks 12-52. complete SC during the 7 previous days before week 52

Secondary CA rate at weeks 12 and 26; punctual abstainer rate (PAR) defined as patient's rate who did not smoke within 7 days prior to follow-up visit with exhaled CO level of < 10 ppm at weeks 12, 26 and 52; AEs; nicotine substitute consumption

Notes

New for 2022 update

Funding by "Programme Hospitalier de Recherche Clinique", Ministère de la Santé, Pfizer.

Author declaration of interests: "All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Couturaud reports having received research grant support from Pfizer and fees for board memberships or symposia from Bayer and Astra Zeneca and having received travel support from Bayer, Daiichi Sankyo, Leo Pharma, Intermune and Actelion. Dr. Le Mao declares he has no conflict of interest related to this research. Dr. Tromeur declares she has no conflict of interest related to this research. Dr. Paleiron declares he has no conflict of interest related to this research. Dr. Sanchez reports having received research grant support from Bayer, Daiichi Sankyo and Portola Pharmaceuticals, and fees or non-financial support for consultancy activities from Actelion, GlaxoSmithKline, Boehringer Ingelheim and Chiesi. Dr Gagnadoux declares he has no conflict of interest related to this research. Dr Jouneau reports grants from AIRB, Boehringer Ingelheim, LVL, Novartis and Roche, and personal fees from Actelion, AIRB, AstraZeneca, BMS, Boehringer Ingelheim, Chiesi, GSK, LVL, Mundipharma, Novartis, Pfizer and Roche. Dr A. Magnan reports personal fees and non-financial support from GlaxoSmithKline, Novartis, Boehringer Ingelheim, AstraZeneca, Stallergnes, ALK, MundiPharma, Teva, Menarini and Meda Pharma, during the past 5 years. Dr Hayem-Vannimemus declares she has no conflict of interest related to this research. Dr Dansou declares she has no conflict of interest related to this research. Dr Proust reports fees for consulting from Novartis and personal fees or nonfinancial support from AstraZeneca, Boehringer, Chiesi, Mundifarma, Glaxo-Smith-Klein, Novartis, Pearl, Portola, Roche, Sanofi, and Teva. Ms Dion declares he has no conflict of interest related to this research. Dr Larhantec declares he has no conflict of interest related to this research. Ms Le Brestec declares she has no conflict of interest related to this research. Dr Dewitte declares he has no conflict of interest related to this research. Dr Roche declares he has no conflict of interest related to this research. Dr Leroyer reports having received research grant support from Pfizer and fees for board memberships or symposia from Bayer and Astra Zeneca and having received travel support from Bayer, Daiichi Sankyo, Leo Pharma, Intermune and Actelion. [...] The funding source was not involved in designing or conducting the study, collecting, managing, analysing or interpreting the data, preparing, reviewing or approving the manuscript, or deciding to submit this for publication. An academic steering committee assumed overall responsibility for all these steps. Dr Couturaud takes responsibility for data access and integrity of the data."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Investigators obtained patient randomisation numbers and treatment group assignments through a central computerised internet-based system."
Allocation concealment (selection bias)	Low risk	"Investigators obtained patient randomisation numbers and treatment group assignments through a central computerised internet-based system."
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence biochemically validated
Incomplete outcome data (attrition bias)	Low risk	Attrition rates similar between study arms

Nicotine receptor partial agonists for smoking cessation (Review)

Le Mao 2020 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Study registered: NCT01694732. Prespecified outcomes reported
Other bias	Unclear risk	"The main limitation of our study is the small sample size due to premature interruption in relation with the premature interruption of pharmaceutical funding (the study was co-financed by an institutional French grant and pharmaceutical grant)."

Lerman 2015
Study characteristics

Methods	Country: USA and Canada Setting: community Aim: to evaluate whether a genetically informed biomarker of nicotine clearance, the nicotine metabolite ratio (NMR; 3'-hydroxycotinine:cotinine), predicts response to NRT or varenicline for SC Study design: 4-site NMR-stratified multicentre, placebo-controlled RCT
Participants	1246 smokers, aged 18–65 years old and reported smoking ≥ 10 CPD for ≥ 6 months (verified with exhaled CO > 10 ppm). 44% female, mean age 46, baseline average CPD 18
Interventions	<ul style="list-style-type: none"> Placebo pill + placebo patch Nicotine patch + placebo pill - 11 weeks of patches to match the duration of varenicline after the TQD: 21 mg (6 weeks), 14 mg (2 weeks), and 7 mg (3 weeks) Varenicline + placebo patch - 12 weeks (including 1 week before the TQD), 2 x 1 mg/day (titrated for first week) <p>Participants were assigned in a 1:1:1 ratio, by NMR group. All participants received interactive behavioural support. This included 1 in-person session pre-quit, and 4 x 15-min follow-up telephone calls.</p>
Outcomes	Primary: 7-day PPA at EoT (week 11) to estimate the pharmacological effect by NMR group during the medication period. Abstinence was biochemically verified with exhaled CO < 8 ppm. Secondary end points were side-effects, withdrawal symptoms, and 6-month and 12-month quit rates
Notes	New for 2022 update Funding by National Institute on Drug Abuse, National Cancer Institute, National Human Genome Research Institute, National Institute on General Medical Sciences, Abramson Cancer Centre at the University of Pennsylvania, Commonwealth of Pennsylvania Department of Health, Canadian Institutes of Health Research, Canada Foundation for Innovation, Ontario Ministry of Research and Innovation. Pfizer Inc. provided varenicline and placebo pills at no cost. Author declaration of interests: "Lerman received study medication and placebo, as well as support for medication packaging, from Pfizer. She has also consulted to Gilead, and has been a paid expert witness in litigation against tobacco companies. Cinciripini served on the scientific advisory board of Pfizer Pharmaceuticals, conducted educational talks sponsored by Pfizer on smoking cessation from 2006-2008, and has received grant support from Pfizer. Schnoll received medication and placebo free of charge from Pfizer for a different project, and has consulted to Pfizer and GlaxoSmithKline. George has had both investigator-initiated and industry-sponsored grants from Pfizer in the past 12 months, and serves on a Data Monitoring Committee for Novartis. Benowitz has served as a consultant to several pharmaceutical companies that market smoking cessation medications and has been a paid expert

Lerman 2015 (Continued)

witness in litigation against tobacco companies. Tyndale has acted as a consultant to pharmaceutical companies, primarily on smoking cessation. The remaining authors report no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Biostatistician, independent of study investigators, developed the randomisation procedure which was integrated into a centralised data management system. Subjects were randomised to the treatment arms in a 1:1:1 ratio. Randomisation was stratified by baseline NMR status and study site, and blocked in blocks of 12 patients (4/treatment block) to ensure approximate balance"
Allocation concealment (selection bias)	Low risk	Allocation performed using centralised data management system
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates similar between study arms
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported

Littlewood 2017
Study characteristics

Methods	Country: USA Setting: at home with in-person study visits (unclear setting) Aim: to evaluate the effectiveness of varenicline for SC, and examine the influence of psychological factors on treatment outcome Study design: double-blind, placebo-controlled, RCT
Participants	205 current cigarette smokers interested in quitting, 34% female, mean age 34, baseline average CPD 16
Interventions	<ul style="list-style-type: none"> • Placebo • Varenicline - 2 x 1 mg/day (titrated for first week) Participants were randomised in a 1:1 ratio. Interventions lasted 12 weeks. All participants received in-person interactive behavioural support, comprising a 30-min baseline counselling session and a 10-20-min follow-up at weeks 2, 6, and 12.
Outcomes	<ul style="list-style-type: none"> • CA for the past month, biochemically confirmed with exhaled CO < 6 ppm • Average number CPD • 7-day PPA
Notes	New for 2022 update Funding by National Institute on Drug Abuse (NIDA) 1R01DA025074-01A2.

Nicotine receptor partial agonists for smoking cessation (Review)

Littlewood 2017 (Continued)

Author declaration of interests: "The authors declare that they have no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Urn-randomisation used
Allocation concealment (selection bias)	Low risk	"In order to maintain the blind, the pharmacist controlled the pre-generated urn randomization schedule and packed varenicline tablets in opaque capsules with microcrystalline cellulose, an inert powder commonly used in packaging medications."
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff measuring the outcome were blinded to allocation. Abstinence biochemically validated.
Incomplete outcome data (attrition bias) All outcomes	High risk	52% of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No trial registration but reports expected outcomes

Mercie 2018
Study characteristics

Methods	Country: France Setting: 30 HIV clinics in French hospitals Aim: to assess the efficacy and safety of varenicline with counselling to aid SC in people living with HIV Study design: randomised, parallel, double-blind, multicentre, placebo-controlled phase 3 trial
Participants	248 people living with HIV who had smoked at least 10 CPD for ≥ 1 year. Participants were motivated to stop smoking, were not dependent on another psychoactive substance. Participants with no history of depression or suicide attempt were eligible. 17% female, mean age 45, baseline number of CPD 20
Interventions	Participants were randomised on a 1:1 ratio. Intervention duration was 12 weeks <ul style="list-style-type: none"> • Placebo • Varenicline - 2 x 1 mg/day (titrated for first week) All participants received interactive, in-person, behavioural support comprising 10-15 sessions over 1 year
Outcomes	Primary: proportion of smokers continuously abstinent from week 9-week 48, biochemically verified by exhaled CO < 10 ppm
Notes	New for 2022 update Funding by ANRS, Emerging Infectious diseases, Pfizer.

Mercie 2018 (Continued)

Author declaration of interests: "The institution of JR has received funds from Institut National de la Santé et de la Recherche Médicale (Inserm)-France Recherche Nord et Sud Sida-hiv hépatites (ANRS). XD has received grant support from Pfizer. J-MM is a member of scientific advisory boards of Merck laboratories, Gilead, Bristol-Myers Squibb, ViiV Healthcare, and Janssen and has received grant support from Merck laboratories and Gilead. BS has received honoraria for seminars from Merck laboratories, Gilead, and Janssen and support for the IAS 2014 conference from Merck laboratories. The institution of CF and GC has received grant support from Inserm-ANRS and Pfizer. GC has received grant support for International Workshop on HIV and Hepatitis Observational Databases from Gilead, Tibotec-Janssen, Roche, Merck laboratories, Janssen Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, ViiV Healthcare, Mylan, Abbvie, and Abbott and grant support for ongoing clinical trials of Inserm-ANRS from Gilead, Tibotec-Janssen, Merck laboratories, Boehringer Ingelheim, and Abbott. All other authors declare no competing interests."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation (1:1) was done centrally via electronic case report software (CS software, Ennov-Clinsight), on the basis of a list generated with SAS software, version 9.2 (PROC PLAN procedure, block size 8)"
Allocation concealment (selection bias)	Low risk	"Only the trial statistician (JA) had access to the randomisation list during the trial."
Blinding (performance bias and detection bias) All outcomes	Low risk	CO ≤ 10 ppm and "Patients and investigators were masked to treatment group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"71 (58%) participants in the varenicline group versus 81 (65%) in the placebo group completed follow-up at 48 weeks"
Selective reporting (reporting bias)	Unclear risk	Not all prespecified outcomes reported in results paper. However, authors state "Other objectives described in the protocol will be reported elsewhere".

Nahvi 2014a
Study characteristics

Methods	Country: USA Setting: 3 urban outpatient clinics for substance use disorder (SUD) in the Bronx, NY Aim: to test the efficacy and safety of varenicline for SC among opioid-dependent people on a maintenance regimen Study design: randomised quadruple-blind controlled trial Dates conducted: August 2009-September 2011
Participants	112 smokers in methadone treatment for substance abuse, aged 18+, CPD 5+, motivated to quit within next 6 months. Allocated 57 varenicline, 55 placebo. 52% women, 54% Hispanic, mean CPD 15, mean FTND 4
Interventions	<ul style="list-style-type: none"> Varenicline: 12-week standard regimen, titrated for 1st week Control: identical placebo tablets and regimen

Nahvi 2014a (Continued)

All participants set a TQD 1 week after treatment began. All were offered structured, brief (≤ 10 min) individual in-person counselling by a physician or tobacco specialist at baseline and at 2-, 4-, 8- and 12-week visits. All participants were also offered free quitline support

Outcomes	7-day PPA at 12 and 24 weeks Validation: expired CO < 8 ppm
Notes	New for 2016 update Funding: National Center for Research Resources grant UL1 RR025750 to SN, and the National Institute on Drug Abuse grants K23 DA025736 to SN and R25 DA023021 to SN and JHA Author declaration of interests: "The authors have no connection with the tobacco, alcohol, pharmaceutical or gaming industries or anybody substantially funded by one of these organizations. The Albert Einstein College of Medicine Office of Biotechnology and Business Development receives funding from Pfizer, which manufactures varenicline; neither that office nor Pfizer had any role in the study design, analyses or decision to submit the manuscript for publication. None of the authors have direct or indirect funding from Pfizer"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment group allocation was computer-generated, and stratified by the three clinic sites in blocks of six within each stratum"
Allocation concealment (selection bias)	Low risk	"a central data manager concealed the allocation sequence using a password-protected file, assigned subjects to treatment groups and faxed pre-printed medication orders to the study pharmacist. The pharmacist prepared the research medication by compounding varenicline tablets or placebo lactose powder to create identical-appearing capsules. The pharmacist marked medication bottles with subjects' study identification numbers, and delivered medications for individual study subjects to clinical sites, where they were distributed to each subject by the research assistant"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The pharmacist prepared the research medication by compounding varenicline tablets or placebo lactose powder to create identical-appearing capsules. The pharmacist marked medication bottles with subjects' study identification numbers, and delivered medications for individual study subjects to clinical sites, where they were distributed to each subject by the research assistant" "All subjects, research assistants, counsellors and physicians were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses during treatment (varenicline 6, placebo 9) and during follow-up (varenicline 2, placebo 3) fully reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry reported in results paper

Nakamura 2007

Study characteristics

Methods	Country: Japan
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Nicotine receptor partial agonists for smoking cessation (Review)

Nakamura 2007 (Continued)

Setting: 19 study sites
 Aim: to test efficacy, safety and tolerability of 3 doses of varenicline over 12 weeks

Dates conducted: not stated
 Study design: double-blind, placebo-controlled, parallel-group RCT

Participants	<p>619 healthy Japanese adult volunteers, aged 20-75, smoking ≥ 10 CPD. Allocated to varenicline 0.25 mg x 2/day (153), 0.5 mg x 2/day (156), 1.0 mg x 2/day (156) or placebo x 2/day (154). 1 participant withdrew before treatment, and is excluded from ITT denominator. 1 road traffic accident death removed from varenicline group at 52 weeks</p> <p>Participants stratified by level of nicotine dependence, measured by Tobacco Dependence Screener scale (≥ 5) and by FTND. 515 (83.3%) classified as nicotine-dependent</p> <p>Demographic data only supplied for nicotine-dependent group (515/618): 75% men, mean age 39.8, mean CPD 24, mean FTND score 5.6</p> <p>Exclusion criteria: standard pharmacotherapy trial criteria, + use of NRT within last 30 days, use of pipe tobacco, snuff, chewing tobacco, cigars within last 30 days and throughout trial</p>
Interventions	<ul style="list-style-type: none"> • Varenicline 0.25 mg x 2/day • Varenicline 0.50 mg x 2/day • Varenicline 1.00 mg x 2/day • Placebo tablet x 2/day <p>Treatment period 12 weeks, 1st week titrated dosage. All participants received a SC booklet <i>Clearing the Air</i> at baseline, + brief counselling (≤ 10 min) at each clinic visit. Weekly visits throughout treatment phase, plus a 5-min phone call at TQD and +3 days post-TQD</p> <p>In follow-up phase, clinic visits at weeks 13, 16, 24, 36, 44 and 52, plus brief phone calls at weeks 20, 28, 32, 40 and 48</p>
Outcomes	<p>Primary outcome: CO-validated CAR at 9-12 weeks</p> <p>Secondary outcomes: CO-validated CAR at 9-24 weeks and 9-52 weeks; 7-day PPA at weeks 2, 12, 24 and 52</p> <p>Validation was by expired CO ≤ 10 ppm</p> <p>Other outcomes: withdrawal symptoms (using MNWS, QSU-brief and mCEQ), AEs</p> <p>Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis)</p> <p>Attrition in treatment phase was 6.4%, losses to follow-up 11.4% of treatment completers (excluding 1 death)</p>
Notes	<p>Trial was funded by Pfizer Inc</p> <p>New for 2008 update</p> <p>Author declaration of interests: "Dr. Nakamura has received research contracts from Pfizer Japan Inc. (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), and Sanofi-Aventis K.K. (Tokyo, Japan), and a research grant from Pfizer Research Foundation (Tokyo, Japan). Dr. Oshima has received research contracts from Pfizer Japan Inc"</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated list of random numbers"
Allocation concealment (selection bias)	Low risk	"randomized to 1 of the 4 treatment groups in a 1:1:1:1 ratio using a central procedure"
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blinding of subjects and investigators was maintained throughout the study".

Nicotine receptor partial agonists for smoking cessation (Review)

101

Nakamura 2007 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No comment on level or handling of missing data
Selective reporting (reporting bias)	High risk	CA rates for all participants reported, but demographics, withdrawal and craving measures, and PPA for nicotine-dependent group only

NCT01162239
Study characteristics

Methods	Country: USA Setting: outpatient medical care Aim: to assess the efficacy of the relapse prevention treatment to other extended treatments, such as health education, brief contact, and varenicline Study design: open-label parallel 4-arm RCT
Participants	271 adult smokers, smoking 5+ CPD, who have all completed 12-week course of varenicline + counselling 38.9% female, mean age 48.9.
Interventions	<ul style="list-style-type: none"> Extended brief contact Extended health education Extended relapse prevention - varenicline Extended relapse prevention - long-term varenicline - 12 weeks of varenicline treatment at standard dosage of 2 x 0.5 mg/day, plus ongoing access to varenicline for up to 40 additional weeks <p>All participants in all trial arms receive 12 weeks of varenicline treatment at standard dosage of 2 x 0.5 mg/day</p>
Outcomes	Primary: 7-day PPA at weeks 12, 24, 52, 64, 104 Biochemically verified with exhaled CO at < 8 ppm Secondary: comparison of combined extended vs brief treatment at weeks 24 and 52
Notes	New for 2022 update Funding by Pfizer (manufacturer-funded study), and National Institute on Drug Abuse Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on randomisation method (trial registry only)
Allocation concealment (selection bias)	Unclear risk	No information provided (trial registry only)
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label (and no placebo used in standard varenicline duration arm)

Nicotine receptor partial agonists for smoking cessation (Review)

NCT01162239 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up < 50% and similar between arms
Selective reporting (reporting bias)	Low risk	No evidence of selected reporting. All abstinence outcomes reported as planned

Niaura 2008
Study characteristics

Methods	Country: USA Setting: 5 research centres Aim: to test the efficacy and safety of varenicline in smokers allowed to modify their own dosage regimen Dates conducted: December 2001-June 2003 Study design: double-blind placebo-controlled RCT
Participants	320 healthy adult volunteers, aged 18-65, smoking ≥ 10 CPD. Allocated to varenicline (160), or placebo (160) 52% men, 91% white, mean age 42, mean CPD 22, mean FTND score 5.4 Exclusion criteria: standard pharmacotherapy trial criteria, + use of NRT within last 3 months
Interventions	<ul style="list-style-type: none"> 0.5 mg varenicline tablets, from 1-4 per day, as wished Placebo tablets, from 1-4 per day, as wished Treatment period 12 weeks, 1st week titrated dosage up to 0.5 mg x 2/day. All participants received a SC booklet <i>Clearing the Air</i> at baseline, + brief counselling (≤ 10 min) at each clinic visit. Weekly visits throughout treatment phase In follow-up phase, clinic visits at weeks 13, 24, and 52 weeks, plus monthly phone calls between visits
Outcomes	Primary outcome: CAR at 4-7, 9-12 and 9-52 weeks Validation was by expired CO ≤ 10 ppm Secondary outcomes: CO-confirmed CAR at 9-24 weeks; CO-confirmed 7-day PPA Other outcomes: mean modal dosage; withdrawal symptoms (using MNWS, QSU-brief and mCEQ), AEs Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 22% in varenicline group and 29% in placebo group; losses to follow-up by week 52 were 36% from varenicline group and 43% from placebo group
Notes	The trial was funded by Pfizer Inc New for 2010 update Author declaration of interests: " KEW, KRR, and CBB are employees of Pfizer and have stock or stock options in Pfizer. RN has received consulting fees from Pfizer, GlaxoSmithKline, Sanofi-Aventis, Merck, Constella, and LLC. DEJ has received consulting fees from Nabi Biopharmaceutical and receives research support from Pfizer, Nabi Biopharmaceutical, and Sanofi-Aventis. FTL serves on speakers' bureaus for Pfizer and Merck and is a consultant on an advisory panel with Pfizer. JTH received grant support from Pfizer. JEP received grant support from Merck, DepoMed, Pfizer, Novartis, Takeda, Sanofi-Aventis, Symbolon, TAP, and GlaxoSmithKline. Editorial support was provided by Ray Beck, Jr, PhD of Envision Pharma and was funded by Pfizer, Inc. "

Risk of bias

Bias	Authors' judgement	Support for judgement
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Nicotine receptor partial agonists for smoking cessation (Review)

Niaura 2008 (Continued)

Random sequence generation (selection bias)	Low risk	"randomly permuted blocks and a pseudo-random number generator"
Allocation concealment (selection bias)	Low risk	"participants were assigned in a 1:1 ratio to varenicline treatment or placebo in the numerical order that they were accepted to the study"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind" but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data imputed if prior and subsequent abstinence confirmed, otherwise assumed still smoking
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Nides 2006
Study characteristics

Methods	Country: USA Setting: 7 research centres Aim: to test efficacy, tolerability and safety of 3 doses of varenicline over 6 weeks Dates conducted: February 2000-January 2003 Study design: phase 2 double-blind placebo-controlled RCT
Participants	638 healthy volunteer smokers, aged 18-65, smoking at least 10 CPD on average. 48% men, 87% white, average age 42, average CPD 20, mean FTND 5.5. Allocated to varenicline group 1 (128), group 2 (128), group 3 (127), bupropion (128), placebo (127) Exclusion criteria: standard pharmacotherapy trial criteria, + use of bupropion within previous 12 months, use of NRT within past 3 months
Interventions	<ul style="list-style-type: none"> Varenicline tartrate 0.3 mg x 1/day for 6 weeks, + 1 week placebo Varenicline tartrate 1.0 mg x 1/day for 6 weeks, + 1 week placebo Varenicline tartrate 1.0 mg x 2/day for 6 weeks, + 1 week placebo Bupropion 150 mg x 2/day (titrated in week 1) for 7 weeks Placebo tablets x 2/day for 7 weeks <p>All groups received self-help booklet <i>Clearing the Air</i> at baseline, + brief (≤ 10 min) counselling at weekly clinic visits throughout treatment phase. At each visit smoking status reported and verified; lab samples taken at screening, baseline and weeks 1, 2, 4, 6 and 7 Follow-up phase (optional): clinic visits at weeks 12, 24, 52 for brief counselling, smoking status and vital signs. Phone calls every 4 weeks from week 16</p>
Outcomes	Primary outcome: continuous verified 4-week abstinence for any part of treatment period Secondary outcomes: CQR weeks 4-7; CQR from week 4 to weeks 12, 24, and 52 Other outcomes: weight change; reduction of craving and withdrawal using MNWS, QSU-brief and mCEQ; AEs Validation was by expired CO ≤ 10 ppm Trial report ITT analysis based on numbers treated (N = 626); for consistency our MA used numbers randomised (N = 638). Attrition was 30% during treatment period, 25% of follow-up consenters lost during follow-up phase

Nides 2006 (Continued)

Notes

Previous users of bupropion > 12 months before were not excluded, unlike Gonzalez and Jorenby trials; prior use ranged from 13% to 20.6% across groups
 Denominator in trial report is all treated; we have used all randomised in our MA
 The trial was funded by Pfizer Inc

Author declaration of interests: "Dr Nides has received research grants, consulting fees, and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline. Dr Oncken has received research grants, consulting fees, and honoraria from Pfizer; received, at no cost, nicotine replacement and placebo products from GlaxoSmithKline for smoking cessation studies; and received honoraria from Pri-Med. Dr Gonzalez reports having received research contracts from Pfizer, Sanofi-Aventis, GlaxoSmithKline and Nabi Biopharmaceuticals; consulting fees and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline; and owning 5 shares of Pfizer stock. Dr Rennard has had or currently has a number of relationships with companies that provide product and/or services relevant to outpatient management of chronic obstructive pulmonary disease. These relationships include serving as a consultant (Adams, Almirall, Altana, Array Biopharma, AstraZeneca, Aventis, Biolipox, Centocor, Dey, Critical Therapeutics, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Ono Pharma, Otsuka, RJ Reynolds, Roche, Sankyo, Schering-Plough, Scios, and Wyeth); advising regarding clinical trials (Altana, AstraZeneca, Aventis, Centocor, GlaxoSmithKline, Novartis, Pfizer, and Philip Morris); speaking at continuing medical education programs; and performing funded research at both basic and clinical levels (Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis). He owns no stock in any pharmaceutical companies. Drs Watsky and Reeves and Mr Anziano are employees of Pfizer and own Pfizer stock or have stock options."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated using a method of randomly permuted blocks and a pseudo-random number generator"
Allocation concealment (selection bias)	Low risk	"assigned ... medication to subjects in numerical order of acceptance into the study"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind", "to preserve treatment blinding"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

O'Malley 2018
Study characteristics

Methods	Country: USA Setting: home, 2 x outpatient substance abuse treatment and research facilities Aim: to test the efficacy of varenicline with medical management for patients with alcohol use disorder and comorbid smoking seeking alcohol treatment, and to evaluate the secondary effects on smoking abstinence Study design: phase 2, randomised, double-blind, parallel-group, placebo-controlled trial
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Nicotine receptor partial agonists for smoking cessation (Review)

O'Malley 2018 (Continued)

Participants	<p>131 adult smokers with alcohol use disorder. Eligible participants met alcohol-dependence criteria and reported heavy drinking (≥ 5 drinks for men and ≥ 4 drinks for women) ≥ 2 times per week and smoking ≥ 2 times per week.</p> <p>29.8% female, mean age 42.7, baseline average CPD 11.4</p> <p>Exclusion criteria: current, clinically significant disease or abnormality; diagnosis of a serious psychiatric illness; current suicidal ideation or lifetime history of suicidal behavior; risk of aggression; current diagnosis of drug dependence; risk of clinically significant alcohol withdrawal; medications in the past 3 months to treat alcohol or tobacco dependence; psychotropic medications in the past month. Women of childbearing age could not be pregnant or nursing and had to be practicing effective contraception.</p>
Interventions	<ul style="list-style-type: none"> • Placebo • Varenicline 2 x 1 mg/day <p>Intervention duration was 16 weeks. Participants did not receive any behavioural support for SC - solely for alcohol use reduction.</p>
Outcomes	<ul style="list-style-type: none"> • Percentage of heavy drinking days weeks 9-16 • No heavy drinking days weeks 9-16 • Prolonged smoking abstinence weeks 13-16
Notes	<p>New for 2022 update</p> <p>Funding by grants from the National Institutes of Health and by the State of Connecticut Department of Mental Health and Addiction Services. Pfizer provided varenicline and placebo pills at no cost.</p> <p>Author declaration of interests: "Dr O'Malley reported having been a consultant or an advisory board member for Alkermes, Amygdala, Arkeo, Cerecor, Mitsubishi Tanabe, Opiant, Pfizer; a member of the American Society of Clinical Psychopharmacology Alcohol Clinical Trials Initiative supported by Abbott, Amygdala, Ethypharm, Lilly, Lundbeck, Otsuka, Pfizer, Arbor Pharmaceuticals, and Indivior; a coinvestigator on studies receiving donated medications from Astra Zeneca, Novartis; a site principal investigator for a multisite trial by Lilly; and a scientific panel member for Hazelden Foundation. Dr Petrakis reported being a consultant to Alkermes. Dr Fucito reported registering with the US Patent and Trademark Office the name and content of a web-based program to help with sleeping and drinking (ie, Call it a Night). No other disclosures were reported"</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization list was generated by our study statistician (R.G.) and was implemented through a web-based system (Endpoint Systems)."
Allocation concealment (selection bias)	Low risk	"The randomization list was generated by our study statistician (R.G.) and was implemented through a web-based system (Endpoint Systems)."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants, treatment providers, and research staff were blind to the assignment throughout the study" and abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	"N=94 (71.8%) provided data at the 12 month follow-up" Similar between arms
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported

Oncken 2006

Study characteristics

Methods	<p>Country: USA Setting: 10 research centres Aim: to evaluate efficacy and safety of 4 varenicline dose regimens</p> <p>Dates conducted: not stated Study design: phase 2 double-blind placebo-controlled RCT</p>
Participants	<p>647 healthy volunteer smokers, aged 18-65, smoking at least 10 CPD. 49.5% men, 80% white, average CPD 21, mean FTND 5.5. Allocated to group 1 (129), group 2 (130), group 3 (129), group 4 (130) or placebo (129)</p> <p>Exclusion criteria: standard pharmacotherapy trial criteria, + use of NRT or bupropion within last 3 months; use of marijuana or tobacco other than cigarettes with last month</p>
Interventions	<ul style="list-style-type: none"> • 0.5 mg non-titrated (2/day for 12 weeks) • 0.5 mg titrated (week 1 1/day, weeks 2-12 2/day) • 1.0 mg non-titrated (2/day for 12 weeks) • 1.0 mg titrated (0.5 mg 1/day for 3 days, 0.5 mg 2/day for 4 days, 1.0 mg 2/day weeks 2-12) • Placebo tablets 2/d 12 weeks <p>All groups received self-help booklet at baseline, + brief (≤ 10 min) counselling at weekly clinic visits throughout treatment phase, and phone call 3 days post-TQD. At each visit smoking status reported and CO verified; vital signs, weight and AEs. Urine, blood tests and ECGs at screening, baseline, weeks 1, 2, 4, 7 and 12 Follow-up phase: smoking status + CO measured at weeks 13, 24, 52; self-reported status by phone at weeks 16, 20, 28, 32, 36, 40, 44</p>
Outcomes	<p>Primary outcome: continuous verified 4-week abstinence at weeks 4-7 and 9-12 Secondary outcomes: continuous verified abstinence at weeks 2-12 and 9-52; 7-day PPA throughout treatment phase and at weeks 12, 24 and 52 Other outcomes: weight change; craving and withdrawal changes using MNWS and mCEQ; AEs Validation was by expired CO ≤ 10 ppm Cessation analyses were ITT (all participants randomised), while tolerability and safety analyses were based only on those known to have used the intervention drug (N = 627). Attrition was 27% during treatment phase, and 22% of follow-up consenters lost in follow-up phase</p>
Notes	<p>For cessation analyses, titrated and non-titrated results were reported separately and pooled. 24-week continuous cessation data supplied by study authors The trial was funded by Pfizer Inc</p> <p>Author declaration of interests: "Dr Oncken has received research grants, consulting fees, and honoraria from Pfizer; nicotine replacement and placebo products from GlaxoSmithKline at no cost for smoking cessation studies; and honoraria from Pri-Med. Dr Gonzales has received research contracts, consulting fees, and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline and owns 5 shares of Pfizer stock that he received as a gift from his parents. Dr Rennard has had or currently has a number of relationships with companies who provide products and/or services relevant to outpatient management of chronic obstructive pulmonary disease. These relationships include serving as a consultant (for Adams, Almirall, Altana, Array Biopharma, AstraZeneca, Aventis, Biolipox, Centocor, Dey, Critical Therapeutics, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Ono Pharma, Otsuka, RJ Reynolds, Roche, Sankyo, Schering-Plough, Scios, and Wyeth), advising regarding clinical trials (Altana, AstraZeneca, Aventis, Centocor, GlaxoSmithKline, Novartis, Pfizer, and Philip Morris), speaking at continuing medical education programs and performing funded research at both basic and clinical levels (Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis). He does not own any stock in any pharmaceutical companies. Dr Nides has received research grants, consulting fees, and honoraria from Pfizer, Sanofi-Avenits, and GlaxoSmithKline. Drs Watsky and Reeves and Messrs Billing and Anziano are employees of Pfizer and own Pfizer stock or hold Pfizer stock options."</p>

Oncken 2006 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"Eligible subjects were randomly assigned to 1 of 5 groups"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Subjects and investigators were blinded to the study drug treatment [, and] were not encouraged to guess their treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing COs or visits OK if confirmed abstinent before and after missed measure
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Pastorino 2022
Study characteristics

Methods	Study design: RCT Country: Italy Setting: community Recruitment method: volunteers were recruited through press releases, social networks, television, and other media.
Participants	869 participants in a lung-screening trial who smoked. 44% female. Median age 60. Heavy smokers
Interventions	<ul style="list-style-type: none"> • Behavioural support only • Behavioural support plus 40 days of cytosine (standard dose) • Behavioural support plus 84 days of cytosine (standard dose)
Outcomes	CA at 52 weeks - verified by CO \leq 9 ppm
Notes	Study funding: "Funded by the Scientific Directorate Fondazione IRCCS Istituto Nazionale Tumori, Italian Association for Cancer Research AIRC (AIRC 5x1000 ID 12162, extension 2017-2020), Investigation Grant from the Foundation AIRC for the Research on Cancer (AIRC IG 2019, ID 23244), and Ricerca Corrente of the Italian Ministry of Health. The work of SG is partially supported by an Investigation Grant from the Foundation AIRC for the Research on Cancer (AIRC IG 2021, ID 25987) and by the Italian League Against Cancer (LILT, Milan). The fundings had no role in the design of the study; collection, analysis, and interpretation of data; writing of the manuscript, or the decision concerning submission." Author declaration of interests: "We declare no competing interests." Study authors provided additional results data upon request.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Nicotine receptor partial agonists for smoking cessation (Review)

Pastorino 2022 (Continued)

Random sequence generation (selection bias)	Unclear risk	Stated randomised but method not specified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	A placebo was not used in the arm that did not receive cytisine.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates under 50% however data are not available on how many were followed up in the cytisine arms when they were split by length of treatment - thus we can not see if differential attrition occurred
Selective reporting (reporting bias)	Low risk	Prespecified smoking-related outcomes reported

Qin 2021
Study characteristics

Methods	Study design: RCT Country: China Setting: China–Japan Friendship hospital in Beijing Recruitment method: via a trial site, a hotline of SC, advertisements in the community from February 2019–June 2020
Participants	136 smokers diagnosed with COPD randomised; 2.9% female, average age 62; average CPD 19.21; FTND mode 0-3
Interventions	<ul style="list-style-type: none"> Varenicline, 2 mg/day for 12 weeks Bupropion, 150 mg/day for 12 weeks <p>Common components, quote: "Participants received a counseling session for more than 60 min when they began medication at week 0, and they also received up to 10 min of counseling at weeks 1, 2, 4, 6, 9, 12, and 24."</p>
Outcomes	SC: abstinence at 24 weeks (no further details given). Validated by CO ≤ 10 ppm
Notes	<p>Study funding: "This study was supported by the Capital Health Development Research Project in China (Grant No. 2018-2-4066), the National Natural Science Foundation of China (Grant No. 81720108001) and the National Key R&D Program of China (Grant No. 2017YFC1309400)."</p> <p>Author declaration of interests: "The authors report no conflicts of interest in this work."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A biostatistician, independent of the study used Proc Plan in SAS version 9.4 (SAS Institute) to generate a table of random digit to randomly assign the numbers to the two groups. (the number of the random seed is 87,654,321)."

Qin 2021 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "To ensure random concealment, the group information assigned to each participant was put in a sealed, and opaque envelope."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Because of the different medication packaging, only statisticians were blinded to medication allocation however, all participants received an active evidence-based smoking cessation pharmacotherapy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Only 8/68 and 7/68 lost in the varenicline and bupropion arms respectively."
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry reported

Rennard 2012
Study characteristics

Methods	<p>Countries: Argentina, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, Italy, Korea, Mexico, Taiwan, UK, USA</p> <p>Setting: 33 research centres</p> <p>Aim: to evaluate efficacy and safety of varenicline allowing a self-selected quit date</p> <p>Dates conducted: September 2008-December 2009</p> <p>Study design: double-blind placebo-controlled RCT</p>
Participants	<p>659 healthy volunteer smokers, aged 18-75, motivated to quit, smoking at least 10 CPD. 60% men, mean age 43, 68% white, mean CPD 21, mean FTND 5.5, 66% had tried to quit at least once before. Allocated to varenicline (493) or placebo (166)</p> <p>Exclusion criteria: standard pharmacotherapy trial criteria, + use of NRT, bupropion, clonidine or nortriptyline within last 3 months, ever used varenicline; use of marijuana or tobacco other than cigarettes with last month</p>
Interventions	<ul style="list-style-type: none"> Varenicline 1 mg x 2/day, titrated in 1st week Placebo inactive tablets, same regimen <p>Participants could choose their own quit date between days 8 and 35</p> <p>Treatment period was 12 weeks. All participants received <i>Clearing the Air: Quit smoking today</i> booklet at baseline, + brief counselling (≤ 10 min) at each clinic visit. Weekly visits throughout treatment phase, and in follow-up phase clinic visits at weeks 13, 16, 20 and 24. Phone calls at weeks 14, 18 and 22</p>
Outcomes	<p>Primary outcome: CO-validated CAR at 9-12 weeks</p> <p>Secondary outcomes: CO-validated CAR at 9-24 weeks; 7-day PPA at weeks 12 and 24</p> <p>Other outcomes: AEs, SAEs; timing and number of quit attempts</p> <p>Validation was by expired CO ≤ 10 ppm</p> <p>Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition to end of study (24 weeks) was 12.4% from varenicline, 20.5% from placebo</p>
Notes	<p>New for 2012 update</p> <p>Additional information supplied by the study authors</p> <p>The study was funded and managed by Pfizer Inc</p> <p>Author declaration of interests: "SR, JH, PC, EK, and TR did not receive any financial support with respect to the writing or development of this manuscript. Funding from Pfizer Inc. has been received by the authors or their institutions for the following in the 36 months prior to submission: research grants (JH, PC, EK, and TR); advisory board membership (SR and JH); reimbursement for travel and accom-</p>

Nicotine receptor partial agonists for smoking cessation (Review)

110

Rennard 2012 (Continued)

modation expenses (SR, PC, EK, and TR); lectures/speaker bureau (PC); consultancy (EK); and development of educational materials (EK and TR). CA, LSA, and CR are employees of Pfizer Inc. JH has received consulting fees from several non-profit and for-profit entities that develop or promote smoking cessation products or that advocate for tobacco control measures."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a predefined, central, computer-generated randomization sequence...assigned subjects in a 3:1 ratio". Block size: 4, stratified by centre
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple-blind (participant, care-giver, investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and attrition rates fully reported
Selective reporting (reporting bias)	Low risk	All predicted and expected outcomes reported

Rigotti 2010
Study characteristics

Methods	Country: 15 countries in Europe, Asia, Americas Setting: 39 research centres Aim: to evaluate efficacy and safety of varenicline in patients with stable CVD Dates conducted: February 2006-August 2008 Study design: phase 3 double-blind placebo-controlled RCT
Participants	714 adult smokers, aged 35-75, smoking at least 10 CPD, with stable CVD and motivated to quit. 79% men, 80% white, mean CPD 22, mean FTND 5.6. Allocated to varenicline (355) or placebo (359), stratified by site Exclusion criteria: standard pharmacotherapy trial criteria, + use of NRT or bupropion within previous month. All had been diagnosed for at least 2 months with CVD, but not hypertension alone
Interventions	<ul style="list-style-type: none"> Varenicline 1.0 mg 2/day for 12 weeks, including week 1 at titrated dose Placebo tablets as above Both groups received brief (≤ 10 min) counselling at weekly clinic visits throughout treatment phase, and phone call 3 days post-TQD. At each visit smoking status reported and CO verified; vital signs, weight and AEs. Urine, blood tests and ECGs at screening, baseline, weeks 12 and 52 Follow-up phase: smoking status + CO measured at weeks 13, 16, 24, 32, 40 and 52; counselling and self-reported status by phone at weeks 14, 20, 28, 36 and 44
Outcomes	Primary outcome: CO-validated CAR at weeks 9-12 Secondary outcomes: CO-validated CAR at weeks 9-52 and 9-24; 7-day PPA at weeks 12, 24 and 52 Other outcomes: AEs; SAEs; cardiovascular events; changes in blood pressure and heart rate Validation was by expired CO ≤ 10 ppm

Nicotine receptor partial agonists for smoking cessation (Review)

Rigotti 2010 (Continued)

Cessation analyses were ITT (all participants randomised minus deaths), while tolerability and safety analyses were based only on those known to have used the intervention drug (N = 703). Attrition was 17.5% from the varenicline group and 20.3% from the placebo group during treatment phase, and 14.9% varenicline and 19.5% placebo who did not complete the study. This includes 2 deaths in the varenicline group and 5 in the placebo group by 52-week follow-up

Notes

New for 2010 update

Study funding: "This study was funded by Pfizer Inc. Editorial support for the development of this manuscript was provided by Alexandra Bruce, PhD, of UBC Scientific Solutions and was funded by Pfizer Inc."

Author declaration of interests: "Drs Rigotti, Pipe, Benowitz, and Tonstad have consulted for Pfizer. Dr Rigotti has been the site principal investigator for clinical trials of smoking cessation medications funded by Pfizer, sanofi-aventis, and Nabi Biopharmaceuticals. Dr Pipe has received educational and research support in the past from Bristol-Myers Squibb, Johnson & Johnson, GlaxoSmithKline, and Merrell-Dow. Drs Benowitz and Tonstad served on the scientific planning committee for this study and have been paid consultants to Pfizer and other pharmaceutical companies that are developing and/or marketing smoking cessation medications. Dr Benowitz has been a paid expert witness in litigation against tobacco companies. At the time of the study, his family owned a small amount of Pfizer stock, but no longer does. Dr Tonstad has been the site principal investigator for clinical trials of smoking cessation medication and other medications funded by Pfizer and other pharmaceutical companies. Dr Arteaga is a statistical director at Pfizer Inc, supporting the varenicline studies. Dr Garza is a senior medical director of clinical research and development at Pfizer Inc, and the medical monitor for this study. The other authors report no conflicts."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study sponsor conducted the randomization centrally using a computer-generated list that prespecified the order of treatment allocation"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as "double-blind" (participants and study implementation). Cardiovascular outcomes "were reviewed separately and adjudicated under blinded conditions by an independent event committee made up of 3 board-certified cardiologists"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses conducted; participants who missed a visit but had validated abstinence at next visit were considered continuously abstinent. But 52-week status had to be attended and confirmed
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Rohsenow 2017
Study characteristics
Methods

Country: USA

Setting: university offices in Rhode Island, USA

Aim: to compare varenicline with transdermal nicotine (NRT) for smokers with current substance use disorders (SUD) for effects on smoking abstinence

Nicotine receptor partial agonists for smoking cessation (Review)

Rohsenow 2017 (Continued)

Study design: double-blind double-placebo-controlled randomised design, stratifying by MDD history

Participants	<p>137 adult smokers in substance-use disorder treatment, who were substance abstinent < 12 months, and smoked 10+ CPD for the past 6 months. 47% female, mean age 39.6, baseline CPD 19.5</p> <p>Participants did not need to be motivated to quit</p> <p>Exclusion criteria: hallucinations/delusions, current SC treatment, contraindications for either medication, using medications affected by SC (antipsychotics, warfarin, theophylline and insulin), suicidal ideation, not willing to try to quit smoking and, substance use reported on the day of or before recruitment or positive breath alcohol at recruitment</p>
Interventions	<ul style="list-style-type: none"> Varenicline: 12 weeks of 2 x 1 mg/day (titrated for first week) NRT: 21 mg/day, decreasing to 7 mg/day
Outcomes	<p>Primary: 7-day smoking PPA at 3 months</p> <p>Secondary: 7-day PPA at 6 months; quantity and frequency of smoking and substance use at 3 and 6 months; within-treatment abstinence; medication adherence; depressive symptoms</p>
Notes	<p>New for 2022 update</p> <p>Funding by a personal grant 1R01DA024652 from the National Institute on Drug Abuse and Department of Veterans Affairs</p> <p>Author declaration of interests: "All authors report no financial interests or potential conflicts of interest except for the following: R.M.S. has received travel and honorarium from D&A Pharma and has received consultant fees from CT Laboratorie"</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Urn randomization [32] to medication condition (1: 1 assignment) was stratified by gender, median score on the Fagerström Test for Nicotine Dependence [33] from a previous study [28] and history of MDD. The randomization program was run by the Project Manager, who concealed the assignment from all other staff."
Allocation concealment (selection bias)	Low risk	"Urn randomization [32] to medication condition (1: 1 assignment) was stratified by gender, median score on the Fagerström Test for Nicotine Dependence [33] from a previous study [28] and history of MDD. The randomization program was run by the Project Manager, who concealed the assignment from all other staff."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind trial with placebo patch and placebo tablets used (double placebo). Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	23/60 and 25/77 did not complete follow-ups for primary outcome at 3 months but information not stated for 6 months; however multiple imputation sensitivity analysis has been done (supplementary materials) which the study authors claim did not change the conclusion
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry reported

Rose 2013

Study characteristics

Methods	<p>Country: USA Setting: Duke University Medical Center, Durham, NC</p> <p>Aim: "Given the safety and tolerability profile of nicotine replacement therapy, our rationale in this study was to use nicotine replacement therapy as an initial line of treatment, and then identify early on which smokers are unlikely to benefit from nicotine alone" Study design: randomised double-blind parallel-arm adaptive treatment trial in 2 phases</p> <p>Dates conducted: not stated</p>
Participants	<p>606 adult smokers, motivated to quit, aged 18-65, mean CPD 10+ for 3 years, expired CO level 10+ ppm. 46% women, 63% white, mean CPD 21.7, mean FTND 5.8. Participants could receive up to USD 320 for study participation</p>
Interventions	<p>2-phase study</p> <p>All participants seen weekly for 2 weeks before TQD, and attended 4-6 sessions after the TQD. At each session, participant received brief (< 15 min) support, + clinical trial materials. Smoking diaries, expired CO, withdrawal symptoms and reports of AEs were collected each time. Participants were recontacted at 6 months, and those reporting abstinence were invited to return to give a CO sample</p> <p>All participants were given open-label active NRT patch, either 42 mg/day (baseline CO > 30 ppm) or 21 mg/day (baseline CO < 30 ppm) for 2 weeks; dose reductions allowed if side effects dictated. At 1 week, participants were classified as 'responders' (reduced ad lib smoking by > 50%, CO-verified) or 'non-responders' (< 50%)</p> <ul style="list-style-type: none"> • Phase 1 (12 weeks) <ul style="list-style-type: none"> ◦ Non-responders only (N = 371-36 who withdrew, = 335) allocated to: <ul style="list-style-type: none"> ■ double-blind varenicline, stopping NRT (N = 112) ■ double-blind augmentation of NRT with bupropion (N = 109) ■ continuation on open-label NRT alone (N = 114) ◦ All participants received dummy (placebo) versions of the other 2 treatments as well as their own active treatment. • Phase 2 <ul style="list-style-type: none"> ◦ 235 responders after week 1 assessed at 1st week after TQD (week 3). Lapsers (N = 105) were assigned a 2nd TQD 1 week later, and were allocated to the same 3 double-blind treatment conditions as Phase 1 non-responders. <ul style="list-style-type: none"> ■ double-blind varenicline, stopping NRT (N = 36) ■ double-blind augmentation of NRT with bupropion (N = 34) ■ continuation on open-label NRT alone (N = 35) <p>Non-lapsers (N = 130) remained on open-label NRT throughout study duration</p> <p>All participants received dummy (placebo) versions of the other 2 treatments as well as their own active treatment.</p> <p>47 participants were excluded from the analysis (27 Phase 1, 20 Phase 2) because of using contra-indicated medications during the study or failing to meet other entry requirements. 1 individual died before EoT, and 1 was excluded for extreme CO change from the mean sample range</p>
Outcomes	<p>Primary: CAR at weeks 8-11</p> <p>Secondary: CA from TQD for 11 weeks (EoT); 7-day PPA at 6 months: CA from TQD to 6 months</p> <p>Validation: CO ≤ 10 ppm</p> <p>AEs and SAEs (reported, but not by treatment group)</p>
Notes	<p>Phase 1 and Phase 2 groups combined for varenicline vs NRT analysis</p>

Nicotine receptor partial agonists for smoking cessation (Review)

Rose 2013 (Continued)

New for 2016 update

Study funding: "Supported by a grant to Duke University from Philip Morris USA. Nicotine patches were donated by GlaxoSmithKline. The companies had no role in the planning or execution of the study, data analysis, or publication of results."

Author declaration of interests: "Dr. Rose has served as a consultant for Targacept and Philip Morris USA and has a patent purchase agreement with Philip Morris International. Both authors have received research funding from Philip Morris USA."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported; exclusions for protocol violations or contra-indicated medicines. 1 death and 1 'rogue' CO reading excluded
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from trial registry all reported
Other bias	Unclear risk	Unexplained disparity between CONSORT (N = 103) and Results table (N = 108) denominators for rescue varenicline group

Scharfenberg 1971
Study characteristics

Methods	Country: East Germany Aim: to test the efficacy of cytisine for SC Setting: SC clinic, Magdeburg, July-December 1967 Study design: double-blind placebo-controlled randomised trial
Participants	1214 smokers recruited from 1452 applicants through smoking clinics and via initial press releases. 88.2% male. 2.5% of participants smoked < 10 CPD, 42.4% 10-20 CPD, 48.9% 21-30 CPD, 5.2% > 30 CPD 40.4% had smoked > 20 years. 40.6% had tried to quit at least once before Randomised to cytisine (607) or placebo (607) Exclusion criteria not stated (214 volunteers excluded at initial screening)
Interventions	<ul style="list-style-type: none"> 20-day course of cytisine. 1.5 mg tablets: days 1-3 6/day; days 4-12 5/day; days 13-16 4/day; days 17-20 3/day Placebo tablets, same regimen Behavioural support: none
Outcomes	Self-reported abstinence at 4 weeks, 6 months and 2 years

Nicotine receptor partial agonists for smoking cessation (Review)

Scharfenberg 1971 (Continued)

ITT analysis. Attrition rate 34% by longest follow-up

Notes Study funding: not reported
Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"a numbered pouch"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Not stated

Schnoll 2019

Study characteristics

Methods	Country: USA Setting: unclear Aim: to determine if extended-use varenicline should be considered for treating tobacco use among cancer patients Study design: placebo-controlled parallel RCT
Participants	207 adult smokers with a diagnosis of cancer or a recurrence within the past 5 years, and smoking ≥ 5 cigarettes per week. Participants were motivated to quit. 50.7% female, mean age 58.5, and baseline average CPD 13.4 Exclusion criteria: daily use of nicotine products other than cigarettes, unstable substance abuse/dependence in the last year
Interventions	<ul style="list-style-type: none"> Standard varenicline - 12 weeks of varenicline 2 x 1 mg/day (titrated for first week) + 12 weeks of placebo Extended varenicline - 24 weeks of varenicline 2 x 1 mg/day (titrated for first week) <p>Participants were randomised 1:1. All participants had 7 x SC counselling sessions over 24 weeks (4 x in-person, 3 x by telephone).</p>
Outcomes	Primary: 7-day biochemically confirmed abstinence at weeks 24 and 52
Notes	New for 2022 update

Nicotine receptor partial agonists for smoking cessation (Review)

Schnoll 2019 (Continued)

Funding by R01 CA165001 and K24 DA045244. Pfizer provided medication and placebo free of charge.

Author declaration of interests: "Drs. Schnoll and Hitsman receive medication and placebo free from, and provide consultation to, Pfizer. Drs. Schnoll and Dr. Kalhan have consulted for GlaxoSmithKline. Dr. Schnoll consults with Curaleaf."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The study statistician provided a randomization procedure (1:1) to the Penn Investigational Drug Service (IDS), which distributed pills."
Allocation concealment (selection bias)	Low risk	"The study statistician provided a randomization procedure (1:1) to the Penn Investigational Drug Service (IDS), which distributed pills. All personnel, except IDS, were blinded to assignment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Objective verification and participants blinded during the second 12 weeks (first 12 weeks were open-label as all participants received varenicline)
Incomplete outcome data (attrition bias) All outcomes	Low risk	77% and 75% in the 2 arms completed study according to flow-chart
Selective reporting (reporting bias)	Low risk	Outcomes are reported as planned on clinical trials record

Stein 2013
Study characteristics

Methods	Country: USA Setting: 9 methadone-maintained treatment centres in New England Aim: "[to] test varenicline versus placebo, and include a comparison condition of combination nicotine replacement therapy" Study design: randomised 3-armed double-blind controlled trial Dates conducted: December 2008-January 2012 Analysis: sample sizes of 132 (varenicline) and 44 (placebo) estimated to give 80% power to detect quit rates of 20% and 2.5% respectively; the study was not powered to detect differences between varenicline and combination NRT
Participants	315 adult methadone-maintained smokers, smoking 10+ CPD, willing to set a quit date within the 1st week Allocated 3:1:3 to varenicline (137): placebo (45): combination NRT (133). Mean age 39.9, 47.6% women, 78.5% white, mean CPD 20, mean FTND 5.7
Interventions	<ul style="list-style-type: none"> Varenicline: 24-week course of varenicline tablets, 1st week titrated Placebo: 24-week course of identical tablets and regimen Combination NRT: 24-week course of NRT patch (42 mg for > 30 CPD, 21 mg if < 30 CPD), + ad lib nicotine gum (4 mg) as needed <p>All participants received a standardised 15-min session of advice to quit (5As model: Ask, Advise, Assess, Assist, and Arrange), and were asked to set a TQD for 8 days' time. All made monthly visits for support and top-up medication. Participants were paid USD 30 for the baseline assessment and USD 40 for the 6-month assessment</p>

Stein 2013 (Continued)

Outcomes	<p>Primary: 7-day PPA at 6 months</p> <p>Secondary: CA from week 2 to 6 months; for non-quiters: CPD reduction in the 28 days prior to 6-month assessment</p> <p>Validation: CO < 8 ppm; urinary cotinine in varenicline and placebo participants claiming abstinence</p>
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Notes	<p>Funding: "Funding for this study was provided by the National Cancer Institute (RO1 CA129226). Dr. Stein is a recipient of a NIDA Mid-Career Investigator Award (K24 DA00512). NCI and NIDA had no further role in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication."</p> <p>New for 2016 update</p> <p>Author declaration of interests: "No conflict declared"</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants were randomized to treatment after completing the baseline assessment". No further information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind"; research assistants were "blind to participant group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to treatment and follow-up reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in trial registry reported

Steinberg 2011

Study characteristics

Methods	<p>Country: New Jersey, USA</p> <p>Setting: Robert Wood Johnson Hospital (584-bed, university-based)</p> <p>Aim: to evaluate efficacy and safety of varenicline in hospital inpatients</p> <p>Dates conducted: August 2007-March 2009</p> <p>Study design: phase III triple-blind pilot RCT</p>
Participants	<p>79 adult smokers, aged 18+, smoking 10+ CPD; randomised to varenicline (40) or placebo (39)</p> <p>59% men, mean age: 51, 72% white, 57% > 20 CPD, 40% FTND > 6</p> <p>Admission diagnoses 57% CVD, 14% orthopaedic, 13% pulmonary, 16% other</p> <p>Exclusion criteria: standard pharmacotherapy criteria, + current use of any SC medications</p>
Interventions	<ul style="list-style-type: none"> Varenicline 1.0 mg x 2/day for 12 weeks, including week 1 at titrated dose Placebo tablets as above

Steinberg 2011 (Continued)

Initial visit by Clinic Co-ordinator of local Tobacco Dependence Program for 5-10 min counselling Subsequent sessions of 15-min post-discharge

After discharge, data collection sessions at 4, 12 and 26 weeks, + 1 phone call at 2 weeks with research nurse USD 25 gift card for attendance at each follow-up visit

Outcomes

Primary outcome: 7-day PPA at 26 weeks

Secondary outcomes: 7-day PPA at 4, 12 weeks. Repeated PPA at 4, 12 and 24 weeks. AEs and SAEs; withdrawal and craving on MNWS; motivation; CPD; utilisation of outpatient services; composite medical outcome

Validation: CO validation \leq 8 ppm. Self-report accepted if unable to attend

Notes

Study was funded and support by Robert Wood Johnson Foundation and Pfizer

Repeated PPA at 4, 12 and 24 weeks used as strictest definition of abstinence and included in main MA

New for 2012 update

Author declaration of interests: "Dr. Steinberg had previously received honoraria for educational programs from Pfizer (2006–2009). The other authors declare that they have no conflicts of interest to disclose."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized in a 1:1 ratio through centralized telephone randomization process by the study statistician and hospital research pharmacist"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"The subject, research nurse, and treatment staff were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis conducted; unvalidated smoking status included where ascertained for non-attenders, but % of unvalidated status not reported
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered, except for detailed identification of SAEs

Steinberg 2018
Study characteristics
Methods

Country: USA

Setting: community

Aim: to conduct a proof-of-concept RCT of varenicline for smokers willing to reduce, but not quit smoking

Study design: parallel, placebo-controlled RCT

Steinberg 2018 (Continued)

Participants	<p>53 current adult smokers, smoking at least 10 CPD for the past 6-months, and interested in cutting down, but not in quitting in the next 30 days. 49.2% female, mean age 44.3, baseline average CPD 15</p> <p>Exclusion criteria: any past use of varenicline, current use of bupropion/nortriptyline/nicotine preparations, use of tobacco products other than cigarettes more than once per month, currently receiving tobacco use disorder counselling, alcohol use disorder, drug abuse, psychosis, depression or suicidal ideation</p>
Interventions	<ul style="list-style-type: none"> • Placebo • Varenicline 2 x 1 mg/day (titrated for the first week) <p>Participants were randomised on a 1:1 ratio. All participants received in-person interactive behavioural support, which comprised 3 x 20-min and 1 x 35-min counselling visits</p>
Outcomes	<p>Relevant outcomes</p> <ul style="list-style-type: none"> • Cigarette reduction goal (> 50% reduction) at 6 months • Mean CPD over time at 1, 3 and 6 months • Exhaled CO at 3 months and EoT • Number of quit attempts
Notes	<p>New for 2022 update.</p> <p>Abstinence data were provided upon request by study authors</p> <p>Funding by Global Research Award for Nicotine Dependence (GRAND) grant #WS777117 – An independent competitive grants program supported by Pfizer. Pfizer had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.</p> <p>Author declaration of interests: "MLS and JMW have consulted for and received unrestricted educational grants and research grant support from Pfizer. SE-L has no conflicts to declare."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized to active or placebo varenicline using an urn randomization procedure"
Allocation concealment (selection bias)	Unclear risk	Concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates 12% in placebo arm and 29% in varenicline arm
Selective reporting (reporting bias)	Low risk	Abstinence a prespecified outcome, but results not published. However, abstinence data were provided upon request by study authors

Tashkin 2011
Study characteristics

Methods	<p>Country: USA (17 centres), Spain (3 centres), France (4 centres), Italy (3 centres) Setting: 27 research centres</p> <p>Aim: to test efficacy and safety of varenicline in smokers with COPD</p> <p>Dates conducted: May 2006-April 2009 Study design: double-blind placebo-controlled RCT</p>
Participants	<p>504 adult smokers with mild-to-moderate COPD, aged 35+, smoking 10+ CPD, motivated to quit; allocated to varenicline (250), or placebo (254). 62% men, mean age 57, CPD 24-25, FTND score 5.9-6.2 Treatment groups were comparable at baseline Exclusion criteria: standard pharmacotherapy trial criteria, + treatment with systemic corticosteroids or hospitalised for COPD in previous 4 weeks</p>
Interventions	<ul style="list-style-type: none"> • Varenicline 1.0 mg x 2/day for 12 weeks, preceded by 1 week titrated dose • Placebo tablets as above <p>Both groups received SC educational booklet, + brief (≤ 10 min) counselling at weekly clinic visits throughout treatment phase, and phone call 3 days post-TQD. At each visit smoking status reported and CO verified; throughout treatment and at week 52 lung function, respiratory symptoms, weight, blood pressure, pulse, temperature, ECGs, haematology and serum chemistry assessed, + AEs Follow-up phase: smoking status + CO measured at weeks 13, 16, 24, 32, 40, 48 and 52; counselling and self-reported status by phone at weeks 14, 20, 28, 36 and 44</p>
Outcomes	<p>Primary outcome: CO-validated CAR at weeks 9-12 Secondary outcomes: CO-validated CAR at weeks 9-52 and 9-24; 7-day PPA at weeks 12, 24 and 52 Other outcomes: AEs; SAEs; weight change Validation was by expired CO ≤ 10 ppm Cessation analyses were ITT (all participants randomised), while tolerability and safety analyses were based only on those known to have used the intervention drug (N = 499). Attrition was 17% in the varenicline group and 24% in the placebo group during treatment phase, and 29% varenicline and 38% placebo who did not complete the study. This includes 2 deaths in the varenicline group and 1 in the placebo group</p>
Notes	<p>The study was funded by Pfizer Inc New for 2010 update</p> <p>Author declaration of interests: "The authors have reported to the CHEST the following conflicts of interest: Dr Tashkin received grant support from Pfizer Inc and Nabi Pharmaceuticals and fees for attending advisory board meetings from Pfizer Inc. Dr Hays received a research grant from Pfizer Inc for the conduct of the clinical trial described in this manuscript. In the past 3 years, Dr Rennard has been a consultant or a member of an advisory board for Able Associates, Adelphi Research, Almirall/Prescott, APT Pharma/Britnall, Aradigm, AstraZeneca, Boehringer Ingelheim, Chiesi, CommonHealth, Consult Complete, COPDForum, Data-Monitor, Decision Resources, Defined Health, Dey, Dunn Group, Eaton Associates, Equinox, Gerson, GlaxoSmithKline, Infomed, KOL Connection, M Pankove, MedaCorp, MDRx Financial, Mpex, Novartis, Nycomed, Oriel Therapeutics, Otsuka, Pennside Partners, Pfizer Inc (varenicline), Pharma Ventures, Pharmaxis, Price Waterhouse, Propagate, Pulmatrix, Reckner Associates, Recruiting Resources, Roche, Schlesinger Medical, SciMed, Sudler and Hennessey, TargeGen, Theravance, UBC, Uptake Medical, and VantagePoint Management. Dr Rennard has lectured for the American Thoracic Society, AstraZeneca, Boehringer Ingelheim, California Allergy Society, Creative Educational Concept, France Foundation, Information TV, Network for Continuing Ed, Novartis, Pfizer, and SOMA and has received industry-sponsored grants from AstraZeneca, Biomarck, Centocor, Mpex, Nabi Pharmaceuticals, Novartis, and Otsuka. Ms Ma and Drs Lawrence and Lee are all employees of Pfizer Inc, own Pfizer Stock, and have Pfizer stock options."</p>

Risk of bias
Nicotine receptor partial agonists for smoking cessation (Review)

Tashkin 2011 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"participants were randomized"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double blind" but details not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	All expected and predicted outcomes covered

Tonstad 2011
Study characteristics

Methods	<p>Countries: France, Spain, Belgium, Sweden, Denmark, Norway Setting: 22 research centres</p> <p>Aim: to test the efficacy and safety of dianicline for SC</p> <p>Dates conducted: June 2006-June 2007 Study design: double-blind placebo-controlled parallel group RCT</p> <p>Study name: EURODIAN study</p>
Participants	<p>602 healthy adult volunteers, smoking 10+ CPD within previous 2 months, aged 18+; allocated to dianicline (300), or placebo (302). 42% men, mean age 45, mean CPD 21, mean previous quit attempts 3.4, mean FTND score 5.75. Treatment groups were comparable at baseline</p> <p>Exclusion criteria: standard pharmacotherapy trial criteria, plus any quit attempt in previous 3 months, any use of bupropion, NRT, tobacco other than cigarettes 3+ times in previous 3 months</p>
Interventions	<ul style="list-style-type: none"> Dianicline 40 mg twice/day for 7 weeks (not titrated) Placebo inactive tablets, same regimen <p>TQD was set for days 3-7 following baseline visit</p> <p>All participants received standardised brief counselling (≤ 10 min, based on <i>Smoke-Free and Living It</i>) at each visit</p> <p>Weekly visits throughout weeks 1-7, then (for treatment completers) at weeks 8, 10, 14, 18, 22 and 26</p> <p>Smoking status and brief advice at each visit</p> <p>Participants completed smoking diaries</p>
Outcomes	<p>Primary outcome: CO-confirmed CAR for weeks 4-7</p> <p>Secondary outcomes: CO-confirmed CAR at 26 weeks. PPA weeks 4-7</p> <p>Validation by expired CO < 10 ppm (all visits) and plasma cotinine ≤ 8 $\mu\text{g/L}$ (weeks 4 and 7)</p> <p>Other outcomes: AEs, SAEs; craving and withdrawal symptoms</p> <p>Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis)</p>

Tonstad 2011 (Continued)

25.2% varenicline and 23% placebo participants did not complete the study. AE-related dropouts were 4.3% varenicline and 7.6% placebo

Notes

New for 2012 update

The trial was funded by Sanofi-Aventis. "The sponsor did not play a role in writing of the manuscript"

Author declaration of interests: "Serena Tonstad and Philip Tønnesen have received honoraria for lectures and advising from sanofi-aventis, Pfizer, Novartis, and GlaxoSmithKline, all manufacturers of drugs for smoking cessation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a predefined, central, and computer-generated randomization accessed through an Interactive Voice Response System assigned participants on a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants and investigators were blinded to drug treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts fully reported
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Tsai 2007

Study characteristics

Methods	<p>Country: Taiwan and Korea Setting: 5 sites in each country</p> <p>Aim: to test the efficacy and safety of varenicline for SC in Taiwanese and Korean smokers</p> <p>Dates conducted: February 2005-March 2006 Study design: double-blind placebo-controlled RCT</p>
Participants	<p>250 healthy adult volunteers, motivated to quit, aged 18-75; allocated to varenicline (126), or placebo (124). 89% men, mean age 40.3, BMI < 15 or > 38 or weight < 45.5 kg, mean CPD 24, mean FTND score 5.1 Treatment groups were comparable at baseline Exclusion criteria: standard pharmacotherapy trial criteria</p>
Interventions	<ul style="list-style-type: none"> Varenicline 1.0 mg x 2/day Placebo tablet x 2/day <p>Treatment period 12 weeks, 1st week titrated dosage. All participants received a SC booklet <i>Clearing the Air</i> at baseline, + brief counselling (≤ 10 min) at each clinic visit. Clinic visits at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, 12, plus a 5-min phone call at +3 days post-TQD, and at weeks 5, 7, 9, 11 In follow-up phase, clinic visits at weeks 13, 16, 20, 24 plus brief phone calls at weeks 14, 18, 22</p>

Nicotine receptor partial agonists for smoking cessation (Review)

Tsai 2007 (Continued)

Outcomes	<p>Primary outcome: CO-validated CAR at 9-12 weeks Secondary outcomes: CO-validated CAR at 9-24 weeks; 7-day PPA at weeks 12 and 24 Validation was by expired CO \leq 10 ppm Other outcomes: withdrawal symptoms (using MNWS, QSU-brief and mCEQ), AEs Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 2.8%, losses to follow-up 2.5% of treatment completers</p>
Notes	<p>Trial was funded by Pfizer Inc New for 2008 update</p> <p>Author declaration of interests: "Drs. Tsai and Cho have been members of Pfizer-sponsored advisory panels and, together with Drs. Cheng, Kim, and Hsueh, were investigators for a Pfizer-sponsored clinical trial."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly permuted blocks" (block size=4)
Allocation concealment (selection bias)	Low risk	Web- and telephone-based assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, investigators, study staff and sponsor personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information, but very high compliance rates
Selective reporting (reporting bias)	Unclear risk	All expected and predicted outcomes covered

Tsukahara 2010

Study characteristics

Methods	<p>Country: Japan Setting: cessation clinic in Fukuoka University Hospital</p> <p>Aim: to test the efficacy and safety of varenicline for SC in Japanese smokers</p> <p>Dates conducted: August 2008-November 2009 Study design: open-label RCT Study name: the VN-SEESAW Study</p>
Participants	<p>32 adult smokers, motivated to quit, allocated to varenicline (16) or nicotine patch (16). 75% men, mean age 46, mean CPD 28 (varenicline), 25 (patch), mean Brinkman index score (CPD x years smoking) 702. 71% had tried to quit previously, and 7% had used nicotine patches before Standard pharmacotherapy trial exclusion criteria, plus attendance at any SC clinic during previous 12 months</p>
Interventions	<ul style="list-style-type: none"> Open-label varenicline 1.0 mg x 2/day for 12 weeks, following 1 week titration Open-label nicotine patch for 8 weeks (52.5 mg/day for 4 weeks, 35 mg/day for 2 weeks, 17.5 mg/day for 2 weeks)

Nicotine receptor partial agonists for smoking cessation (Review)

Tsukahara 2010 (Continued)

No non-treatment or placebo control group
Varenicline group received 8 clinic visits and nicotine group 5 visits over 12 weeks, with 5 brief counselling sessions (≤ 10 min)

Outcomes
CO-confirmed CAR at 9-12 weeks, and self-reported at 9-24 weeks by phone interview
Validation by expired CO < 8 ppm at 12 weeks, but not at 24 weeks
Other outcomes: safety and tolerability by week 12, using MNWS at weeks 2, 4, 8 and 12. Also used Stress Check List and Strait-trait Anxiety Inventory
Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis)
Attrition in treatment phase was 12.5% from each group

Notes
The study was supported by the Japanese Ministry of Education, Science and Culture, Fukuoka University and FU-Global program
New for 2010 update

Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"by computer" allocating men: women 3:1 to reflect Japanese smoking prevalence (M: 40%, F: 12%)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and personnel were not blinded to treatment. However, both groups received an active licensed SC treatment and there is no reason to believe that participants would have favoured one over the other.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Tuisku 2016

Study characteristics

Methods	Country: Finland Setting: community Aim: to investigate the efficacy of varenicline and the nicotine patch as a SC aid in volunteer daily smokers in their twenties Study design: parallel, placebo-controlled RCT
Participants	288 current smokers aged 18-26 year-old, who had smoked daily for at least the past month, and smoked ≥ 100 cigarettes in their life. Participants were motivated to quit. 50.2% of participants were female, median age was 21, and average CPD at baseline 14 Exclusion criteria: current drug or alcohol abuse, known allergy towards medications used in the study, lactation, pregnancy or intention to become pregnant during the study period

Nicotine receptor partial agonists for smoking cessation (Review)

Tuisku 2016 (Continued)

Interventions	<p>Light smokers were randomly assigned into 2 groups:</p> <ul style="list-style-type: none"> • Placebo patch for 8 weeks • NRT - nicotine patch 10 mg/16 h for 8 weeks <p>Heavy smokers were randomly assigned into two groups:</p> <ul style="list-style-type: none"> • NRT - nicotine patch 15 mg/16 h for 8 weeks • Varenicline - 12 weeks 2 x 1 mg/day (titrated for first week)
Outcomes	<p>Primary: self-reported smoking abstinence at week 12</p> <p>Secondary: self-reported smoking abstinence at weeks 4 and 26; self-reported abstinence verified by saliva cotinine level at week 12</p>
Notes	<p>New for 2022 update</p> <p>Funding by Ministry of Social Affairs and Health, Finland; Finnish Research Foundation of the Pulmonary Disease; Finnish Medical Society Duodecim</p> <p>Author declaration of interests: "The authors declare no conflict of interest."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After assessment... at the baseline visit, simple randomisation with a computer-generated random list... was used to allocate study subjects into the different treatment groups"
Allocation concealment (selection bias)	Unclear risk	No information reported on allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence was self-reported, however placebo or another licensed treatment were used as comparators and behavioural support was balanced between groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were similar between study arms.
Selective reporting (reporting bias)	High risk	It appears 12-month follow-up was planned (NCT01531049) but is not reported in the published paper.

Tulloch 2016
Study characteristics

Methods	<p>Country: Canada</p> <p>Setting: community</p> <p>Aim: to evaluate smoking abstinence with standard nicotine patch, extended use of combined formulations of NRT, or varenicline</p> <p>Study design: parallel RCT</p>
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Tulloch 2016 (Continued)

Participants	<p>737 smokers, including those with medical and psychiatric comorbidities, motivated to quit. 46.6% female, mean age 48.61, baseline average CPD 23.2</p> <p>Exclusion criteria: use of NRT or varenicline for > 72 consecutive h in the past month; serious cardiac arrhythmias or a myocardial infarction or cerebral vascular accident within the previous 10 days; severe or unstable angina pectoris; end-stage renal disease or use of cimetidine; alcohol or substance abuse in the previous 3 months; unstable psychiatric symptoms; an inability to understand English or French. Women were excluded if pregnant, lactating, or likely to become pregnant in the next year.</p>
Interventions	<ul style="list-style-type: none"> • Nicotine patch - up to 10 weeks of patches (21 mg daily maximum dose) • Combination NRT - up to 22 weeks of nicotine patches (35 mg daily maximum dose) and gum or inhaler for up to 22 weeks • Varenicline - 2 x 1 mg/day for up to 24 weeks <p>All participants received 6 x 15-min cessation counselling interactive behavioural support from experienced nurses.</p>
Outcomes	<p>Primary: CO-confirmed CA rates from weeks 5–52.</p> <p>Secondary: CA rates from weeks 5–10 and 5–22; CO-confirmed 7-day PPA at weeks 10, 22, and 52</p>
Notes	<p>New for 2022 update</p> <p>Funding by the Heart and Stroke Foundation of Ontario. Study authors have previously received research grants and delivered educational presentation for Pfizer.</p> <p>Author declaration of interests: "AP and RR have received research grants from Pfizer. AP and BR have been paid for developing and delivering educational presentations for Pfizer. AP is on the advisory board for Pfizer and Johnson & Johnson."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated using a computer generated algorithm in Statistical Analysis Software (SAS program) by a researcher not involved in the study and blinded to the identity of participants."
Allocation concealment (selection bias)	Low risk	"Randomization numbers were placed in opaque, sealed, and consecutively numbered envelopes and opened following the completion of the baseline data collection."
Blinding (performance bias and detection bias) All outcomes	Low risk	Open-label with higher intensity medication provided in the combination NRT arm than the nicotine patch arm.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was < 50% and comparable between arms.
Selective reporting (reporting bias)	Low risk	Abstinence was reported as stated in trial register (NCT01623505)

Vinnikov 2008

Study characteristics

Nicotine receptor partial agonists for smoking cessation (Review)

Vinnikov 2008 (Continued)

Methods	Country: Kyrgyzstan Setting: Mining company (Kumtor Operating Company) Aim: to test the efficacy and safety of cytisine for SC in a workplace setting Study design: double-blind placebo-controlled parallel-group RCT
Participants	197 adult smokers, aged 20+, smoking at least 15 CPD, no prior use of cytisine, and motivated to quit Randomised to cytisine (100) or placebo (97). 26 (15 cytisine, 11 placebo) who took no medication were excluded from trial report 97% men, mean age 39, mean CPD 22, mean FTND 5.3, 86% had tried to quit previously; mean previous quit attempts 3.3 Exclusion criteria: standard pharmacotherapy trial criteria
Interventions	Tabex tablets (1.5 mg cytisine): <ul style="list-style-type: none"> • first 3 days: 6 tablets/day; reduce smoking by half • days 4-12: 5 tablets/day; stop smoking completely • days 13-16: 4 tablets/day • days 17-20: 3 tablets/day • days 21-22: 2 tablets/day • days 23-25: 1 tablet/day Placebo tablets, same regimen Treatment period was 25 days, with TQD Day 5. All participants received "behavior counselling" (no further detail)
Outcomes	Primary outcome: CO-validated CAR from day 5 to week 8 Secondary outcome: CO-validated CAR from day 5 to week 26 Validation was by expired CO \leq 8 ppm Other outcomes: change in health-related QoL measures, changes in body weight, AEs, SAEs Attrition to 8 weeks was 6 in cytisine group and 7 in placebo group; to 26 weeks 10 in cytisine group and 16 in placebo group
Notes	New for 2012 update Additional information supplied by the study author Study funding: not reported Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done by independent statistician in an Excel programme and the randomization key was kept by an independent person"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"Nor patients neither investigators did not know where Tabex and where placebo were"; "follow-up was blind"
Incomplete outcome data (attrition bias)	Unclear risk	26 participants who did not take a single treatment dose were excluded from denominators by authors (restored to our MAs)

Nicotine receptor partial agonists for smoking cessation (Review)

Vinnikov 2008 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Expected and predicted outcomes reported
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Walker 2014
Study characteristics

Methods	Country: New Zealand Setting: National Quitline Aim: "a non-inferiority trial to investigate whether cytisine was at least as effective as nicotine-replacement-therapy" Study design: parallel-group non-inferiority RCT Dates conducted: March 2011-February 2013
Participants	1310 daily smokers, callers to the NZ National Quitline, aged 18+, motivated to quit. Allocated to cytisine (655) or to open-label NRT (655). Mean age 38, 57% women, 33% NZ Maori, mean CPD 19, mean FT-ND 5.4
Interventions	<ul style="list-style-type: none"> 25-day course of cytisine (Tabex) tablets, + NRT vouchers in case they needed them after completing the cytisine course Usual care, i.e. 8-week course of NRT (patch, gum or lozenge), tailored to dependence level, supplied by vouchers <p>All participants received standard Quitline support, i.e. average 3 x 10-15-min calls over 8 weeks</p>
Outcomes	Self-reported CAR (5 cigarettes or fewer) at 1 month CAR and 7-day PPA (no smoking) at 1 week, 1 month, 2 months and 6 months. AEs Validation: none used
Notes	Funding by Health Research Council of New Zealand; cytisine supplied at no cost by Sopharma New for 2016 update Author declaration of interests: "Dr. McRobbie reports receiving lecture fees from Johnson & Johnson and grant support from Pfizer. No other potential conflict of interest relevant to this article was reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated, by computer ... in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	"Randomization was stratified with the use of minimization according to sex, ethnicity (Maori, Pacific Islander, or non-Maori and non-Pacific Islander), and cigarette dependence, which was determined by means of the Fagerström Test of Cigarette Dependence, in which smokers were assigned to one of two groups: those with scores of 5 or lower, indicating lower dependence, and those with scores greater than 5, indicating greater dependence"
Blinding (performance bias and detection bias)	High risk	"Participants and researchers collecting outcome data were aware of treatment allocation"

Nicotine receptor partial agonists for smoking cessation (Review)

Walker 2014 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported. By 6 months, 182 cytisine participants (28%) lost to follow-up, and 16 withdrawals; 173 NRT participants (26%) lost to follow-up, and 14 withdrawals. 19 cytisine users crossed over to NRT, and 1 NRT user crossed over to cytisine. ITT analyses conducted
Selective reporting (reporting bias)	Low risk	Prespecified outcomes from protocol all reported
Other bias	Unclear risk	Cytisine was supplied free, while NRT users had to pay a nominal charge (NZD 3 for an 8-week course of each NRT item).

Walker 2021
Study characteristics

Methods	Country: New Zealand Setting: community pharmacy (for drug distribution), participants' homes Aim: to determine whether cytisine was at least as effective as varenicline in supporting smoking abstinence for ≥ 6 months in New Zealand indigenous Māori or <i>whānau</i> (extended-family) of Māori Study design: open-label, parallel, RCT
Participants	679 adult daily smokers who identified as Māori or <i>whānau</i> of Māori, motivated to quit in the next 2 weeks, and were eligible for subsidised varenicline. 69.6% female, mean age 43, baseline average CPD 15.5 Exclusion criteria: pregnant/breastfeeding; currently using SC medication (including e-cigarettes); enrolled in another cessation programme/study; used varenicline or cytisine in the previous 12 months; known hypersensitivity; self-reported moderate/severe renal impairment; treatment for active/latent tuberculosis; heart attack, stroke or severe angina within the previous 2 weeks; uncontrolled high blood pressure; history of seizures
Interventions	<ul style="list-style-type: none"> Varenicline - 2 x 1.5 mg/day (titrated for first week). Cytisine - days 1–3: 6 x 1.5 mg/day; days 4–12: 5 x 1.5 mg/day; days 13–16: 4 x 1.5 mg/day; days 17–20: 3 x 1.5 mg/day; and days 21–25: 2 x 1.5 mg/day. A maintenance dose of cystine 2 x 1.5 mg/day was added for day 26 to week 12 to match the treatment duration of varenicline. <p>All participants received low-intensity cessation behavioural support from the prescribing doctor and community stop-smoking services or a research assistant.</p>
Outcomes	Primary: CA at 6 months (verified with exhaled CO < 9 ppm) Secondary outcomes measured at 1, 3, 6 and 12 months post-quit date included: self-reported CA, 7-day PPA, CPD, time to (re)lapse, AEs, treatment adherence/compliance and acceptability, nicotine withdrawal/urge to smoke and healthcare utilization/health-related QoL
Notes	New for 2022 update Funding by the Health Research Council of NZ. Manufacturer supplied the treatment free of charge. Author declaration of interests: "All authors report grants from the Health Research Council of New Zealand and non-financial support from Achieve Life Sciences during the conduct of the study. N. W., C.B. and M.V. V.P. report grants from Pfizer, grants from the Health Research Council of New Zealand, outside the submitted work; and has previously undertaken two trials of e-cigarettes for smoking cessation [with e-cigarettes purchased from a NZ e-cigarette on-line retailer (NZVAPOR, https://www.nz-

Nicotine receptor partial agonists for smoking cessation (Review)

130

Walker 2021 (Continued)

vapor.com/), e-liquid for one trial purchased from Nicopharm, Australia (<https://www.nicopharm.com.au/>) and nicotine patches supplied by the NZ Government via their contract with Novartis (Sydney, Australia)]. Neither NZVAPOR nor Nicopharm have links with the tobacco industry. C.B. also reports personal fees from the Moffat Cancer Center, University of Florida, USA, and personal fees from Virginia Commonwealth University, USA outside the submitted work. J.B. also reports personal fees from New Zealand Ministry of Health Natural Health Products (NHPs) Regulations Subcommittee on the Permitted Substances List (member of subcommittee 2016–17), non-financial support from Uppsala Monitoring Centre, Sweden (who manages the technical and scientific aspects of the WHO Programme for International Drug Monitoring); honorary consultant and herbal safety signal reviewer (2004–current), outside the submitted work. None of the above parties had any role in the design, conduct, analysis or interpretation of the trial findings or writing of the resulting publication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomization was undertaken, with varying block sizes. The randomization sequence was prepared by the trial statistician using R and loaded into the REDCap database, which was the accessed by the study doctor via a computer at the point of randomization."
Allocation concealment (selection bias)	Low risk	"Block randomization was undertaken, with varying block sizes. The randomization sequence was prepared by the trial statistician using R and loaded into the REDCap database, which was the accessed by the study doctor via a computer at the point of randomization."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Abstinence was verified by a researcher or community-based cessation provider, using standardized exhaled carbon monoxide (CO) measurement with a Bedfont Smokerlyzer".
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 39% of participants in both groups were followed up at 6 months (12 months is unclear) although these numbers do not match main results table. Methods say multiple imputation used but not clear what effect this had on findings.
Selective reporting (reporting bias)	Low risk	Outcomes reported match the trial protocol paper

Wang 2009
Study characteristics

Methods	Country: China (10 sites), Singapore (3 sites), Thailand (2 sites) Aim: to test the efficacy and safety of varenicline for SC in Chinese, Singaporean and Thai smokers Dates conducted: not stated Study design: double-blind placebo-controlled RCT
Participants	333 healthy adult volunteers, aged 18-75; allocated to varenicline (165), or placebo (168). 97% men, mean age 39, BMI > 15 and < 38 or weight > 45.5 kg, mean CPD 20, mean FTND score 5.4. Treatment groups were comparable at baseline. 58% had never tried to quit before Exclusion criteria: standard pharmacotherapy trial criteria, plus any use of NRT or bupropion in previous 6 months
Interventions	<ul style="list-style-type: none"> Varenicline 1.0 mg x 2/day

Nicotine receptor partial agonists for smoking cessation (Review)

Wang 2009 (Continued)

- Placebo tablet x 2/day

Treatment period 12 weeks, 1st week titrated dosage. All participants received a SC booklet at baseline, + brief counselling (≤ 10 min) at each clinic visit, except for weeks 5 and 7, when counselling was conducted by phone

In follow-up phase, clinic visits at weeks 13, 16, 20, 24 plus brief phone calls at weeks 14, 18, 22. Dosing and CO checked at each visit, and lab samples taken at weeks 12 and 24

Outcomes	<p>Primary outcome: CO-confirmed CAR for weeks 9-12</p> <p>Secondary outcomes: CO-confirmed CAR for weeks 9-24; 7-day PPA at 24 weeks</p> <p>Validation by expired CO < 10 ppm</p> <p>Other outcomes: AEs; long-term quit rates</p> <p>Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis)</p> <p>Attrition in treatment phase was 3.0% in varenicline group, and 3.6% in placebo group. By week 24, 4.2% of had dropped out of each group</p>
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Notes	<p>The trial was funded by Pfizer Inc New for 2010 update</p> <p>Author declaration of interests: "Pfizer Inc. funded the study and was involved with its design, analysis and writing the manuscript. All authors had complete access to all relevant data. Dahlia Garza and Simon Davies are employees of Pfizer Inc., and therefore hold shares in the company. Editorial support was provided by Aideen Young, PhD, of UBC Scientific Solutions and funded by Pfizer Inc. None of the other authors hold shares in any companies. Chen Wang and Dan Xiao are affiliated with the WHO Collaborating Centre for Tobacco or Health. WHO had no role in the study's funding, design, analysis or write-up."</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"eligible subjects were randomized in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information, but very high compliance rates
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

West 2011

Study characteristics

Methods	<p>Country: Poland Setting: SC clinic in Warsaw</p> <p>Aim: to test the efficacy and safety of cytisine for SC with minimal counselling and support</p> <p>Dates conducted: December 2007-September 2010</p>
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Nicotine receptor partial agonists for smoking cessation (Review)

West 2011 (Continued)

	Study design: single-centre, double-blind placebo-controlled parallel-group RCT
Participants	<p>740 healthy adults, smoking 10+ CPD, motivated to quit. Randomised to cytisine (370) or placebo (370)</p> <p>46.5% men, mean age 48, mean CPD 23, prior quit attempts 82%, mean FTND 6.2</p> <p>Exclusions were current psychiatric disorder or any medical condition contraindicated on cytisine label</p>
Interventions	<p>Tabex tablets (1.5 mg cytisine):</p> <ul style="list-style-type: none"> • first 3 days: 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 <p>Placebo tablets, same regimen</p> <p>Treatment period was 25 days. Quitting advice, randomisation and drugs dispensed at baseline visit; phone calls at TQD + 1 week later (+ optional clinic visit). Clinic visit 4 weeks post-TQD, then phone calls at 6 months and 12 months, with visit to confirm abstinence if claimed. Behavioural support was minimal, to simulate likelihood of real-world conditions in countries where Tabex is available</p>
Outcomes	<p>Primary: CO-validated abstinence 12 months after EoT. Abstinence defined as smoking < 5 cigarettes during preceding 6 months, and none in week before visit</p> <p>Secondary outcomes: sustained CO-validated abstinence at 6-month follow-up; 2-week PPA at 4 weeks; 7-day PPA at 12 months</p> <p>Validation was expired CO < 10 ppm</p> <p>Attrition: 79 (cytisine) and 89 (placebo) participants were lost to follow-up over 12 months. Drug discontinuation or reduction rates similar in both groups: 6.2% for cytisine and 4.6% for placebo</p> <p>Other outcomes: AEs, SAEs</p>
Notes	<p>New for 2012 update</p> <p>The trial was funded by the UK National Prevention Research Initiative, Cancer Research UK, and the National Institute for Health Research</p> <p>Author declaration of interests: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"performed by a statistician at Sopharma, who generated a list of study-group assignments for 740 participants with nQuery Advisor software. Assignments were made in variable block sizes of either 20 (10 cytisine, 10 placebo) or 10 (5 and 5)"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"Trial staff and participants were unaware of the group assignments and the randomization scheme"
Incomplete outcome data (attrition bias)	Low risk	Dropouts and attrition fully reported

Nicotine receptor partial agonists for smoking cessation (Review)

West 2011 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes reported
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Westergaard 2015
Study characteristics

Methods	Country: Denmark Aim: to evaluate the effect of varenicline on tobacco cessation in young smokers suffering from asthma Dates conducted: not stated Study design: double-blind placebo-controlled RCT
Participants	52 young (aged 19-40) smokers with asthma, randomised to varenicline (26) or placebo (26). CPD \geq 10; FTND 5.6
Interventions	<ul style="list-style-type: none"> Varenicline: presumed standard regimen: varenicline 1.0 mg x 2/day Placebo tablet x 2/day No further details
Outcomes	Primary: presumed PPA at 12 weeks Secondary: presumed PPA at 0, 6, 24 weeks Validation by expired CO < 10 ppm Also assessed asthma symptom score, general health quality score (15D) and methacholine challenge
Notes	Study funding: "The Respiratory Research Unit has received financial support from Pfizer Inc. [WS807136] in relation to the conduction of the present study. Furthermore, the Varenicline and placebo tablets were provided by Pfizer Inc. Pfizer Inc. has not been involved in study design, in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication." Author declaration of interests: not reported Author supplied further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated. ""randomized, placebo-controlled, double-blinded trial"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated. "double-blinded"

Westergaard 2015 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated; ITT analysis conducted
Selective reporting (reporting bias)	Unclear risk	Not stated

Williams 2007
Study characteristics

Methods	Country: USA and Australia Setting: 9 research centres (8 USA, 1 Australia) Aim: to test the safety of long-term (12 months) use of varenicline in smokers trying to quit Study design: double-blind placebo-controlled RCT Dates conducted: October 2003-March 2005
Participants	377 adult smokers, aged 18-75, smoking at least 10 CPD. 49.9% men, 88.6% white, average CPD at baseline 23, mean FTND 5.5 in treatment group, 6.05 in control group. Allocated to varenicline (251) or placebo (126) Exclusion criteria: standard pharmacotherapy trial criteria, + no use of NRT, antidepressants, antipsychotics, naltrexone during study period
Interventions	<ul style="list-style-type: none"> Varenicline 1 mg x 2/day, titrated for first week Placebo inactive tablets, same regimen <p>All participants received booklet <i>Clearing the Air</i>. Brief counselling (≤ 10 min) at each visit TQD was 1st day of week 1 visit (7-10 days post-randomisation) Treatment period was 52 weeks. Weekly visits throughout weeks 1-8, then every 4 weeks to week 52, + week 53 assessment Blood and urine samples taken at screening, baseline, weeks 2, 12, 24, 36, 52 (or early termination) Complete physical exam at baseline, weeks 24 and 52; BP, pulse and weight measured at all visits, ECG at screening, baseline, weeks 2, 24 and 52 (or early termination)</p>
Outcomes	Primary outcome: safety of smokers treated continuously with varenicline over 52 weeks, measured at week 53 by level and tolerability of AEs and incidence of SAEs Secondary outcome: 7-day CO-verified PPA at all clinic visits (expired CO ≤ 10 ppm) Other outcomes: weight change; changes in vital signs Attrition was 46.2% in varenicline group, 53.2% in control group by end of study
Notes	This was a safety study, with cessation rates collected as a secondary outcome The trial was funded and conducted by Pfizer Inc In the first version of this review, this trial appeared as Reeves 2006 (unpublished data) Author declaration of interests: "Kathryn E. Williams, Karen R. Reeves, Clare B. Billing, Jr, Ann M. Pennington, and Jason Gong are all employees of Pfizer and were involved in designing the study, data monitoring, data management, statistical analysis, and interpretation of the results, as well as the drafting, editing, and reviewing of this manuscript"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation 2:1 varenicline to placebo. No detailed information reported

Nicotine receptor partial agonists for smoking cessation (Review)

Williams 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing CO and/or visit taken as smokers
Selective reporting (reporting bias)	Low risk	Primary outcome was safety, so minimal cessation data

Williams 2012

Study characteristics

Methods	<p>Countries: Canada, USA Setting: 12 sites Aim: to evaluate primarily safety, but also efficacy of varenicline in smokers with schizophrenia or schizoaffective disorders</p> <p>Dates conducted: May 2008-April 2010 Study design: double-blind placebo-controlled RCT. Sample size [120] was considered sufficient to detect a between-group difference in 7-day PPA "for a medium effect size"</p>
Participants	128 adults, diagnosed with stable schizophrenia or schizoaffective disorders, smoking at least 15 CPD and motivated to quit. Randomised to varenicline (85) or placebo (43). 77% men aged 18-75
Interventions	<ul style="list-style-type: none"> Varenicline 1.0 mg x 2/d for 12 weeks, including week 1 at titrated dose Placebo tablets as above <p>Weekly clinic visits, for safety and efficacy, ≤ 30-min counselling sessions; after treatment phase, clinic visits at weeks 13, 16, 20, 24, with brief phone calls at weeks 14, 18 and 22. Follow-up sessions included brief (≤ 10 min) counselling. AEs collected to 30 days after treatment, and neuropsychiatric AEs to week 24</p>
Outcomes	<p>Primary outcome: N of participants with AEs and SAEs from baseline to 30 days after EoT (12 weeks). N of participants with psychiatric AEs, including suicidal ideation or behaviour</p> <p>Secondary outcomes: CO-confirmed PPA at weeks 12 and 24; 50%+ reduction in CPD; change in CPD from baseline. Assessments on mood and psychiatric scales</p> <p>Validation was by exhaled CO ≤ 10 ppm</p> <p>Dropouts in treatment phase: 14 (varenicline), 3 (placebo); follow-up phase: 10 (varenicline), 3 (placebo) 1 varenicline participant died during follow-up phase</p>
Notes	<p>The study was funded by Pfizer</p> <p>New for 2012 update</p> <p>Author declaration of interests: "Dr Williams has received research support from the National Institutes of Health (NIH [National Institute of Mental Health and National Institute on Drug Abuse]) and Pfizer and has received further support from Pfizer for advisory board membership and product support. Dr Anthenelli provides consultancy and/or advisory services for Pfizer and GlaxoSmithKline, and his laboratory receives funding support from the National Institute on Alcohol Abuse and Alcoholism, the De-</p>

Nicotine receptor partial agonists for smoking cessation (Review)

Williams 2012 (Continued)

partment of Veterans Affairs, Pfizer, Nabi Biopharmaceuticals, and sanofi-aventis. He has also received honoraria from Pfizer. Dr Morris has received research support from Pfizer. Drs Thompson and Yunis and Ms Treadow are employees of and shareholders in Pfizer. Dr George has received consulting fees from Pfizer, sanofi-aventis, Novartis, Eli Lilly, Prepharm, AstraZeneca, and Janssen; has received research support from Pfizer and Sepracor; and has received grant support relevant to the study medication from the NIH, Canadian Institutes of Health Research, Canada Foundation for Innovation, and the Ontario Mental Health Foundation"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized (2:1) to varenicline or placebo ... and were stratified according to antipsychotic medication type (typical vs atypical)."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not yet reported
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in trial registry reported

Windle 2018
Study characteristics

Methods	Country: 40 centres in USA and Canada Setting: hospitals Aim: to determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction Study design: double-blind placebo-controlled multicentre RCT Study name: evaluation of varenicline in SC for patients post-acute coronary syndrome (EVITA) Dates conducted: not stated
Participants	302 adult smokers, aged 18+, smoking 10+ CPD, interested in trying to quit, hospitalised in USA or Canada for acute coronary syndrome (MI or unstable angina). Mean age 55, 25% women, mean CPD 21.5 Allocated to varenicline (151) or placebo (151) Exclusions: excessive alcohol, history of panic disorder, psychosis, bipolar disease, dementia, renal or hepatic impairment, current or recent drug use, history of suicidal ideation/attempt or family history of suicide
Interventions	<ul style="list-style-type: none"> Varenicline 12 weeks, titrated 1st week Placebo 12 weeks, titrated 1st week Medication was begun in hospital. All participants received low-intensity counselling

Nicotine receptor partial agonists for smoking cessation (Review)

Windle 2018 (Continued)

Follow-up at weeks 1, 2 and 8 by phone, and clinic visits at weeks 4, 12, 24 and 52

Outcomes

Primary: 7-day PPA at week 24

Secondary: CAR at all follow-up visits, 7 day PPA at other follow-up visits, $\geq 50\%$ reduction in CPD

Measures of side effects and SAEs

Validation: CO ≤ 10 ppm

Notes

New for 2016 update

Study funding: "EVITA was an investigator-initiated trial that received funding and the study drug and placebo from Pfizer Inc. Pfizer had no role in the design, conduct, analysis, interpretation of data, or reporting of the EVITA trial."

Author declaration of interests: "Shamir Mehta reports funding from AstraZeneca, Boston Scientific, Bayer and Abbott. Beth Abramson has received grants or research support from AstraZeneca and Sanofi; honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Fournier, Merck, Pfizer, Servier and Sanofi; and consulting fees from Amgen, Bayer, Boehringer Ingelheim, Sanofi and Servier. She authored Heart Health for Canadians. Mark Eisenberg, Payam Dehghani, François Grondin and Mina Madan received honoraria from Pfizer for providing continuing medical education on SC. No other competing interests were declared"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized to either varenicline or matching placebo... Randomization was performed by enrolling center personnel and stratified by center using a computer-generated list of permuted blocks of 2 and 4"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as "double-blind", but no further detail. Abstinence biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in trial registry reported

Wong 2012

Study characteristics

Methods

Country: Canada
Setting: 2 Toronto hospitals

Aim: "to determine the effectiveness and safety of a perioperative SC intervention including varenicline and counseling versus placebo and counseling to increase short- and long-term abstinence in surgical patients"

Study design: randomised placebo-controlled double-blind trial

Wong 2012 (Continued)

Dates conducted: June 2008-November 2010

Participants	286 non-cardiac elective surgery patients, smoking 10+ CPD, no abstinence > 3 months in last year, scheduled for surgery in the next 8-30 days. Allocated to varenicline (151) or placebo (135). Mean age 52.6, 47% women, mean CPD 17.4, mean FTND 4.8
Interventions	<ul style="list-style-type: none"> • Varenicline: 12 weeks standard regimen, 1st week titrated • Placebo: Identical-looking tablets and regimen <p>All participants received 2 standardised 15-min counselling sessions by researchers, 1 in pre-op clinic and 1 24 h after surgery, supplemented by written materials. All participants retained the same counsellor throughout the process</p> <p>Weekly counselling phone calls for 4 weeks, and at the end of 8 weeks. From 3-12 months, phone calls every 4 weeks for smoking status, nicotine dependence, stage of change, CPD, brief (< 5 min) counselling. TQD was set for 24 h before surgery, and medication begun 7 days before TQD</p> <p>Participants were invited to visit the hospital at 3, 6, and 12 months, for assessment and testing. Participants unable to visit the hospital were sent a self-test urinary kit</p>
Outcomes	7-day PPA at 12 months; abstinence on TQD; 7-day PPA at 3 months and 6 months. Self-reported changes in CPD and stage of change at 3, 6 and 12 months
	Validation: expired CO and urinary cotinine (cut-offs not given)
Notes	<p>Supported by Canadian academic institutes and Pfizer Canada</p> <p>New for 2016 update</p> <p>Author declaration of interests: "Dr. Chapman holds the GSK-CIHR Research Chair in Respiratory Health Care Delivery. Dr. Wong is a recipient of a Merit Research Award from the Department of Anesthesia at the University of Toronto, Toronto, Ontario, Canada."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Smokers were randomly assigned to receive varenicline (Pfizer Inc., Kirkland, Quebec, Canada) or matching placebo using a computer-generated randomization list at each center. A stratified randomization with blocks of 40, based on the smoker's stage of change, was employed because the stage of change may predict successful abstinence from smoking."
Allocation concealment (selection bias)	Low risk	"The patient assignments were placed into sequentially numbered, opaque sealed envelopes, and were kept by an independent research pharmacist at each center who was not involved with patient care or outcome assessments. For each patient, the research pharmacist opened the envelope and provided the research coordinator with the medication or placebo (lactose, identical in appearance) according to the randomization schedule."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The patients, healthcare personnel, and research staff were blinded to the randomization throughout the study period."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported: varenicline: 6 discontinued treatment, 11 discontinued follow-up. Placebo: 6 discontinued treatment, 10 discontinued follow-up. ITT analyses conducted
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in trial registry reported

Nicotine receptor partial agonists for smoking cessation (Review)

139

Yang 2016

Study characteristics

Methods	Country: China Setting: hospital Study design: parallel randomised trial
Participants	78 male smokers, motivated to quit, with a diagnosis of COPD Mean age 58, baseline average CPD 5
Interventions	<ul style="list-style-type: none"> No medication Varenicline 2 x 1 mg/day
Outcomes	PA at 24 weeks. Self-reported
Notes	New for 2022 update Study funding: not reported Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated randomised but methods not reported
Allocation concealment (selection bias)	Unclear risk	Concealment not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rate unclear
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Zawertailo 2020

Study characteristics

Methods	Country: Canada Setting: inpatient or outpatient treatment clinic Aim: to evaluate if varenicline would be a safe and efficacious treatment for tobacco dependence in people with alcohol dependence
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Zawertailo 2020 (Continued)

Study design: randomised, placebo-controlled, double-blind pilot study

Participants	<p>31 daily dependent smokers, aged 18-65 years, also in treatment for alcohol dependence. Eligible participants smoked at least 10 CPD; and scored ≥ 3 on the Fagerstrom Test of Nicotine Dependence (FT-ND). 26.7% were female, mean age 44.6, baseline average CPD 18.4</p> <p>Exclusion criteria: serious medical condition requiring immediate investigation or treatment, current pregnancy or breastfeeding, current psychiatric disorder excluding alcohol use disorder and tobacco dependence, any known contraindication to using varenicline, inability to provide informed written consent, or inability or unwillingness to attend weekly study visits for 12 consecutive weeks</p>
Interventions	<ul style="list-style-type: none"> Varenicline 2 x 1.5 mg/day (first week titrated) Placebo <p>All participants received weekly individual in-person SC counselling for 12 weeks</p>
Outcomes	<p>Primary: abstinence from smoking (defined as no smoking during the last 4 weeks) at the EoT. Self-reported abstinence was biochemically verified using exhaled CO of < 10 ppm</p> <p>Secondary: abstinence from smoking at 6 months, biochemically confirmed using exhaled CO of < 10 ppm</p>
Notes	<p>New for 2022 update</p> <p>Funding by Pfizer and the Ministry of Health, the Canadian Institutes of Health Research</p> <p>Author declaration of interests: "L.Z. is currently receiving investigator-initiated funding from Pfizer, Inc, and peer-reviewed grant funding from the Ontario Ministry of Health and the Canadian Institutes of Health Research. B.L.F. has obtained funding from Pfizer (GRAND Awards, including salary support) for investigator-initiated projects. P.S. has received funding from the Ontario Ministry of Health, Canadian Institutes of Health Research, Canadian Centre on Substance Abuse, Public Health Agency of Canada, Pfizer, Inc/Canada, Ontario Lung Association, and Canadian Cancer Society Research Institute. He has received honoraria for speaking engagements and consulting from Pfizer Canada, Inc, ABBVie, Bristol-Myers Squibb, Evidera, Inc, Johnson & Johnson Group of Companies, Medcan Clinic, Inflexion, Inc, V-CC Systems, Inc, MedPlan Communications, Kataka Medical Communications, Miller Medical Communications, NVision Insight Group, Sun Life Financial, and Myelin & Associates For the remaining authors, no conflicts of interest are declared."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated by the CAMH Research Pharmacy",
Allocation concealment (selection bias)	Low risk	"Both participants and study staff were blinded to the randomization assignment" with allocation performed by the CAMH Research Pharmacist, who were not involved in recruitment.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both participants and study staff were blinded to the randomization assignment." "Self-reported abstinence at each weekly visit was confirmed with expired CO of less than 10 ppm using a Bedfont Smokelyzer."
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/15 (placebo) and 4/16 (varenicline) dropped out. 21/31 participants attended 6 months follow-up
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported

Nicotine receptor partial agonists for smoking cessation (Review)

141

Zhang 2022
Study characteristics

Methods	<p>Study design: RCT</p> <p>Country: Canada</p> <p>Recruitment method (quote): "The primary method of recruitment was by word of mouth and Facebook advertisement. Interested participants were directed to the study website, where they could indicate their consent for participation and complete eligibility questionnaires"</p>
Participants	2461 smokers; 56% female, average age 46.5, 46.9% of bupropion group and 44.9% of varenicline group smoked 11-20 CPD
Interventions	<ul style="list-style-type: none"> Bupropion 150 mg once daily for first 3 days, then twice daily for the remainder of 12 weeks. Starting 7 days prior to TQD Varenicline 0.5 mg once daily for first 3 days, then 0.5 mg twice daily for next 4 days, then 1 mg twice daily for the remainder of 12 weeks. Starting 7 days prior to TQD <p>Common components: weekly motivational emails</p>
Outcomes	<ul style="list-style-type: none"> SC: point prevalence measured at 52 weeks. Not biochemically verified AEs: measured at 12 weeks
Notes	<p>Study funding: "This research was funded by Global Research Awards for Nicotine Dependence (GRAND), a peer-reviewed research grant competition funded by Pfizer Pharmaceuticals [Zawertailo (GRAND2012) WS2391913]. The study's funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report, and had no decision to submit the article for publication. Dr. Le Foll is supported by a clinician-scientist award from the Department of Family and Community Medicine and by the Addiction Psychiatry Chair of the Department of Psychiatry of University of Toronto. Dr. Selby is supported by a clinician-scientist award from the Department of Family and Community Medicine and CAMH."</p> <p>Author declaration of interests: "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; PS reports receiving funding and/ or honoraria from Pfizer Inc./Canada, Shoppers Drug Mart, Bhasin Consulting Fund Inc., Patient-Centered Outcomes Research Institute, ABBVie, and Bristol-Myers Squibb; BLF and LZ both receive support from Pfizer Global Research Awards in Nicotine Dependence (GRAND) Award Program; there are no other relationships or activities that could appear to have influenced the submitted work. BLF also reports grants from Brainsway, grants from Bioprojet, grants from Alkermes, grants from Canopy, grants from ACS, non-financial support from Aurora, outside the submitted work."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Study quote: "Participants were randomly assigned to one of two medication arms (varenicline or bupropion) using permuted-block randomization in a 1:1 ratio in blocks of 100."</p> <p>Protocol quote: "The randomization process will be computerized."</p>
Allocation concealment (selection bias)	Low risk	Protocol quote: "The randomization process will be computerized."
Blinding (performance bias and detection bias) All outcomes	Low risk	Study quote: "Participants were not blinded to treatment since their health care provider signing the prescription form was required to know which drug

Nicotine receptor partial agonists for smoking cessation (Review)

142

Zhang 2022 (Continued)

was being prescribed to their patient." However, both study groups received active smoking cessation pharmacotherapy treatment.

The abstinence outcome was not biochemically verified, however, study arms received the same behavioural support.

Incomplete outcome data (attrition bias) All outcomes	Low risk	The overall number of participants lost at the 52-week follow-up was > 50% in each condition. However, a complete case sensitivity analysis (section 3.5.2) did not change findings at the 52-week follow-up (i.e. no difference between conditions)
Selective reporting (reporting bias)	Unclear risk	Not all prespecified outcomes from trial registry reported in main results paper. However, SC outcomes are reported.

Zincir 2013
Study characteristics

Methods	Study design: RCT Country: Turkey Setting: outpatient SC clinic in a hospital Recruitment method: patients who presented at the SC outpatient clinic were included in the study on a voluntary basis
Participants	300 participants randomised; average age: 45.8 in those who stopped smoking and 40.8 in those who continued smoking; average boxes of cigarettes per year: 23.62 in those who stopped smoking and 23.26 in those who continued smoking; mean FTND: 5.9 in those who stopped smoking and 6.7 in those who continued smoking
Interventions	<ul style="list-style-type: none"> Bupropion 150 mg/day, started a week before the quit day and continued from day 1-3, raised to 300 mg daily on day 4, with this dose maintained until the end of week 12 Varenicline 0.5 mg daily, raised to 1 mg daily at day 4, then to 2 mg daily at day 8, with this dose maintained until the end of week 12 NRT: administered using either a nicotine patch or nicotine gum, or a combination of both. Nicotine patches were used in their 3 forms containing 21, 14 and 7 mg of nicotine, and in cases of excessive nicotine craving, 2 mg nicotine gum was used. For each dose of nicotine patches, 4 weeks of administration in decreasing doses was recommended. The nicotine gum was started between 12 and 24 doses (2 mg) a day and gradually decreased.
Outcomes	<ul style="list-style-type: none"> SC: definition not specified; measured at 24-28 weeks from study start AEs: measured for unspecified period
Notes	Funding: not reported Author declaration of interests: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...they were randomized to the pharmacological therapy groups" Comment: no further information given

Zincir 2013 (Continued)

Allocation concealment (selection bias)	Unclear risk	Quote: "...they were randomized to the pharmacological therapy groups" Comment: no further information given
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "This was a naturalistic clinical follow-up study." Comment: those involved in the study were therefore unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	300 participants were randomised and 251 completed the study. Therefore 49/300 (16.3%) were lost to follow-up overall. However, it is impossible to establish the number lost to follow-up by group.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Other bias	High risk	Quote: "no adverse event was reported during the study". This is highly unlikely to be correct when considering standard definitions of AEs. There is no explanation of how AEs were assessed in this study. In addition, the wording of the paper makes the final follow-up slightly unclear. After discussion we judged final follow-up to be 24-28 weeks from study start, although quit rates are higher than would be expected at this time point.

AE: adverse event; **BMI:** Body Mass Index (kg/m²); **CA:** continuous abstinence; **CAR:** Continuous Abstinence Rate; **cnRT:** combined nicotine replacement therapy; **CO:** carbon monoxide; **COPD:** chronic obstructive pulmonary disease; **CPD:** cigarettes per day; **CQR:** continuous quit rate; **CVD:** cardiovascular disease; **DSM-IV:** *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*; **ECG:** electrocardiogram; **EtO:** end of treatment; **FTND:** Fagerström Test for Nicotine Dependence; **ITT:** intention-to-treat; **LOCF:** last observation carried forward; **MA:** meta-analysis; **MDD:** major depressive disorder; **MI:** motivational interviewing; **MIMS:** Monthly Index of Medical Specialities; **mCEQ:** Modified Cigarette Evaluation Questionnaire; **MNWS:** Minnesota Nicotine Withdrawal Scale; **NCT:** National Clinical Trials (ClinicalTrials.gov registry); **NRT:** nicotine replacement therapy; **PA:** prolonged abstinence; **PPA:** point-prevalence abstinence; **ppm:** parts per million; **QoL:** quality of life; **QSU-brief:** Brief Questionnaire of Smoking Urges; **RCT:** randomised controlled trial; **SAE:** serious adverse event; **SC:** smoking cessation; **TQD:** target quit date

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brandon 2011	Short-term (15 days) RCT, to test craving and psychological reward; cessation was not an outcome. Previously included but excluded for 2023 update
Bullen 2018	Study tested effect of e-cigarettes as an adjunct to varenicline
Burststein 2006	RCT of tolerability and safety of varenicline in 24 elderly (≥ 65) smokers for 1 week. Not a cessation trial
Chantix 2006	Tested NRT alone or varenicline + NRT for 12 days to test safety and side effects of co-administration. Not a cessation trial
Cui 2012	Open-label non-randomised pre/post study of 36 HIV+ participants; all received varenicline
Dezee 2013	RCT in which all participants were given varenicline; intervention tested was in-person vs internet counselling
Dutra 2012	53 participants with schizophrenia given varenicline + cognitive behavioural therapy. Abstinence assessed at 12 weeks (end of treatment)
Ebbert 2009a	Open-label, single-arm Phase II study, for safety and efficacy of varenicline plus bupropion

Nicotine receptor partial agonists for smoking cessation (Review)

Study	Reason for exclusion
Ebbert 2009b	Cohort analysis of 104 participants on varenicline + NRT and 135 participants treated prior to release of varenicline (93% used NRT)
Ebbert 2011b	Pilot study of varenicline for smokeless tobacco users. 12-week outcome (EoT) reported, not long-term post-treatment. Previously included but excluded for 2023 update
Ebbert 2014	RCT in which all participants were given varenicline; the intervention being tested was bupropion vs placebo. See also Hong 2011
Evins 2014	Relapse prevention study that recruited already abstinence participants. Previously included but excluded for 2023 update
Faessel 2009	Outcomes were safety, tolerability and pharmacokinetics, not smoking cessation. Previously included but excluded for 2023 update
Fagerström 2010	431 smokeless tobacco users in Norway and Sweden, randomised to varenicline or placebo; CAR assessed at 12 and 26 weeks. Previously included but excluded for 2023 update
Falk 2014	Varenicline was used for alcohol reduction, not for smoking
Fatemi 2013	3-arm RCT of varenicline, bupropion and placebo; only assessed to end of treatment (12 weeks).
Ferketich 2012	Pilot study of varenicline vs NRT; participants could choose their treatment; intervention being tested was the addition of a lung cancer screening programme
Ferketich 2013	Safety of varenicline among smokers enrolled in the Lung HIV study. Participants could choose varenicline or NRT, and were only followed for 3 months.
Fertig 2015	Study testing effect of varenicline on alcohol dependence
Frye 2013	Participants followed only until EoT (12 weeks)
Fucito 2011	Primary outcome was effects on drinking behaviour. Smoking status only measured at end of study (8 weeks)
Garza 2011	110 abstinent smokers treated with varenicline or placebo, to assess incidence and severity of neuropsychiatric symptoms; not a cessation trial. Previously included but excluded for 2023 update
Granatowicz 1976	No control group
Gray 2012	Pilot study of varenicline vs bupropion in older adolescents; outcome was reduction rather than cessation, and participants were only followed for 3 months.
Hajek 2011	101 smokers randomised to preloaded varenicline or placebo; abstinence not measured beyond 12 weeks
Hajek 2013	All were given varenicline, with the intervention tested being the addition of a NRT patch. Only followed to 3 months
Hajek 2015	Follow-up under 6 months. Previously included but excluded for 2023 update
Hartwell 2014	Varenicline for drinking and smoking; smoking topography and pharmacogenetics rather than smoking cessation
Hawk 2012	RCT of extended pre-TQD varenicline vs standard regimen; all participants got varenicline, and were followed only until end of treatment (12 weeks)

Study	Reason for exclusion
Hong 2011	Secondary analysis to Ebbert 2014 , looking at depression in recipients of varenicline + bupropion vs varenicline alone
Hoogsteder 2014	All participants were given open-label varenicline; the intervention being tested was the addition of NicVAX.
Hsueh 2014	Open-label cohort study of smokers taking varenicline or NRT
Hsueh 2021	Study not randomized. Participants chose their own treatment.
Hughes 2011	218 smokers not ready to quit assigned to varenicline or placebo for 2-8 weeks for cigarette reduction. Previously included but excluded for 2023 update
IRCT20100127003210N	Study not randomised
Jain 2014	RCT of smokeless tobacco users. Follow-up of 12 weeks
Jennings 2014	Only followed to 16 weeks
Jiménez-Ruiz 2013	Not an RCT
Kempe 1967	Observational uncontrolled study
Koegelenberg 2014	All participants took varenicline; the intervention being tested was the addition of NRT.
Maliszewski 1972	Uncontrolled study of 14 smokers on a 25-day course of cytisine (Tabex); followed up for 2 weeks
Marakulin 1984	Follow-up 6 weeks
McClure 2013	Laboratory study following an RCT of varenicline in a programmed lapse; abstinence only to 4 weeks. Previously included but excluded for 2023 update
McCull 2008	RCT of varenicline's potential as an abuse drug in smokers and non-smokers; not a smoking cessation trial
McNaughton 2013	All participants received varenicline; the intervention being tested, as a relapse prevention aid, was interactive voice response phone calls
Meszaros 2013	Pilot study (10 participants, only 4 completers), only followed to 3 months; objective was reduction, not cessation. Previously included but excluded for 2023 update
Metelitsa 1987	Uncontrolled study
Mitchell 2012	Varenicline was for drinking reduction, not smoking cessation; only followed for 12 weeks. Previously included but excluded for 2023 update
Mocking 2013	7-day administration of varenicline for emotional and cognitive processing in non-smokers
Monova 2004	Follow-up was 60 days
Nahvi 2014b	Follow-up under 6 months
Nahvi 2020	Study tested an intervention for improving adherence to varenicline
NCT00387946	Follow-up under 6 months

Study	Reason for exclusion
NCT00502216	Study of varenicline and naltrexone for tolerability and weight gain in smokers, not cessation
NCT00554840	Follow-up under 6 months
NCT00828113	Relapse prevention study that recruited already abstinent participants. Previously included but excluded for 2023 update
NCT01093937	Follow-up under 6 months
NCT01413516	Follow-up under 6 months
NCT01532232	Study terminated
NCT01574703	Tobacco abstinence not measured
NCT01592695	Different levels of behavioural support between study arms
NCT01639560	Follow-up under 6 months
NCT01771627	Follow-up under 6 months
NCT01772641	Follow-up under 6 months
NCT01806779	All participants got varenicline; the addition of bupropion was the intervention being tested.
NCT01892813	Different levels of behavioural support between study arms
NCT02048917	Follow-up under 6 months
NCT02147132	Cross-over trial
NCT02271919	Follow-up under 6 months
NCT02501265	Study testing the addition of bupropion to a subset of participants receiving varenicline
NCT03709823	Follow-up under 6 months
Nides 2021	Follow-up under 6 months
Nollen 2011	All participants received varenicline, but half received extended counselling and half a single session. Cessation only measured to 3 month end point
Ostrovskaja 1994	Uncontrolled study
Park 2011	RCT of 49 smokers with lung cancer randomised to varenicline or placebo; follow-up only for 12 weeks to EoT
Patterson 2010	Short-term (3-week) study of propensity to relapse with working memory deficits after 10 days of varenicline
Paun 1968	Controlled trial of cytisine (Tabex) (366 smokers) vs placebo (239 smokers) but followed only for 8 weeks. Observational study of 230 cytisine-users followed for 26 weeks, but no comparator group
Pfeifer 2019	Did not measure smoking cessation as an outcome

Study	Reason for exclusion
Pfizer 2006	Follow-up under 6 months
Poling 2010	RCT of varenicline in 31 methadone-maintained smokers; trial lasted 3 months, and reduction was an outcome of interest (only 3-month abstinence was reported)
Ramon 2014	RCT in which all participants received varenicline; intervention being tested was the addition of NRT
Rose 2014	RCT of varenicline versus varenicline + bupropion, in smokers who had failed to quit on NRT. All got varenicline
Schlienz 2014	4 weeks treatment with varenicline; outcome was impact on behavioural economic indices, not smoking cessation
Schmidt 1974	Non-randomised trial
Schnoll 2011	RCT of open-label varenicline + counselling; intervention being tested was recruitment strategies, not smoking cessation
Shim 2011	60 smokers with schizophrenia randomised to varenicline or placebo for 8 weeks; assessment at end of treatment, reduction but not abstinence rates reported
Sicras-Mainar 2010	Multicentre observational non-randomised non-controlled study
Smith 2013	Follow-up under 6 months
Stapleton 2008	Non-randomised trial
Stoyanov 1972	Observational study with no comparator group and short but unstated length of follow-up
Swan 2010	All participants were given varenicline (treated as an included study for 2012 update)
Tonstad 2006	Relapse prevention study that recruited already abstinent participants. Previously included but excluded for 2023 update
Tønnesen 2013	Relapse prevention study that recruited already abstinent participants. Previously included but excluded for 2023 update.
Weiner 2011	Follow-up under 6 months
Zatonski 2006	Uncontrolled observational study

CAR: Continuous Abstinence Rate; **EOt:** end of treatment; **NRT:** nicotine replacement therapy; **RCT:** randomised controlled trial; **TQD:** target quit date

Characteristics of studies awaiting classification *[ordered by study ID]*

[Wiratmoko 2013](#)

Methods

Participants

Interventions

Nicotine receptor partial agonists for smoking cessation (Review)

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Wiratmoko 2013 (Continued)

Outcomes

Notes

Abstract only; further details awaited

Yujie 2014

Methods

Participants

Interventions

Outcomes

Notes

Abstract only; further details awaited

Characteristics of ongoing studies [ordered by study ID]

Berlin 2019

Study name	Randomised trial of electronic cigarettes with or without nicotine in smoking cessation (ECSMOKE)
Methods	Randomised, placebo-controlled, double-blind, double-dummy, multicentre, parallel-group trial
Participants	At least 650 adults smoking at least 10 CPD in the past year, motivated to quit, aged 18-70
Interventions	<ul style="list-style-type: none"> e-cigarette without nicotine plus placebo tablets of varenicline e-cigarette with nicotine (12 mg/mL) plus placebo tablets of varenicline e-cigarette without nicotine plus 0.5 mg varenicline tablets
Outcomes	Continuous smoking abstinence rate during the last 4 weeks of the treatment period. Validated by self-report and expired CO < 8 ppm at 12 and 24 weeks after treatment initiation
Starting date	17 October 2018
Contact information	Ivan Berlin, +33142161678, ivan.berlin@aphp.fr
Notes	Study funding: Programme Hospitalier de Recherche Clinique (PHRC) National 2015, Ministry of Health, France

Caponnetto 2019

Study name	Efficacy of smoking cessation with varenicline plus counselling for e-cigarettes users (VAREVAPE)
Methods	Randomised, double-blind, placebo-controlled, parallel 2-group trial
Participants	140 participants that exclusively smoke e-cigarettes daily for > 3 months 140 'dual users' that use e-cigarettes daily for > 3 months, who also smoke at least one combustible CPD All motivated to quit

Nicotine receptor partial agonists for smoking cessation (Review)

Caponnetto 2019 (Continued)

Interventions	<ul style="list-style-type: none"> • Counselling plus varenicline 1 mg twice a day • Counselling plus matched placebo
Outcomes	Continuous smoking abstinence rate between weeks 9-24. Validated by self-report and expired CO < 10 ppm, and saliva cotinine levels < 7 ng/mL
Starting date	June 2019
Contact information	Pasquale Caponnetto: p.caponnetto@unict.it
Notes	Study funding: Pfizer, GRAND, Global Research Award for Nicotine Dependence

ChiCTR1900021400

Study name	Individual tobacco cessation research based on nicotine metabolite ratio in smoking patients with chronic obstructive pulmonary disease: a randomized controlled trial
Methods	Parallel-group RCT
Participants	224 participants aged 18-85 years who meet the diagnostic criteria for both COPD and tobacco dependency, who have been smoking for > 5 years, with at least 10 CPD for the past 12 months. Exhaled CO > 10 ppm
Interventions	<ul style="list-style-type: none"> • Varenicline • Bupropion
Outcomes	Smoking abstinence rate. Nicotine metabolite ratio
Starting date	18 February 2019
Contact information	Xiao Dan, +86138111374263, danxiao@263.net
Notes	Study funding: The China-Japan Friendship Hospital

IRCT20200719048133N1

Study name	Efficacy of varenicline for smoking cessation among persistent smokers after coronary artery revascularization: a randomized placebo controlled clinical trial
Methods	Double-blind, randomised, placebo-controlled trial
Participants	600 participants that are male, > 18 years, and a current daily smoker of ≥ 5 CPD. Must also have a history of coronary artery revascularisation 9-12 months prior to the study
Interventions	<ul style="list-style-type: none"> • Varenicline 0.5 mg once a day for 3 days, 0.5 mg twice a day for 4 days, 1 mg twice a day for 12 weeks • Placebo, following same regimen
Outcomes	Continuous smoking abstinence rate at the end of 26 weeks' follow-up, by self-report and validated by a close relative
Starting date	22 August 2020

Nicotine receptor partial agonists for smoking cessation (Review)

IRCT20200719048133N1 (Continued)

Contact information	Masoumeh Lotfi Tokaldany, +982188029256, lotfi213366@yahoo.co.uk
Notes	Study funding: Tehran University of Medical Sciences

Lawson 2021

Study name	Extended pre-quit varenicline to assist in quitting smoking (EVarQuit)
Methods	Parallel group, placebo-controlled RCT
Participants	320 participants, smoking at least 10 CPD for the past 6 months, expired CO > 7 ppm, motivated to quit
Interventions	<ul style="list-style-type: none"> • Extended run-in group: 4 weeks of varenicline • Standard run-in group (comparator): 3 weeks placebo, plus 1 week of varenicline • Both groups will receive 11 weeks of varenicline post run-in, after their target quit date
Outcomes	Continuous smoking abstinence at 12 and 26 weeks post-quit date, self-report but bioverified
Starting date	01 October 2017
Contact information	Larry Hawk, lhawk@buffalo.edu
Notes	Study funding: state University of New York at Buffalo, National Cancer Institute, Pfizer

NCT00906386

Study name	Methadone maintenance treatment and smoking cessation (MMTASC)
Methods	Randomised, double-blind, placebo-controlled trial
Participants	112 people who smoke and are on methadone maintenance for opioid dependence
Interventions	Varenicline 1.0 mg x 2/day vs placebo for 12 weeks
Outcomes	7-day PPA at 26 weeks
Starting date	May 2009
Contact information	Milan Khara
Notes	Current status unknown

NCT01243203

Study name	Smoking cessation program in the preadmission clinic: the use of a teachable moment
Methods	Double-blind, parallel-group RCT

Nicotine receptor partial agonists for smoking cessation (Review)

NCT01243203 (Continued)

Participants	300 adults scheduled for elective surgery, aged 18+, smoking 10+ CPD
Interventions	Varenicline vs placebo
Outcomes	Abstinence at 24 and 52 weeks
Starting date	November 2007
Contact information	Francis Chung
Notes	Study funding: Pfizer

NCT01312909

Study name	Smoking cessation study in healthy adolescent smokers
Methods	Phase IV randomised, triple-blind, placebo-controlled trial
Participants	300 healthy adolescents (12-19 years) smoking at least 5 CPD, with at least 1 failed quit attempt
Interventions	Varenicline 1 mg x 2/day vs varenicline 0.5 mg x 2/day vs placebo
Outcomes	CA at weeks 9-12, 9-24, 9-52; 7-day PPA at weeks 12, 24, 52; reduction in CPD
Starting date	April 2011
Contact information	Pfizer Inc
Notes	Study funding: Pfizer

NCT01800019

Study name	The Canadian HIV Quit Smoking Trial: tackling the co-morbidities of depression and cardiovascular disease in HIV+ smokers (CANQUIT)
Methods	Open-label, 4-arm, factorial RCT
Participants	256 adults who are HIV+ and smoke, 5+ CPD, willing to set a quit date
Interventions	<ul style="list-style-type: none"> • NRT • NRT + HIV-tailored quit smoking counselling • Varenicline • Varenicline + HIV-tailored quit smoking counselling
Outcomes	7-day PPA and 4-week CA at week 48, CO-verified
Starting date	January 2014
Contact information	Louise Balfour, PhD, Ottawa Hospital Research Institute
Notes	Study funding: CIHR Research Operating Grant

Nicotine receptor partial agonists for smoking cessation (Review)

NCT02106637

Study name	Early in-hospital initiation of pharmacotherapy for smoking cessation, patients after ACS
Methods	Double-blind, parallel-group RCT
Participants	300 adult smokers with ACS
Interventions	Varenicline vs placebo
Outcomes	CA at 1 month, 6 months, 1 year after hospitalisation; SAE rate
Starting date	June 2014
Contact information	Ilan Goldenberg, MD, Ilan.Goldenberg@sheba.health.gov.il
Notes	

NCT02162849

Study name	Reward sensitivity and pharmacotherapy for smoking cessation
Methods	Double-blind, parallel-group RCT
Participants	90 adults who smoke, 5+ CPD
Interventions	Varenicline + placebo patch vs nicotine patch + placebo tablet; all get behavioural counselling
Outcomes	CA at EoT, 3 months and 6 months
Starting date	April 2015
Contact information	Paul Cinciripini
Notes	

NCT02378714

Study name	Behavioral activation and varenicline for smoking cessation in depressed smokers
Methods	Parallel-group, placebo-controlled RCT
Participants	Adults who smoke with MDD
Interventions	<ul style="list-style-type: none"> • Standard behavioral smoking cessation treatment plus placebo varenicline • Behavioral activation for smoking cessation plus placebo varenicline • Standard behavioral smoking cessation treatment plus active varenicline • Behavioral activation for smoking cessation plus active varenicline
Outcomes	Bioverified PPA at 27 weeks; AE and SAE rates

Nicotine receptor partial agonists for smoking cessation (Review)

NCT02378714 (Continued)

Starting date	24 July 2015
Contact information	Brian Hitsman, Ph.D. Northwestern University
Notes	Study funding: 1R01CA184211-01A1 (U.S. NIH Grant/Contract)

NCT02460900

Study name	Optimizing smoking cessation for people with HIV/AIDS who smoke
Methods	Randomised factorial trial
Participants	Adults who smoke and have HIV/AIDS
Interventions	<ul style="list-style-type: none"> • Varenicline and standard care • Placebo and standard care • Positively Smoke Free and placebo • Positively Smoke Free and varenicline
Outcomes	7-day PPA at 24 weeks
Starting date	July 2016
Contact information	Principal Investigators: Seth Himelhoch, MD, MPH and Deanna Kelly, PharmD, University of Maryland School of Medicine
Notes	

NCT02856581

Study name	Reducing surgical complications in patients with newly diagnosed lung cancer who smoke cigarettes
Methods	Parallel group, placebo-group, phase III, RCT
Participants	23 participants, aged > 18, with a new diagnosis of lung cancer with surgery scheduled 10 days-12 weeks after randomisation. Have smoked daily/nearly every day for previous 6 months, and at least 1 puff in the previous 7 days. Motivated to quit
Interventions	<ul style="list-style-type: none"> • Varenicline for 12 weeks, plus behavioural intervention • Placebo for 12 weeks, plus behavioural intervention
Outcomes	<ul style="list-style-type: none"> • Primary outcomes: mortality, rehospitalisation, incidence of pulmonary complications, incidence of intensive care unit admissions, incidence of unspecific wound infection, incidence of anastomotic failure • Secondary outcomes: change in QoL, length of hospital stay, smoking abstinence rates as measured by self-report and salivary cotinine testing
Starting date	29 September 2017
Contact information	Ivana Croghan, ivana.croghan@mayo.edu

Nicotine receptor partial agonists for smoking cessation (Review)

NCT02856581 (Continued)

Notes Study funding: Alliance for Clinical Trials in Oncology, National Cancer institute, Pfizer

NCT02991781

Study name	Combined bio- and neuro- feedback vs. varenicline use for smoking cessation
Methods	RCT
Participants	Unemployed adults < 35 who smoke (subgroup of a larger trial population)
Interventions	<ul style="list-style-type: none"> • Biofeedback and neurofeedback training • Varenicline use for smoking cessation • Sham neurofeedback • Passive control
Outcomes	Abstinence at 2 years
Starting date	January 2017
Contact information	Principal Investigator: Panos Bamidis, Ass. Prof, Medical School, Aristotle University of Thessaloniki
Notes	

NCT03365362

Study name	Achieving smoking cessation milestones in opioid treatment patients: a randomised 2x2 factorial trial of directly observed and long-term varenicline
Methods	2 x 2 factorial, placebo-controlled, RCT
Participants	450 participants, aged > 18, currently smoking at least 5 CPD and > 100 in their lifetime, motivated to quit, receiving methadone or buprenorphine in an opioid treatment programme > 3 months
Interventions	<ul style="list-style-type: none"> • Long-term varenicline - 24 weeks of standard dose • Short-term varenicline - 12 weeks of standard dose, then matched placebo weeks 13-24 • Directly observed therapy - varenicline from opioid treatment programme nurses at the same time as methadone • Self-administered varenicline
Outcomes	<ul style="list-style-type: none"> • Primary outcomes: initial abstinence (period of > 24 h smoking abstinence), time to lapse, time to relapse (7 consecutive days of self-reported smoking) • Secondary outcomes: durability of tobacco abstinence, validated by exhaled CO at week 28 and week 52, cigarettes smoked/day, nicotine dependence, QoL
Starting date	25 October 2018
Contact information	Shadi Nahvi, snahvi@montefiore.org
Notes	Study funding: Albert Einstein College of Medicine, NIH, Pfizer, National Institute on Drug Abuse

Nicotine receptor partial agonists for smoking cessation (Review)

NCT03557294

Study name	Varenicline OTC trial on efficacy and safety (VOTC)
Methods	Parallel-group, placebo-controlled, RCT
Participants	307 participants, aged ≥ 21 , daily smoking with exhaled CO > 10 ppm or positive urine cotinine, motivated to quit
Interventions	<ul style="list-style-type: none"> Days 1-3, 0.5 mg varenicline once daily; days 4-7, 0.5 mg twice daily; day 8 to end, 1 mg twice daily Days 1-3, 0.5 mg varenicline once daily; day 4 to end: 0.5 mg twice daily 0.0 mg placebo comparator
Outcomes	Smoking abstinence, validated by self-report and exhaled CO
Starting date	07 May 2018
Contact information	Not reported
Notes	Study funding: Arizona State University, National Institute on Drug abuse, Los Angeles Clinical Trials, University of Nevada, Reno, Pfizer

NCT04011280

Study name	Novel pharmacotherapy approaches in smokers with serious mental illness
Methods	Phase IV, double-blind, randomised, parallel-group RCT
Participants	60 participants, 18-70 years, with a diagnosis of bipolar disorder or schizophrenia spectrum disorder, smoke > 10 CPD, exhaled CO > 10 ppm, motivated to quit
Interventions	<ul style="list-style-type: none"> Low-dose varenicline: 0.5 mg twice daily with 0.5 mg daily titration over 1 week Standard-dose varenicline: 1.0 mg twice daily with standard titration
Outcomes	Primary: feasibility of combining ACT (Acceptance and Commitment Therapy) with different varenicline regimens Secondary: nicotine-metabolite ratio
Starting date	15 July 2019
Contact information	Benjamin McKenna, bmckenna@ucsd.edu
Notes	Study funding: University of California, San Diego, Veterans Medical Research Foundation, University of California

NCT04015414

Study name	Varenicline versus cytisine for smoking cessation in the primary care setting in Croatia and Slovenia - a randomised controlled trial
Methods	Parallel-group, RCT
Participants	380 participants, > 18 years, currently smoking, motivated to quit

Nicotine receptor partial agonists for smoking cessation (Review)

NCT04015414 (Continued)

Interventions	<ul style="list-style-type: none"> Varenicline - starting 1 week prior to patient's target quit date Cytisine - following standard manufacturer's dosing protocol
Outcomes	Self-reported 7-day abstinence from tobacco (primary outcome: 12-weeks following TQD)
Starting date	14 July 2020
Contact information	Stjepan Oreskovin, +385912858247, sooreskov@gmail.com Jeffrey Ashburner, 617/724-3828, jasburner@mgh.harvard.edu
Notes	Study funding: University of Zagreb, University of Ljubljana School of Medicine, University of Zagreb School of Medicine, Harvard Medical School

NCT04188873

Study name	Optimized chronic care for smokers: developing and implementing integrated clinical systems in interventions in primary care - cessation trial
Methods	2x2x2 factorial design, RCT
Participants	608 participants, > 18 years, smoking > 4 CPD for the previous 6 months
Interventions	<p>Factorial trial with the following arms:</p> <ul style="list-style-type: none"> 12-week varenicline with minimal counselling 12-week varenicline with 4-week preparation varenicline and minimal counselling 24-week varenicline with minimal counselling 24-week varenicline with 4-week preparation varenicline and minimal counselling 12-week varenicline with intensive counselling 12-week varenicline with 4-week preparation varenicline and intensive counselling 24-week varenicline with intensive counselling 24-week varenicline with 4-week preparation varenicline and intensive counselling 12-week C-NRT with minimal counselling 12-week C-NRT with 4-week preparation C-NRT and minimal counselling 24-week C-NRT with minimal counselling 24-week C-NRT with 4-week preparation C-NRT and minimal counselling 12-week C-NRT with intensive counselling 12-week C-NRT with 4-week C-NRT and intensive counselling 24-week C-NRT with intensive counselling 24-week C-NRT with 4-week preparation C-NRT and intensive counselling
Outcomes	Complete 7-day abstinence - 12-months post-TQD, validated by exhaled CO < 5 ppm
Starting date	10 December 2020
Contact information	Megan Piper, 608-265-4572, mep@ctri.wisc.edu Stevens Smith, 608-262-7563, sss@ctri.wisc.edu
Notes	Study funding: University of Wisconsin, Madison, National Cancer Institute

NCT04525755

Study name	A translational randomized clinical trial of varenicline sampling to promote smoking cessation and scalable treatment dissemination
Methods	Parallel-group, open-label RCT
Participants	648 participants, > 18 years, daily smoker (25+ days/previous month, and > 5 CPD), smoking for > 1, motivated to quit
Interventions	<ul style="list-style-type: none"> Varenicline 0.5 mg twice/day, for 28 days NRT, for 28 days No intervention (control)
Outcomes	Primary: 7-day self-reported abstinence Secondary: reduction in smoking by 50%, any quit attempts, use of smoking cessation medication
Starting date	08 February 2021
Contact information	Lisa Coles, 843-876-2291, colesl@musc.edu Amy Boatright, 843-876-2440, boatright@musc.edu
Notes	Study funding: Medical University of South Carolina

NCT04604509

Study name	PISCES I: Precision implemented smoking cessation evaluation study
Methods	Parallel-group, open-label RCT
Participants	2010 participants, > 18 years, smoking > 5 CPD, motivated to quit
Interventions	<ul style="list-style-type: none"> Varenicline daily for 6 weeks NRT for 6 weeks Participants continue to receive varenicline as in group I or NRT as in group II for 6 additional weeks Participants switch to a different therapy and receive varenicline or NRT for 6 additional weeks (depending on which group originally assigned to) Higher-dose varenicline or NRT Varenicline or NRT, plus bupropion Varenicline plus NRT <p>All groups have behavioural counselling</p>
Outcomes	Primary: EoT 7-day PPA, expired CO, abstinence at 12 weeks
Starting date	04 August 2020
Contact information	Paul Cinciripini, 713-745-3822, pcinciri@mdanderson.org
Notes	Study funding: MD Anderson Cancer Center, National Cancer Institute

NCT05102123

Study name	PREVENT: PeRiopEratiVE smokiNg cessaTion Trial
Methods	2x2 factorial, RCT
Participants	1720 participants, > 18 years, scheduled to undergo surgery within 28 days, currently smoking (> 100 cigarettes over lifetime and smoke every day in last 30 days)
Interventions	<ul style="list-style-type: none"> • Cytisine and text messaging behavioural support • Placebo and text messaging behavioural support • Cytisine only • Placebo only
Outcomes	Primary: complete abstinence from quit date to 6 months post-randomisation, verified by exhaled CO < 10 ppm
Starting date	01 April 2022
Contact information	Emily Di Sante, 905-297-3479, emily.disante@phri.ca Jessica Vincent, 905-297-3479 ext 40635, jessica.vincent@phri.ca
Notes	Study funding: Population Health Research Institute

NCT05311085

Study name	Cytisine and e-cigarettes with supportive text-messaging for smoking cessation (Cess@Tion)
Methods	RCT
Participants	Adults who smoke
Interventions	<ul style="list-style-type: none"> • 12 weeks of cytisine • 12 weeks of a nicotine e-cigarette • 12 weeks of cytisine and 12 weeks of a nicotine e-cigarette
Outcomes	CA at 6 months
Starting date	May 2022
Contact information	Natalie Walker, PhD, n.walker@auckland.ac.nz Chris Bullen, PhD MBChB, c.bullen@auckland.ac.nz
Notes	

Reid 2010

Study name	Varenicline versus transdermal nicotine patch for smoking cessation in patients with coronary heart disease
Methods	Randomised open-label trial
Participants	60 adult smokers

Nicotine receptor partial agonists for smoking cessation (Review)

Reid 2010 *(Continued)*

Interventions	Varenicline or NRT patch for 12 weeks
Outcomes	CO-confirmed CA for weeks 12-26
Starting date	April 2009
Contact information	Robert Reid
Notes	

Russo 2021

Study name	Efficacy and safety of smoking cessation with varenicline tartrate in diabetic smokers (DIASMOKE)
Methods	Randomised, double-blind, placebo-controlled trial
Participants	300 adults with type 2 diabetes, who smoke
Interventions	Varenicline 1 mg x 2/day for 12 weeks vs placebo
Outcomes	CA at week 24 and week 52; AEs
Starting date	June 2011
Contact information	Riccardo Polosa
Notes	Study funding: supported by grant WS5086648 from GRAND (Global Research Award for Nicotine Dependence), an independently reviewed competitive grants programme funded by Pfizer Inc.

TCTR20180312001

Study name	Efficacy safety and health-related quality of life (HRQoL) of cytisine in smoking cessation
Methods	Double-blind, RCT
Participants	130 participants, 18-65 years, current smoker > 10 CPD, motivated to quit
Interventions	<ul style="list-style-type: none"> • Cytisine • Placebo
Outcomes	<ul style="list-style-type: none"> • PPA rate at 4, 12, 24 and 48 weeks, verified by self-report and exhaled CO lung function • Self-reported relapse rate • QoL
Starting date	01 May 2018
Contact information	Sunee Lertsinudom, 081-6617237, lsunee@kku.ac.th
Notes	Study funding: Government Pharmaceuticals Organization, Thailand

Tindle 2020

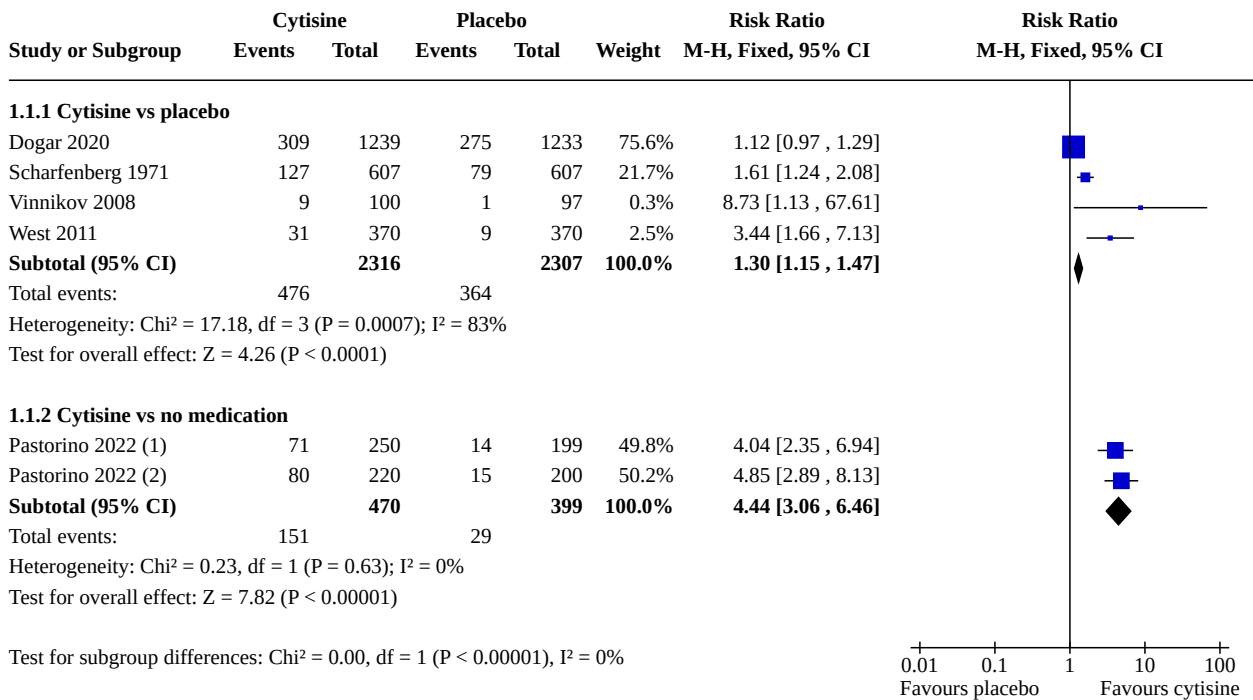
Study name	STudying Partial-agonists for Ethanol and Tobacco Elimination in Russians with HIV (St PETER HIV)
Methods	Parallel group, placebo-controlled, RCT
Participants	400 participants with HIV and alcohol dependence, who smoke
Interventions	<ul style="list-style-type: none"> • Varenicline + NRT placebo • Varenicline placebo + NRT • Cytisine + NRT placebo • Cytisine placebo + NRT
Outcomes	Smoking cessation at 12 months Percent heavy drinking days in past 30 days
Starting date	19 July 2017
Contact information	hilary.tindle@vumc.org
Notes	Study funding: "This work was supported by grants from the National Institute on Alcohol Abuse and Alcoholism (NI AAA) in support of URBAN ARCH :U01AA020780 , U24AA020779, U24AA020778 ; and by the Providence/ Boston Center for AIDS Research (P30AI042853) and Tennessee Center for AIDS Research (P30AI110527). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health."

ACS: acute coronary syndrome; **AE:** adverse event; **CA:** continuous abstinence; **CIHR:** Canadian Institutes of Health Research; **C-NRT:** combined nicotine replacement therapy; **CO:** carbon monoxide; **COPD:** chronic obstructive pulmonary disease; **CPD:** cigarettes per day; **e-cigarette:** electronic cigarette; **MDD:** major depressive disorder; **NRT:** nicotine replacement therapy; **PPA:** point-prevalence abstinence; **ppm:** parts per million; **QoL:** quality of life; **RCT:** randomised controlled trial; **SAE:** serious adverse event; **TQD:** target quit date

DATA AND ANALYSES
Comparison 1. Cytisine vs placebo or no medication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Abstinence at longest follow-up	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 Cytisine vs placebo	4	4623	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.15, 1.47]
1.1.2 Cytisine vs no medication	1	869	Risk Ratio (M-H, Fixed, 95% CI)	4.44 [3.06, 6.46]
1.2 Adverse events	4	4052	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.07, 1.39]
1.3 Serious adverse events	3	3781	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.78, 1.37]

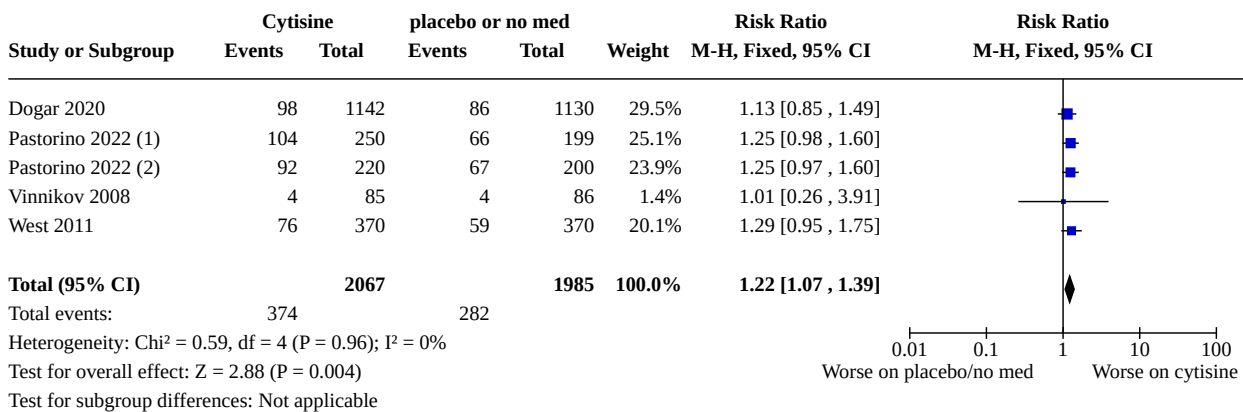
Analysis 1.1. Comparison 1: Cytisine vs placebo or no medication, Outcome 1: Abstinence at longest follow-up



Footnotes

- (1) 40 day duration of cytisine; control arm split
- (2) 84 day duration of cytisine; control arm split

Analysis 1.2. Comparison 1: Cytisine vs placebo or no medication, Outcome 2: Adverse events



Footnotes

- (1) 40 day duration of cytisine; control arm split
- (2) 80 day duration of cytisine; control arm split

Analysis 1.3. Comparison 1: Cytisine vs placebo or no medication, Outcome 3: Serious adverse events

Study or Subgroup	Cytisine		placebo or no med		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dogar 2020	53	1142	46	1130	50.9%	1.14 [0.77, 1.68]	
Pastorino 2022 (1)	48	470	34	299	45.8%	0.90 [0.59, 1.36]	
West 2011	4	370	3	370	3.3%	1.33 [0.30, 5.92]	
Total (95% CI)		1982		1799	100.0%	1.04 [0.78, 1.37]	
Total events:	105		83				
Heterogeneity: Chi ² = 0.80, df = 2 (P = 0.67); I ² = 0%							
Test for overall effect: Z = 0.25 (P = 0.80)							
Test for subgroup differences: Not applicable							

Footnotes

(1) 40 day and 80 day cytisine arms combined

Comparison 2. Cytisine: longer vs shorter duration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Abstinence at longest follow-up	1	470	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.98, 1.67]
2.1.1 84 days vs 40 days	1	470	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.98, 1.67]

Analysis 2.1. Comparison 2: Cytisine: longer vs shorter duration, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Longer duration		Shorter duration		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.1.1 84 days vs 40 days							
Pastorino 2022	80	220	71	250	100.0%	1.28 [0.98, 1.67]	
Subtotal (95% CI)		220		250	100.0%	1.28 [0.98, 1.67]	
Total events:	80		71				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.84 (P = 0.07)							
Total (95% CI)		220		250	100.0%	1.28 [0.98, 1.67]	
Total events:	80		71				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.84 (P = 0.07)							
Test for subgroup differences: Not applicable							

Comparison 3. Cytisine vs varenicline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Abstinence at longest follow-up	2	2131	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.66, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Nausea	2	2017	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.33, 0.50]
3.3 Abnormal dreams	2	2017	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.50, 0.73]
3.4 Insomnia	2	2017	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.10]
3.5 Headache	2	2017	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.33]
3.6 Depression	1	679	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.12, 74.47]
3.7 Suicidal ideation	2	2017	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
3.8 SAEs	2	2017	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.44, 1.03]

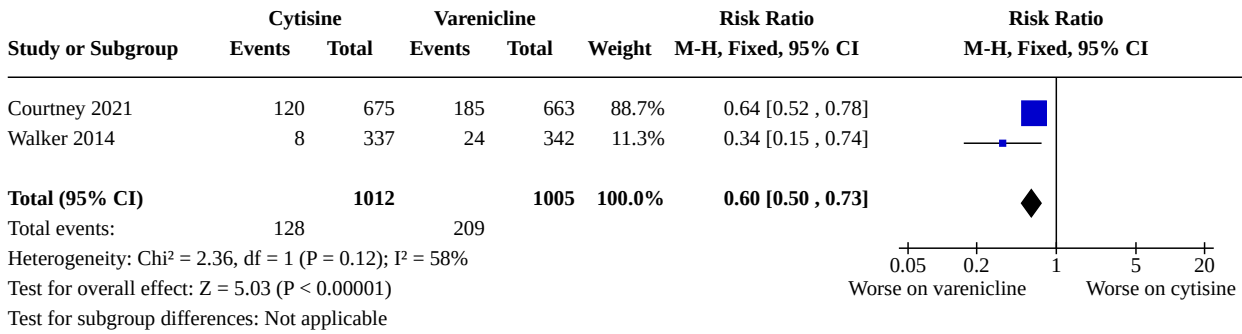
Analysis 3.1. Comparison 3: Cytisine vs varenicline, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Cytisine		Varenicline		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Courtney 2021	85	725	97	727	69.1%	0.88 [0.67, 1.15]	
Walker 2021	32	342	43	337	30.9%	0.73 [0.48, 1.13]	
Total (95% CI)		1067		1064	100.0%	0.83 [0.66, 1.05]	
Total events:	117		140				
Heterogeneity: Chi ² = 0.48, df = 1 (P = 0.49); I ² = 0%							
Test for overall effect: Z = 1.55 (P = 0.12)							
Test for subgroup differences: Not applicable							

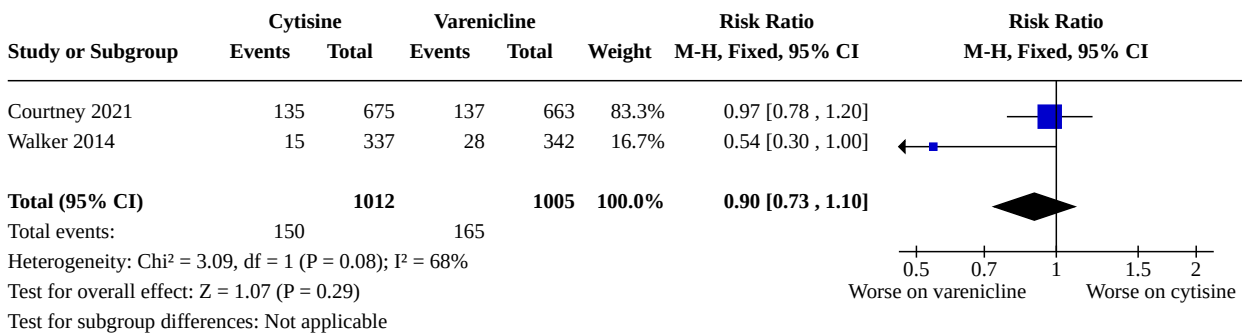
Analysis 3.2. Comparison 3: Cytisine vs varenicline, Outcome 2: Nausea

Study or Subgroup	Cytisine		Varenicline		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Courtney 2021	79	675	198	663	78.8%	0.39 [0.31, 0.50]	
Walker 2014	25	337	54	342	21.2%	0.47 [0.30, 0.74]	
Total (95% CI)		1012		1005	100.0%	0.41 [0.33, 0.50]	
Total events:	104		252				
Heterogeneity: Chi ² = 0.49, df = 1 (P = 0.48); I ² = 0%							
Test for overall effect: Z = 8.35 (P < 0.00001)							
Test for subgroup differences: Not applicable							

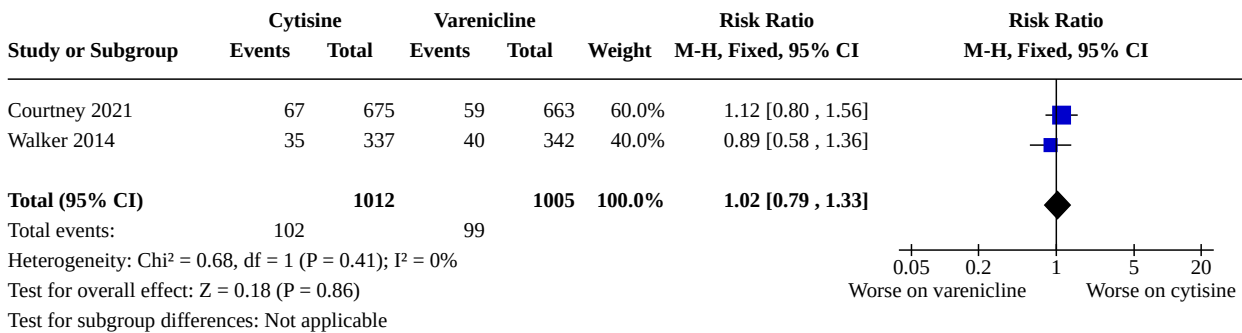
Analysis 3.3. Comparison 3: Cytisine vs varenicline, Outcome 3: Abnormal dreams



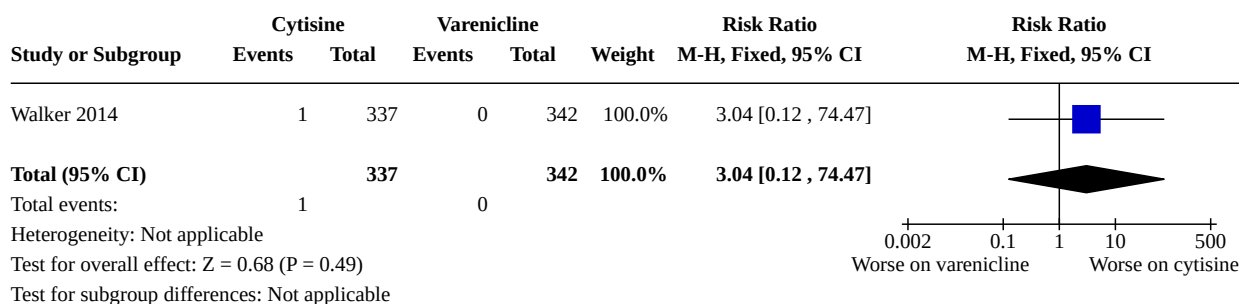
Analysis 3.4. Comparison 3: Cytisine vs varenicline, Outcome 4: Insomnia



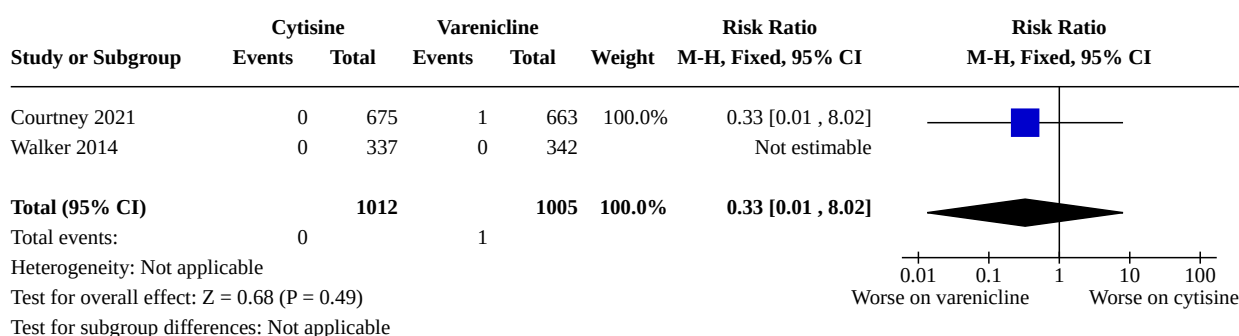
Analysis 3.5. Comparison 3: Cytisine vs varenicline, Outcome 5: Headache



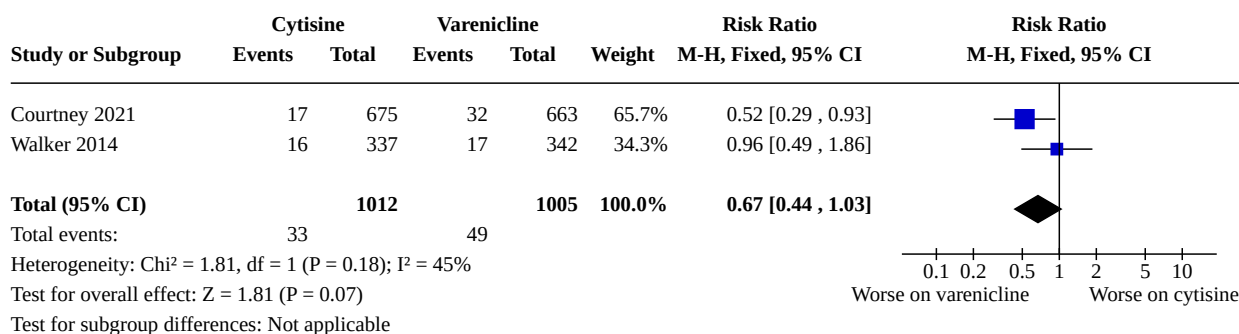
Analysis 3.6. Comparison 3: Cytisine vs varenicline, Outcome 6: Depression



Analysis 3.7. Comparison 3: Cytisine vs varenicline, Outcome 7: Suicidal ideation



Analysis 3.8. Comparison 3: Cytisine vs varenicline, Outcome 8: SAEs



Comparison 4. Cytisine vs NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Abstinence at longest follow-up	1	1310	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.13, 1.80]
4.2 Nausea	1	1310	Risk Ratio (M-H, Fixed, 95% CI)	15.00 [3.60, 62.51]
4.3 SAEs	1	1310	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.76, 1.75]

Analysis 4.1. Comparison 4: Cytisine vs NRT, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Cytisine		NRT		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Walker 2014	143	655	100	655	100.0%	1.43 [1.13 , 1.80]	
Total (95% CI)		655		655	100.0%	1.43 [1.13 , 1.80]	
Total events:	143		100				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.03 (P = 0.002)							
Test for subgroup differences: Not applicable							

Analysis 4.2. Comparison 4: Cytisine vs NRT, Outcome 2: Nausea

Study or Subgroup	Cytisine		NRT		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Walker 2014	30	655	2	655	100.0%	15.00 [3.60 , 62.51]	
Total (95% CI)		655		655	100.0%	15.00 [3.60 , 62.51]	
Total events:	30		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.72 (P = 0.0002)							
Test for subgroup differences: Not applicable							

Analysis 4.3. Comparison 4: Cytisine vs NRT, Outcome 3: SAEs

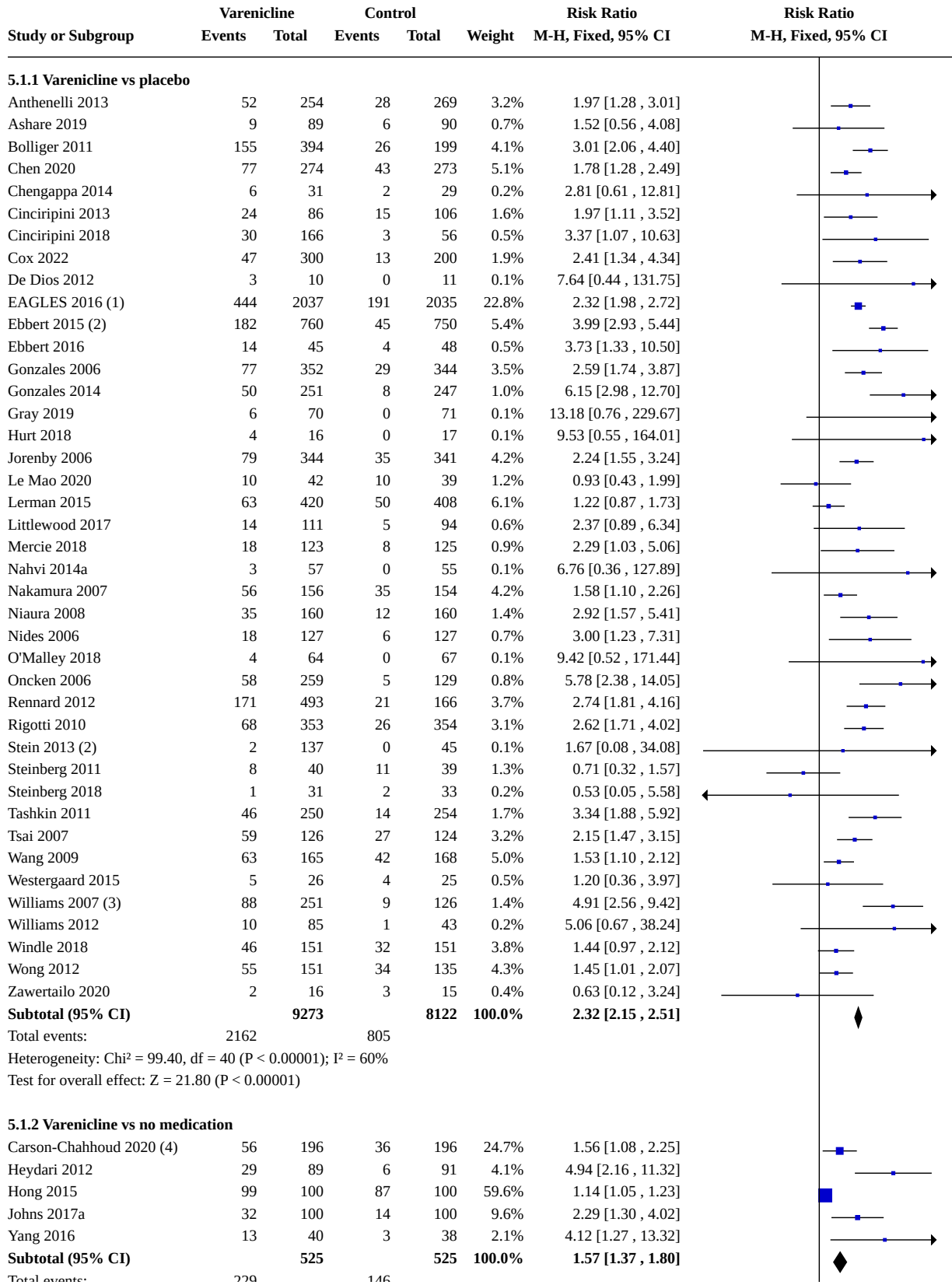
Study or Subgroup	Cytisine		NRT		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Walker 2014	45	655	39	655	100.0%	1.15 [0.76 , 1.75]	
Total (95% CI)		655		655	100.0%	1.15 [0.76 , 1.75]	
Total events:	45		39				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
Test for subgroup differences: Not applicable							

Comparison 5. Varenicline 2 mg per day vs placebo or no medication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Abstinence at longest follow-up	46		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Varenicline vs placebo	41	17395	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [2.15, 2.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1.2 Varenicline vs no medication	5	1050	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.37, 1.80]
5.2 Nausea	36	17080	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [2.44, 2.80]
5.3 Insomnia	35	16803	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.27, 1.47]
5.4 Abnormal dreams	32	16211	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.67, 1.97]
5.5 Headache	31	16326	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.03, 1.19]
5.6 Depression	32	15922	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.20]
5.7 Suicidal ideation	22	12343	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.44, 1.08]
5.8 SAEs	26	14356	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.01, 1.48]
5.9 Neuropsychiatric SAEs (not deaths)	22	7846	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.29]
5.10 Cardiac SAEs, including deaths	18	7151	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.79, 1.84]

Analysis 5.1. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 1: Abstinence at longest follow-up



Analysis 5.1. (Continued)

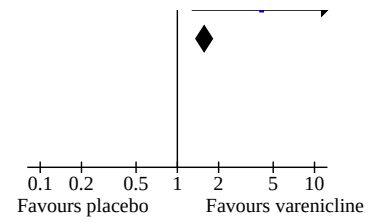
Subtotal (95% CI)	525	525	100.0%	1.57 [1.37, 1.80]
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Total events: 229 146

Heterogeneity: $\text{Chi}^2 = 76.18, \text{df} = 4 (P < 0.00001); I^2 = 95\%$

Test for overall effect: $Z = 6.36 (P < 0.00001)$

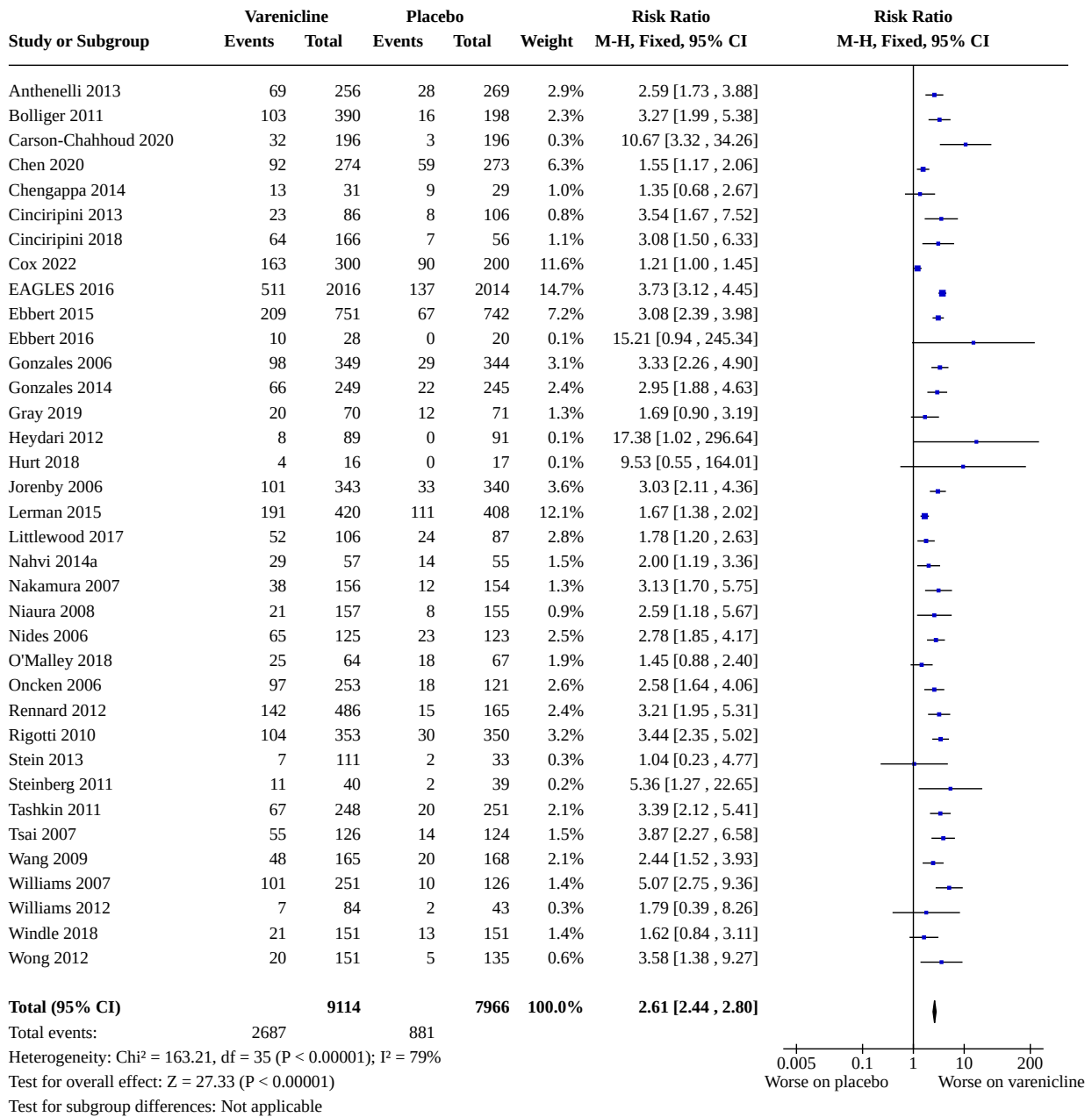
Test for subgroup differences: $\text{Chi}^2 = 0.00, \text{df} = 1 (P < 0.00001), I^2 = 0\%$



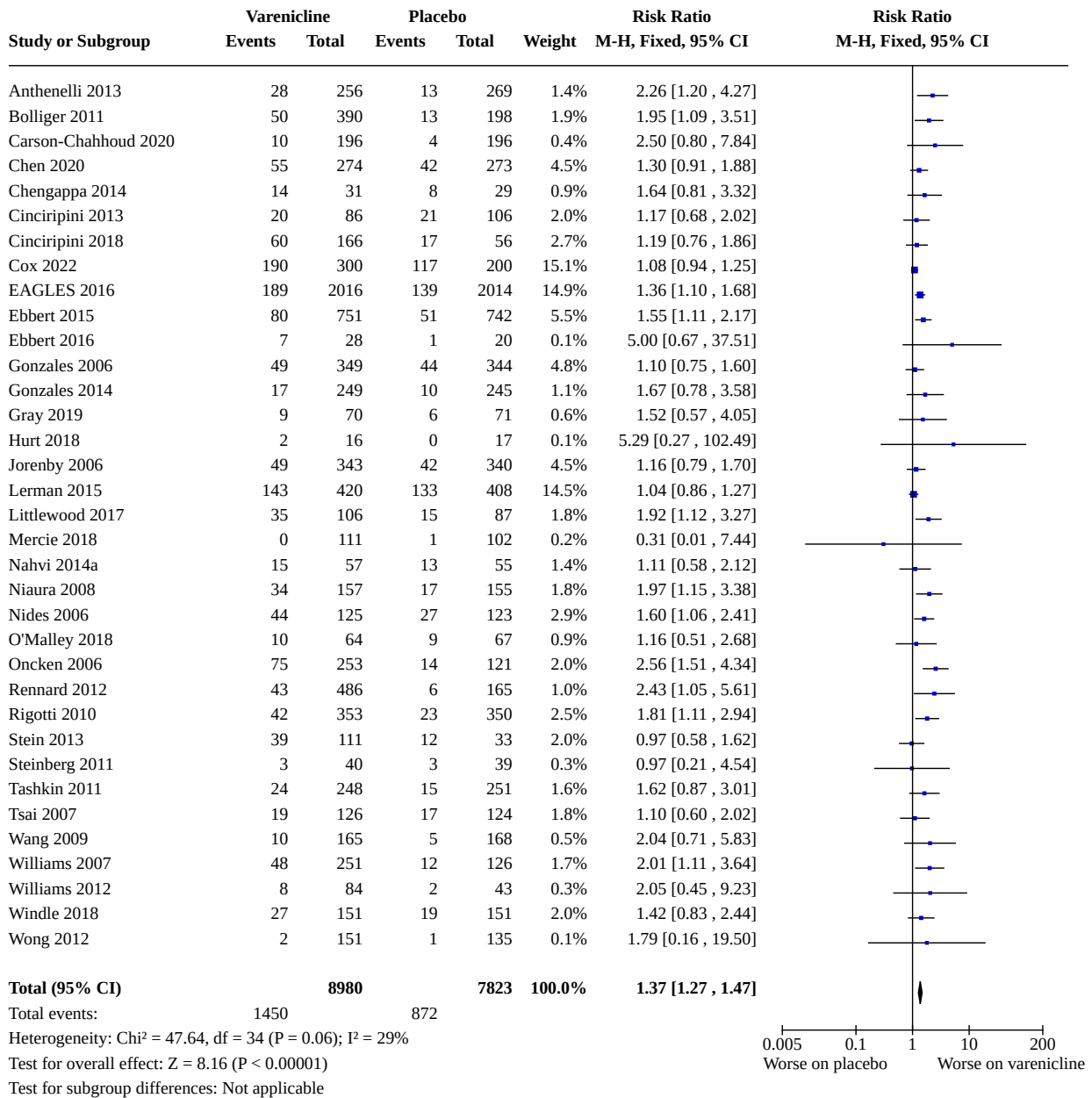
Footnotes

- (1) Extrapolated from % reported quit
- (2) 24 weeks of treatment
- (3) 52 weeks of treatment
- (4) 24-month follow-up

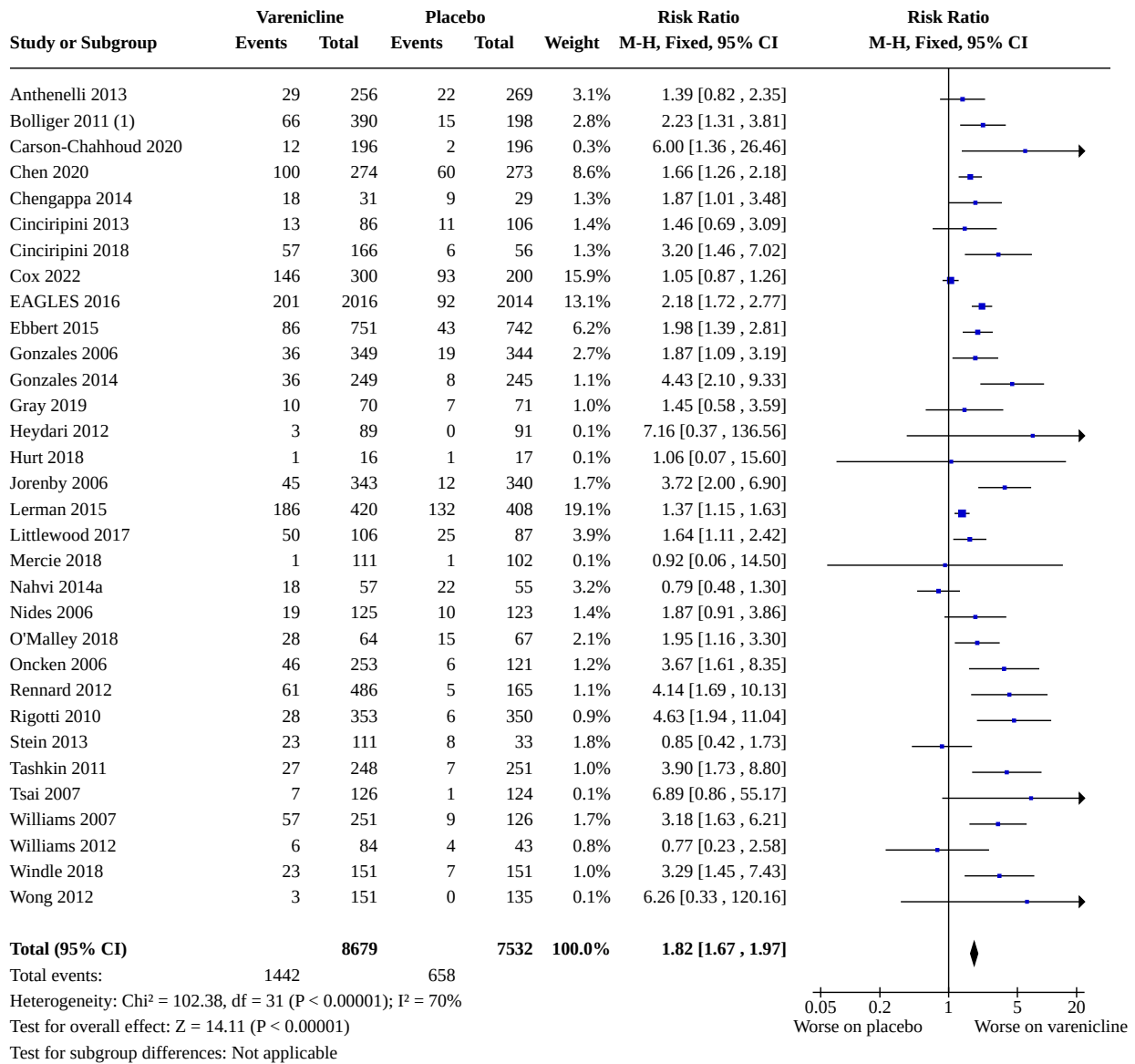
Analysis 5.2. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 2: Nausea



Analysis 5.3. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 3: Insomnia



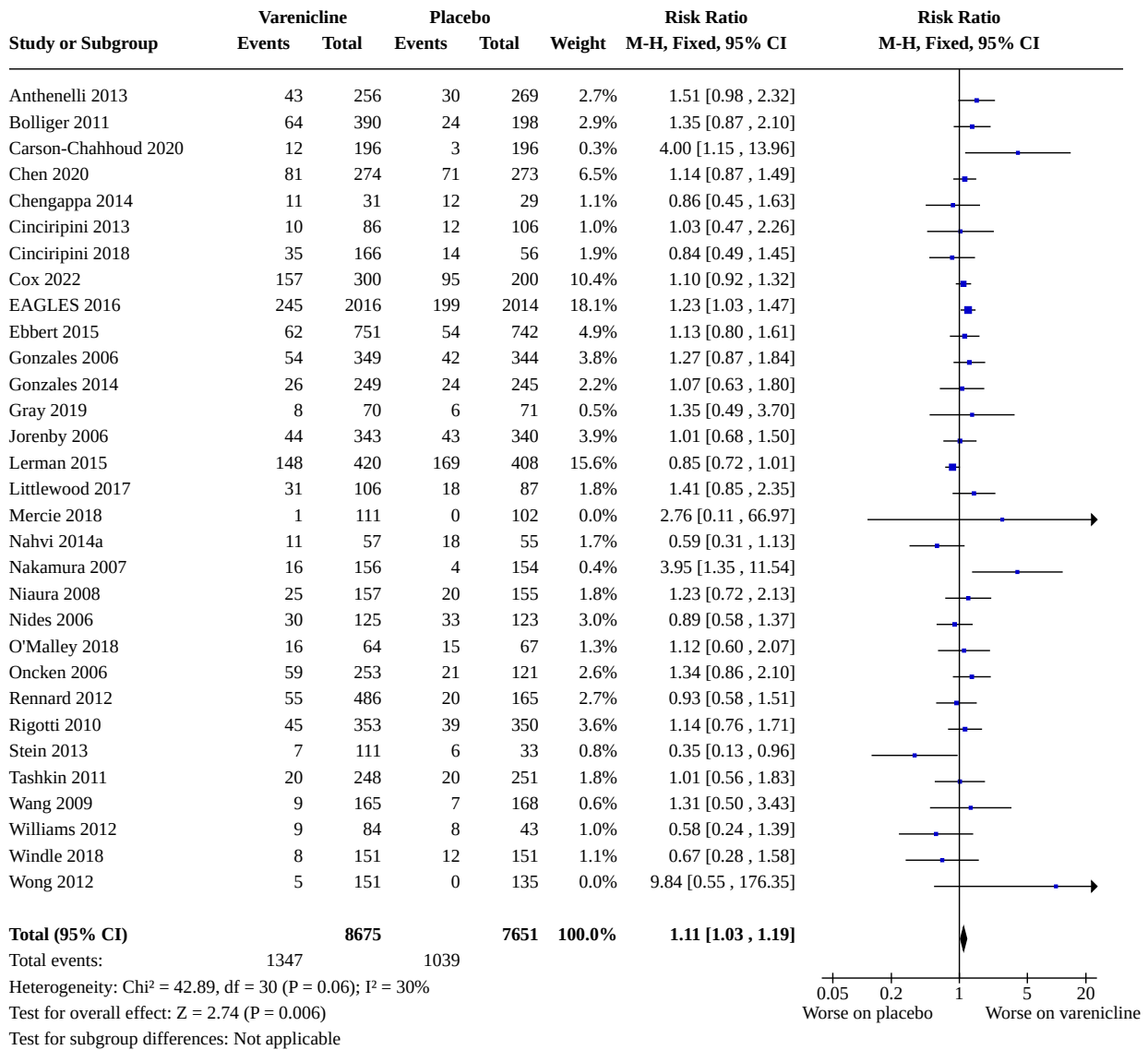
Analysis 5.4. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 4: Abnormal dreams



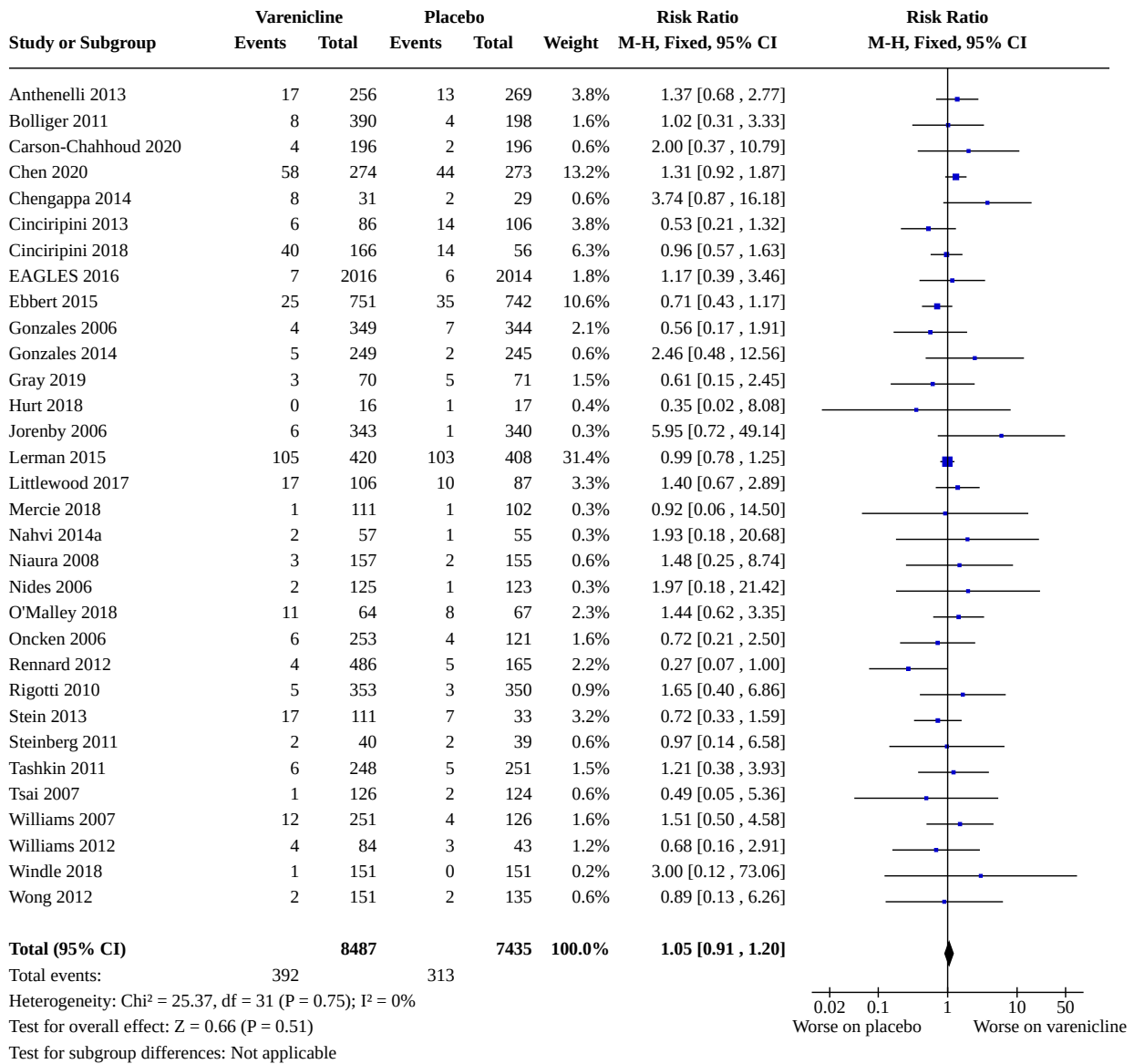
Footnotes

(1) all sleep disorders grouped together

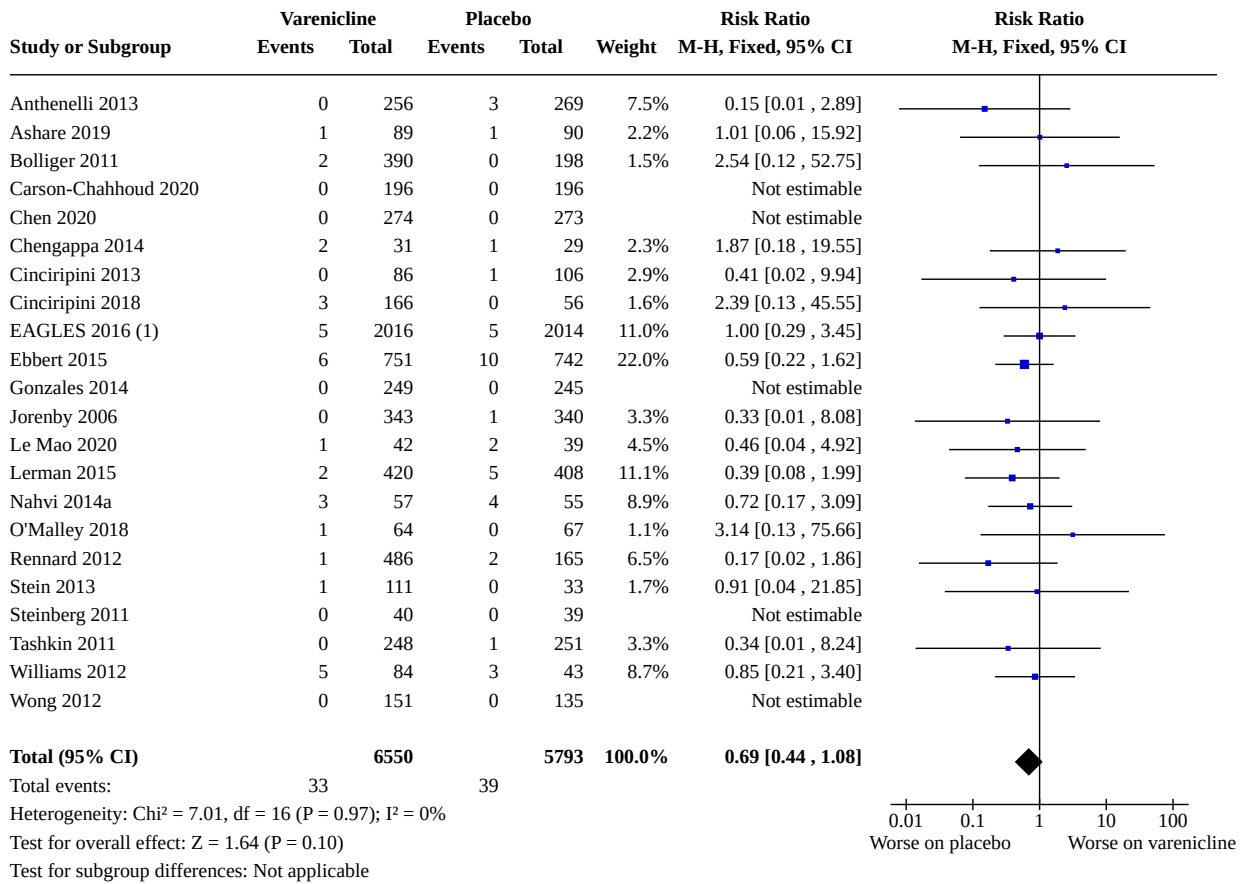
Analysis 5.5. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 5: Headache



Analysis 5.6. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 6: Depression



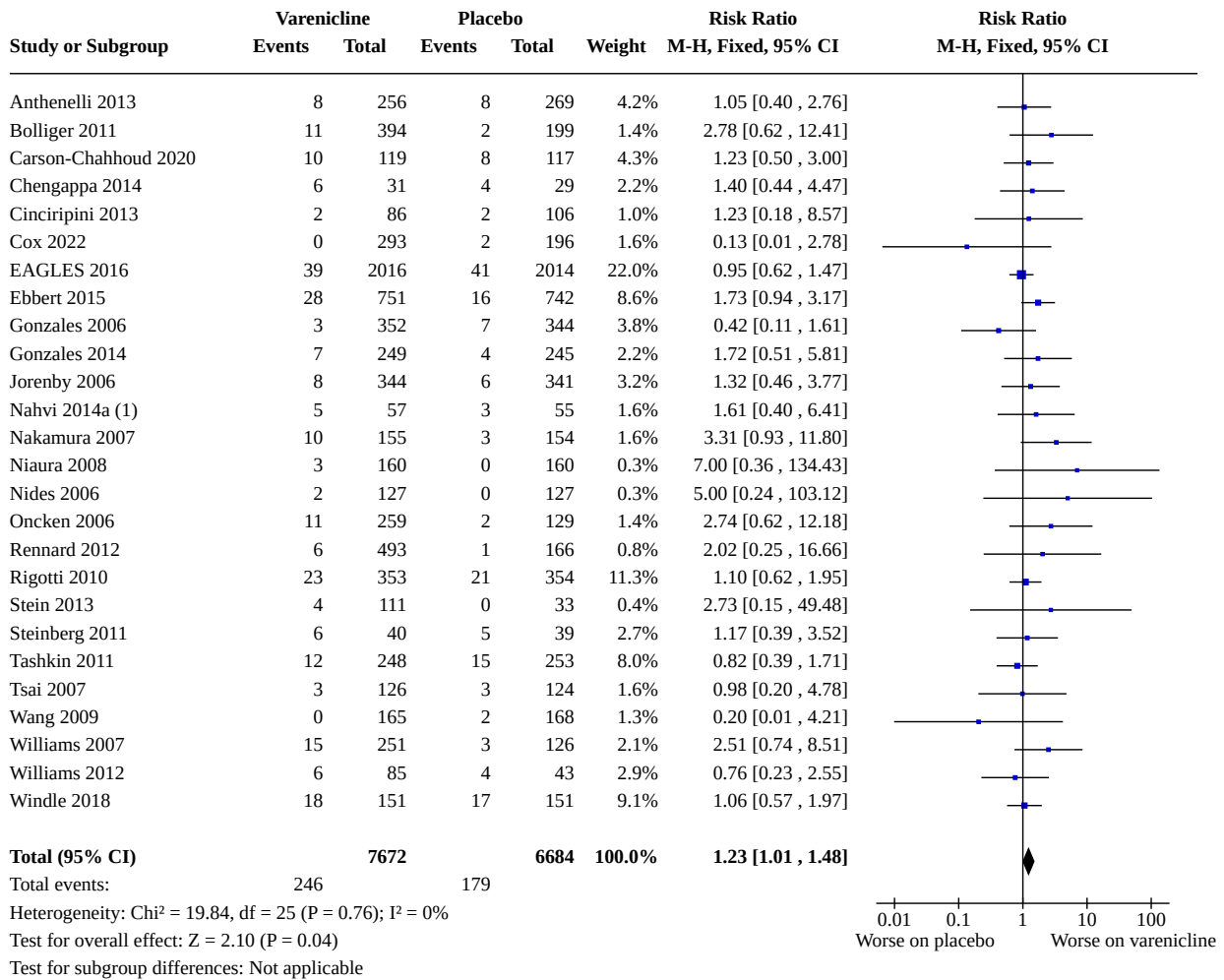
Analysis 5.7. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 7: Suicidal ideation



Footnotes

(1) All 5 events occurred in the psychiatric cohort

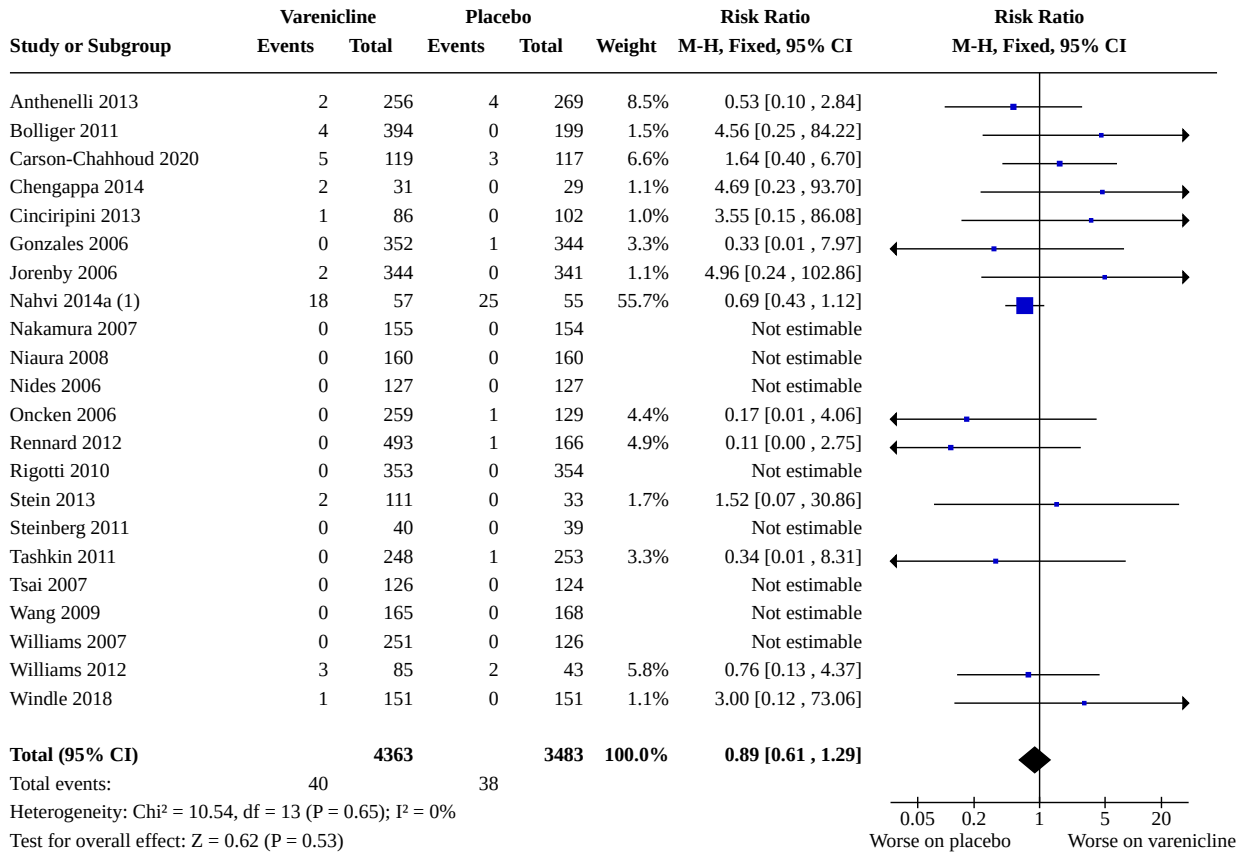
Analysis 5.8. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 8: SAEs



Footnotes

(1) in methadone-maintained patients

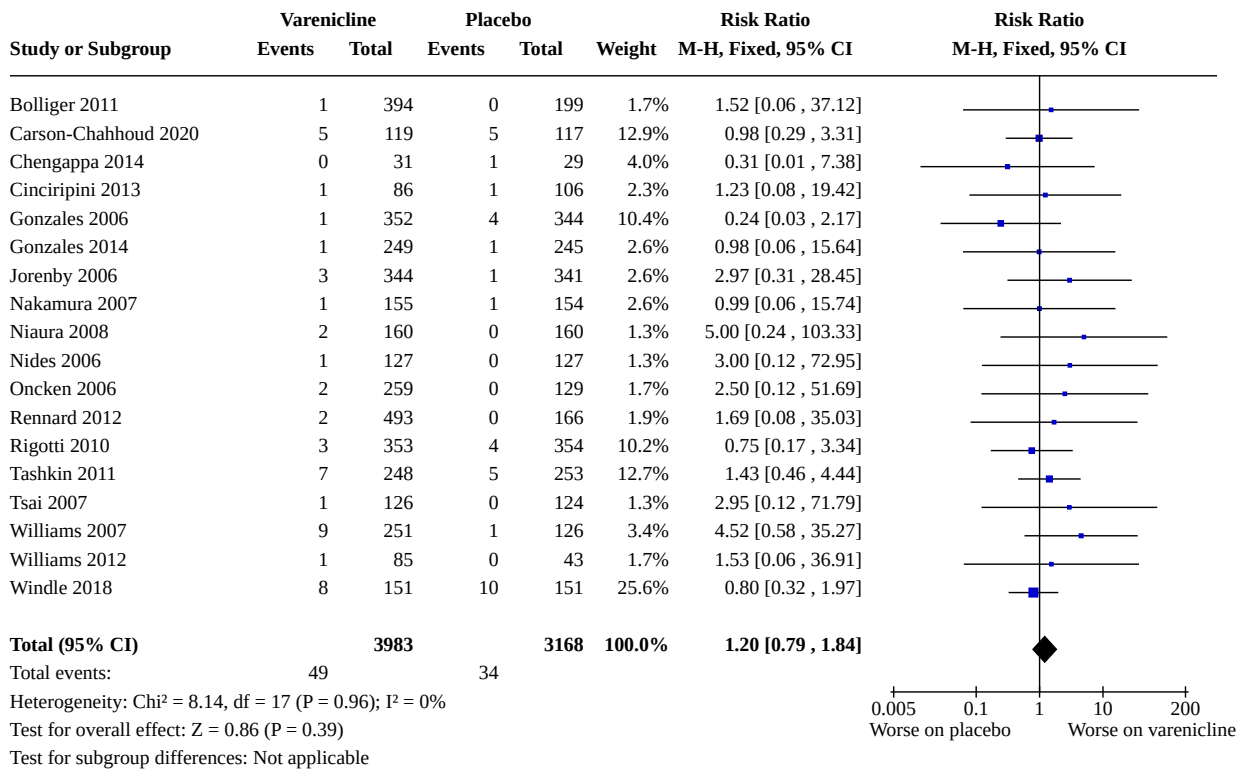
Analysis 5.9. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 9: Neuropsychiatric SAEs (not deaths)



Footnotes

(1) in methadone-maintained patients

Analysis 5.10. Comparison 5: Varenicline 2 mg per day vs placebo or no medication, Outcome 10: Cardiac SAEs, including deaths



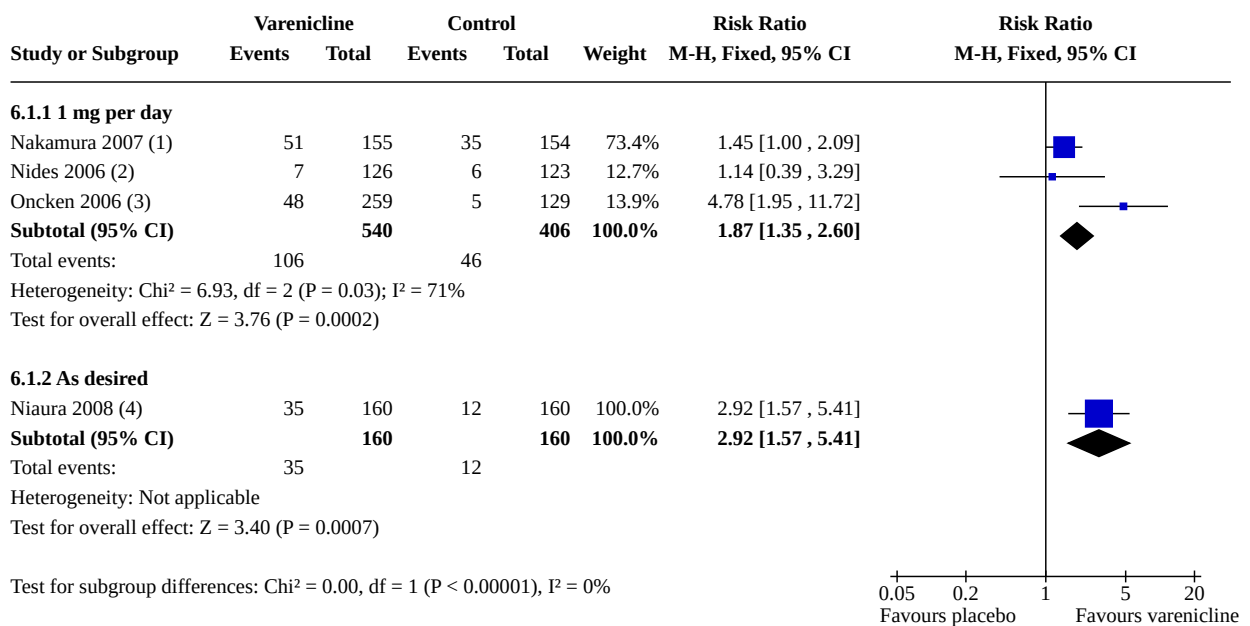
0.005 0.1 1 10 200
Worse on placebo Worse on varenicline

Comparison 6. Varenicline: variations in usage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Low-dose varenicline vs placebo	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1.1 1 mg per day	3	946	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.35, 2.60]
6.1.2 As desired	1	320	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [1.57, 5.41]
6.2 Higher-dose varenicline versus lower-dose varenicline	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.2.1 2 mg per day vs 1 mg per day	4	1563	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.97, 1.30]
6.2.2 2 mg per day vs 0.3 mg per day	1	253	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.89, 3.84]
6.2.3 1 mg per day vs 0.3 mg per day	1	254	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.28, 1.81]
6.3 Longer vs standard duration varenicline	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3.1 24 weeks vs 12 weeks	2	1458	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
6.3.2 52 weeks vs 12 weeks	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.70, 2.43]
6.4 6 week vs 1 week preloading	1	242	Risk Ratio (M-H, Fixed, 95% CI)	5.60 [2.24, 14.02]

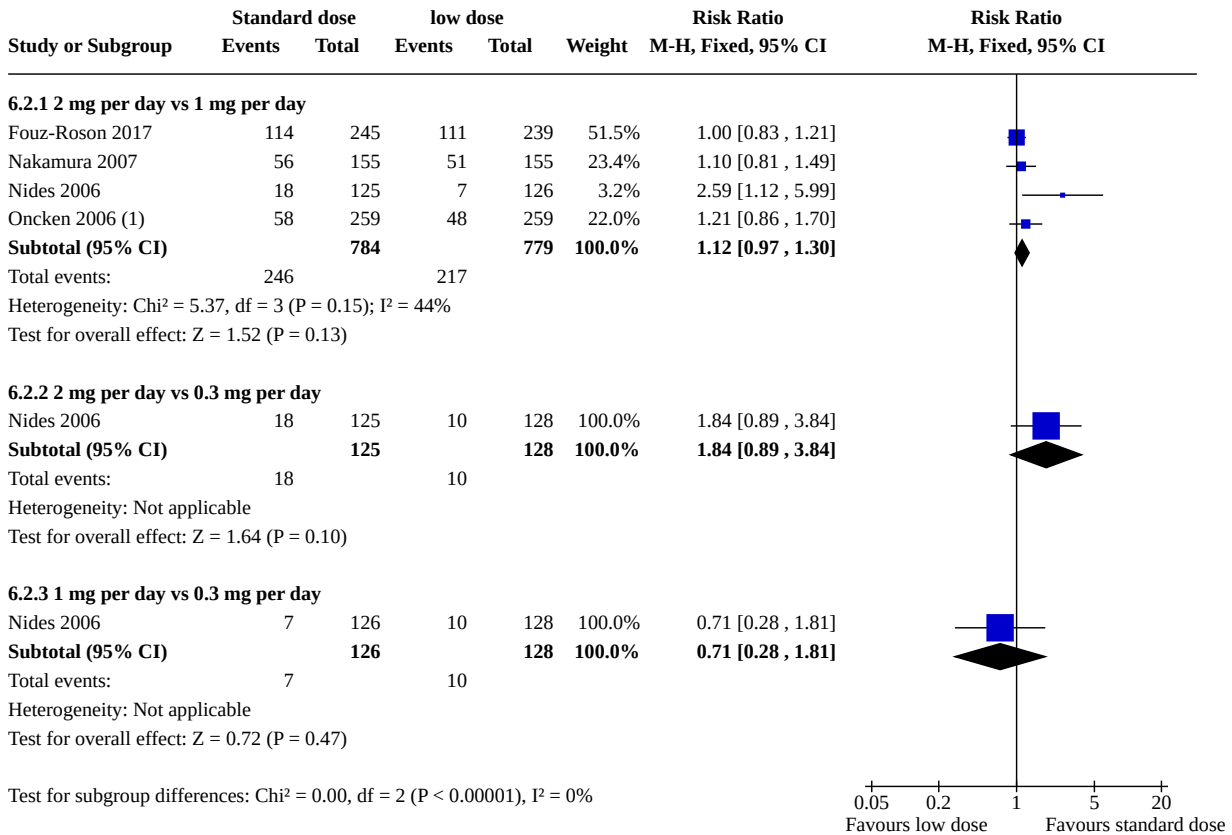
Analysis 6.1. Comparison 6: Varenicline: variations in usage, Outcome 1: Low-dose varenicline vs placebo



Footnotes

- (1) 0.5 mg twice a day
- (2) 1 mg once a day
- (3) 0.5 mg twice a day (titrated and non-titrated combined)
- (4) ad lib, between 0.5 and 2.0 mg daily

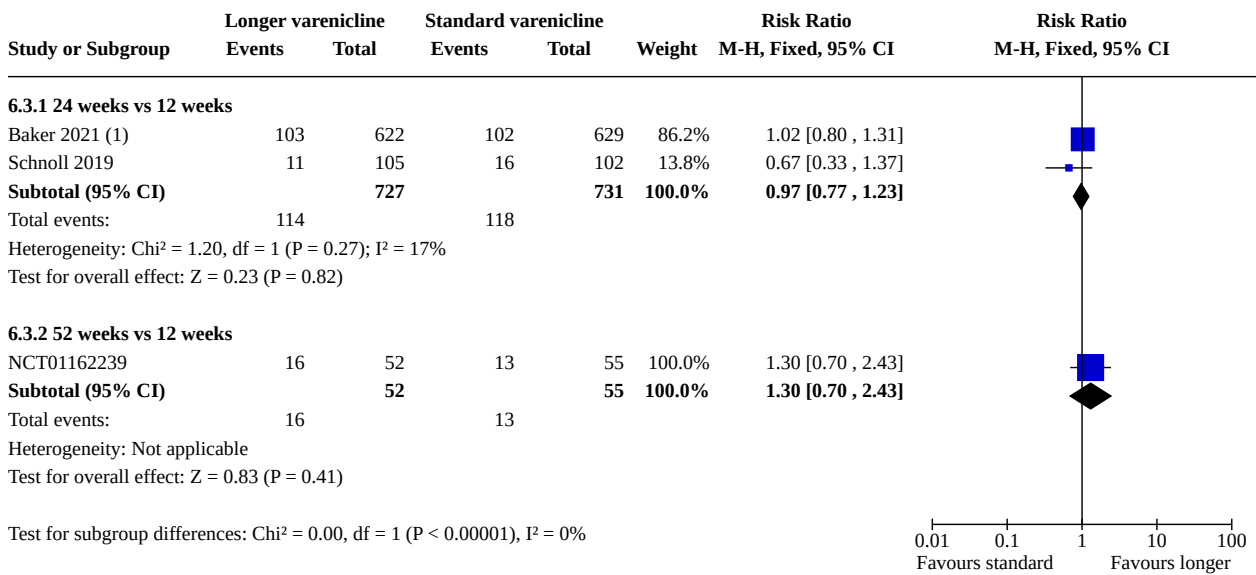
Analysis 6.2. Comparison 6: Varenicline: variations in usage, Outcome 2: Higher-dose varenicline versus lower-dose varenicline



Footnotes

(1) Titrated and non-titrated arms combined

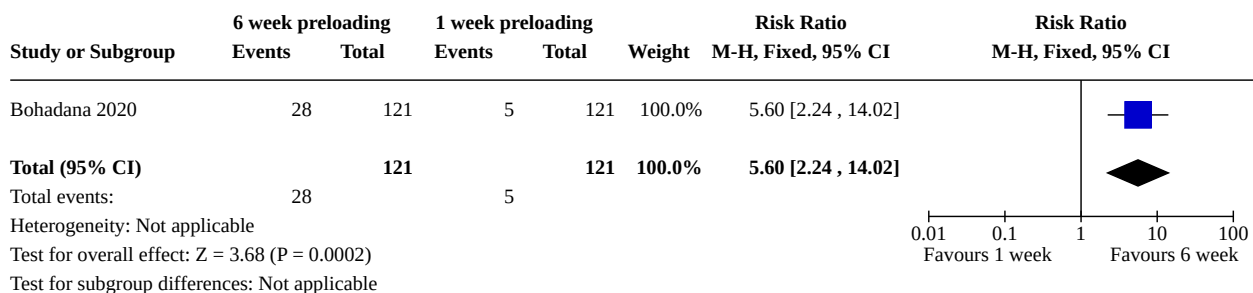
Analysis 6.3. Comparison 6: Varenicline: variations in usage, Outcome 3: Longer vs standard duration varenicline



Footnotes

(1) Combining arms with and without NRT

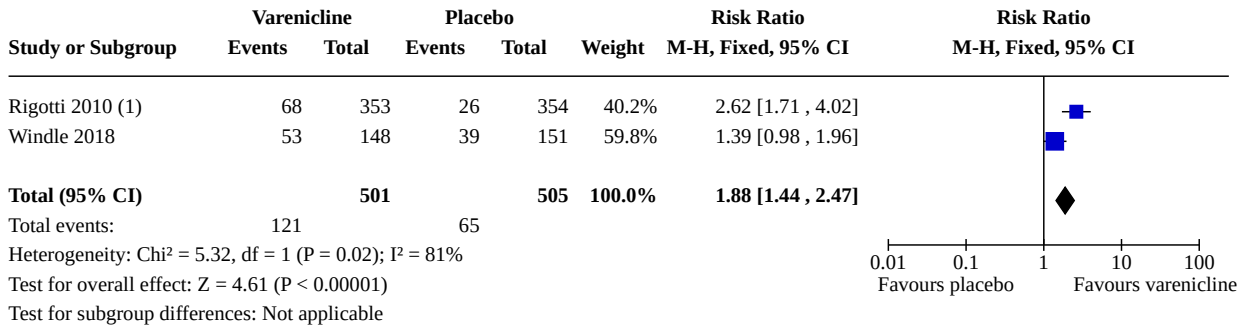
Analysis 6.4. Comparison 6: Varenicline: variations in usage, Outcome 4: 6 week vs 1 week preloading



Comparison 7. Varenicline (vs placebo or no medication) in specific patient groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Cardiovascular disease	2	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.44, 2.47]
7.2 COPD	4	860	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.28, 1.69]
7.3 Asthma	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.38, 4.14]
7.4 Schizophrenia/bipolar/psychiatric disorder	3	2245	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.78, 2.86]
7.5 Depression	2	745	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.45, 3.24]
7.6 Substance use disorder/methadone-maintained at 24 weeks	2	294	Risk Ratio (M-H, Fixed, 95% CI)	3.72 [0.50, 27.59]
7.7 Alcohol-dependence	3	195	Odds Ratio (M-H, Fixed, 95% CI)	3.01 [0.92, 9.92]
7.8 HIV	2	427	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.06, 3.63]

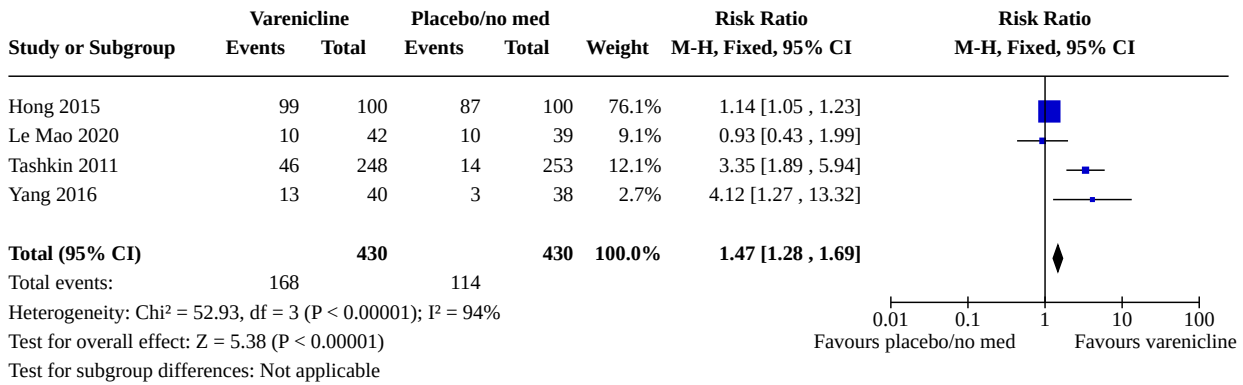
Analysis 7.1. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 1: Cardiovascular disease



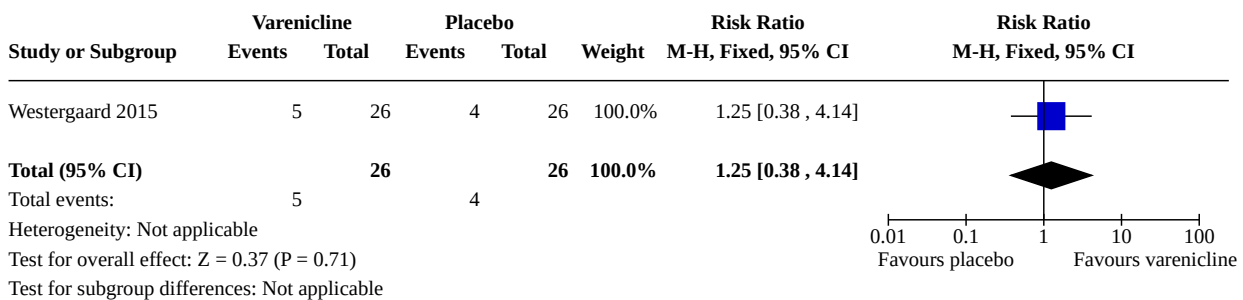
Footnotes

(1) 52 wk follow-up

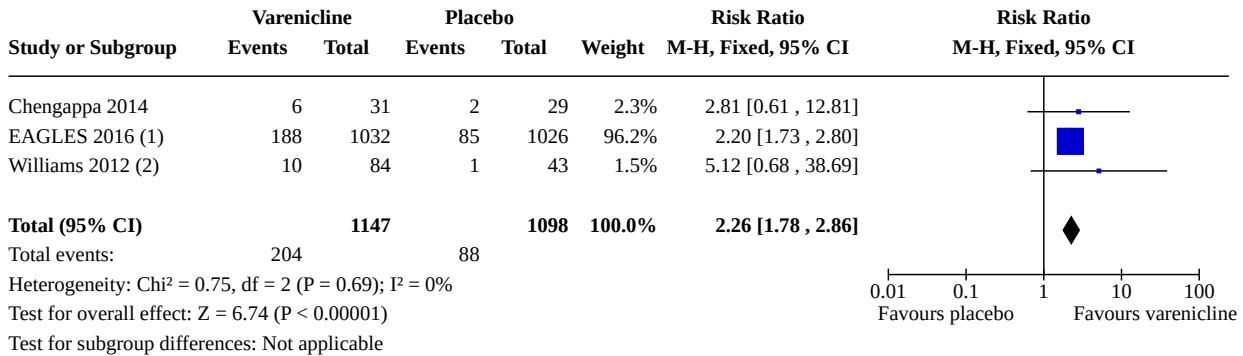
Analysis 7.2. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 2: COPD



Analysis 7.3. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 3: Asthma



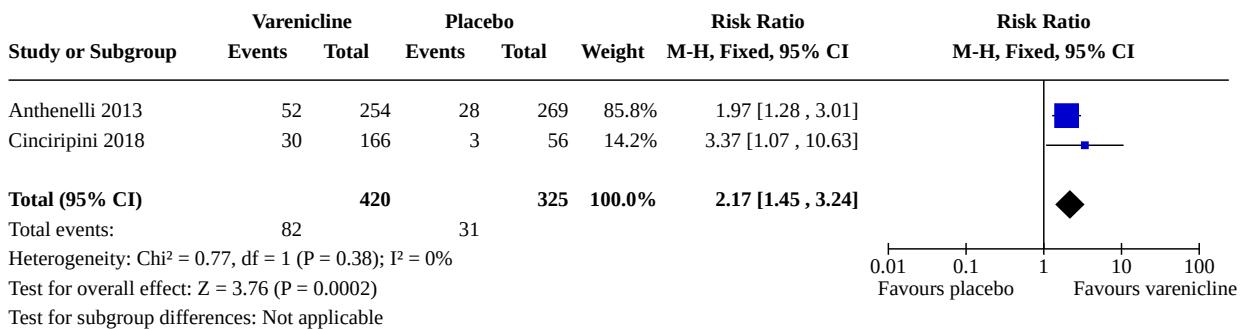
Analysis 7.4. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 4: Schizophrenia/bipolar/psychiatric disorder



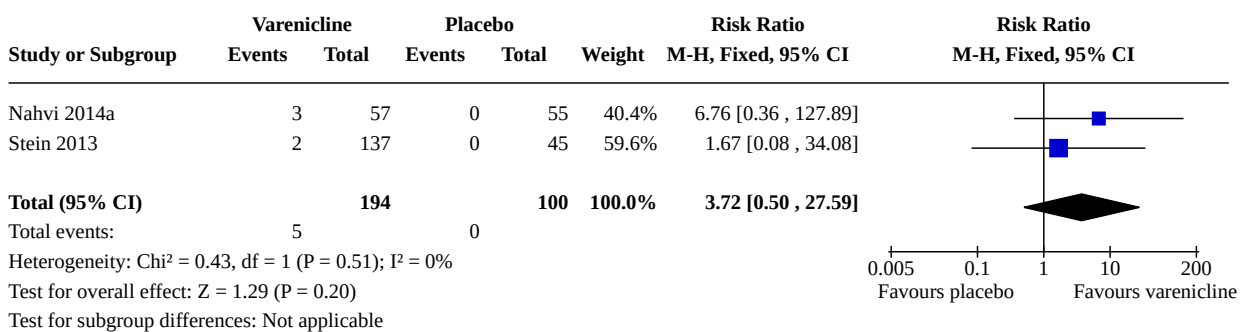
Footnotes

- (1) Extrapolated from % reported quit
- (2) 7-day PPA at 24 weeks

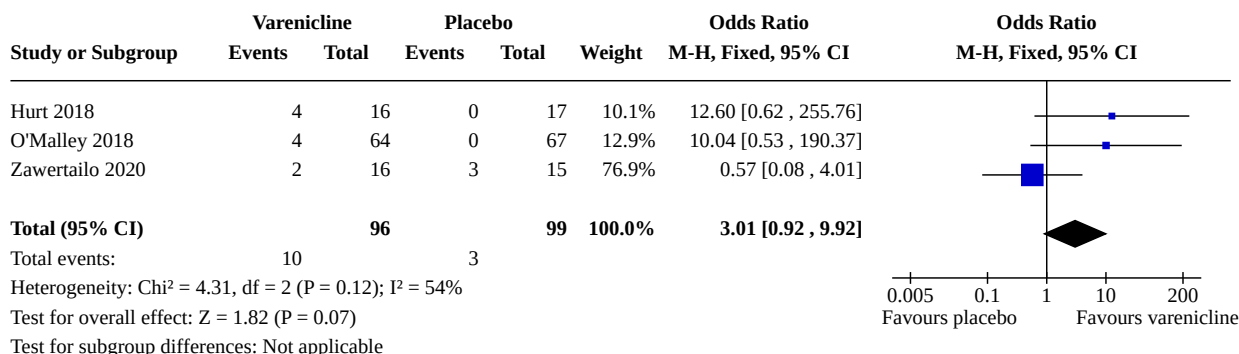
Analysis 7.5. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 5: Depression



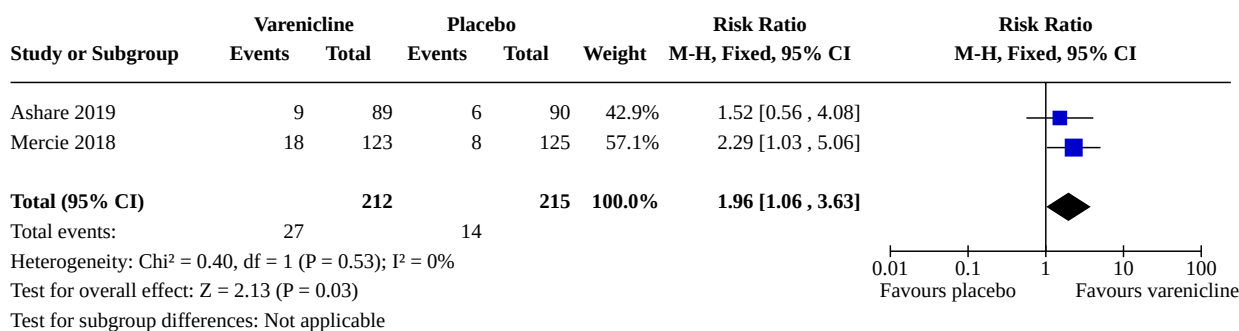
Analysis 7.6. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 6: Substance use disorder/ methadone-maintained at 24 weeks



Analysis 7.7. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 7: Alcohol-dependence



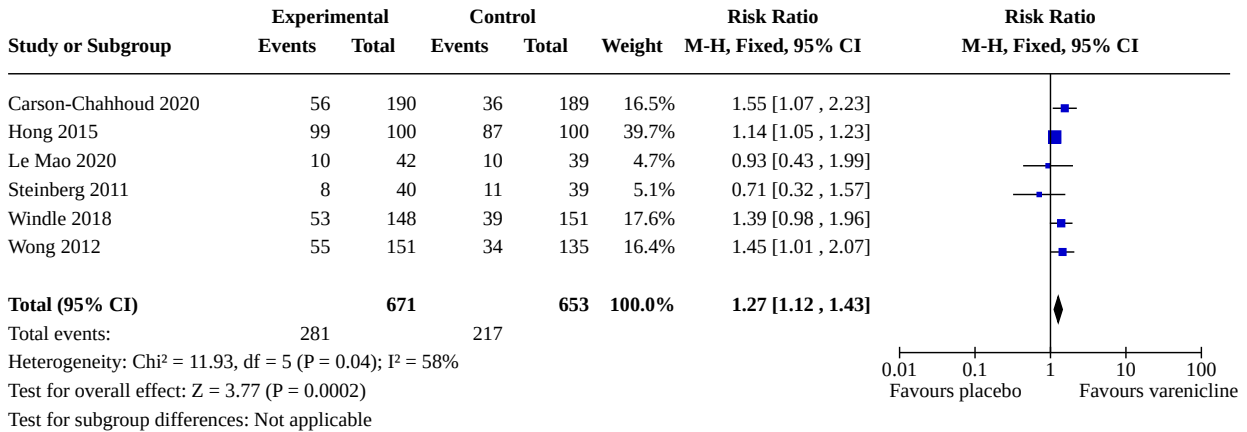
Analysis 7.8. Comparison 7: Varenicline (vs placebo or no medication) in specific patient groups, Outcome 8: HIV



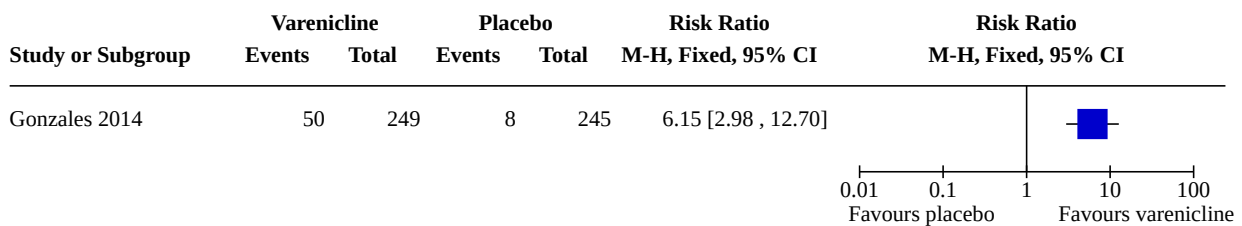
Comparison 8. Varenicline in specific settings/subgroups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Hospital inpatients/perioperative patients	6	1324	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.12, 1.43]
8.2 Smokers with a previous quit attempt on varenicline	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.3 Light or heavy smokers	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.3.1 Light smokers	2	114	Risk Ratio (M-H, Fixed, 95% CI)	4.16 [1.58, 10.97]

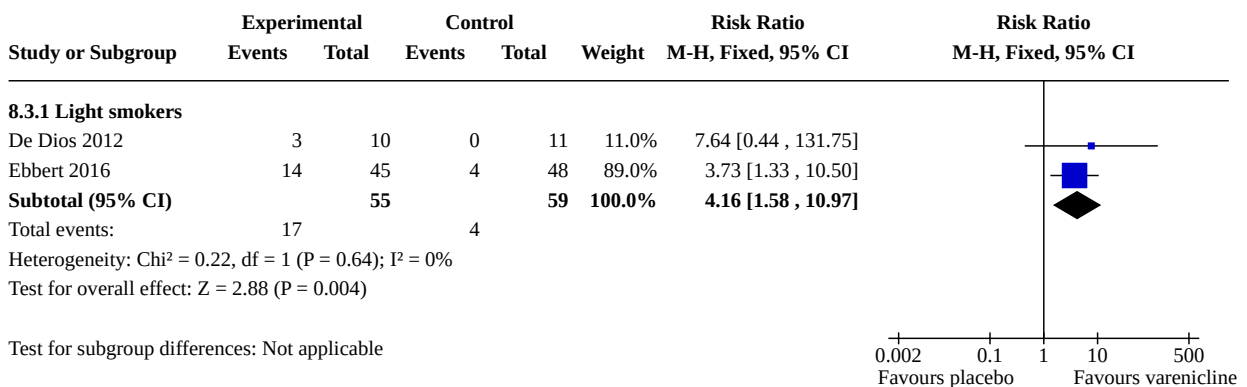
**Analysis 8.1. Comparison 8: Varenicline in specific settings/
subgroups, Outcome 1: Hospital inpatients/perioperative patients**



**Analysis 8.2. Comparison 8: Varenicline in specific settings/subgroups,
Outcome 2: Smokers with a previous quit attempt on varenicline**



Analysis 8.3. Comparison 8: Varenicline in specific settings/subgroups, Outcome 3: Light or heavy smokers



Comparison 9. Varenicline vs bupropion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Abstinence at longest follow-up	9	7560	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.25, 1.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Nausea	4	5808	Risk Ratio (M-H, Fixed, 95% CI)	2.46 [2.20, 2.75]
9.3 Insomnia	6	6789	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.93]
9.4 Abnormal dreams	4	5808	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.39, 1.76]
9.5 Headache	3	4888	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.06, 1.45]
9.6 Depression	2	4210	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.35, 2.35]
9.7 Suicidal ideation	2	4210	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.18, 21.93]
9.8 SAEs	5	5317	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.31]
9.9 Neuropsychiatric SAEs (not deaths)	2	866	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.16, 7.04]
9.10 Cardiac SAEs, including deaths	2	866	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.33, 30.18]

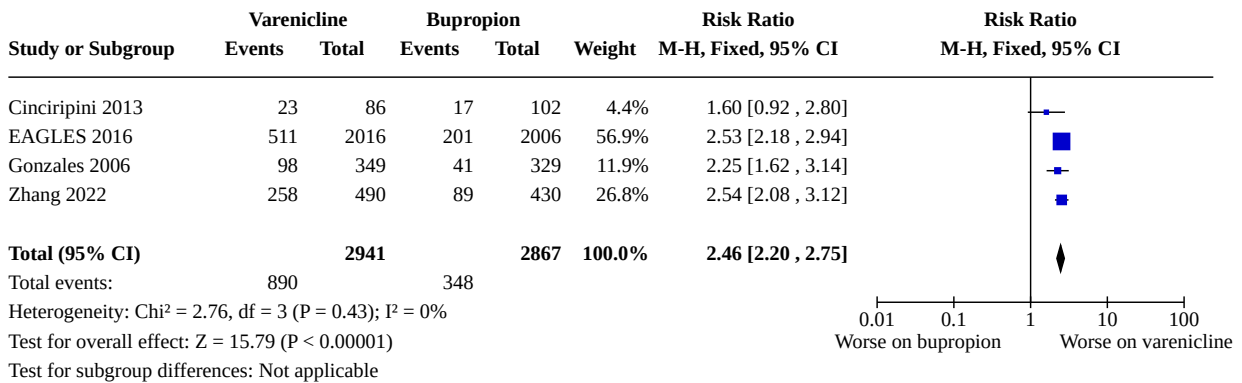
Analysis 9.1. Comparison 9: Varenicline vs bupropion, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Varenicline		Bupropion		Weight	Risk Ratio		Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Benli 2017	34	244	10	161	1.8%	2.24	[1.14, 4.41]	
Cinciripini 2013	24	86	23	102	3.1%	1.24	[0.75, 2.03]	
EAGLES 2016 (1)	444	2037	330	2034	49.3%	1.34	[1.18, 1.53]	
Gonzales 2006	77	352	53	329	8.2%	1.36	[0.99, 1.86]	
Jorenby 2006	79	344	50	342	7.5%	1.57	[1.14, 2.17]	
Nides 2006	18	125	8	126	1.2%	2.27	[1.02, 5.02]	
Qin 2021 (2)	28	68	18	68	2.7%	1.56	[0.96, 2.53]	
Zhang 2022	160	499	121	465	18.7%	1.23	[1.01, 1.50]	
Zincir 2013	73	101	44	77	7.5%	1.26	[1.01, 1.59]	
Total (95% CI)		3856		3704	100.0%	1.36	[1.25, 1.49]	
Total events:	937		657					
Heterogeneity: Chi ² = 6.30, df = 8 (P = 0.61); I ² = 0%								
Test for overall effect: Z = 6.98 (P < 0.00001)								
Test for subgroup differences: Not applicable								

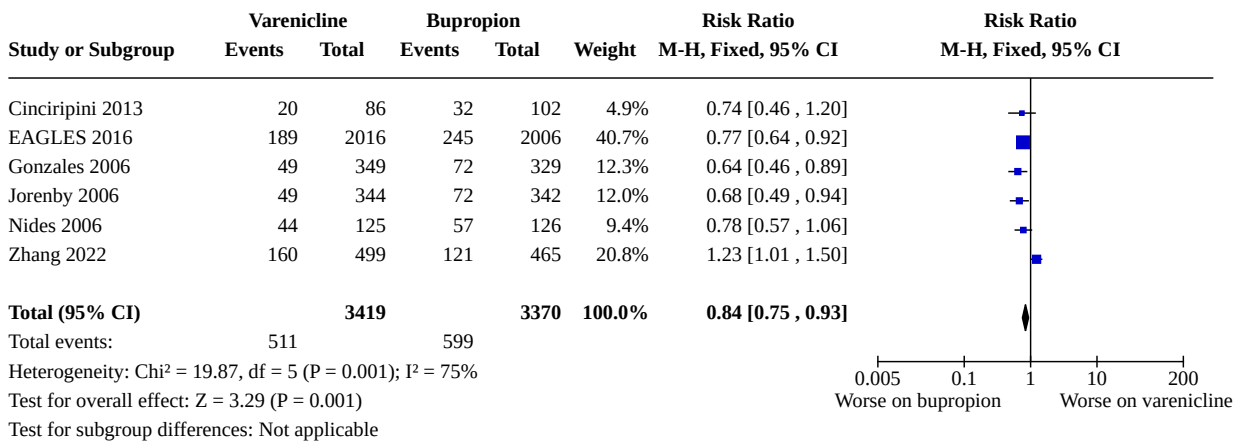
Footnotes

- (1) Extrapolated from % reported quit
- (2) Bupropion at lower than standard dose

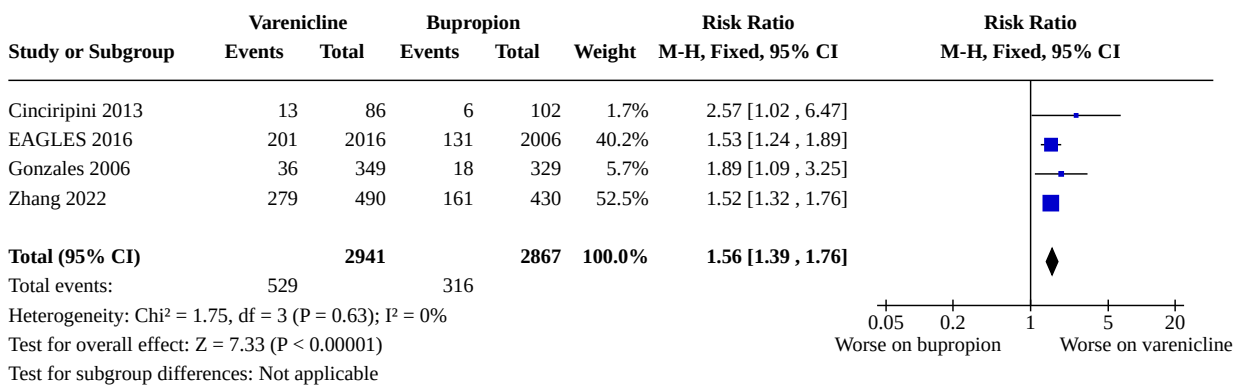
Analysis 9.2. Comparison 9: Varenicline vs bupropion, Outcome 2: Nausea



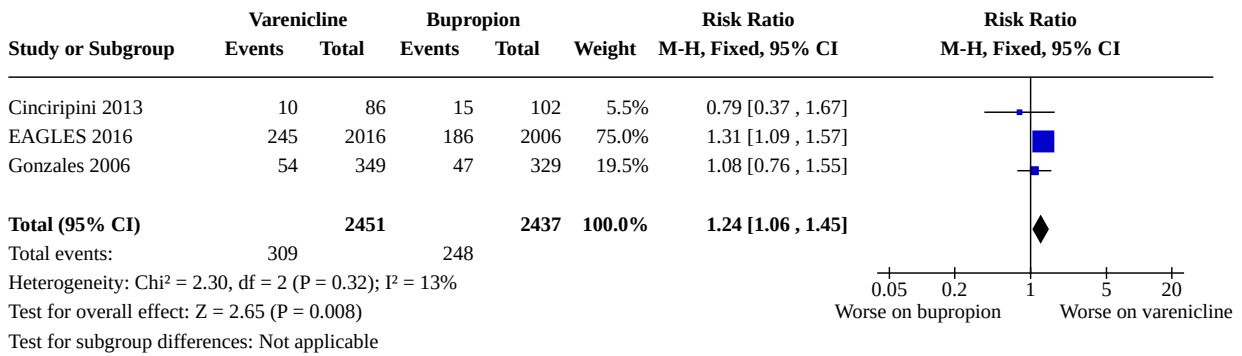
Analysis 9.3. Comparison 9: Varenicline vs bupropion, Outcome 3: Insomnia



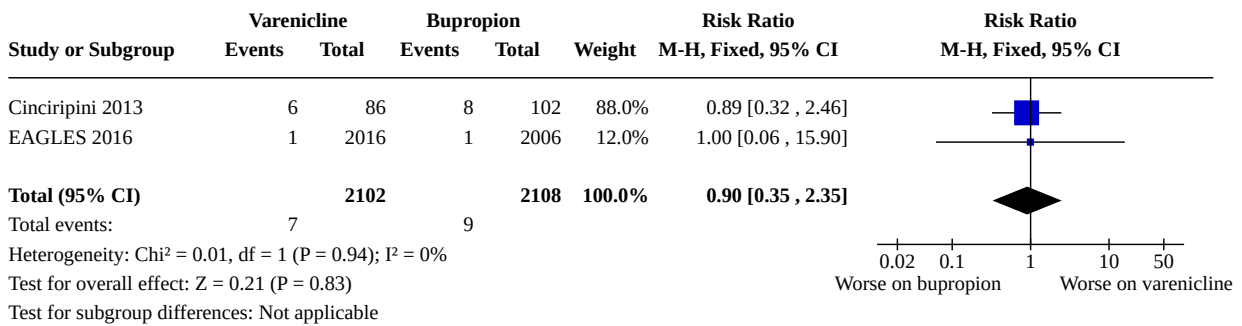
Analysis 9.4. Comparison 9: Varenicline vs bupropion, Outcome 4: Abnormal dreams



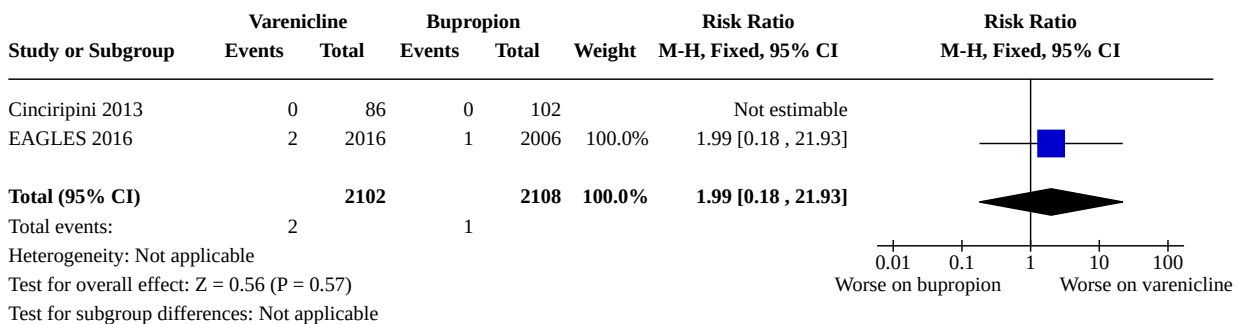
Analysis 9.5. Comparison 9: Varenicline vs bupropion, Outcome 5: Headache



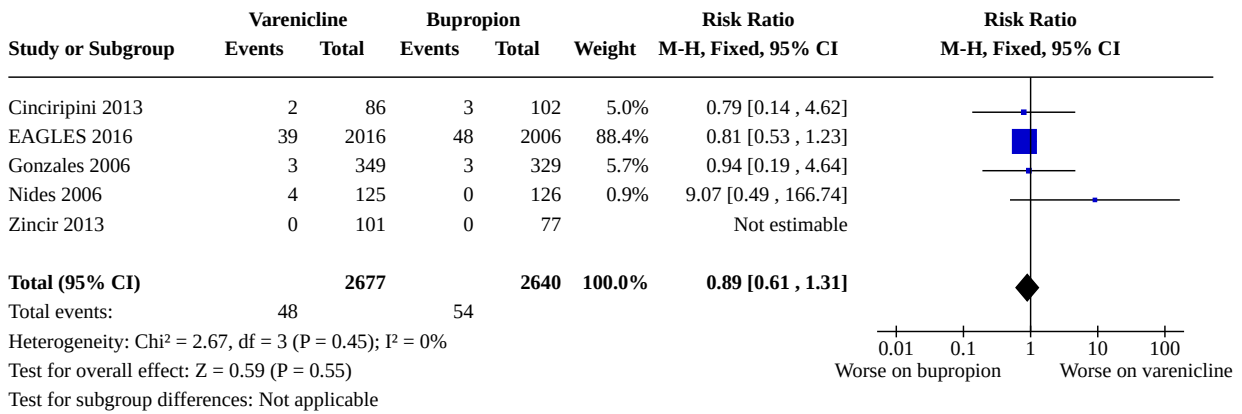
Analysis 9.6. Comparison 9: Varenicline vs bupropion, Outcome 6: Depression



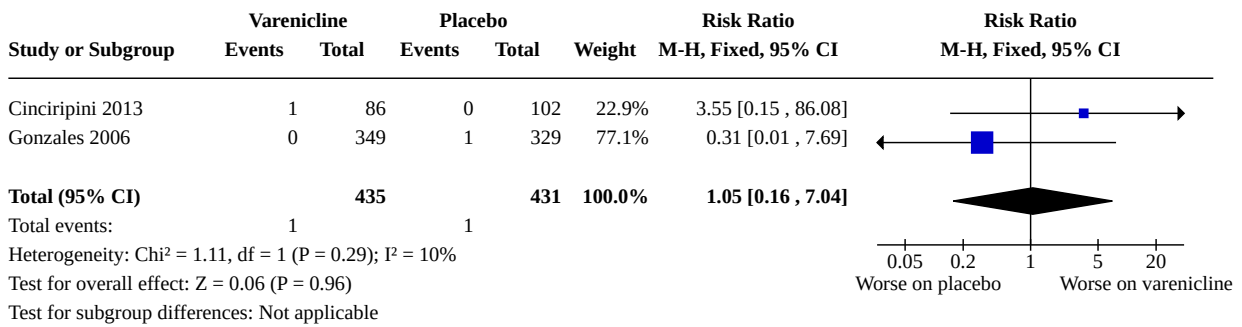
Analysis 9.7. Comparison 9: Varenicline vs bupropion, Outcome 7: Suicidal ideation



Analysis 9.8. Comparison 9: Varenicline vs bupropion, Outcome 8: SAEs



Analysis 9.9. Comparison 9: Varenicline vs bupropion, Outcome 9: Neuropsychiatric SAEs (not deaths)



Analysis 9.10. Comparison 9: Varenicline vs bupropion, Outcome 10: Cardiac SAEs, including deaths



Comparison 10. Varenicline vs NRT monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Abstinence at longest follow-up	11	7572	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.14, 1.37]
10.2 Nausea	6	6500	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [2.41, 3.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Insomnia	5	6319	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.96, 1.21]
10.4 Abnormal dreams	4	5803	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.05]
10.5 Headache	4	6287	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.01, 1.28]
10.6 Depression	3	5541	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.76, 1.16]
10.7 Suicidal ideation	2	4876	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.87, 28.77]
10.8 SAEs	6	6535	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.99]
10.9 Neuropsychiatric SAEs (not deaths)	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.10 Cardiac SAEs, including deaths	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

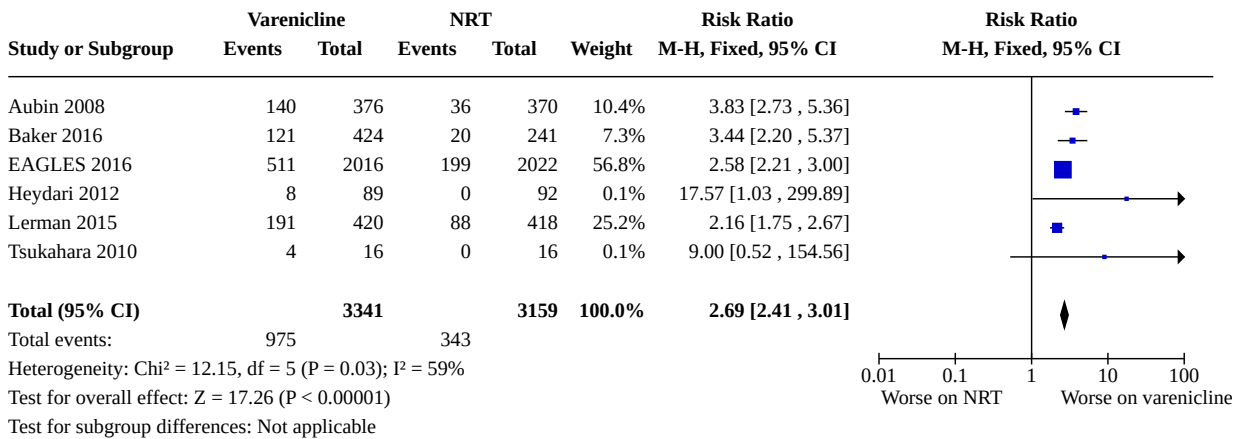
Analysis 10.1. Comparison 10: Varenicline vs NRT monotherapy, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Varenicline		NRT		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Aubin 2008 (1)	145	376	126	370	18.7%	1.13 [0.94, 1.37]	
Baker 2016	100	424	55	241	10.3%	1.03 [0.77, 1.38]	
De Dios 2012	3	10	0	11	0.1%	7.64 [0.44, 131.75]	
EAGLES 2016 (2)	444	2037	320	2038	47.1%	1.39 [1.22, 1.58]	
Heydari 2012 (1)	52	89	47	92	6.8%	1.14 [0.88, 1.49]	
Lerman 2015	63	420	69	418	10.2%	0.91 [0.66, 1.24]	
Rohsenow 2017	7	77	2	60	0.3%	2.73 [0.59, 12.66]	
Rose 2013 (3)	11	138	9	136	1.3%	1.20 [0.52, 2.81]	
Tsukahara 2010 (1)	7	16	7	16	1.0%	1.00 [0.46, 2.19]	
Tuisku 2016	11	60	5	51	0.8%	1.87 [0.70, 5.03]	
Tulloch 2016	36	247	23	245	3.4%	1.55 [0.95, 2.54]	
Total (95% CI)		3894		3678	100.0%	1.25 [1.14, 1.37]	
Total events:	879		663				
Heterogeneity: Chi ² = 13.85, df = 10 (P = 0.18); I ² = 28%							
Test for overall effect: Z = 4.96 (P < 0.00001)							
Test for subgroup differences: Not applicable							

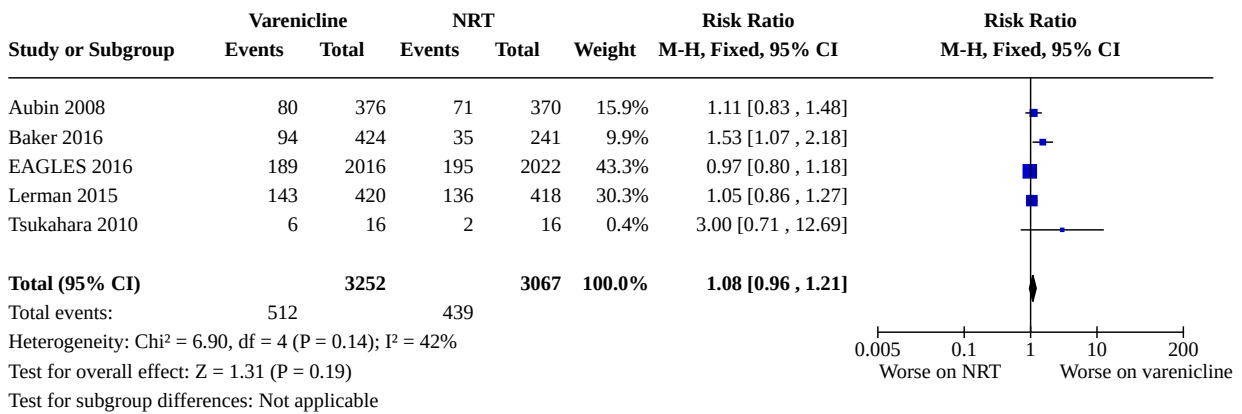
Footnotes

- (1) Open-label, unblinded
- (2) extrapolated from % reported quit
- (3) Rescue treatments for non-responders or relapsers, Phases 1 and 2 combined

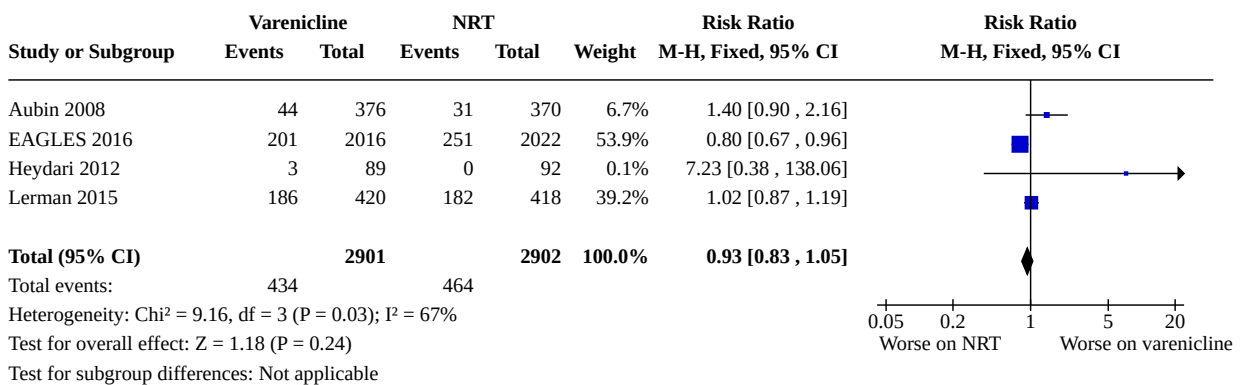
Analysis 10.2. Comparison 10: Varenicline vs NRT monotherapy, Outcome 2: Nausea



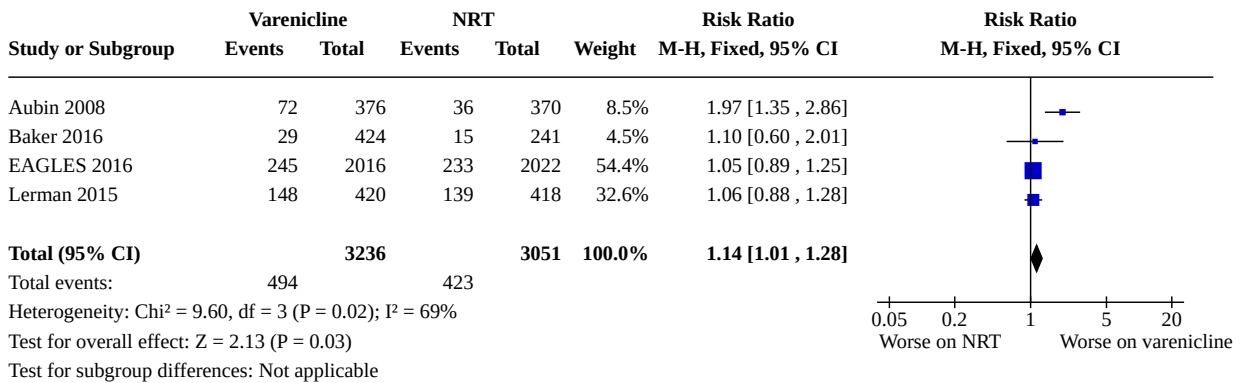
Analysis 10.3. Comparison 10: Varenicline vs NRT monotherapy, Outcome 3: Insomnia



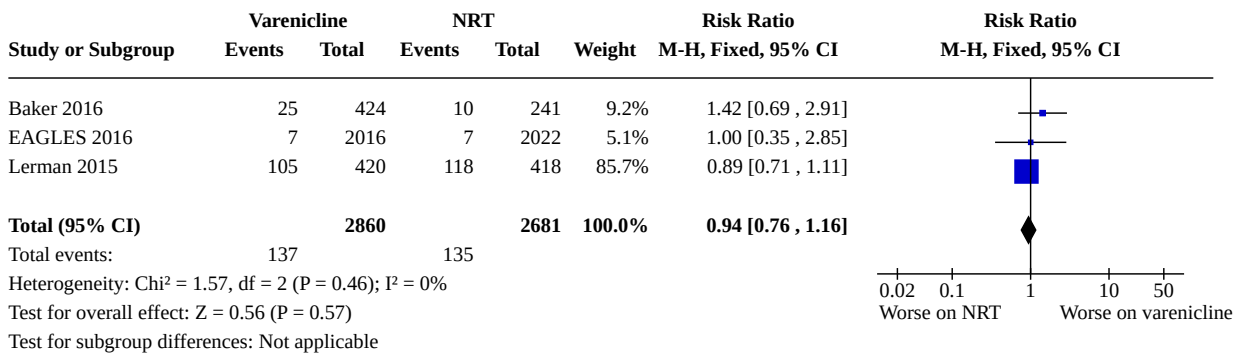
Analysis 10.4. Comparison 10: Varenicline vs NRT monotherapy, Outcome 4: Abnormal dreams



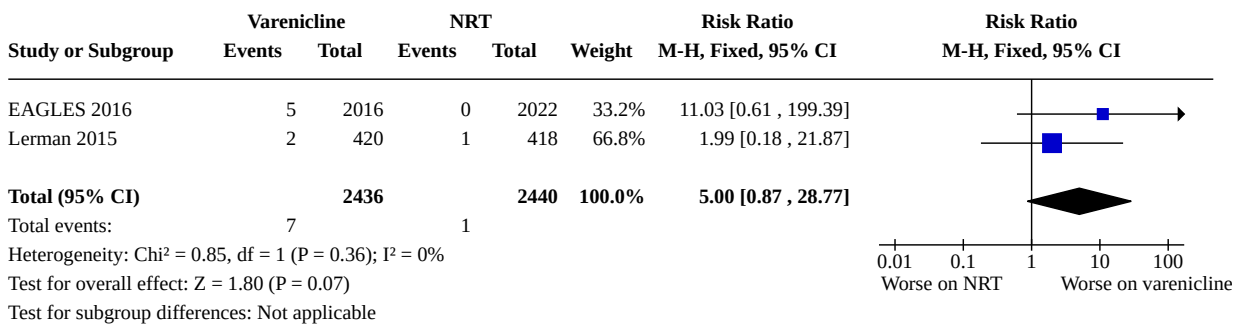
Analysis 10.5. Comparison 10: Varenicline vs NRT monotherapy, Outcome 5: Headache



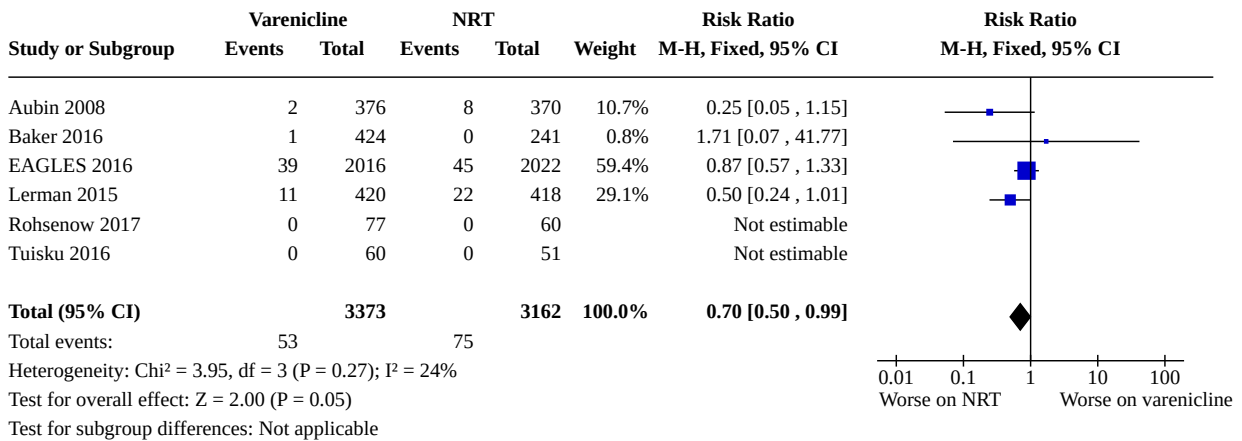
Analysis 10.6. Comparison 10: Varenicline vs NRT monotherapy, Outcome 6: Depression



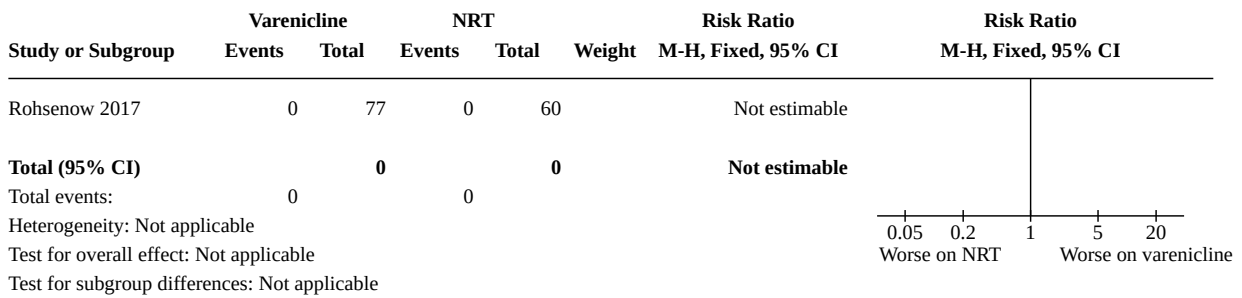
Analysis 10.7. Comparison 10: Varenicline vs NRT monotherapy, Outcome 7: Suicidal ideation



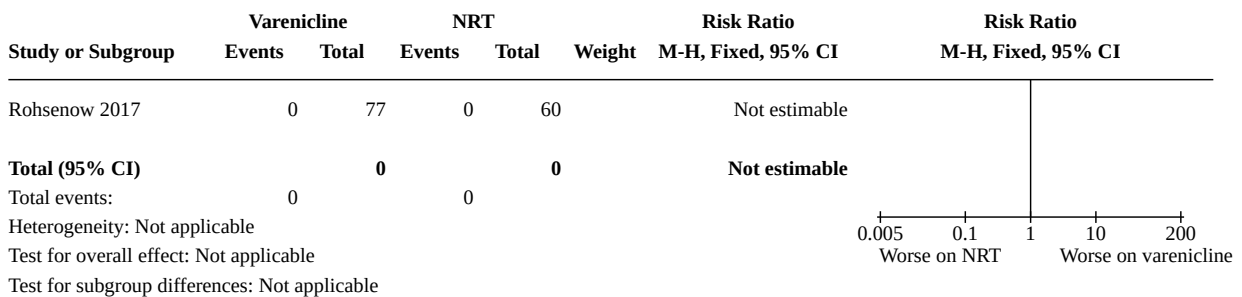
Analysis 10.8. Comparison 10: Varenicline vs NRT monotherapy, Outcome 8: SAEs



Analysis 10.9. Comparison 10: Varenicline vs NRT monotherapy, Outcome 9: Neuropsychiatric SAEs (not deaths)



Analysis 10.10. Comparison 10: Varenicline vs NRT monotherapy, Outcome 10: Cardiac SAEs, including deaths



Comparison 11. Varenicline vs combination NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Abstinence at longest follow-up	5	2344	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.20]
11.2 Nausea	3	1609	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.45, 2.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Insomnia	3	1609	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.15, 1.70]
11.4 Abnormal dreams	1	549	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.22, 2.08]
11.5 Headache	3	1609	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.23]
11.6 Depression	3	1609	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.83, 1.40]
11.7 Suicidal ideation	2	764	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.06, 14.79]
11.8 SAEs	4	1852	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.49, 9.46]
11.9 Neuropsychiatric SAEs (not deaths)	2	764	Risk Ratio (M-H, Fixed, 95% CI)	4.69 [0.23, 96.50]
11.10 Cardiac SAEs, including deaths	2	819	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.88]

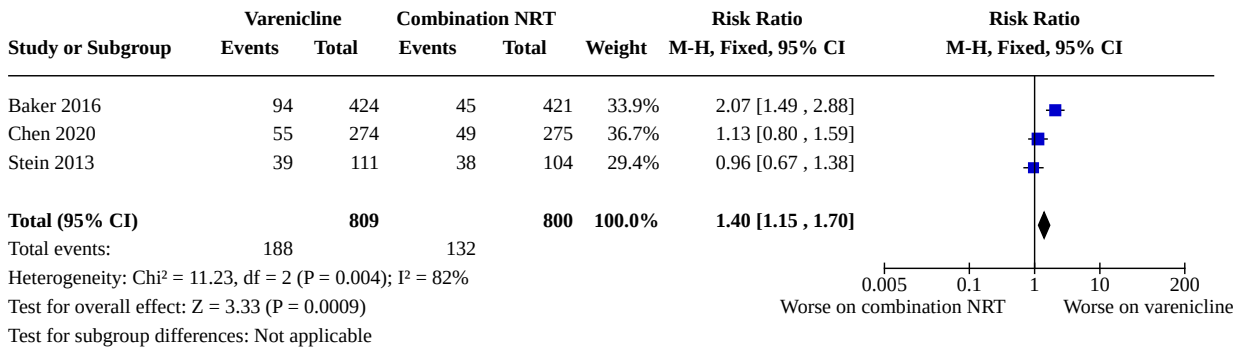
Analysis 11.1. Comparison 11: Varenicline vs combination NRT, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Varenicline		NRT		Weight	Risk Ratio		Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Baker 2016	81	424	85	421	37.4%	0.95 [0.72, 1.24]			
Chen 2020	77	274	68	275	29.7%	1.14 [0.86, 1.50]			
Ikonomidis 2017	38	94	44	94	19.3%	0.86 [0.62, 1.20]			
Stein 2013	2	137	2	133	0.9%	0.97 [0.14, 6.79]			
Tulloch 2016	36	247	29	245	12.8%	1.23 [0.78, 1.94]			
Total (95% CI)		1176		1168	100.0%	1.02 [0.87, 1.20]			
Total events:		234	228						
Heterogeneity: Chi ² = 2.53, df = 4 (P = 0.64); I ² = 0%									
Test for overall effect: Z = 0.29 (P = 0.77)									
Test for subgroup differences: Not applicable									

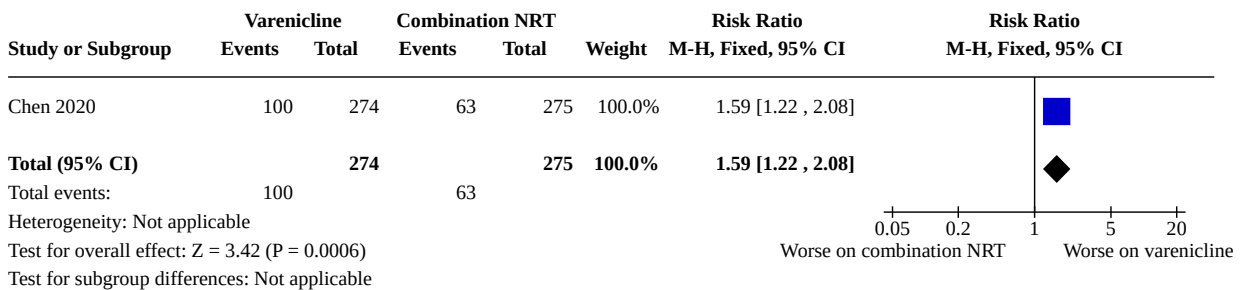
Analysis 11.2. Comparison 11: Varenicline vs combination NRT, Outcome 2: Nausea

Study or Subgroup	Varenicline		Combination NRT		Weight	Risk Ratio		Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Baker 2016	121	424	62	421	50.0%	1.94 [1.47, 2.55]			
Chen 2020	92	274	53	275	42.5%	1.74 [1.30, 2.34]			
Stein 2013	7	111	9	104	7.5%	0.73 [0.28, 1.89]			
Total (95% CI)		809		800	100.0%	1.76 [1.45, 2.15]			
Total events:		220	124						
Heterogeneity: Chi ² = 3.78, df = 2 (P = 0.15); I ² = 47%									
Test for overall effect: Z = 5.69 (P < 0.00001)									
Test for subgroup differences: Not applicable									

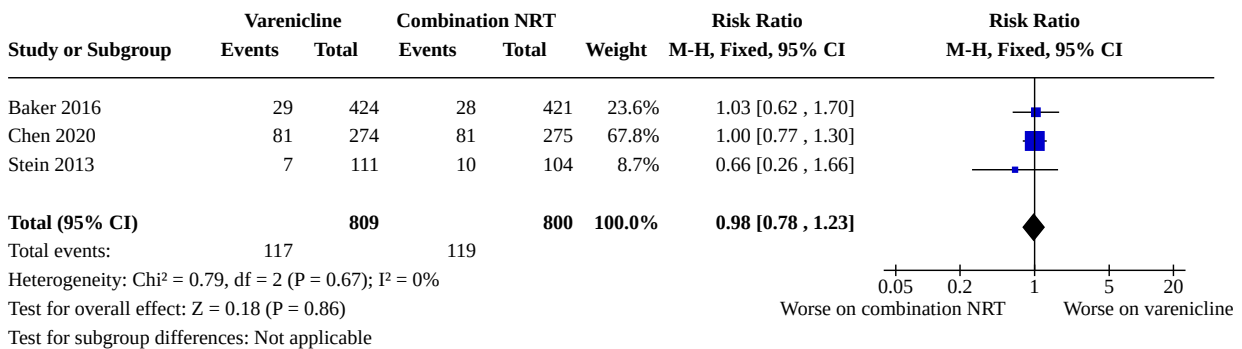
Analysis 11.3. Comparison 11: Varenicline vs combination NRT, Outcome 3: Insomnia



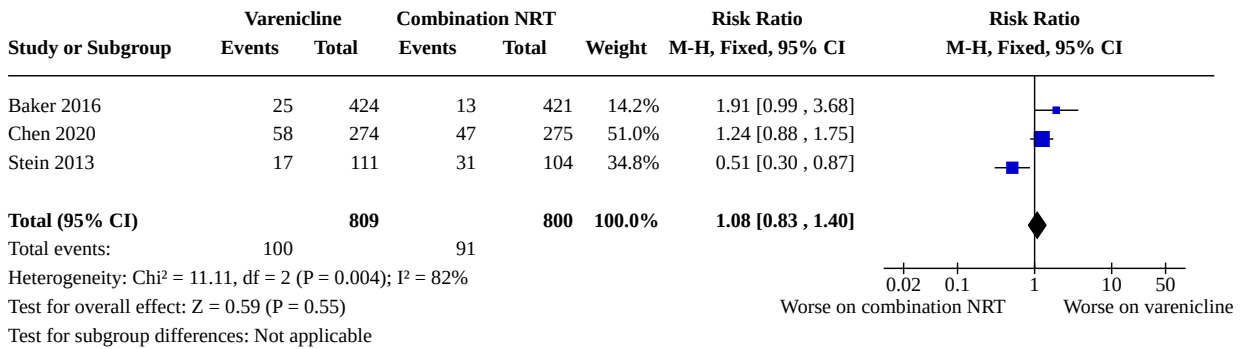
Analysis 11.4. Comparison 11: Varenicline vs combination NRT, Outcome 4: Abnormal dreams



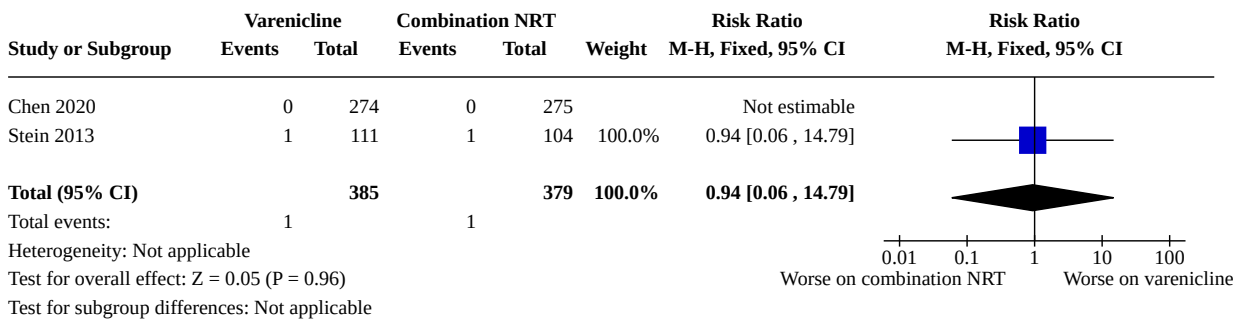
Analysis 11.5. Comparison 11: Varenicline vs combination NRT, Outcome 5: Headache



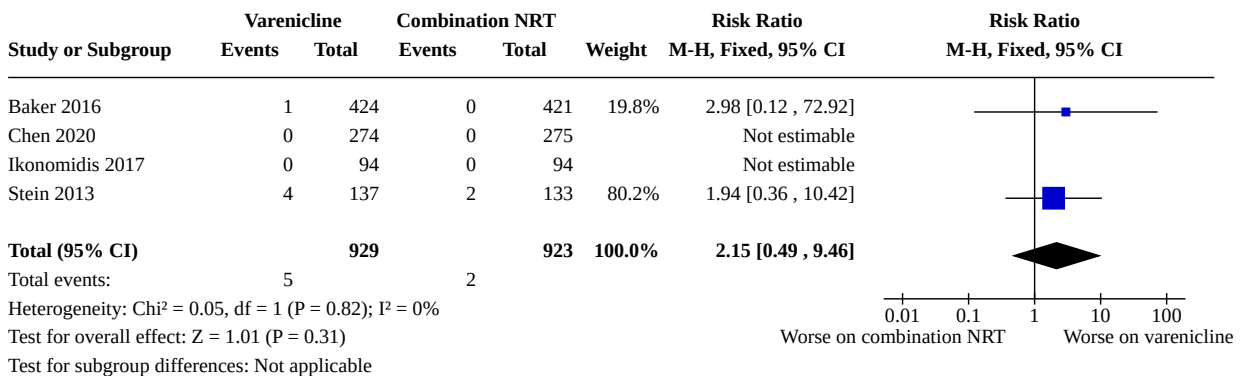
Analysis 11.6. Comparison 11: Varenicline vs combination NRT, Outcome 6: Depression



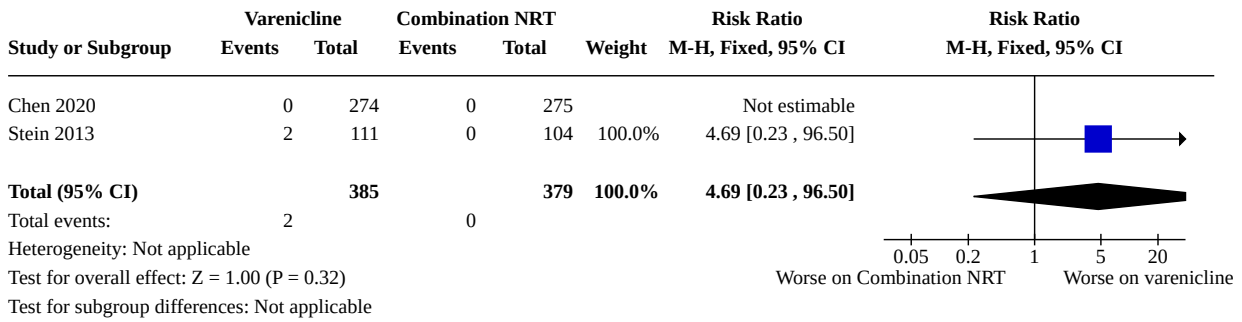
Analysis 11.7. Comparison 11: Varenicline vs combination NRT, Outcome 7: Suicidal ideation



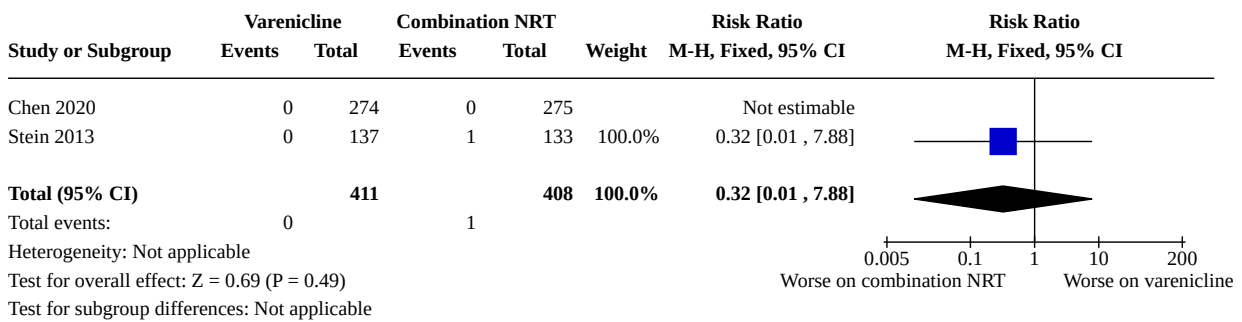
Analysis 11.8. Comparison 11: Varenicline vs combination NRT, Outcome 8: SAEs



Analysis 11.9. Comparison 11: Varenicline vs combination NRT, Outcome 9: Neuropsychiatric SAEs (not deaths)



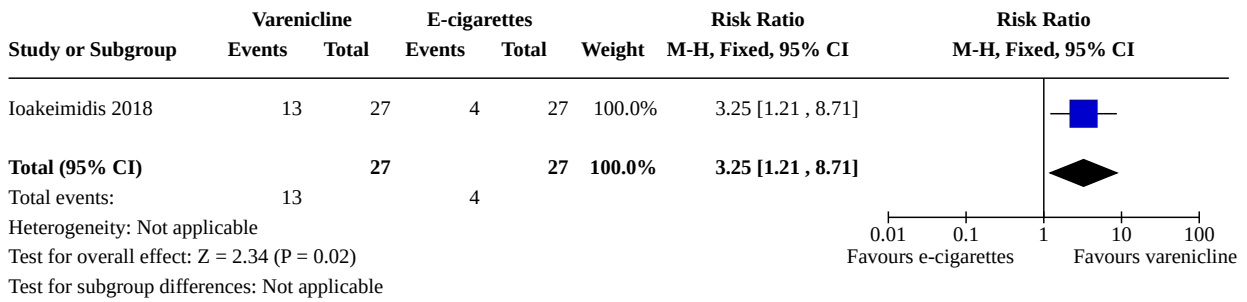
Analysis 11.10. Comparison 11: Varenicline vs combination NRT, Outcome 10: Cardiac SAEs, including deaths



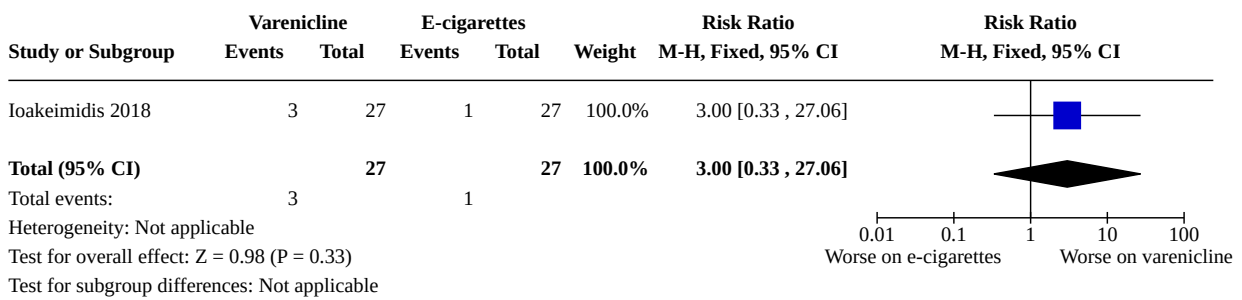
Comparison 12. Varenicline vs e-cigarettes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Abstinence at longest follow-up	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [1.21, 8.71]
12.2 Nausea	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.33, 27.06]
12.3 SAEs	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.4 Neuropsychiatric SAEs (not deaths)	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.5 Cardiac SAEs, including deaths	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

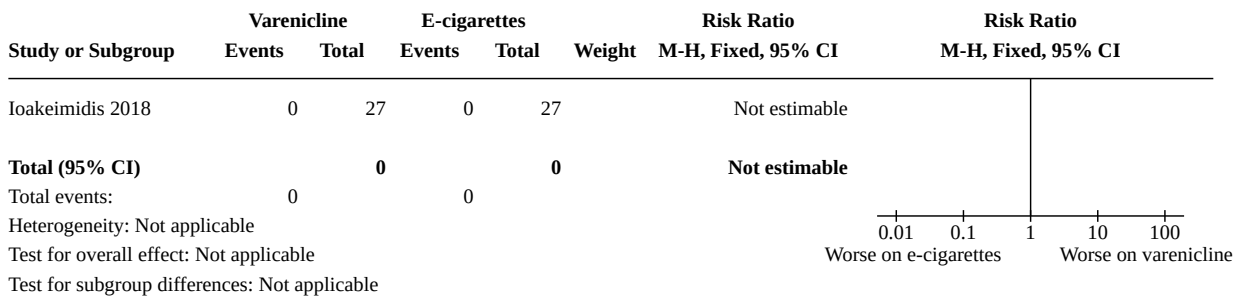
Analysis 12.1. Comparison 12: Varenicline vs e-cigarettes, Outcome 1: Abstinence at longest follow-up



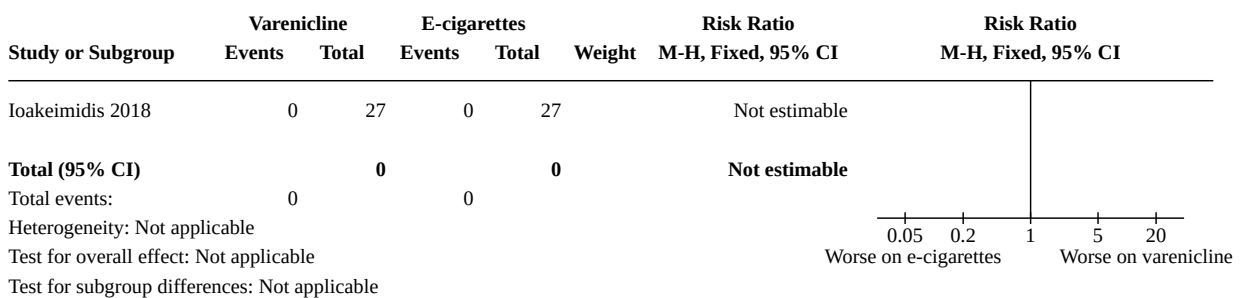
Analysis 12.2. Comparison 12: Varenicline vs e-cigarettes, Outcome 2: Nausea



Analysis 12.3. Comparison 12: Varenicline vs e-cigarettes, Outcome 3: SAEs



Analysis 12.4. Comparison 12: Varenicline vs e-cigarettes, Outcome 4: Neuropsychiatric SAEs (not deaths)



Analysis 12.5. Comparison 12: Varenicline vs e-cigarettes, Outcome 5: Cardiac SAEs, including deaths

Study or Subgroup	Varenicline		E-cigarettes		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ioakeimidis 2018	0	27	0	27		Not estimable	
Total (95% CI)		0		0		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

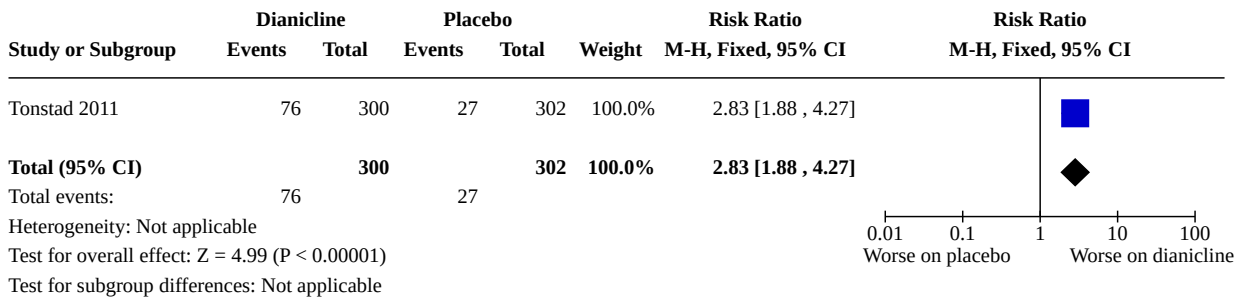
Comparison 13. Dianicline vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Abstinence at longest follow-up	1	602	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.82, 1.75]
13.2 Nausea	1	602	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [1.88, 4.27]
13.3 Headache	1	602	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.82, 1.85]
13.4 Depression	1	602	Risk Ratio (M-H, Fixed, 95% CI)	8.05 [1.01, 63.99]
13.5 Serious adverse events	1	602	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.20, 4.95]
13.6 Cardiac SAEs, including deaths	1	602	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.02]

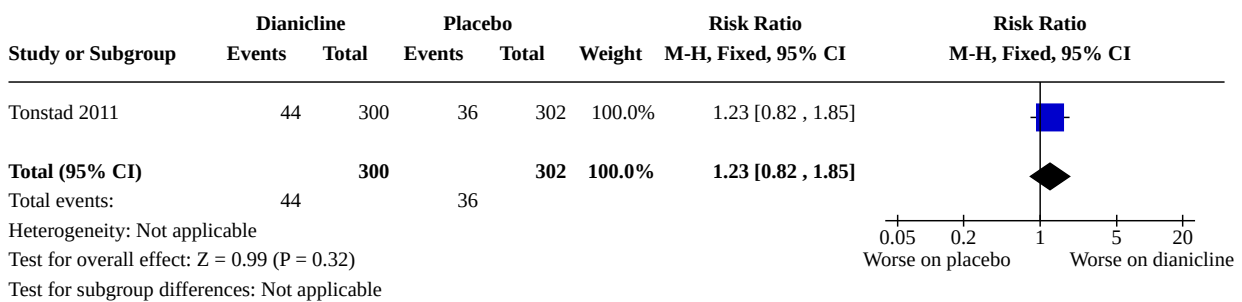
Analysis 13.1. Comparison 13: Dianicline vs placebo, Outcome 1: Abstinence at longest follow-up

Study or Subgroup	Dianicline		Placebo		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Tonstad 2011	50	300	42	302	100.0%	1.20 [0.82, 1.75]	
Total (95% CI)		300		302	100.0%	1.20 [0.82, 1.75]	
Total events:	50		42				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.94 (P = 0.35)							
Test for subgroup differences: Not applicable							

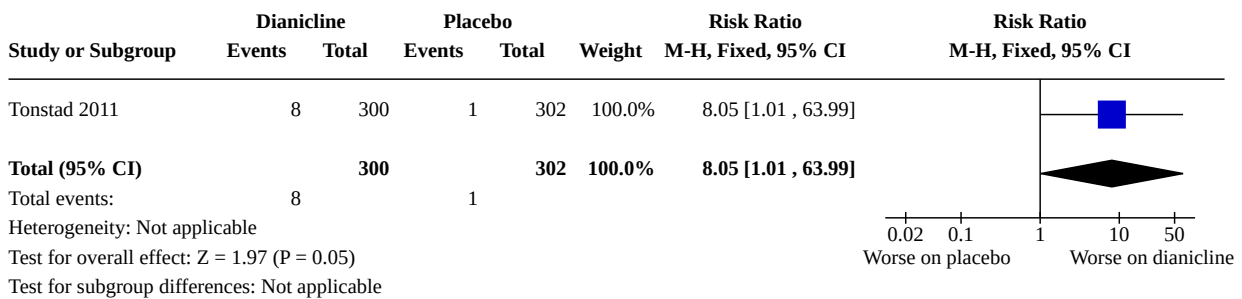
Analysis 13.2. Comparison 13: Dianicline vs placebo, Outcome 2: Nausea



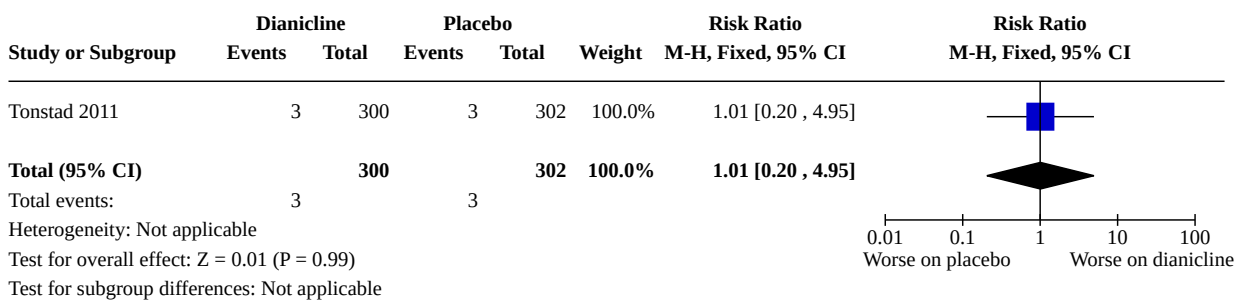
Analysis 13.3. Comparison 13: Dianicline vs placebo, Outcome 3: Headache



Analysis 13.4. Comparison 13: Dianicline vs placebo, Outcome 4: Depression



Analysis 13.5. Comparison 13: Dianicline vs placebo, Outcome 5: Serious adverse events



Analysis 13.6. Comparison 13: Dianicline vs placebo, Outcome 6: Cardiac SAEs, including deaths

Study or Subgroup	Dianicline		Placebo		Weight	Risk Ratio		Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Tonstad 2011	1	300	1	302	100.0%	1.01 [0.06 , 16.02]		
Total (95% CI)		300		302	100.0%	1.01 [0.06 , 16.02]		
Total events:	1		1					
Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (P = 1.00) Test for subgroup differences: Not applicable								

APPENDICES

Appendix 1. Search strategy

CTAG Specialised Register (CRS web)

1. (cytisine or Tabex or dianicline or varenicline or champix or chantix):TI,AB,MH,EMT,XKY,KY,KW
 2. MeSH DESCRIPTOR Nicotine WITH AG AI
 3. MeSH DESCRIPTOR Nicotinic Agonists
 4. MeSH DESCRIPTOR Nicotinic Antagonists
 5. nicotinic agonist*:TI,AB,MH,EMT,XKY,KY,KW
 6. nicotinic antagonist*:TI,AB,MH,EMT,XKY,KY,KW
 7. nicotin* NEAR2 partial:TI,AB,MH,EMT,XKY,KY,KW
- #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

Appendix 2. Glossary of tobacco-related terms

Term	Definition
Abstinence	A period of being quit, i.e. stopping the use of cigarettes or other tobacco products. May be defined in various ways; see also: point prevalence abstinence; prolonged abstinence; continuous/sustained abstinence
Biochemical verification	Also called 'biochemical validation' or 'biochemical confirmation' A procedure for checking a tobacco user's report that he or she has not smoked or used tobacco. It can be measured by testing levels of nicotine or cotinine or other chemicals in blood, urine, or saliva, or by measuring levels of carbon monoxide in exhaled breath or in blood.
Bupropion	A pharmaceutical drug originally developed as an antidepressant, but now also licensed for smoking cessation; trade names Zyban, Wellbutrin (when prescribed as an antidepressant)
Carbon monoxide (CO)	A colourless, odourless, highly poisonous gas found in tobacco smoke and in the lungs of people who have recently smoked, or (in smaller amounts) in people who have been exposed to tobacco smoke. May be used for biochemical verification of abstinence.
Cessation	Also called 'quitting' The goal of treatment to help people achieve abstinence from smoking or other tobacco use, also used to describe the process of changing behaviour.
Continuous abstinence	Also called 'sustained abstinence'

(Continued)

	A measure of cessation often used in clinical trials involving avoidance of all tobacco use since the quit day until the time the assessment is made. The definition occasionally allows for lapses. This is the most rigorous measure of abstinence.
'Cold turkey'	Quitting abruptly, and/or quitting without behavioural or pharmaceutical support.
Craving	A very intense urge or desire (to smoke) See: Shiffman 2004
Dopamine	A neurotransmitter in the brain that regulates mood, attention, pleasure, reward, motivation and movement
Efficacy	Also called 'treatment effect' or 'effect size' The difference in outcome between the experimental and control groups
Harm reduction	Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g. potentially reduced exposure products (PREPs), smokeless tobacco
Lapse/slip	Terms sometimes used for a return to tobacco use after a period of abstinence. A lapse or slip might be defined as a puff or two on a cigarette. This may proceed to relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may have their effect by helping people recover from a lapse.
nAChR	Neural nicotinic acetylcholine receptors Areas in the brain that are thought to respond to nicotine, forming the basis of nicotine addiction by stimulating the overflow of dopamine
Nicotine	An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking
Nicotine replacement therapy (NRT)	A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence while users are learning to be tobacco-free. The nicotine dose can be taken through the skin, using patches, by inhaling a spray, or by mouth using gum or lozenges.
Outcome	Often used to describe the result being measured in trials that is of relevance to the review. For example smoking cessation is the outcome used in reviews of ways to help smokers quit. The exact outcome in terms of the definition of abstinence and the length of time that has elapsed since the quit attempt was made may vary from trial to trial.
Pharmacotherapy	A treatment using pharmaceutical drugs, e.g. nicotine replacement therapy, bupropion
Point prevalence abstinence (PPA)	A measure of cessation based on behaviour at a particular point in time, or during a relatively brief specified period, e.g. 24 hours, 7 days. It may include a mixture of recent and long-term quitters. cf. prolonged abstinence, continuous abstinence
Prolonged abstinence	A measure of cessation that typically allows a 'grace period' following the quit date (usually of about two weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging. See: Hughes 2003
Relapse	A return to regular smoking after a period of abstinence
Secondhand smoke	Also called passive smoking or environmental tobacco smoke (ETS)

(Continued)

A mixture of smoke exhaled by smokers and smoke released from smouldering cigarettes, cigars, pipes, bidis, etc. The smoke mixture contains gases and particulates, including nicotine, carcinogens and toxins.

Self-efficacy	The belief that one will be able to change one's behaviour, e.g. to quit smoking
SPC [Summary of Product Characteristics]	Advice from the manufacturers of a drug, agreed with the relevant licensing authority, to enable health professionals to prescribe and use the treatment safely and effectively.
Tapering	A gradual decrease in dose at the end of treatment, as an alternative to abruptly stopping treatment
Titration	A technique of dosing at low levels at the beginning of treatment, and gradually increasing to full dose over a few days, to allow the body to get used to the drug. It is designed to limit side effects.
Withdrawal	A variety of behavioural, affective, cognitive and physiological symptoms, usually transient, which occur after use of an addictive drug is reduced or stopped. See: Shiffman 2004

WHAT'S NEW

Date	Event	Description
4 May 2023	New search has been performed	New searches conducted 29 April 2022 adding 45 new studies
4 May 2023	New citation required and conclusions have changed	New searches conducted 29 April 2022. Analyses and conclusions updated

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 1, 2007

Date	Event	Description
31 January 2016	New citation required and conclusions have changed	Additional comparisons. Analyses expanded and restructured. SAE information updated
31 January 2016	New search has been performed	39 trials of varenicline now included
16 May 2013	Amended	Minor change made to labelling on forest plot.
14 March 2012	New search has been performed	Seven new included studies (5 varenicline, 1 cytosine, 1 dianicline) and 14 new excluded studies added, plus safety data.
14 March 2012	New citation required and conclusions have changed	Safety profile modified, as new possible cardiovascular and psychiatric adverse events information incorporated. Efficacy findings unchanged but confirmed.
13 January 2011	Amended	Vinnikov trial of cytosine added to Studies awaiting Classification, for inclusion in next update.

Nicotine receptor partial agonists for smoking cessation (Review)

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Date	Event	Description
8 November 2010	New search has been performed	Six new RCTs added; sources of funding added for all trials. On-going trials section expanded.
8 November 2010	New citation required and conclusions have changed	Surveillance data and secondary analyses do not support fears about safety. Efficacy conclusions strengthened but unchanged.
17 July 2008	Amended	Date of last search amended (2007 corrected to 2008); Source of support added.
12 May 2008	New citation required and conclusions have changed	Three new included trials, switch in the MA metric from OR to RR, updated background section and new safety information.
15 March 2008	New search has been performed	New search conducted.
30 August 2007	Amended	Converted to new review format.
15 November 2006	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

JL-B led this review update, updating the text and analyses. JL-B, AT, AH, and NL screened for new studies and JL-B, AT, AH, LH, TRF, and KT performed data extraction and study evaluation. All authors contributed to text and findings, and approved the final version of the review.

DECLARATIONS OF INTEREST

JL-B is employed by the University of Oxford to work as a Managing Editor for the Cochrane Tobacco Addiction Review Group. He was not involved in the editorial process for this review. Core infrastructure funding for the Cochrane Tobacco Addiction Group is provided by the NIHR to the University of Oxford. JLB has no conflicts of interest.

TF: none known

KT published an opinion piece on varenicline (Davies 2017). KT is on the Specialist Register in the UK as a Consultant in Public Health Medicine, employed by the University of Bristol as an Associate Professor in Public Health Medicine, and currently holds Honorary status as a Consultant in Public Health at South Gloucestershire Council, and is Clinical Director for the NIHR CRN West of England. KT has no conflicts of interest.

AH: none known

AT: none known

LH: none known

NL is employed by the University of Oxford to work as a Managing Editor for the Cochrane Tobacco Addiction Review Group. She was not involved in the editorial process for this review. Core infrastructure funding for the Cochrane Tobacco Addiction Group is provided by the NIHR to the University of Oxford. NL has written pieces for *The Conversation* on the findings of Cochrane Reviews assessing the effects of treatments for smoking cessation. These are evidence-based and not based on personal opinion. NL receives funding from CRUK and the NIHR (a part of the NHS) who both have interests in people stopping smoking and run educational campaigns, and in the latter case provide treatment to encourage people to stop smoking. NL has no conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update we did some restructuring of the meta-analyses and summary of findings tables to better present the evidence available, including adding analyses of adverse events for comparisons of varenicline with other pharmacotherapies. We excluded previously included studies as these studies recruited already-abstinent participants ([Evins 2014](#); [Tonstad 2006](#); [Tønnesen 2013](#); [NCT00828113](#)), and because follow-up was under six months ([Hajek 2015](#)). We also excluded [Brandon 2011](#); [Ebbert 2011b](#); [Faessel 2009](#); [Fagerström 2010](#); [Garza 2011](#); [Hughes 2011](#); [McClure 2013](#); [Meszaros 2013](#); [Mitchell 2012](#), which had previously been included for data on harms only but do not meet all inclusion criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

*Alkaloids [adverse effects]; Bupropion [adverse effects]; *Electronic Nicotine Delivery Systems; Nicotine [adverse effects]; Nicotinic Agonists [adverse effects]; *Smoking Cessation [methods]; Tobacco Use Cessation Devices; Varenicline [adverse effects]

MeSH check words

Humans