

Question:

How does bupropion compare with placebo for promoting smoking cessation in adolescents and adults?

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23 September 2020

<https://doi.org/10.1002/cca.3204>

Answer

High-certainty evidence shows bupropion is more effective than placebo for enhancing smoking cessation success; however, treatment with the antidepressant may also increase rates of adverse events.

High-certainty evidence supports the use of the antidepressant bupropion for increasing smoking abstinence rates at six months or later, compared with placebo or no pharmacotherapy (154 versus 94 per 1000 people; all results on average).

Adverse events such as abnormal test findings, clinically significant symptoms and signs, and worsening of underlying disease were more common in those receiving bupropion than placebo (743 versus 650 events per 1000 people), as were psychiatric adverse events (325 versus 259 events per 1000 people), and more participants receiving bupropion withdrew from trials due to adverse events (75 versus 55 per 1000 people). However, little or no difference was detected in rates of serious adverse events (19 versus 16 events per 1000 people; moderate-certainty evidence) and deaths (1 versus 1 per 1000 people).

For a comparison of bupropion with varenicline or nicotine replacement therapies, see [CCA 3205](#); for effects of adding bupropion or fluoxetine to other treatments, see [CCA 3206](#).

Comparisons

1. Bupropion versus placebo/no pharmacotherapy

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> **OUTCOME 1.1 Smoking cessation – follow-up: ≥ 6 months**

Narrative result

46 RCTs with 17866 participants found that more people ceased smoking with bupropion than with placebo/no pharmacotherapy.^[1]

Subgroup analyses were conducted on level of behavioral support (multisession group support, multisession individual counseling, low-intensity support, unspecified) and mental health disorders (psychiatric and non-psychiatric conditions). All were consistent with the main analysis apart from the analysis of low-intensity support which was underpowered to draw conclusions.

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 high certainty. [See Summary of findings from Cochrane Review](#)

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of bupropion (RR 1.64, 95% CI 1.52 to 1.77).

Review: Antidepressants for smoking cessation
 Comparison: 1 Bupropion versus placebo/no pharmacotherapy control
 Outcome: 1 Smoking cessation

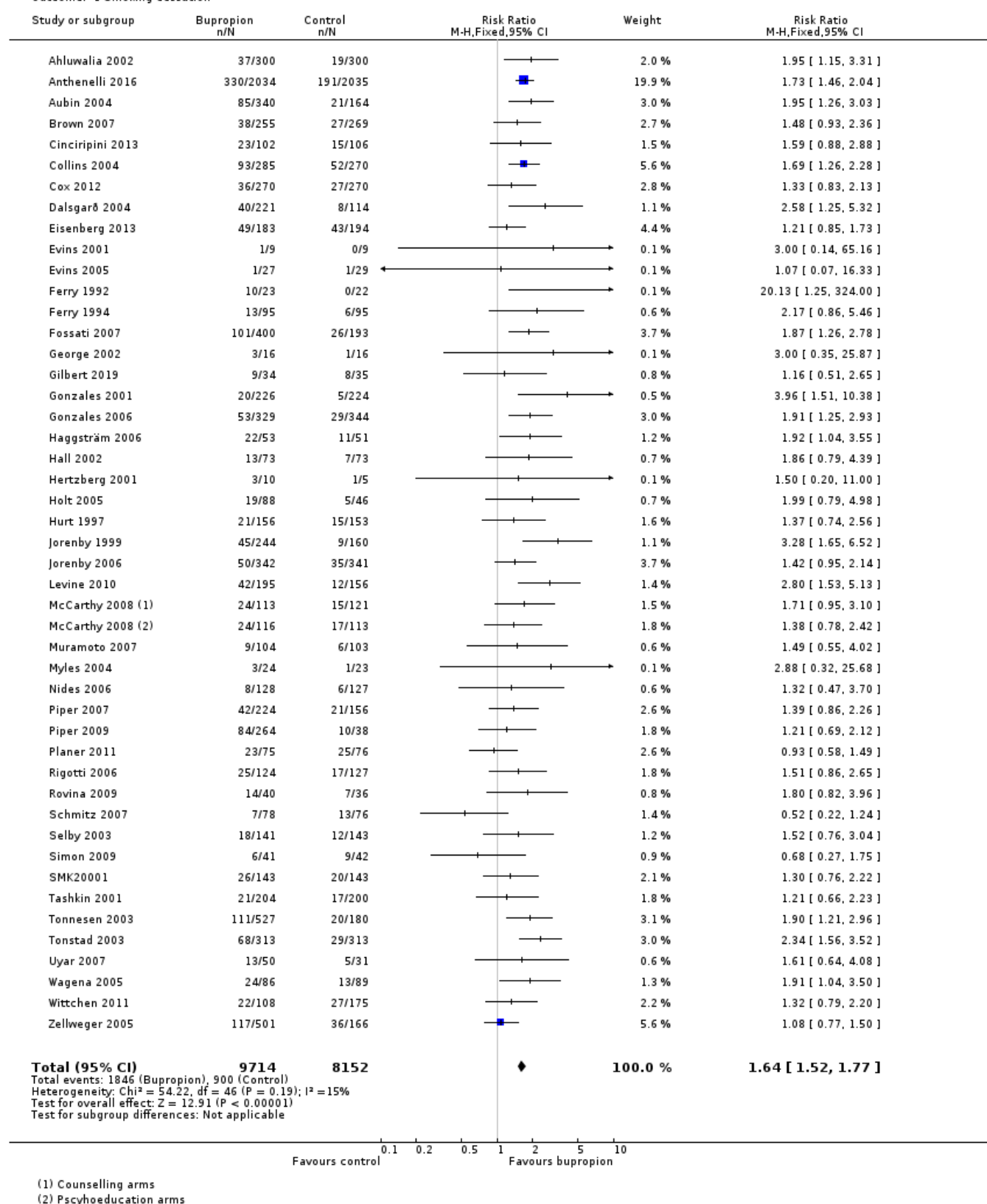


Figure 1

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

154 per 1000 people (95% CI 143 to 166) with bupropion compared with 94 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> OUTCOME 1.2 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.[\[2\]](#)

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.2.1 Adverse events – [subgroup: Adverse events of any severity]

Narrative result

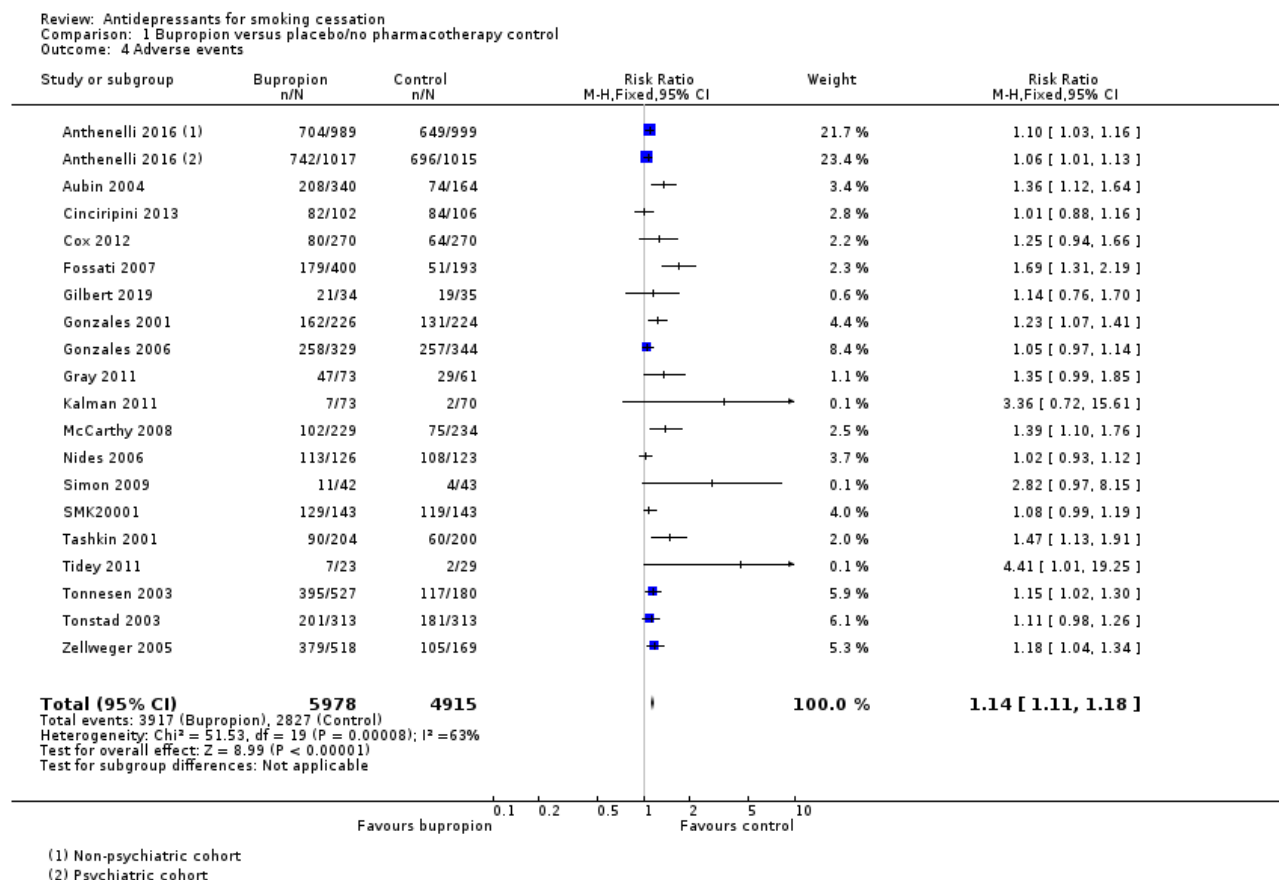
19 RCTs with 10893 participants found that more people had adverse events of any severity with bupropion than with placebo/no pharmacotherapy. Adverse events included abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, and progression or worsening of underlying disease[\[3\]](#)

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the nineteen studies, twelve failed to report adequate allocation concealment and/or random sequence generation, twelve did not report adequate blinding of participants/carers/outcome assessors and three had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo/no pharmacotherapy (RR 1.14, 95% CI 1.11 to 1.18).

**Figure 2**[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

743 per 1000 people (95% CI 721 to 764) with bupropion compared with 650 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.2.2 Adverse events – [subgroup: Psychiatric]

Narrative result

Six RCTs with 4439 participants found that more people had psychiatric adverse events with bupropion than with placebo/no pharmacotherapy. Psychiatric adverse events included any adverse events relating to mental health other than suicide, which was reported as a serious adverse event.^[4]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the six studies, five 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.

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo/no pharmacotherapy (RR 1.25, 95% CI 1.15 to 1.37).

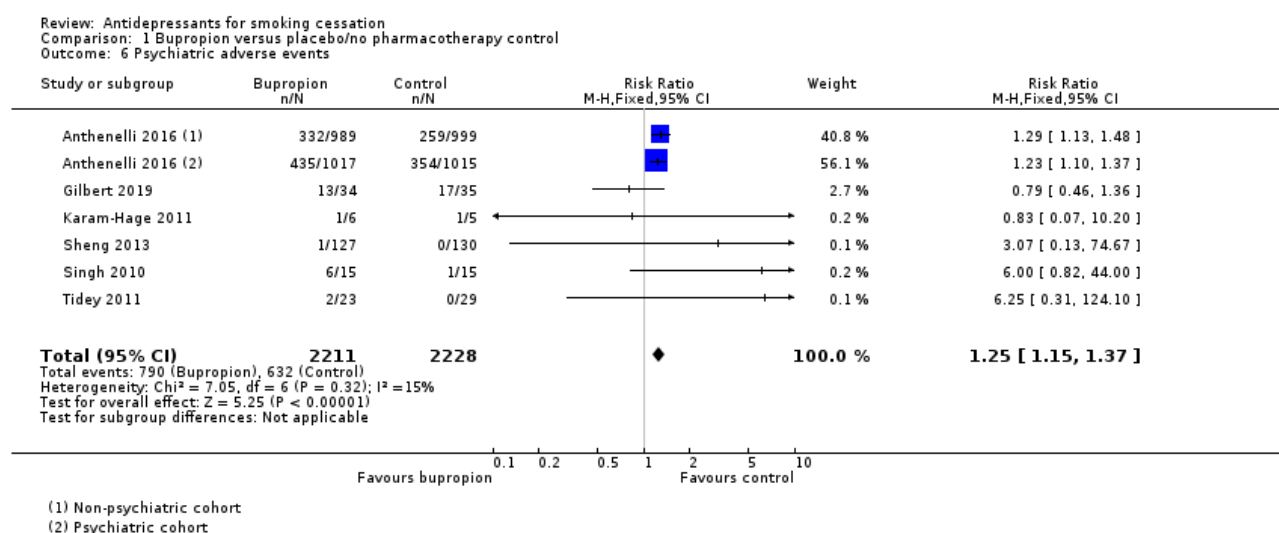


Figure 3

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

325 per 1000 people (95% CI 299 to 354) with bupropion compared with 259 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.2.3 Adverse events – [subgroup: Anxiety]

Narrative result

11 RCTs with 7406 participants found that more people experienced anxiety with bupropion than with placebo/no pharmacotherapy.[5]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the eleven studies, seven failed to report adequate allocation concealment and/or random sequence generation, seven did not report adequate blinding of participants/carers/outcome assessors and four had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo/no pharmacotherapy (RR 1.42, 95% CI 1.21 to 1.67).

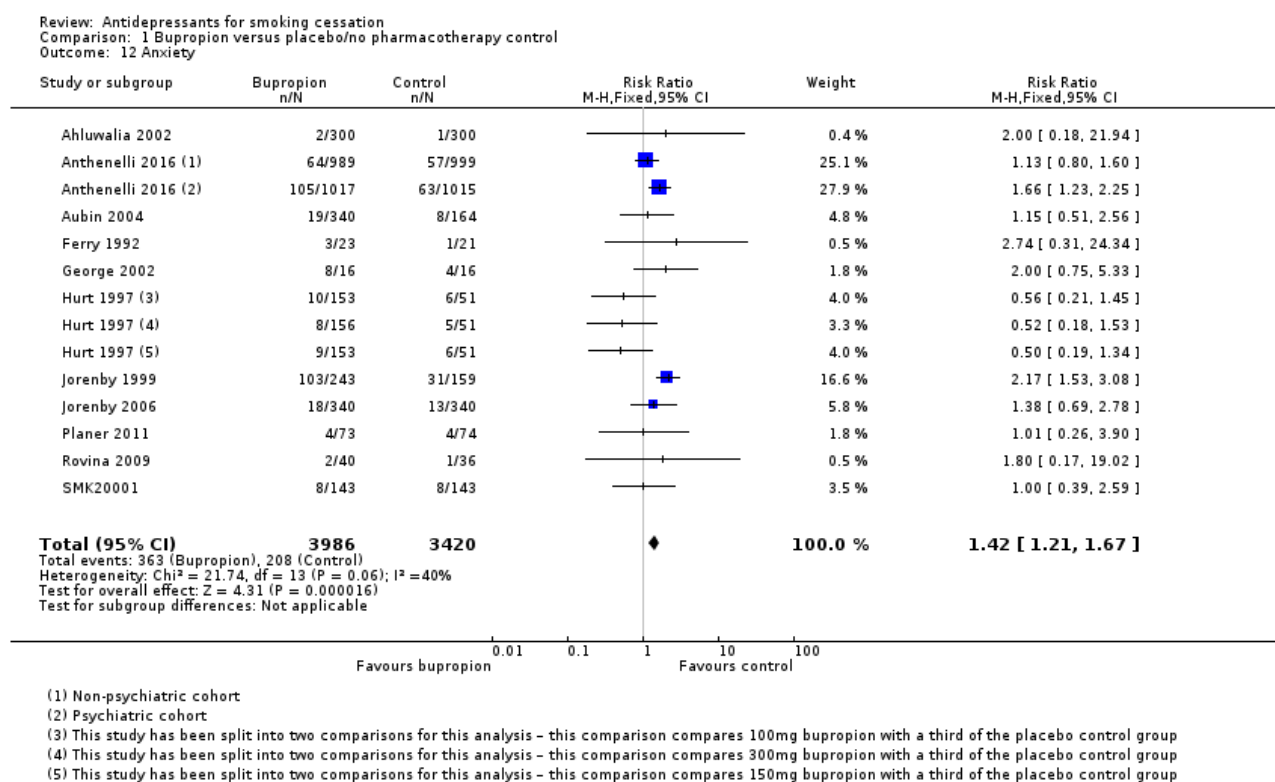


Figure 4

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Forest plot from Cochrane Review

Absolute effect

81 per 1000 people (95% CI 69 to 95) with bupropion compared with 57 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. *Antidepressants for smoking cessation*. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.2.4 Adverse events – [subgroup: Insomnia]

Narrative result

22 RCTs with 11077 participants found that more people had insomnia with bupropion than with placebo/no pharmacotherapy.[6]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the twenty-two studies, thirteen failed to report adequate allocation concealment and/or random sequence generation, sixteen did not report adequate blinding of participants/carers/outcome assessors and eight had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo/no pharmacotherapy (RR 1.78, 95% CI 1.62 to 1.96).

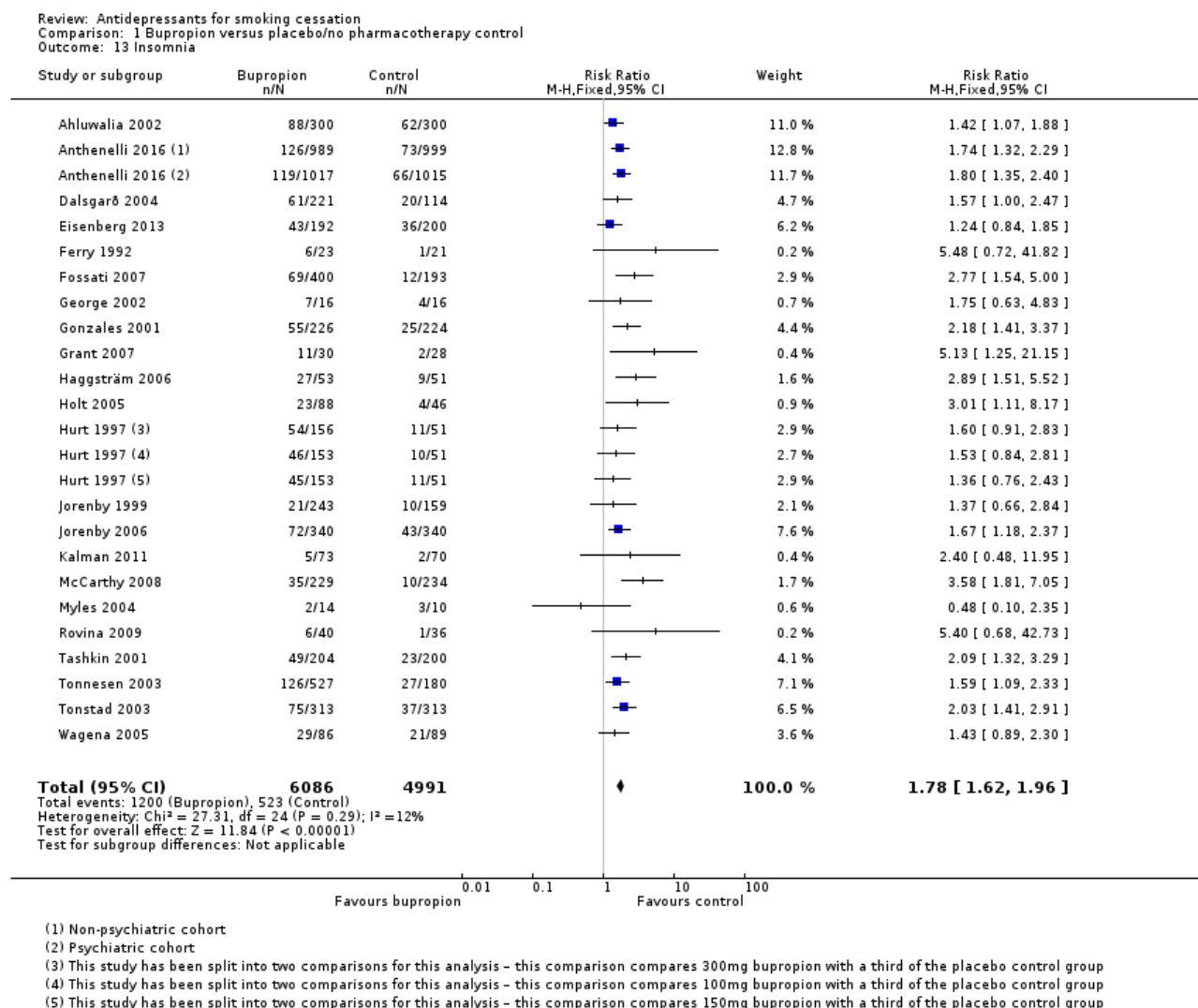


Figure 5

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Forest plot from Cochrane Review

Absolute effect

130 per 1000 people (95% CI 118 to 143) with bupropion compared with 73 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#).

Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD000031. DOI:

10.1002/14651858.CD000031.pub5. 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, overdoses and suicide attempts. All analyses found little or no difference between bupropion and placebo/no pharmacotherapy; most were underpowered. Click below for details.[\[7\]](#)

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#).

Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD000031. DOI:

10.1002/14651858.CD000031.pub5. Search date May 2019

➤ **Subgroup analysis 1.3.1 Serious adverse events – [subgroup: Serious adverse events of any severity]**

Narrative result

21 RCTs with 10625 participants found no statistically significant difference between groups.[\[8\]](#)

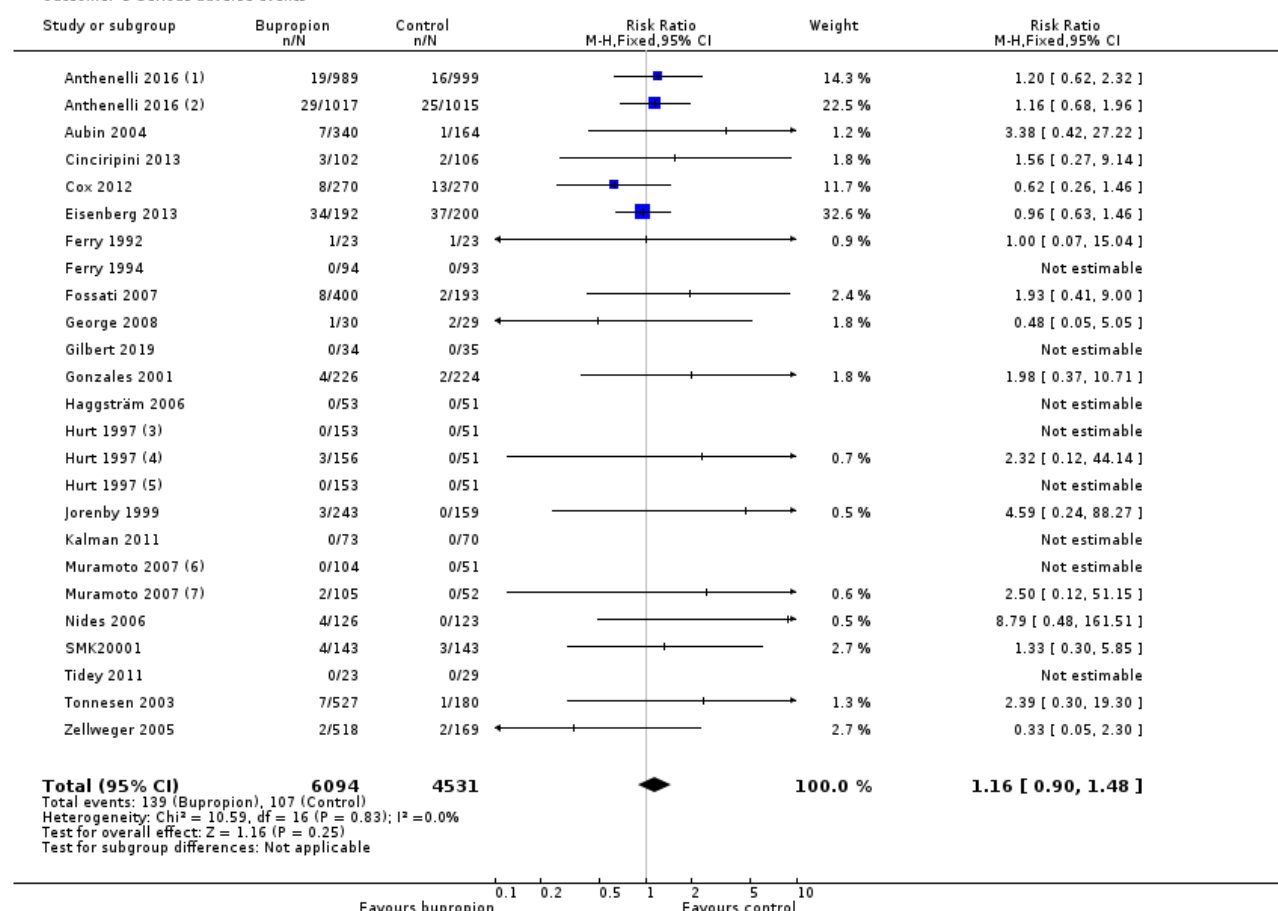
Quality of the evidence

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](#)

Relative effect or mean difference

There was no statistically significant difference between groups (RR 1.16, 95% CI 0.90 to 1.48).

Review: Antidepressants for smoking cessation
 Comparison: 1 Bupropion versus placebo/no pharmacotherapy control
 Outcome: 5 Serious adverse events



(1) Non-psychiatric cohort

(2) Psychiatric cohort

(3) This study has been split into two comparisons for this analysis - this comparison compares 100mg bupropion with a third of the placebo control group

(4) This study has been split into two comparisons for this analysis - this comparison compares 300mg bupropion with a third of the placebo control group

(5) This study has been split into two comparisons for this analysis - this comparison compares 150mg bupropion with a third of the placebo control group

(6) This study has been split into two comparisons for this analysis - this comparison compares 300mg bupropion with half the placebo control group

(7) This study has been split into two comparisons for this analysis - this comparison compares 150mg bupropion with half the placebo control group

Figure 6

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

19 per 1000 people (95% CI 14 to 24) with bupropion compared with 16 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.3.2 Serious adverse events – [subgroup: Seizures]

Narrative result

13 RCTs with 7344 participants found no statistically significant difference between groups.[9]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the thirteen studies, eight failed to report adequate allocation concealment and/or random sequence generation, eleven did not report adequate blinding of participants/carers/outcome assessors and three had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was no statistically significant difference between groups (RR 2.93, 95% CI 0.64 to 13.37).

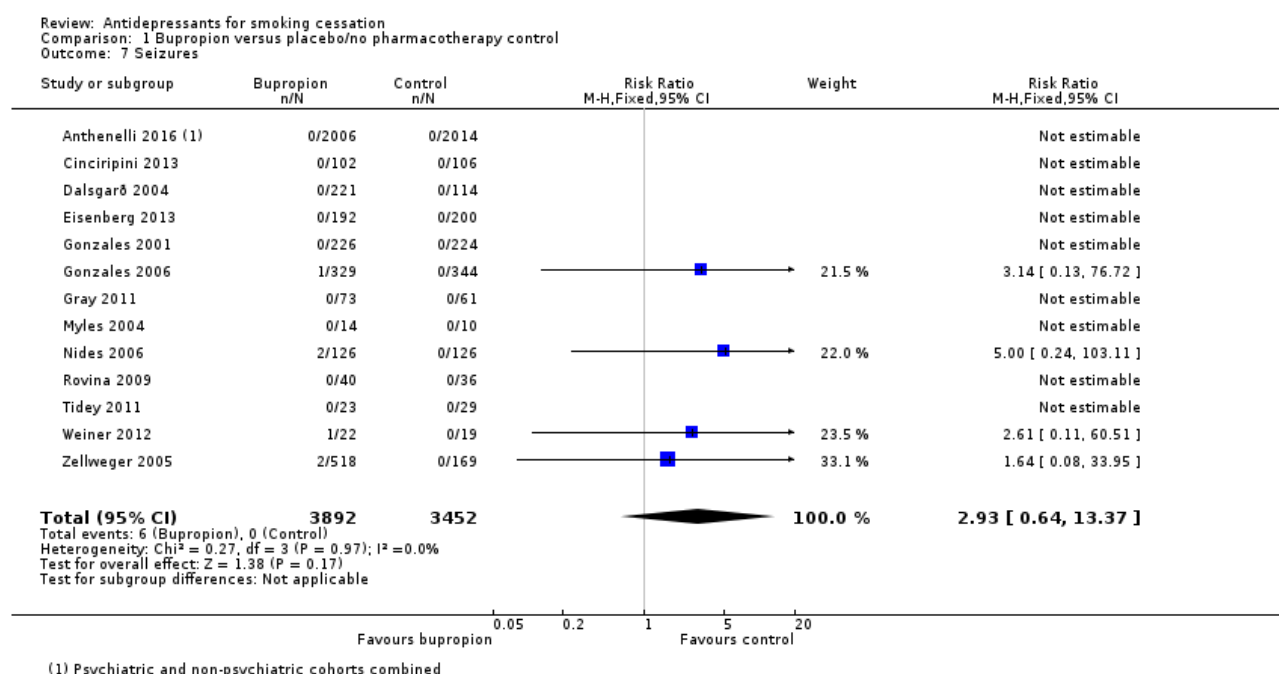


Figure 7

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

We could not calculate absolute results for this outcome because of low event rates.

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.3.3 Serious adverse events – [subgroup: Overdoses]

Narrative result

Five RCTs with 5585 participants found no statistically significant difference between groups.[10]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the five 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.

Relative effect or mean difference

There was no statistically significant difference between groups (RR 2.15, 95% CI 0.23 to 19.86).

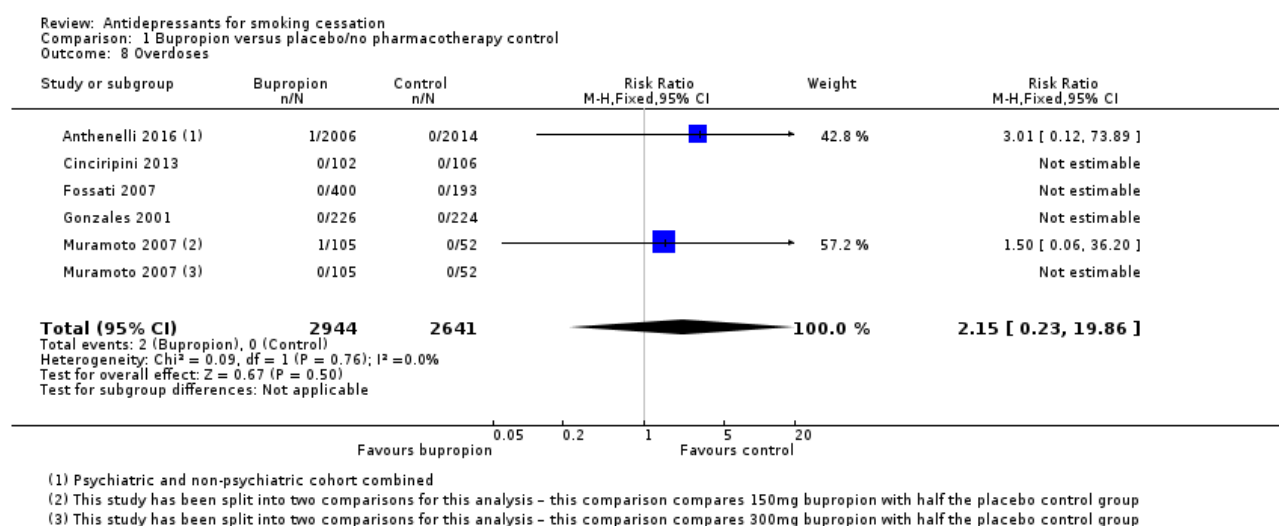


Figure 8

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Forest plot from Cochrane Review

Absolute effect

We could not calculate absolute results for this outcome because of low event rates.

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.3.4 Serious adverse events – [subgroup: Suicide attempts]

Narrative result

Ten RCTs with 6484 participants found no statistically significant difference between groups.[\[11\]](#)

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the ten studies, eight failed to report adequate allocation concealment and/or random sequence generation, six did not report adequate blinding of participants/carers/outcome assessors and two had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was no statistically significant difference between groups (RR 1.62, 95% CI 0.29 to 8.92).

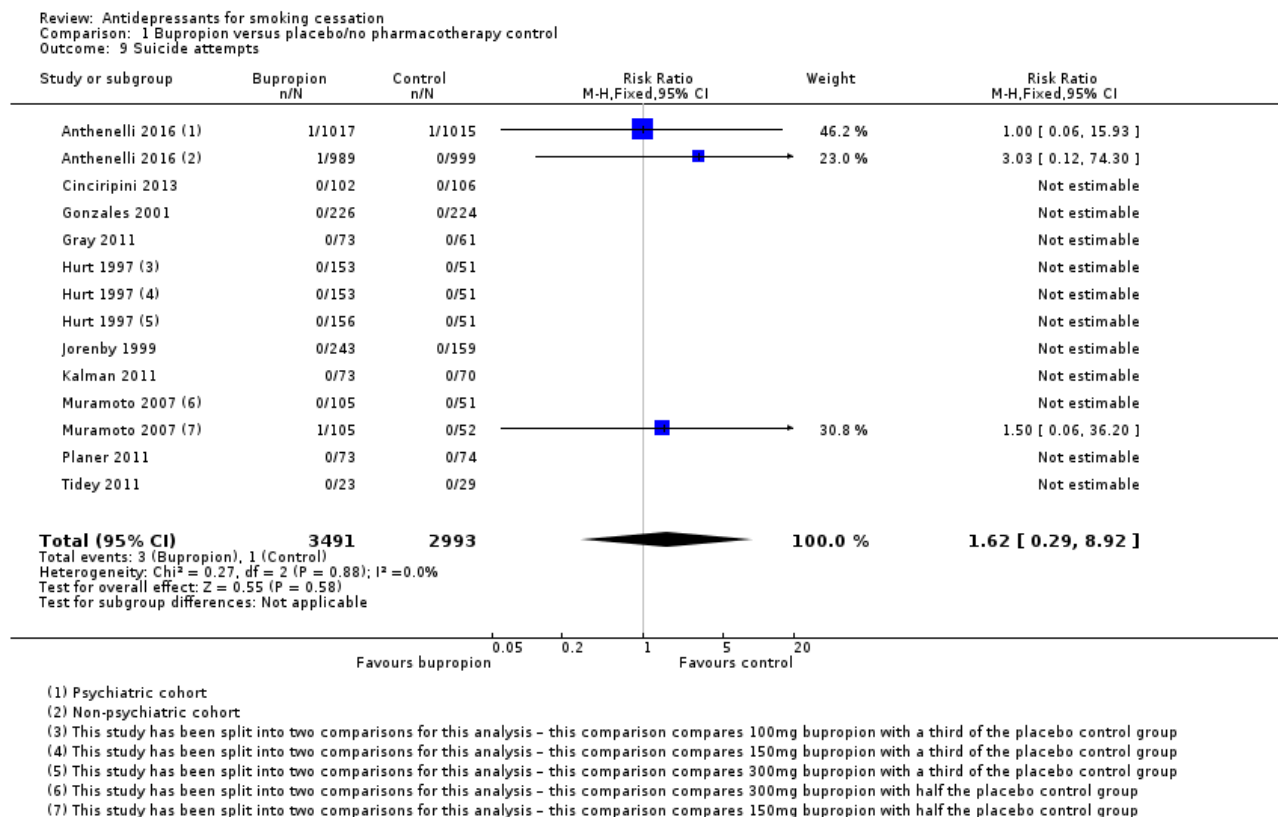


Figure 9

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

We could not calculate absolute results for this outcome because of low event rates.

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

OUTCOME 1.4 Mortality

Narrative result

Mortality was measured as all-cause mortality and deaths by suicide; both analyses found little or no difference between bupropion and placebo/no pharmacotherapy. Click below for details.[\[12\]](#)

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#).

Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD000031. DOI:

10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.4.1 Mortality – [subgroup: All-cause mortality]

Narrative result

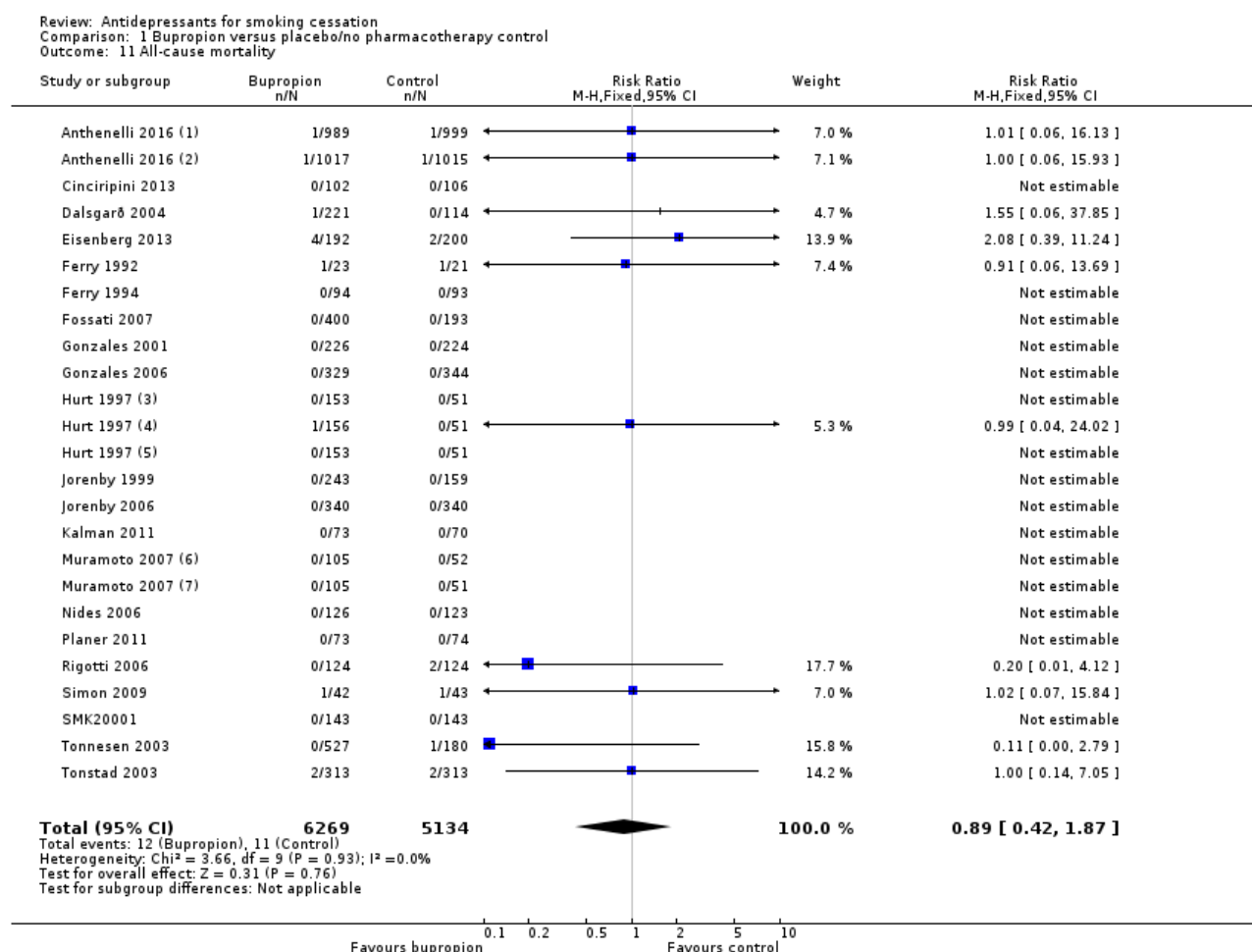
21 RCTs with 11403 participants found no statistically significant difference between groups.[13]

Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the twenty-one studies, twelve failed to report adequate allocation concealment and/or random sequence generation, fourteen did not report adequate blinding of participants/carers/outcome assessors and five had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was no statistically significant difference between groups (RR 0.89, 95% CI 0.42 to 1.87).



(1) Non-psychiatric cohort

(2) Psychiatric cohort

(3) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control group

(4) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control group

(5) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control group

(6) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control group

(7) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control group

Figure 10

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

1 per 1000 people (95% CI 0 to 2) with bupropion compared with 1 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation](#). *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> Subgroup analysis 1.4.2 Mortality – [subgroup: Death by suicide]**Narrative result**

14 RCTs with 8822 participants found no statistically significant difference between groups.^[14]

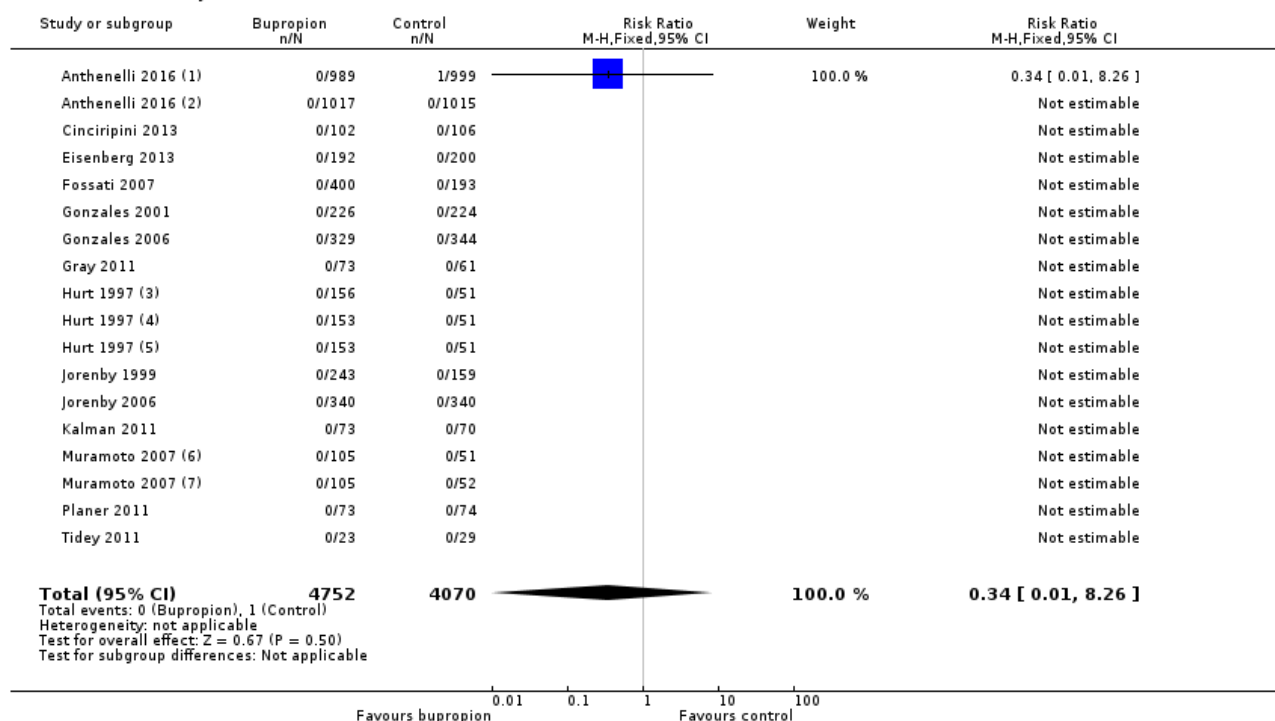
Risk of bias of studies

The reviewers did not perform a GRADE assessment of the quality/certainty of the evidence. Of the fourteen studies, nine failed to report adequate allocation concealment and/or random sequence generation, nine did not report adequate blinding of participants/carers/outcome assessors and two had high or unclear numbers of withdrawals.

Relative effect or mean difference

There was no statistically significant difference between groups (RR 0.34, 95% CI 0.01 to 8.26).

Review: Antidepressants for smoking cessation
 Comparison: 1 Bupropion versus placebo/no pharmacotherapy control
 Outcome: 10 Death by suicide



(1) Non-psychiatric cohort

(2) Psychiatric cohort

(3) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control group

(4) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control group

(5) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control group

(6) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control group

(7) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control group

Figure 11

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

We could not calculate absolute results for this outcome because of low event rates.

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. *Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub5. Search date May 2019

> OUTCOME 1.5 Withdrawals due to adverse events

Narrative result

25 RCTs with 12340 participants found that more people withdrew from treatment due to adverse events with bupropion than with placebo/no pharmacotherapy.[15]

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 high certainty. [See Summary of findings from Cochrane Review](#)

Relative effect or mean difference

There was a statistically significant difference between groups, in favor of placebo/no pharmacotherapy (RR 1.37, 95% CI 1.21 to 1.56).

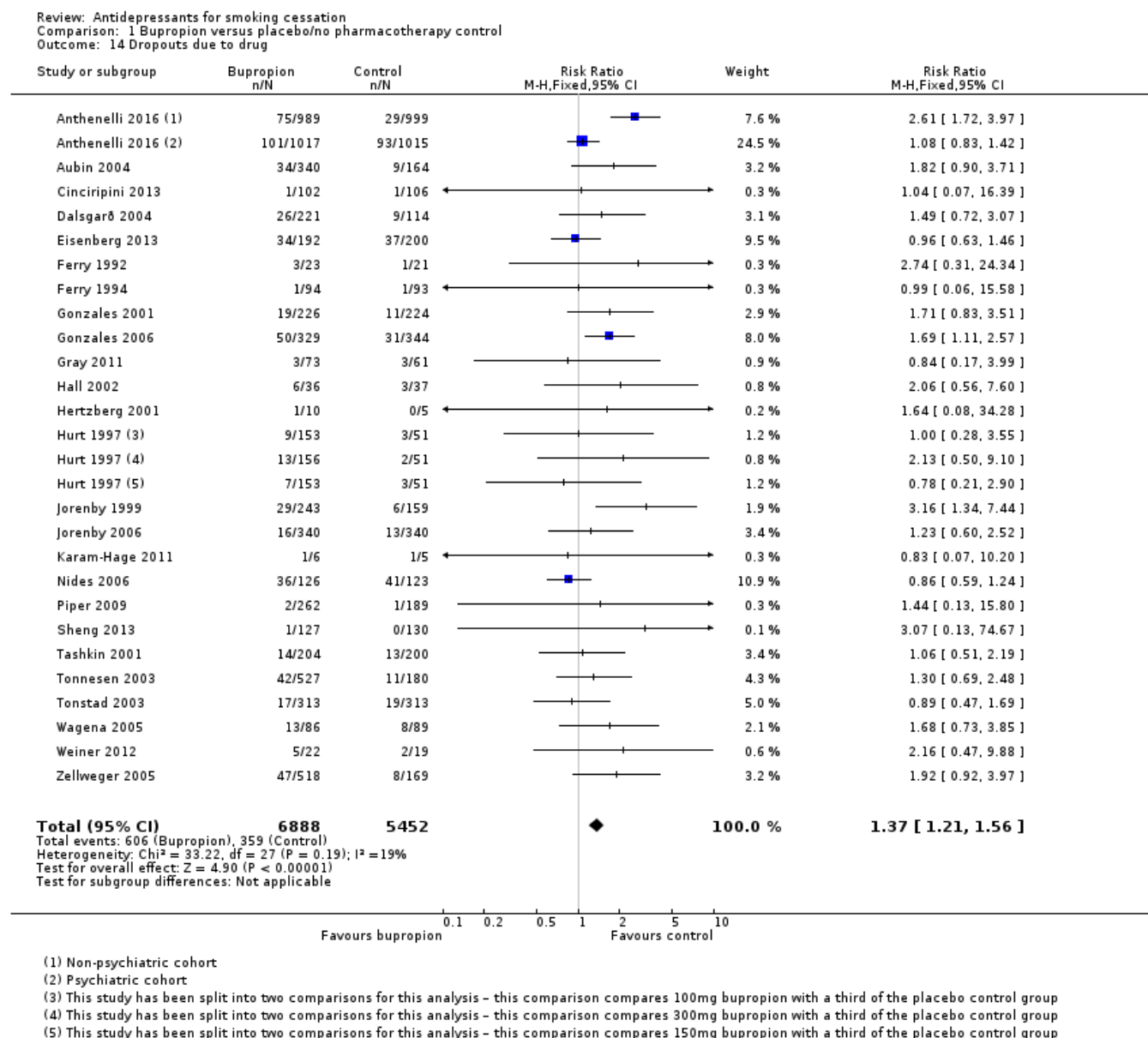


Figure 12

[Open in figure viewer](#)

Forest plot from Cochrane Review

Absolute effect

75 per 1000 people (95% CI 66 to 85) with bupropion compared with 55 per 1000 people with placebo/no pharmacotherapy (calculated using median event rate).

Reference

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. [Antidepressants for smoking cessation.](#)

Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD000031. DOI:

10.1002/14651858.CD000031.pub5. Search date May 2019

Population

Adolescent and adult smokers recruited from the community or from smoking cessation clinics worldwide. Most people received multisession individual counseling (84%) and had non-psychiatric mental health conditions (88%). Pregnant women were excluded

Intervention

Bupropion 100-300 mg/day

Comparator

Placebo/no pharmacotherapy

Additional Information

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