

What are the effects of adding bupropion or fluoxetine to other treatments compared with other treatments alone for people trying to quit smoking?

Notes to Associate Editor from Cochrane Review CD000031 [not for publication]	
Review title	Antidepressants for smoking cessation
Outcomes (Methods > Criteria for considering studies for this review > Types of outcome measures)	<ul style="list-style-type: none"> • Efficacy, measured as smoking cessation <p>For this outcome we only included studies that set out to report smoking cessation rates at least six months after baseline, in line with the standard methods of Cochrane Tobacco Addiction. Where cessation was assessed at multiple intervals, we report only the longest follow-up data. Additionally, where multiple definitions of abstinence are assessed, we report the strictest of these definitions (e.g. continuous/prolonged abstinence over point prevalence abstinence). We also report biochemical validation of abstinence over self-reported abstinence (but it was not necessary for abstinence to have been biochemically validated for a study to be included).</p> <ul style="list-style-type: none"> • Safety, measured as: <ul style="list-style-type: none"> ○ number of people experiencing adverse events (AEs) of any severity (e.g. abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, and progression or worsening of underlying disease) ○ number of people experiencing psychiatric AEs (e.g. adverse events relating to mental health) ○ number of people experiencing serious adverse events (SAEs), i.e. events that result in death, are life-threatening (immediate risk of death), require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, and/or result in congenital anomaly or birth defect (e.g. seizures, overdoses, suicide attempts, death by suicide, all-cause mortality). <p>We also recorded the following SAEs specifically, as these have previously been associated with the use of antidepressants for smoking cessation.</p> <ul style="list-style-type: none"> ○ Number of people experiencing seizures ○ Number of people experiencing overdoses ○ Number of people experiencing suicide attempts ○ Number of people experiencing death by suicide ○ Number of people experiencing all-cause mortality

	<ul style="list-style-type: none"> Tolerability, measured as the number of participants who dropped out of the trial due to adverse events <p>For all safety and tolerability outcomes, we considered studies with follow-up of any length.</p>
	<p>Outcomes chosen by CCA Editor</p> <p>Associate Editor/Clinical Advisor: PLEASE SPECIFY WHETHER ANY OF THESE OUTCOMES SHOULD BE DELETED AND IF THERE ARE ANY OTHER CLINICALLY IMPORTANT OUTCOMES THAT NEED TO BE ADDED</p> <p>Smoking cessation</p> <p>Adverse events</p> <p>Serious adverse events</p> <p>Mortality</p> <p>Withdrawals due to adverse events</p>

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Clinical question	What are the effects of adding bupropion or fluoxetine to other treatments compared with other treatments alone for people trying to quit smoking?
Clinical answer	<p>Low-certainty evidence does not show an additional benefit from adding bupropion (300 mg/day for 7-12 weeks) to nicotine replacement therapy (NRT; 2-4mg/day for 7-12 weeks) compared with providing NRT alone for increasing smoking abstinence rates at six months or later. However very limited evidence suggests that adding bupropion may lead to more adverse events (on average, 588 vs 488 per 1000 people).</p> <p>Limited evidence does not show a difference from adding bupropion to NRT in the number of serious adverse events, deaths, or withdrawals due to adverse events.</p> <p>Moderate-certainty evidence does not show an additional benefit from adding bupropion (50-300 mg/day for 11-12 weeks) to varenicline (0.5-2 mg/day for 11-12 weeks) compared with providing varenicline alone for increasing smoking abstinence rates at six months or later. Limited evidence suggests that adding bupropion may lead to more adverse events (on average, 682 vs 626 per 1000 people).</p> <p>Limited evidence does not show a difference from adding bupropion to varenicline in the number of serious adverse events, deaths, or withdrawals due to adverse events.</p>

	<p>Very limited evidence does not show an additional benefit from adding fluoxetine (10-40 mg/day for 2-6 months) to NRT (7-21 mg/day for 2-6 months) compared with providing NRT alone for increasing smoking abstinence rates at six months or later. No evidence assessed adverse events.</p> <p>For a comparison of bupropion with placebo, see CCA 3204, or for comparison with varenicline or nicotine replacement therapies, see CCA 3205.</p>
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PICOS	
Comparison	Bupropion plus nicotine replacement therapy (NRT) versus NRT alone
Population	Adolescent and adult smokers (average age 17-55 years, 5-58% female in 4 RCTs, 100% male in 1 RCT) who smoked an average of 15-33 cigarettes per day, where reported. Participants had schizophrenia in 2 RCTs, alcoholism in 2 RCTs and cancer in 1 RCT. All participants also received one-to-one or group counseling in person or over the phone delivered as multiple 10-90-minute sessions. Recruited from clinics, schools and mental health centers in the USA (11 RCTs) and the UK (1 RCT). Pregnant women were excluded
Intervention	Bupropion 300 mg/day plus nicotine replacement therapy: nicotine patch 21-42 mg/day and/or nicotine gum 2 mg (9 RCTs); lozenge 2-4 mg (2 RCTs) or choice of NRT (1 RCT) for 7-12 weeks.
Comparator	Nicotine replacement therapy as above plus placebo
Safety alerts	
Outcome 1.1	Smoking cessation – follow-up: ≥ 6 months
Narrative result	12 RCTs with 3487 participants found no statistically significant difference between groups. Subgroup analyses on type of NRT (patch, lozenge or choice) were consistent with the main analysis.
Quality of the evidence	The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was low certainty. See Summary of findings from Cochrane Review
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 1.19, 95% CI 0.94 to 1.51). Forest plot details: CD000031 Analysis 2.1
Quantitative result: absolute effect	238 per 1000 people (95% CI 188 to 300) with bupropion plus NRT compared with 199 per 1000 people with NRT alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Outcome 1.2	Adverse events
Narrative result	Reviewers assessed adverse events of any severity, anxiety and insomnia. Analyses for any severity adverse events and insomnia found that adverse events were more common in those receiving bupropion. Little or no difference between groups was reported for anxiety but the analysis was underpowered. Click below for details.
Reference	CD000031
Search date	May 2019

Subgroup analysis 1.2.1	Adverse events – [subgroup: Adverse events of any severity]
Narrative result	Two RCTs with 313 participants found that more people had adverse events of any severity with bupropion plus NRT than with NRT alone. Adverse events included abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, and progression or worsening of underlying disease
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, both failed to report adequate allocation concealment and/or random sequence generation and did not report adequate blinding of participants/carers/outcome assessors; one had high or unclear numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was a statistically significant difference between groups, in favor of NRT alone (RR 1.21, 95% CI 1.02 to 1.43). Forest plot details: CD000031 Analysis 2.2
Quantitative result: absolute effect	588 per 1000 people (95% CI 496 to 698) with bupropion plus NRT compared with 488 per 1000 people with NRT alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.2.2	Adverse events – [subgroup: Anxiety]
Narrative result	Three RCTs with 1218 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the three studies, two failed to report adequate allocation concealment and/or random sequence generation, none reported adequate blinding of participants/carers/outcome assessors and one had high or unclear numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 1.58, 95% CI 0.97 to 2.56). Forest plot details: CD000031 Analysis 2.9
Quantitative result: absolute effect	4 per 1000 people (95% CI 2 to 6) with bupropion plus NRT compared with 2 per 1000 people with NRT alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.2.3	Adverse events – [subgroup: Insomnia]
Narrative result	Two RCTs with 556 participants found that more people had insomnia with bupropion plus NRT than with NRT alone.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, both failed to report adequate allocation concealment and/or random sequence generation and did not report adequate blinding of participants/carers/outcome assessors; one had high or unclear numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was a statistically significant difference between groups, in favor of NRT alone (RR 1.55, 95% CI 1.24 to 1.93). Forest plot details: CD000031 Analysis 2.8
Quantitative result:	465 per 1000 people (95% CI 372 to 580) with bupropion plus NRT compared with 300 per 1000 people with NRT alone (calculated using median event rate).

absolute effect	
Reference	CD000031
Search date	May 2019
Outcome 1.3	Serious adverse events
Narrative result	Serious adverse events were defined as events that result in death, are life-threatening (immediate risk of death), require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, and/or result in congenital anomaly or birth defect. Reviewers assessed several measures of serious adverse events including serious adverse events of any severity, seizures and suicide attempts. All analyses were underpowered and found little or no difference between bupropion plus NRT and NRT alone; no suicide attempts were reported in either treatment group. Click below for details.
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.3.1	Serious adverse events – [subgroup: Serious adverse events of any severity]
Narrative result	Three RCTs with 607 participants found no statistically significant difference between groups.
Quality of the evidence	The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was very low certainty. See Summary of findings from Cochrane Review
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 1.52, 95% CI 0.26 to 8.89). Forest plot details: CD000031 Analysis 2.3
Quantitative result: absolute effect	6 per 1000 people (95% CI 1 to 37) with bupropion plus NRT compared with 4 per 1000 people with NRT alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.3.2	Serious adverse events – [subgroup: Seizures]
Narrative result	One RCT with 527 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. The study failed to report adequate allocation concealment and/or random sequence generation and did not report adequate blinding of participants/carers/outcome assessors; however, did have low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (OR 2.93, 95% CI 0.12 to 72.31). Forest plot details: CD000031 Analysis 2.4
Quantitative result: absolute effect	We could not calculate absolute results for this outcome because of low event rates.
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.3.3	Serious adverse events – [subgroup: Suicide attempts]

Narrative result	One RCT with 487 participants reported no suicide attempts in either group.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. The study failed to report adequate allocation concealment and/or random sequence generation and did not report adequate blinding of participants/carers/outcome assessors; however, did have low numbers of withdrawals.
Reference	CD000031
Search date	May 2019
Outcome 1.4	Mortality
Narrative result	Mortality was measured as all-cause mortality and deaths by suicide; little or no difference was reported between bupropion plus NRT and NRT alone for all-cause mortality, but the analysis was underpowered; no deaths by suicide were reported in either group. Click below for details.
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.4.1	Mortality – [subgroup: All-cause mortality]
Narrative result	Two RCTs with 731 participants found no statistically significant difference between groups. No deaths were reported in one of the RCTs (487 participants).
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, neither reported adequate allocation concealment and/or random sequence generation or adequate blinding of participants/carers/outcome assessors; however, both had low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 0.68, 95% CI 0.12 to 3.98). Forest plot details: CD000031 Analysis 2.7
Quantitative result: absolute effect	We could not calculate absolute results for this outcome because of low event rates.
Reference	CD000031
Search date	May 2019
Subgroup analysis 1.4.2	Mortality – [subgroup: Death by suicide]
Narrative result	One RCT with 487 participants reported no suicide attempts in either group.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. The study failed to report adequate allocation concealment and/or random sequence generation and did not report adequate blinding of participants/carers/outcome assessors; however, did have low numbers of withdrawals.
Reference	CD000031
Search date	May 2019
Outcome 1.5	Withdrawals due to adverse events
Narrative result	Two RCTs with 538 participants found no statistically significant difference between groups.
Quality of the evidence	The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was low certainty. See Summary of findings from Cochrane Review
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 1.67, 95% CI 0.95 to 2.92). Forest plot details: CD000031 Analysis 2.10

Quantitative result: absolute effect	110 per 1000 people (95% CI 63 to 192) with bupropion plus NRT compared with 66 per 1000 people with NRT alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Outcome 1.6	Adverse events - psychiatric adverse events other than suicide, Serious adverse events - overdoses
Narrative result	Reviewers found no studies assessing these outcomes.
Reference	CD000031
Search date	May 2019
Comparison	Bupropion plus varenicline versus varenicline alone
Population	Adult smokers (average age 39-49 years, 42-55% female in 4 RCTs, 100% male in 1 RCT) who smoked an average of 20-21 cigarettes per day, where reported. In 4/5 RCTs, all participants also received 1.5-3 hours of counseling delivered in-person and via the phone over multiple sessions. Recruited from clinics, universities and research centers in the USA
Intervention	Bupropion 50-300 mg/day plus varenicline 0.5-2 mg/day for 11-12 weeks.
Comparator	Varenicline as above plus placebo
Safety alerts	
Outcome 2.1	Smoking cessation – follow-up: ≥ 6 months
Narrative result	Three RCTs with 1057 participants found no statistically significant difference between groups.
Quality of the evidence	The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was [moderate certainty. See Summary of findings from Cochrane Review
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 1.21, 95% CI 0.95 to 1.55). Forest plot details: CD000031 Analysis 3.1
Quantitative result: absolute effect	241 per 1000 people (95% CI 189 to 307) with bupropion plus varenicline compared with 199 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Outcome 2.2	Adverse events
Narrative result	Reviewers assessed adverse events of any severity, psychiatric adverse events, anxiety and insomnia. All analyses found that adverse events were more common in those receiving bupropion. Click below for details.
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.2.1	Adverse events – [subgroup: Adverse events of any severity]
Narrative result	Four RCTs with 1043 participants found that more people had adverse events of any severity with bupropion plus varenicline than with varenicline alone.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the four studies, three failed to report adequate allocation concealment and/or random sequence generation, two did not report adequate blinding of participants/carers/outcome assessors and one had high or unclear numbers of withdrawals.

Quantitative result: relative effect or mean difference	There was a statistically significant difference between groups, in favor of varenicline alone (RR 1.09, 95% CI 1.02 to 1.17). Forest plot details: CD000031 Analysis 3.2
Quantitative result: absolute effect	682 per 1000 people (95% CI 636 to 731) with bupropion plus varenicline compared with 626 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.2.2	Adverse events – [subgroup: Psychiatric adverse events]
Narrative result	Two RCTs with 835 participants found that more people had psychiatric adverse events with bupropion plus varenicline than with varenicline alone. Psychiatric adverse events included any adverse events relating to mental health other than suicide, which was recorded as a serious adverse event.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, one failed to report adequate allocation concealment and/or random sequence generation; however, both reported adequate blinding of participants/carers/outcome assessors and had low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was a statistically significant difference between groups, in favor of varenicline alone (RR 1.15, 95% CI 1.03 to 1.30). Forest plot details: CD000031 Analysis 3.4
Quantitative result: absolute effect	9 per 1000 people (95% CI 8 to 10) with bupropion plus varenicline compared with 8 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.2.3	Adverse events – [subgroup: Anxiety]
Narrative result	Two RCTs with 499 participants found that more people had anxiety with bupropion plus varenicline than with varenicline alone.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, both failed to report adequate allocation concealment and/or random sequence generation and one did not report adequate blinding of participants/carers/outcome assessors; however, both had low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was a statistically significant difference between groups, in favor of varenicline alone (RR 1.55, 95% CI 1.01 to 2.38). Forest plot details: CD000031 Analysis 3.10
Quantitative result: absolute effect	243 per 1000 people (95% CI 158 to 372) with bupropion plus varenicline compared with 157 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.2.4	Adverse events – [subgroup: Insomnia]
Narrative result	Two RCTs with 499 participants found that more people had insomnia with bupropion plus varenicline than with varenicline alone.

Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, neither reported adequate allocation concealment and/or random sequence generation and one did not report adequate blinding of participants/carers/outcome assessors; however, both had low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was a statistically significant difference between groups, in favor of varenicline alone (RR 1.45, 95% CI 1.14 to 1.84). Forest plot details: CD000031 Analysis 3.11
Quantitative result: absolute effect	523 per 1000 people (95% CI 411 to 667) with bupropion plus varenicline compared with 361 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Outcome 2.3	Serious adverse events
Narrative result	Serious adverse events were defined as events that result in death, are life-threatening (immediate risk of death), require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, and/or result in congenital anomaly or birth defect. Reviewers assessed several measures of serious adverse events including serious adverse events of any severity, seizures, overdoses and suicide attempts. All analyses found little or no difference between bupropion and placebo but were underpowered. No instances of seizures were reported. Click below for details.
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.3.1	Serious adverse events – [subgroup: Serious adverse events of any severity]
Narrative result	Five RCTs with 1268 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the five studies, four failed to report adequate allocation concealment and/or random sequence generation, three did not report adequate blinding of participants/carers/outcome assessors and one had high or unclear numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 1.23, 95% CI 0.63 to 2.42). Forest plot details: CD000031 Analysis 3.3
Quantitative result: absolute effect	34 per 1000 people (95% CI 17 to 66) with bupropion plus varenicline compared with 27 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.3.2	Serious adverse events – [subgroup: Seizures]
Narrative result	One RCT with 221 participants reported no seizures in either group.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. The study failed to report adequate allocation concealment and/or random sequence generation and did not report adequate blinding of participants/carers/outcome assessors; however, it did have low numbers of withdrawals.
Reference	CD000031
Search date	May 2019

Subgroup analysis 2.3.3	Serious adverse events – [subgroup: Overdoses]
Narrative result	Two RCTs with 550 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, both failed to report adequate allocation concealment and/or random sequence generation and one did not report adequate blinding of participants/carers/outcome assessors; however, both had low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 0.34, 95% CI 0.01 to 8.27). Forest plot details: CD000031 Analysis 3.6
Quantitative result: absolute effect	2 per 1000 people (95% CI 0 to 50) with bupropion plus varenicline compared with 6 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.3.4	Serious adverse events – [subgroup: Suicide attempts]
Narrative result	Three RCTs with 1056 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the three studies, two failed to report adequate allocation concealment and/or random sequence generation and one did not report adequate blinding of participants/carers/outcome assessors; however, all had low numbers of withdrawals.
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 0.34, 95% CI 0.04 to 3.27). Forest plot details: CD000031 Analysis 3.7
Quantitative result: absolute effect	1 per 1000 people (95% CI 0 to 13) with bupropion plus varenicline compared with 4 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Outcome 2.4	Mortality
Narrative result	Mortality was measured as all-cause mortality and deaths by suicide. For all-cause mortality, little or no difference was found between bupropion plus varenicline and varenicline alone, but the analysis was underpowered; no instances of death by suicide were reported. Click below for details.
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.4.1	Mortality – [subgroup: All-cause mortality]
Narrative result	Two RCTs with 727 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, one failed to report adequate allocation concealment and/or random sequence generation, one did not report adequate blinding of participants/carers/outcome assessors; however, both had low numbers of withdrawals.
Quantitative result: relative	There was no statistically significant difference between groups (RR 0.34, 95% CI 0.01 to 8.40). Forest plot details: CD000031 Analysis 3.9

effect or mean difference	
Quantitative result: absolute effect	1 per 1000 people (95% CI 0 to 33) with bupropion plus varenicline compared with 4 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Subgroup analysis 2.4.2	Mortality – [subgroup: Death by suicide]
Narrative result	Two RCTs with 727 participants found no instances of death by suicide in either group.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the two studies, one failed to report adequate allocation concealment and/or random sequence generation, one did not report adequate blinding of participants/carers/outcome assessors; however, both had low numbers of withdrawals.
Reference	CD000031
Search date	May 2019
Outcome 2.5	Withdrawals due to adverse events
Narrative result	Four RCTs with 1230 participants found no statistically significant difference between groups.
Quality of the evidence	The reviewers performed a GRADE assessment of the quality of evidence for this outcome at this time point and stated that the evidence was low certainty. See Summary of findings from Cochrane Review
Quantitative result: relative effect or mean difference	There was no statistically significant difference between groups (RR 0.80, 95% CI 0.45 to 1.45). Forest plot details: CD000031 Analysis 3.12
Quantitative result: absolute effect	22 per 1000 people (95% CI 12 to 39) with bupropion plus varenicline compared with 27 per 1000 people with varenicline alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Comparison	Fluoxetine plus nicotine replacement therapy (NRT) versus NRT alone
Population	Adult smokers (average age 40-46 years, 38-62% female) who smoked an average of 21-28 cigarettes per day, where reported. Recruited from cessation clinics in the USA (2 RCTs) and Iceland (1 RCT)
Intervention	Fluoxetine 10-40 mg/day plus nicotine inhaler or patch (7-21 mg/day) for 2-6 months. All participants also received 2-5 hours of one-to-one or group behavior therapy over multiple sessions
Comparator	Nicotine inhaler or patch as above plus placebo
Safety alerts	
Outcome 3.1	Smoking cessation
Narrative result	Three RCTs with 466 participants found no statistically significant difference between groups.
Risk of bias of studies	The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the three studies, two failed to report adequate allocation concealment and/or random sequence generation, two did not report adequate blinding of participants/carers/outcome assessors and two had high or unclear numbers of withdrawals.
Quantitative result: relative	There was no statistically significant difference between groups (RR 0.70, 95% CI 0.48 to 1.03). Forest plot details: CD000031 Analysis 17.1

effect or mean difference	
Quantitative result: absolute effect	161 per 1000 people (95% CI 110 to 237) with fluoxetine plus NRT compared with 231 per 1000 people with NRT alone (calculated using median event rate).
Reference	CD000031
Search date	May 2019
Outcome 3.2	Smoking cessation, Adverse events, Serious adverse events, Mortality, Withdrawals due to adverse events
Narrative result	Reviewers found no studies assessing these outcomes.
Reference	CD000031
Search date	May 2019