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# BUPROPION FOR ADHD: MECHANISMS OF ACTION AND ITS POTENTIAL AS AN ALTERNATIVE TREATMENT — A REVIEW

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**ABSTRACT**

**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood. Its core symptoms are related to executive dysfunction and include inattention, hyperactivity, and impulsivity. As a neurodevelopmental disorder, ADHD requires chronic, long-term treatment. Therefore, it is essential to identify the most effective and safest therapeutic options that minimize the side effects of prolonged pharmacological intervention.
**Aim of the Study:** This article examines the potential role of bupropion in ADHD treatment, focusing on its mechanism of action, efficacy in symptom alleviation, and possible side effects.
**Materials and Methods:** This review was conducted using multiple databases, including PubMed, Scopus, and Google Scholar. The search terms used were: "ADHD", "bupropion", "methylphenidate", "comorbidity", "side effects", and "non-stimulants".
**Summary of Current Knowledge:** ADHD should be managed with both pharmacological and non-pharmacological methods. While methylphenidate is considered first-line pharmacological treatment, it is associated with a relatively high discontinuation rate. Bupropion, as an alternative, may offer effective symptom relief and better tolerability in patients who experience severe side effects from stimulant medications.
**Conclusions:** Bupropion appears to be effective in treating ADHD compared to placebo and is generally well tolerated, especially in contrast to first-line stimulant treatments. It may be a viable alternative for patients who do not tolerate stimulants. However, further research using objective comparative methods is necessary to evaluate the effectiveness and side effect profiles of bupropion versus methylphenidate.

**KEYWORDS**

Bupropion, Methylphenidate, ADHD, Non-Stimulants

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## 1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterized by a high variability of symptoms related to inattention, hyperactivity, and impulsivity. It is estimated that ADHD affects approximately 3–7% of children and adolescents globally, making it one of the most prevalent psychiatric disorders in this age group. [1,2] ADHD is also believed to affect around 2.5% of adults worldwide. [3]

ADHD is diagnosed clinically, based on a comprehensive medical history — especially with input from parents and school staff. Accurate diagnosis often requires the collaboration of a psychiatrist, neurologist, and psychologist. A key diagnostic criterion is the onset of symptoms in childhood. According to the latest diagnostic criteria in ICD-11, symptoms must be present before the age of 12, which is a change from ICD-10, where the threshold was set at age 7. [4]

ADHD symptoms affect three main domains: hyperactivity, impulsivity, and attention deficits. They may include disorganization, forgetfulness, lack of concentration, emotional dysregulation, impulsivity, and poor self-regulation. [3,6] These difficulties must significantly impair daily functioning and be observed in at least two different settings (e.g., home and school). [5]

The core symptoms of ADHD are linked to dysfunctions in executive functioning, primarily regulated by the frontal lobes. [3,7,8,9] Executive functions are higher-order cognitive processes responsible for attention regulation, emotional control, and goal-directed behavior. Impairments in these areas may hinder planning, organization, and self-monitoring. [8]

ADHD is frequently comorbid with other psychiatric conditions such as depression, anxiety disorders, eating disorders, and substance use disorders (SUDs). [3,10,11,14,19] It is estimated that 60–80% of adults

with ADHD have at least one co-occurring condition. [10,19] These comorbidities are often associated with late diagnosis or inadequate treatment in childhood.

ADHD can be managed through both non-pharmacological and pharmacological approaches. [17,18,19] Currently, first-line pharmacological treatment involves stimulant medications such as methylphenidate and amphetamines. [12,13,18,19] However, not all patients tolerate stimulants well, and a subset of individuals either do not respond optimally or experience intolerable side effects. It is estimated that approximately 15% of patients require a change or discontinuation of stimulant medication. [19] Therefore, it is necessary to explore non-stimulant alternatives that are both safe and effective. One such option is bupropion, an antidepressant with non-competitive antagonism of nicotinic acetylcholine receptors. [12,15,16,18]

**Objective of this work**

The aim of this study is to examine the potential use of bupropion in the treatment of ADHD as an alternative to first-line stimulant medications. The article focuses on bupropion's mechanism of action, its efficacy in alleviating symptoms, and its side effect profile.

## 2. Materials and Methods

This review was conducted using multiple databases, including PubMed, Scopus, and Google Scholar. The following search terms were used: "ADHD", "bupropion", "methylphenidate", "comorbidity", "side effects", and "non-stimulants". Articles included in the review were selected based on relevance to the topic, study design (randomized controlled trials, meta-analyses, and clinical studies), and publication in peer-reviewed journals.

## 3. Current state of knowledge

### 3.1 Etiology

There is no single factor or mechanism responsible for the development of ADHD. Its etiopathogenesis involves a combination of genetic and environmental influences. [20]

Neurobiological studies suggest that ADHD may be associated with a reduction in dopamine synaptic markers. [21,22] Additionally, numerous studies have indicated the role of alterations in the norepinephrine system. [23] Supporting this hypothesis is the observed effectiveness of stimulant medications, which enhance central dopamine and norepinephrine activity. [24]

The combined evidence suggests that dysregulation in these neurotransmitter systems plays a central role in the pathophysiology of ADHD.

### 3.2 Current treatment options

Currently, the treatment of ADHD involves both non-pharmacological and pharmacological strategies. Numerous studies have confirmed that the combination of both approaches tends to be the most effective in alleviating symptoms. [19,27]

According to Catalá-López et al., behavioral therapy is the only non-pharmacological intervention with well-established efficacy. [18] This therapy focuses on analyzing behavior patterns and developing skills to manage them effectively. However, some publications also highlight the potential of alternative interventions such as cognitive training and neurofeedback. [17]

Pharmacologically, stimulants—primarily methylphenidate and amphetamine—remain the cornerstone of ADHD treatment. Research indicates that their effectiveness is largely due to the increased extracellular levels of dopamine (DA) and norepinephrine (NE) in the brain. These drugs work by inhibiting the dopamine and norepinephrine transporters, which in turn boosts neurotransmitter activity in key regions such as the cortex and striatum. [24] These areas are involved in executive function regulation, the disruption of which is a hallmark of ADHD. The effectiveness of stimulants is estimated at approximately 70%. [19,31]

However, the use of stimulant medications is associated with adverse effects in around 30% of patients, and up to 15% may require discontinuation due to side effect severity. [Austerman] Notably, Lee et al. observed a strong correlation between methylphenidate treatment and the onset of insomnia and reduced appetite—side effects that can be especially problematic in children. [25,26]

Other medications used in ADHD management include atomoxetine, guanfacine, clonidine, antidepressants, and antipsychotics. These are generally considered second-line therapies or are used as adjunct treatments in cases of comorbidity. Among non-stimulant alternatives, bupropion stands out for its potential effectiveness in treating core ADHD symptoms, particularly inattention. [18,19]

### 3.3 Bupropion – mechanism of action

Although bupropion is classified as an antidepressant, its mechanism of action differs significantly from that of most other drugs in this class. Research indicates that bupropion primarily works by inhibiting the norepinephrine transporter (NET) and the dopamine transporter (DAT). This leads to reduced reuptake and consequently increased availability of both neurotransmitters in the synaptic cleft. [28,30]

According to Shalabi et al., bupropion appears to have minimal influence on serotonergic transmission, which allows it to avoid many of the side effects typically associated with selective serotonin reuptake inhibitors (SSRIs), such as sexual dysfunction. [29] Moreover, bupropion has no significant affinity for other postsynaptic receptors, including acetylcholine, histamine, or β-adrenergic receptors. [30]

This distinct pharmacological profile makes bupropion a potentially favorable option in treating ADHD, particularly in patients who do not tolerate or respond well to stimulant medications.

### 3.4 Bupropion's effectiveness in ADHD treatment

Given that the pathophysiology of ADHD is closely linked to dopaminergic and noradrenergic dysregulation, bupropion may serve as an effective treatment option, especially for individuals who are reluctant to use stimulants or who experience adverse effects from them.

A double-blind, placebo-controlled trial involving 42 adult patients found that six weeks of bupropion treatment led to significantly greater reductions in ADHD symptoms compared to placebo. [31] Similarly, a randomized trial conducted by Timothy et al. with 162 adult patients demonstrated a response rate of 53% in the bupropion group, compared to 31% in the placebo group. [32]

In patients with ADHD and comorbid Substance Use Disorders (SUDs), studies have shown that bupropion can effectively reduce ADHD symptoms, although its impact on substance use outcomes was not statistically significant. [33]

A meta-analysis of five randomized controlled trials including a total of 349 patients confirmed that bupropion was significantly more effective than placebo in alleviating ADHD symptoms. [34] Similar conclusions were drawn in a broader meta-analysis that included 133 double-blind randomized controlled trials across different age groups, which also confirmed the drug's efficacy. [35]

Since ADHD primarily affects children and adolescents, it is essential to evaluate the effectiveness of bupropion in younger populations. A clinical trial involving 109 children aged 6 to 12 years found that bupropion, administered at a dose of 3 to 6 mg/kg per day, was significantly more effective than placebo in reducing ADHD symptoms. Improvements were observed in both hyperactivity and behavioral problems within just three days of treatment. [36] According to Daviss, bupropion may also be effective in adolescents with ADHD, particularly those with comorbid depression or dysthymic symptoms. [37]

While many studies have demonstrated the efficacy of bupropion in reducing ADHD symptoms, it is particularly important to assess how it compares to first-line treatments. A six-week randomized, double-blind study involving 44 patients found comparable efficacy between bupropion (100–150 mg/day) and methylphenidate (20–30 mg/day). [38] Similar results were obtained in a double-blind clinical trial involving 15 patients aged 7 to 17 years. [39]

However, a meta-analysis of 28 clinical trials concluded that while bupropion was more effective than placebo, its efficacy was lower than that of methylphenidate or atomoxetine. [40] In contrast, a 2024 meta-analysis including 31 clinical trials provided more promising results: it found that alternative medications such as bupropion, dasotraline, venlafaxine, and viloxazine were not statistically less effective than methylphenidate in treating ADHD. [41]

### 3.4 Bupropion – side effects

Bupropion is generally considered a well-tolerated medication. The most commonly reported adverse effect is nausea. [42] According to Hamedi et al., frequent side effects include fatigue (57.1% vs. 33.3% in the placebo group), agitation (57.1% vs. 38.1%), anxiety (42.9% vs. 28.6%), insomnia (42.9% vs. 33.3%), somnolence (52.4% vs. 28.6%), and sweating (42.9% vs. 19%). However, these differences were not statistically significant compared to placebo. [31]

Other potential adverse effects during bupropion treatment include headache, irritability, vomiting, dry mouth, palpitations, paresthesia, and constipation. [31,44] Insomnia and anxiety are among the side effects that may lead to treatment discontinuation. [43]

Importantly, bupropion does not affect heart rate nor does it cause an increase in blood pressure. [43] Moreover, unlike many other antidepressants, it does not cause sexual dysfunction, which is a significant advantage. [28]

A rare but serious side effect of bupropion is its potential to lower the seizure threshold, which necessitates caution in patients with seizure risk factors. [43,45]

## 4. Conclusions

Bupropion is a well-tolerated antidepressant that has also demonstrated effectiveness in alleviating symptoms of ADHD. Numerous studies have confirmed its beneficial impact on reducing ADHD symptoms compared to placebo. Additionally, its established antidepressant properties are noteworthy, especially since ADHD often coexists with depression. In such cases, bupropion may help avoid polypharmacy by effectively addressing symptoms of both disorders.

However, it should be noted that most studies conducted to date have involved relatively small patient groups. There is also a lack of large-scale trials directly comparing the effectiveness of bupropion and methylphenidate. Therefore, while bupropion should not be considered a replacement for methylphenidate in ADHD treatment, it appears to be a justified alternative for patients who cannot tolerate or prefer not to use stimulants.

Moreover, methylphenidate treatment is frequently associated with side effects such as tachycardia and reduced appetite, which can limit its use, particularly in children and elderly patients. In these cases, bupropion represents a safer and effective option worthy of consideration.

The potential efficacy of bupropion underscores the importance of exploring therapeutic options beyond stimulants. Nonetheless, further extensive research is necessary to fully evaluate both the benefits and potential risks of alternative ADHD treatments.

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