SVOA Paediatrics
ISSN: 2755-1660

ScienceVolks Open Access

Review Article

Use of Bupropion for Attention-Deficit/Hyperactivity Disorder and Depression in Children and Adolescents

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DOI: https://doi.org/10.58624/SVOAPD.2024.03.087

***Received:** October 25, 2024* ***Published:** November 13, 2024*

Abstract

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders and frequently continues through adolescence and adulthood. Medication is the single most effective treatment for reducing ADHD symptoms and its use is recommended in children with 6 years and older. Nearly two-thirds of children and adolescents with ADHD also have another mental, emotional, or behavioral disorder, including depression disorders. Bupropion is an antidepressant with a mechanism of action potentially relevant to the treatment of ADHD, used in adults for both depression and smoking cessation and eventually as a third line treatment for ADHD.

Objective: This review aims to explore the effectiveness, safety and tolerability of bupropion in children and adolescents with ADHD and depression.

Method: A scientific review was conducted on a careful analysis of the scientific evidence available on the electronic databases: MEDLINE, Embase and the Cochrane Library.

Results: There is little empirical evidence to guide the pharmacological treatment for comorbid ADHD and depression as most treatment studies tend to exclude patients with comorbid disorders. The majority of trials demonstrated bupropion's efficacy in improving ADHD symptoms in children and adolescents, with effects being superior than placebo and most frequently comparable to methylphenidate. Bupropion also appears to be effective in alleviating depressive symptoms in this population, whether with or without ADHD comorbidity. Side effects did not differ significantly in comparison with stimulants and discontinued medication due to adverse reactions was rare.

Conclusions: Current findings have to be interpreted with caution because of the very limited database and frequent use of small sample sizes. Bupropion seems effective and well-tolerated in children and adolescents with ADHD and ADHD-depression comorbidity. It should be considered for treatment of this population, but more randomized controlled trials with larger sample sizes are necessary.

Keywords: *Bupropion, Attention-Deficit/Hyperactivity Disorder, Depression, Children, Adolescents*

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood neuropsychiatric disorders affecting around 5% of school-age children (aged ≤18 years) [1]. It is frequently associated with significant impairment in academic and social functioning, and symptoms often persist through adolescence and adulthood. Pharmacotherapy stands out as the single most effective treatment for reducing ADHD symptoms. Medication is unanimously recommended in children with 6 years and older when symptoms continue to cause a significant impairment after educational and psychosocial interventions, and stimulants are usually the first choice [2].

However, up to 20% of pediatric patients may not respond to stimulants, and 4% discontinue medication due to severe side effects, including headache, nausea, vomiting, and appetite suppression [3]. Additionally, second-line treatments such as atomoxetine and guanfacine seem to have lower effect sizes, reduced tolerability and a worse risk-benefit profile compared to first-line treatment [4].

Comorbidities are common among children and adolescents with ADHD, with nearly two-thirds presenting with concurrent mental, emotional, or behavioral disorders. In adolescents with ADHD, depressive disorders are four times more prevalent than in the general adolescent population [5]. Managing these patients poses significant challenges for clinicians, as both conditions have the potential to exacerbate the symptoms of the other. Depression frequently magnifies the symptoms and dysfunction associated with ADHD, while ADHD may intensify the impairment caused by depression alone. The suicide rate is significantly elevated in individuals with both ADHD and Major Depression (MD) compared to those with MD alone [6].

Despite the common comorbidity of these two entities, evidence-based systematic research on the efficacy and safety of using single or multiple medications in this high-risk patient group has been delayed and many studies on ADHD or depressive disorders tend to exclude patients with comorbidities [5,6]. Even though stimulants can be added to the treatment with antidepressants, they may exacerbate comorbid sleep, mood, and anxiety disorders. Although it is well-documented that the use of psychostimulants in the treatment of ADHD may decrease the risk of substance abuse, their potential for misuse is particularly relevant in adolescence [3].

Bupropion, a dopamine and norepinephrine reuptake inhibitor established as an approved treatment for depression and smoking cessation in adults [7], has emerged as a potential third-line treatment for ADHD [5,8]. In cases of comorbid ADHD and mood disorders in adults, bupropion is being considered as a potential first-line treatment [9]. However, limited research has investigated the effectiveness of bupropion in children and adolescents with ADHD, and even fewer studies have explored its impact in depressive disorders in this population [10].

This review aims to assess the effectiveness, safety and tolerability of bupropion in children and adolescents with ADHD and depression. A comprehensive scientific review was conducted, carefully analyzing evidence from electronic databases, including MEDLINE, Embase and the Cochrane Library.

Body

Clinical trials suggest that bupropion is effective and well-tolerated in treating ADHD symptoms in children and adolescents. Most head-to-head studies indicate that the effect size of bupropion seems comparable to stimulants [3,11]. A double-blind placebo-controlled study reported smaller effect sizes for bupropion compared to methylphenidate in teacher and parent ratings of ADHD symptoms, although memory and performance test results were similar [12]. In a single-blind placebo trial involving adolescents (11-18 years old) with ADHD and comorbid major depressive disorder (MDD) or Persistent Depressive Disorder (PDD), bupropion demonstrated a global response rate of 88% for depressive disorders and 63% for ADHD. Approximately 58% of patients responded to both disorders, 4.2% were exclusively ADHD responders and 29.2% were solely depression responders, with only 8% being non-responders for both conditions [5]. Other retrospective study on the pediatric population reported a significant improvement rate in both depressive and ADHD symptoms [7].

Bupropion is generally well-tolerated, with no significant effects on pulse, mean blood pressure, or weight [7]. However, rare adverse events are described, such as irritability, dizziness, insomnia, decreased appetite, anxiety, headache, nausea/vomiting, fatigue, tremor, tics, xerostomia, rash, and constipation [5,7]. In the single blind placebo trial mentioned earlier, rash (self-limited), irritability, tremor and tics were more frequent compared to placebo. Despite this, no patients discontinued medication due to side effects, and 96% chose to continue bupropion therapy at the study's conclusion [5]. Another study reported a 15% discontinuation rate due to side effects, primarily irritability, thought most adverse symptoms spontaneously resolved [7]. In the adult population, bupropion appears well-tolerated in long-term use, with some studies suggesting a reduction in adverse events with continued treatment [8]. However, the duration of pediatric studies is typically limited to four months [3]. Some studies have reported rare serious adverse events with bupropion use, such as serum sickness-like reactions and seizures [3,8].

The data on these events are contradictory, with some adult studies indicating the safety of antidepressant treatment, including bupropion, in patients with epilepsy, while others suggest an association between antidepressants and seizures, with a risk comparable between SSRI and bupropion [8,13]. Adolescents grappling with both depression and ADHD may be particularly susceptible to developing bipolarity, as each disorder independently contributes to an increased risk [14,15]. Recent studies highlight a higher risk of serious morbidity with bupropion overdose in adolescents compared to SSRI [16].

Conclusions

Examining non-stimulant alternatives for managing ADHD in children and adolescents is imperative, as nearly one-fifth of patients do not respond to stimulants. Additionally, their use may worsen comorbid disorders and potentially lead to misuse or diversion [1]. The frequent comorbidity with depression presents significant challenges in managing these patients, as both conditions can mutually exacerbate the symptoms of the other [6]. Despite this prevalent comorbidity, evidence-based research on the efficacy and safety of pharmacological treatment in this high-risk patient group has encountered delays [5,6]. While severely ill pediatric patients often necessitate multiple medications, the preference is for monotherapy and a simplified treatment plan. Clinical trials indicate that bupropion may effectively improve ADHD symptoms in children and adolescents, producing results comparable to stimulants [3]. Moreover, bupropion seems to have a positive impact in cases of ADHD-depression comorbidity [5]. While generally well tolerated, there is limited information on the long-term tolerability of bupropion in the pediatric population due to the short duration of available studies [3]. Irritability emerges as the most common side effect in children and adolescents [7]. Caution is advised regarding medication-induced irritability and risk of bipolarity when using bupropion in depressed patients particularly with ADHD [5]. Some factors can heighten the risk of seizures. Consequently, it is essential to screen patients for the existence of medical comorbidities or concurrent medications that might reduce the seizure threshold [8]. Considering the risk of serious morbidity with bupropion overdose, evaluating the patient's propensity for self-harm is recommended when contemplating bupropion therapy [16].

Bupropion is effective and generally well-tolerated in treating ADHD and depressive symptoms a in children and adolescents [3,7]. Nevertheless, current findings should be interpreted cautiously due to the limited database and frequent use of small sample sizes. To ascertain the safety of long-term bupropion use in the pediatric population, large prospective placebo-controlled studies are warranted.

Authors' contribution statement

The authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Financing Support

This work has not received any contribution, grant or scholarship.

Ethical Considerations

Confidentiality of Data and Patient Consent: No data from patients were used in this work.

Conflicts of Interest

The authors have no conflicts of interest to declare.

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

Awards and Previous Presentations

A preliminary version of the data presented was disclosed in the context of a poster presentation at the 21st WPA World Congress of Psychiatry, held between October 18 and 21, 2021.

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Citation: Barradas NA, Delgado RM. Use of Bupropion for Attention-Deficit/Hyperactivity Disorder and Depression in Children and Adolescents. *SVOA Paediatrics* 2024, 3:6, 186-189. doi:10.58624/SVOAPD.2024.03.087