

Health Technology Review

# High-Dose Bupropion for Depression

# Key Messages

## What Is the Issue?

- Bupropion is a drug used in the treatment of depression. Bupropion is 1 of many treatment options available for depression and is associated with several side effects as well as the potential for misuse. The risk of side effects may be increased with higher daily doses of bupropion; therefore, it is important to determine the appropriate dosing for bupropion for the treatment of depression.

## What Did We Do?

- To help determine the appropriate dosing of bupropion for the treatment of major depressive disorder and treatment-resistant depression in adults, we sought to identify and summarize studies of the clinical efficacy and safety of high-dose (301 mg per day to 450 mg per day) versus standard-dose ( $\leq 300$  mg per day) bupropion. We also sought to identify and summarize recommendations on the use of high-dose bupropion for the treatment of depression in evidence-based guidelines.
- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence, published since 2014. One reviewer screened articles for inclusion, based on predefined criteria.

## What Did We Find?

- We did not identify any studies that evaluated the clinical efficacy and safety of high-dose versus standard-dose bupropion for the treatment of depression, which met our criteria for this review.
- We did not identify any evidence-based guidelines that included recommendations on the use of high-dose bupropion in adults with depression that met our criteria for this review.

## What Does it Mean?

- We cannot draw conclusions on the use of high-dose bupropion for the treatment of major depressive disorder or treatment-resistant depression in adults due to the lack of identified studies or evidence-based guidelines that met our criteria for this review. Future studies that compare high-dose and standard-dose bupropion for the treatment of depression could aid decision-making around the subject area of appropriate bupropion dosing.

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## Context and Policy Issues

### What Is Major Depressive Disorder and Treatment-Resistant Depression?

Major depressive disorder is defined by a depressed mood or loss of pleasure or interest for at least 2 weeks.<sup>1</sup> For a diagnosis, it must be accompanied by 4 additional symptoms, including weight loss or change in appetite, insomnia or hypersomnia; slowing down or speeding up of physical movements; fatigue or loss of energy, feelings of worthlessness, indecisiveness or diminished ability to concentrate or think; and recurrent thoughts of death or suicide.<sup>1,2</sup> Major depressive disorder causes disability, impairs functioning, has an impact on the quality of life, and can adversely affect the prognosis of physical illnesses.<sup>3</sup> In 2022, 7.6% of people aged 15 and older in Canada experienced a major depressive episode in the previous 12 months.<sup>4</sup> Treatment-resistant depression is a subset of major depressive disorder in which patients do not respond to 2 or more adequate trials of medication.<sup>5</sup> Treatment-resistant depression is estimated to affect approximately 2% of people in Canada (around 700,000 individuals).<sup>5</sup>

### What Is the Current Practice?

There are a range of treatment options used for depression including pharmacotherapy, psychoeducation, psychotherapy, and brain stimulation therapies (for example electroconvulsive therapy).<sup>6</sup> Different treatments for depression can be used alone or in combination. The goals for treatment of depression are symptom remission and return to baseline functioning.<sup>7</sup> Common classes of medications used in the treatment of depression include selective serotonin reuptake inhibitors (for example fluoxetine, paroxetine, fluvoxamine), serotonin and norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), norepinephrine and dopamine reuptake inhibitors (for example bupropion), nonselective cyclic (for example amitriptyline, imipramine, desipramine), and monoamine oxidase inhibitors (for example phenelzine, moclobemide).<sup>8</sup> The choice of medication for depression treatment is usually individualized based on efficacy and tolerability.<sup>7</sup>

### What Is Bupropion?

Bupropion is a drug that is used in the treatment of depression. Its mechanism of action is not fully understood; however, it inhibits the reuptake of norepinephrine and dopamine.<sup>9</sup> Bupropion is indicated for the treatment of major depressive illness and the prevention of major depressive illness with an autumn-winter seasonal pattern.<sup>10</sup> It is available as an extended-release tablet in 150 mg and 300 mg doses.<sup>10</sup> The starting dose is 150 mg per day and the maximum dose is 300 mg per day, which can be given as early as 1 week after treatment initiation.<sup>10</sup> Potential side effects of bupropion include increased heart rate, rhinitis, throat inflammation, insomnia, headache, agitation, dizziness, excessive sweating, weight loss, constipation, dry mouth, nausea, tremor, and blurred vision.<sup>9</sup>

### Why Is it Important to Do This Review?

Intentional misuse of bupropion has been reported.<sup>11</sup> Bupropion overdose is frequently associated with seizures, tachycardia (increased heart rate), and agitation.<sup>11</sup> The risk of seizures with daily doses of bupropion up to 300 mg is 0.1%, but increases to 0.4% with daily doses up to 450 mg.<sup>11</sup> Due to the potential for misuse as well as increased risk of adverse effects with higher daily doses of bupropion, an overview of

studies comparing the efficacy and safety of high-dose versus standard-dose bupropion as well as evidence-based guidelines on the use of high-dose bupropion for the treatment of depression may aid decision-making. This could help to determine the appropriate dosing of bupropion for adults with major depressive disorder or treatment-resistant depression to maximize the effectiveness and minimize the adverse effects and potential misuse.

## Research Questions

1. What is the clinical efficacy and harms of high-dose bupropion (301 mg per day to 450 mg per day) compared to doses up to the maximum licensed dose of bupropion for depression (300 mg)?
2. What are the evidence-based guidelines for the use of high-dose bupropion in adults with depression?

## Methods

### Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International Health Technology Assessment Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were bupropion and depression. The search was completed on December 20, 2024, and limited to English-language documents published since January 1, 2014.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

**Table 1: Selection Criteria**

Criteria	Description
<b>Population</b>	Adults ≥ 18 years with major depressive disorder and/or treatment-resistant depression
<b>Intervention</b>	Bupropion of any dose up to 300 mg (maximum licensed dose)
<b>Comparator</b>	Bupropion doses between 301 mg per day and 450 per day mg

Criteria	Description
<b>Outcomes</b>	Q1: Clinical effectiveness (e.g., symptoms, mood stability, quality of life, cognitive function, functional outcomes) and safety (e.g., misuse, adverse events, morbidity, mortality) Q2: Guideline recommendations
<b>Study designs</b>	Systematic reviews, health technology assessments, randomized controlled trials, nonrandomized and/or observational studies, evidence-based guidelines

## Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), if they were duplicate publications or were published before 2014. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodology were also excluded.

## Summary of Evidence

### Quantity of Research Available

A total of 921 citations were identified in the literature search. Following screening of titles and abstracts, 855 citations were excluded and 66 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, all 76 were excluded for various reasons, and as a result there were no publications that met the inclusion criteria for this report. [Appendix 1](#) presents the PRISMA<sup>12</sup> flow chart of the study selection.

Additional references of potential interest are provided in [Appendix 2](#).

### Summary of Findings

We did not identify any studies that evaluated the clinical efficacy and safety of high-dose versus standard-dose bupropion for the treatment of depression that met our inclusion criteria. We did not identify any evidence-based guidelines that included recommendations on the use of high-dose bupropion in adults with depression.

### Limitations

This report is limited by the quantity of the research available on the use of high-dose versus standard-dose bupropion for the treatment of depression.

## Conclusions and Implications for Decision- or Policy-Making

We cannot draw conclusions on the use of high-dose bupropion for the treatment of depression due to the lack of studies or evidence-based guidelines published in the last 10 years that met our inclusion criteria. Future studies that compare the efficacy and safety of high-dose bupropion (301 mg per day to 450 per day mg) with doses up to the maximum licensed dose of bupropion (300 mg) for the treatment of depression could aid decision-making around the appropriate dosing for this drug.



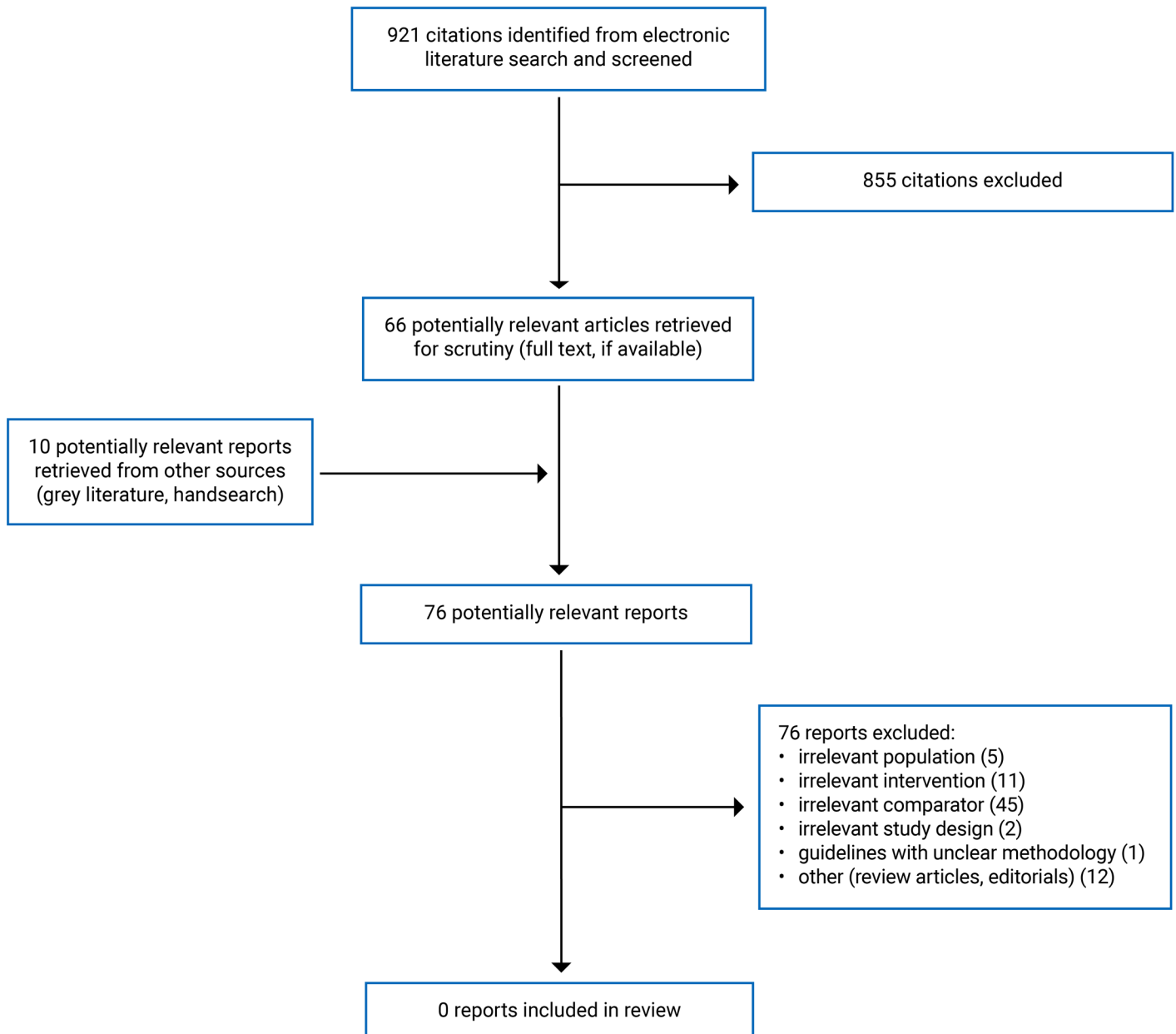
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## Appendix 1: Selection of Included Studies

Please note that this appendix has not been copy-edit.

**Figure 1: PRISMA<sup>12</sup> Flow Chart of Study Selection**



## Appendix 2: References of Potential Interest

Please note that this appendix has not been copy-edited.

### Previous CDA-AMC Reports

Review of guidelines on bupropion for depression. RC1558. 2024: <https://www.cda-amc.ca/review-guidelines-bupropion-depression>. Accessed 2025 Jan 8.

Bupropion for treatment resistant depression. RC1351. 2021: <https://www.cda-amc.ca/bupropion-treatment-resistant-depression>. Accessed 2025 Jan 8.

Bupropion for major depressive disorder or persistent depressive disorder (dysthymia). RC1352. 2021: <https://www.cda-amc.ca/bupropion-major-depressive-disorder-or-persistent-depressive-disorder-dysthymia>. Accessed 2025 Jan 8.

Major depressive disorder – focused critical appraisal of a network meta-analysis. 2020 <https://www.cda-amc.ca/major-depressive-disorder-focused-critical-appraisal-network-meta-analysis>. Accessed 2025 Jan 8.

### Nonrandomized Studies

Fawver J, Flanagan M, Smith T, Drouin M, Mirro M. The association of COMT genotype with bupropion treatment response in the treatment of major depressive disorder. *Brain Behav.* 2020;10(7):e01692. [PubMed](#)

### Guidelines (Not Evidence-Based or With Unclear Methodology)

Individualized antidepressant therapy in patients with major depressive disorder. Novel evidence-informed decision support tool. *Canadian Family Physician.* 2022; 68 (11): 807-814: <https://www.cfp.ca/content/68/11/807>. Accessed 2025 Jan 8. [PubMed](#)

Guidelines for prescribing bupropion. Maidstone (GB): Kent and Medway NHS; 2021: <https://www.kmptformulary.nhs.uk/media/1109/guidelines-for-the-use-of-bupropion-dec-21docx.pdf>. Accessed 2025 Jan 8.

Treatment of adult Major Depressive Disorder (MDD) tool. Toronto (ON): Centre for Effective Practice; 2019: [https://cep.health/media/uploaded/CEP\\_MDD\\_2019.pdf](https://cep.health/media/uploaded/CEP_MDD_2019.pdf). Accessed 2025 Jan 8.



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