Comparative Incidence of Oppositional Defiant and Conduct Disorders in ADHD: Bupropion vs. Stimulant Treatments

ABSTRACT

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is often complicated by comorbid Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), which worsen outcomes. Stimulants, the standard ADHD treatment, may exacerbate aggression and oppositional behaviors, while bupropion, an atypical antidepressant, has emerged as a potential alternative with fewer behavioral risks.

Objective: This study evaluates whether ADHD patients treated with bupropion have lower incidences of ODD and CD compared to those treated with stimulants.

Methods: A retrospective cohort study was conducted using the TriNetX Global Collaborative Network. ADHD patients treated with stimulants (n=372,330) or bupropion (n=132,457) were analyzed. Patients with prior ODD, CD, or tobacco use were excluded. Incidence rates of ODD and CD were compared using measures of association and Kaplan-Meier survival analysis.

Results: The incidence of ODD was significantly higher in the stimulant cohort (1.3%) compared to the bupropion cohort (0.5%) with a risk difference of 0.8% (95% CI: 0.007-0.009) and a risk ratio of 2.7 (95% CI: 2.484-2.934). Similarly, CD incidence was higher in the stimulant cohort (1.9%) versus the bupropion cohort (1.0%), with a risk difference of 0.9% (95% CI: 0.008-0.010) and a risk ratio of 1.864 (95% CI: 1.756-1.978). Kaplan-Meier analysis confirmed higher risks of ODD and CD in stimulant-treated patients.

Conclusion: Bupropion is associated with a lower risk of ODD and CD in ADHD patients compared to stimulants. These findings suggest that bupropion may be a safer alternative for ADHD patients at risk for these comorbid disorders, though further research is needed to confirm these results and explore underlying mechanisms. While this study provides valuable insights, the retrospective design introduces potential limitations, including biases from unmeasured confounders and the risk of incomplete or inaccurate data in the database.

Keywords: *Bupropion, ADHD, ODD, CD, Conduct Disorder*

1. INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterized by persistent symptoms of inattention, hyperactivity, and impulsivity. This

disorder significantly impacts the academic performance, social interactions, and overall quality of life of affected individuals. Globally, ADHD is one of the most commonly diagnosed psychiatric disorders in children and adolescents, with a prevalence ranging from 5% to 10% (Polanczyk et al., 2015). Complicating ADHD is the frequent occurrence of comorbid behavioral disorders, particularly Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD). These comorbidities, marked by defiant, hostile, and antisocial behaviors, can lead to significant impairments in social functioning and increase the risk of more severe psychiatric conditions in adulthood (Morgan et al., 1996; Wolraich et al., 1996; Eiraldi et al., 1997), including higher rates of incarceration and substance use disorder (Erskine et al., 2016). Some studies found that in children with ADHD, showing signs of early conduct disorder was a large risk factor in developing antisocial behavior. However, lack of parental supervision and substance abuse have also been identified as further risk factors (Hoeve et al., 2009; Yockey, King, & Vidourek, 2019). However, these medications can also lead to adverse effects, including insomnia and appetite suppression (De Sousa & Kalra, 2012), as well as increased anxiety in some patients (Coughlin et al., 2015). Some studies show a concern that they may exacerbate aggressive or oppositional behaviors in others (Wigal et al., 2013), particularly when high doses are used or in individuals with certain risk factors. Because of common comorbid aggression seen with ADHD, other combination pharmacological therapy has been practiced, especially in stimulant-refractory cases. Traditionally, antipsychotics like risperidone have been used, but concerns regarding their long-term cardiometabolic side effects, particularly weight gain, have prompted exploration of alternative therapies. Molindone, for instance, has shown promise due to its favorable safety profile with less weight gain, though it requires further study. Additionally, mood stabilizers like divalproex have demonstrated efficacy in reducing aggression, supporting a stepped-care approach to treatment. These findings emphasize the importance of considering both efficacy and long-term safety in treatment strategies (Saylor & Amann, 2014).

Bupropion, an atypical antidepressant with norepinephrine-dopamine reuptake inhibition properties, has emerged as a potential alternative for ADHD treatment, especially for those who cannot tolerate or do not respond well to stimulants (Wilens et al., 2001). While it has been noted that this drug may exacerbate anxiety, other studies have shown that it is comparable to SSRIs in reducing anxiety as well (Naguy & Badr, 2022; Papakostas et al., 2008). Previous studies have indicated that bupropion is effective in managing ADHD symptoms (Daviss et al., 2001) and may be associated with reduced aggression and improved behavioral outcomes in children and adolescents. Systematic reviews have shown that bupropion may be efficacious in treating ADHD in children and can be considered as an alternative nonstimulant medication (Ng, 2017; Nadia & Ricardo-Manuel, 2024). However, comprehensive studies comparing the incidence of ODD and CD in ADHD patients treated with bupropion versus those treated with stimulants are limited. This gap in the literature highlights the need for further research to understand the differential impact of these treatments on comorbid behavioral disorders.

The objective of this study is to evaluate whether ADHD patients treated with bupropion have a lower incidence of ODD and CD compared to those treated with stimulant medications. Utilizing data from the TriNetX global health research network, this study will analyze a large, diverse cohort of adolescents diagnosed with ADHD. By comparing the outcomes of those treated with bupropion and those receiving stimulant therapy, this research aims to provide valuable insights into the potential benefits of bupropion in managing ADHD with comorbid behavioral disorders. The findings could inform clinical practice, potentially guiding treatment decisions to reduce the burden of ODD and CD in adolescents with ADHD.

2. METHODOLOGY

Study Design and Setting

This study employed a retrospective cohort design using data from the TriNetX Global Collaborative Network, a real-time, global health research network. We aimed to compare the incidence of Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) among patients with Attention-Deficit Hyperactivity Disorder (ADHD) treated with either stimulant medications or bupropion. Data were collected from 127 Health Care Organizations (HCOs) within the TriNetX network on Aug 12, 2024. The extraction included all patients within the database who met the defined inclusion criteria, irrespective of the timing of their diagnosis. The data encompassed all relevant diagnoses and treatment records available up to and including the extraction date, with follow-up extending from one day after the ADHD diagnosis through the day of data extraction.

Participants

ODD/Stimulant Cohort
Patients aged 12 to 40 years diagnosed with ADHD (ICD-10 code F90.x) and prescribed stimulant medications (dextroamphetamine [ICD-10 code T45.1] or amphetamine [ICD-10 code T45.1]). Exclusion criteria included prior ODD (ICD-10 code F91.x), history of tobacco use (ICD-10 code F17.x), or bupropion use (ICD-10 code T43.4). This cohort initially included 381,336 patients.

ODD/Bupropion Cohort
Patients aged 12 to 40 years diagnosed with ADHD (ICD-10 code F90.x) and prescribed bupropion (ICD-10 code T43.4). Exclusion criteria included prior ODD (ICD-10 code F91.x) and history of tobacco use (ICD-10 code F17.x). This cohort included 134,100 patients.

CD/Stimulant Cohort
Patients aged 12 to 40 years with ADHD (ICD-10 code F90.x) prescribed dextroamphetamine or amphetamine (ICD-10 code T45.1), excluding those with prior Conduct Disorder (ICD-10 code F91.x) or tobacco use disorder (ICD-10 code F17.x). This cohort included 356,533 patients.

CD/Bupropion Cohort
Patients aged 12 to 40 years with ADHD (ICD-10 code F90.x) prescribed bupropion (ICD-10 code T43.4), excluding those with prior Conduct Disorder (ICD-10 code F91.x) or tobacco use disorder (ICD-10 code F17.x). This cohort included 124,777 patients.

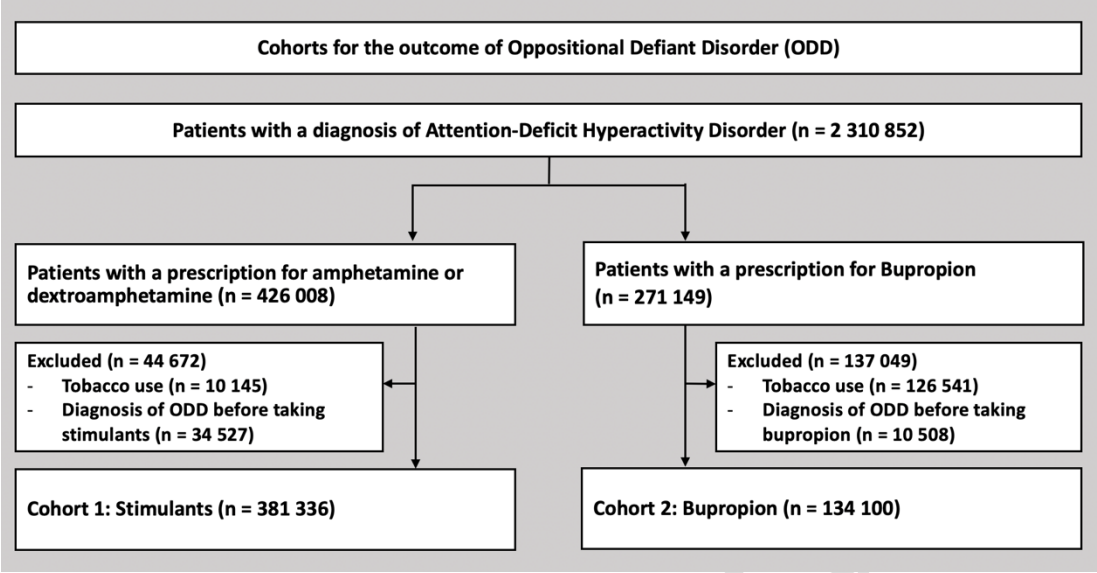

Figure 1. Flowchart of Participant Enrollment in a Retrospective Study on ADHD Treatment with Bupropion vs. Stimulants with Outcome of ODD
This flowchart shows the initial number of patients screened and numbers after excluding prior diagnoses of Oppositional Defiant Disorder (ODD). Tobacco use was also excluded, due to its large association with Bupropion. The chart also illustrates the final number of participants in each treatment group who were included in the two analyses.

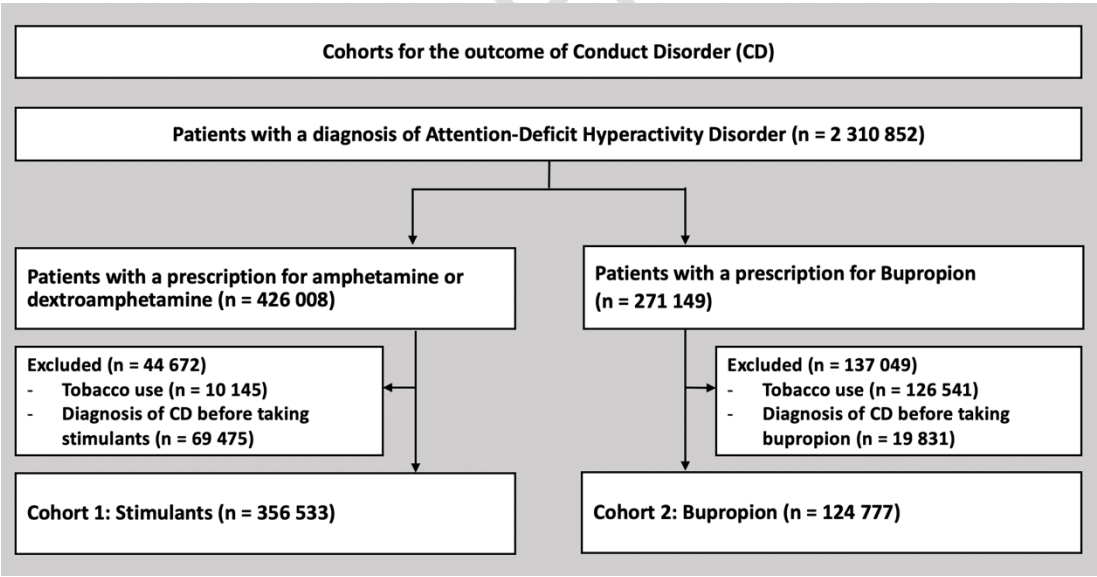

Figure 2. Flowchart of Participant Enrollment in a Retrospective Study on ADHD Treatment with Bupropion vs. Stimulants with Outcome of CD
This flowchart shows the initial number of patients screened and numbers after excluding prior diagnoses of CD. Tobacco use was also excluded, due to its large association with Bupropion.

Index Event and Time Window Definitions

The index event was defined as the first documented diagnosis of ADHD (ICD-10 code F90.x). Outcomes of interest (ODD [ICD-10 code F91.x] and CD [ICD-10 code F91.x]) were tracked from one day after the index event with an open-ended time window. Exclusion criteria for recency were applied, excluding patients with index events more than 20 years prior (9 006 in the stimulant cohort and 1 643 in the bupropion cohort for ODD; 6 947 in Cohort 1 and 1 185 in Cohort 2 for CD).

Outcome Measures

Incidence rates of ODD (ICD-10 code F91.x) and CD (ICD-10 code F91.x) post-index event were the primary outcomes.

Data Sources/Measurement

Data were obtained from the TriNetX network. Measurements of variables, including treatment type and diagnosis, were based on electronic health records and ICD coding. Comparability across groups was ensured through consistent coding practices within the TriNetX network. Access link: https://live.trinetx.com/

Bias

Potential biases include selection bias related to cohort definitions and historical treatment patterns. Efforts to address bias included stringent inclusion and exclusion criteria and validation of cohort definitions. Smoking history was specifically excluded from the analysis due to its potential as a confounding factor associated with higher rates of Oppositional Defiant Disorder and Conduct Disorder.

Study Size

Sample sizes were based on initial queries and inclusion criteria. No formal power analysis was conducted, but the large sample size provided sufficient power to detect meaningful differences.

Statistical Methods

Quantitative variables, such as the incidence rates of outcomes, were analyzed using risk difference, risk ratio, and odds ratio. A significance level of $p < 0.05$ was considered statistically significant. Methods for controlling confounding included statistical adjustments within the TriNetX platform. Missing data were handled by excluding incomplete records from analysis. No formal loss to follow-up occurred as the data were retrospective and complete for the study period. Statistical analyses were performed using TriNetX tools. Methods included risk difference, risk ratio, and odds ratio calculations. Kaplan-Meier survival analysis was used to estimate time to outcome. Sensitivity analyses were conducted to assess robustness of findings under different assumptions.

3. RESULTS

Study Participants

A total of 372 330 patients were included in the stimulant cohort, and 132 457 patients in the bupropion cohort for the ODD analysis. For the Conduct Disorder (CD) analysis, there were 349 586 patients in the stimulant cohort and 123 592 in the bupropion cohort. The number of patients who developed ODD and CD in each cohort is detailed in Table 2 and Table 3. We excluded patients with missing data on key variables and those with incomplete follow-up. Patients were excluded for incomplete records, lack of follow-up data, or if their prescription data did not match the criteria for the respective cohort. Demographic data on participants can be found in table 1 below.

Characteristic	***Stimulants/ ODD***	***Bupropion/ ODD***	***Stimulants/ CD***	***Bupropion/ CD***
Mean Age in Years (SD)	20.6 (8.8)	25.1 (7.09)	21.2 (8.64)	25.4 (6.99)
Gender Distribution				
- Female (%)	45.86%	56.77%	46.82%	57.24%
- Male (%)	51.39%	40.14%	50.17%	39.34%
-Unknown (%)	2.75%	3.09%	3.01%	3.42%
Race Distribution				
- White (%)	71.61%	76.09%	71.81%	75.61%
- Black/African American (%)	9.38%	6.09%	8.6%	5.99%
- Asian (%)	1.77%	2.03%	1.83%	2.07%
- Hispanic/Latino (%)	7.51%	7.3%	7.19%	7.23%
- Other/Unknown (%)	9.73%	8.49%	10.57%	9.1%

Table 1. Characteristics of Study Participants

Demographic and clinical characteristics of participants in the stimulant and bupropion cohorts, including mean age at index, gender distribution, race, and prevalence of comorbidities.

Outcome 1: Oppositional Defiant Disorder (ODD)

Risk Analysis

In a comparative analysis of two cohorts—one consisting of patients prescribed stimulants for Oppositional Defiant Disorder (ODD) and the other of patients prescribed bupropion—significant differences in risk and outcomes were observed. Table 2 shows the number of patients that met the criteria for the two cohorts.

	Patients in Cohort	**Patients with Outcome**	**Risk**
Stimulants	372 330	4 736	1.27%

Bupropion	132 457	624	0.47%

Table 2. Risk of Developing ODD in ADHD Patients Treated with Stimulants or Bupropion

The stimulant cohort (n=372 330) had 4 736 patients who developed the outcome, resulting in a risk of 1.3%. In contrast, the bupropion cohort (n=132 457) had 624 patients with the outcome, translating to a risk of 0.5%.

The risk difference between the two cohorts was calculated to be 0.8% with a 95% confidence interval (CI) of 0.007 to 0.009. The risk ratio was 2.7 (95% CI: 2.484-2.934), indicating that patients in the stimulant cohort were 2.7 times more likely to develop the outcome compared to those in the bupropion cohort. Additionally, the odds ratio was 2.722 (95% CI: 2.503-2.960), further highlighting the increased risk associated with stimulant use.

Kaplan-Meier Survival Analysis

Survival analysis using the Kaplan-Meier method further elucidated differences in outcomes between the two cohorts. For ODD, the survival probability at the end of the time window was 96.23% for the stimulant cohort, compared to 98.78% for the bupropion cohort. The log-rank test yielded a chi-square value of 335.624 with 1 degree of freedom (df), and the difference was statistically significant (P <0.001). The hazard ratio for the stimulant cohort relative to the bupropion cohort was 2.145 (95% CI: 1.973-2.332), indicating a significantly higher risk of the outcome over time for patients in the stimulant cohort.

Number of Instances

The analysis of the number of instances of the outcome revealed a mean of 6.322 instances per patient in the stimulant cohort for ODD, with a standard deviation (SD) of 18.146 and a median of 2 instances. In the bupropion cohort, the mean number of instances was 5.240 (SD: 12.526), with a median of 2 instances. Although the t-test for this comparison yielded a t-value of 1.445 (df=5358) and a p-value of 0.149, indicating no statistically significant difference between the two cohorts.

Outcome 2: Conduct Disorder (CD)

Risk Analysis

The risk analysis revealed that the risk of developing Conduct Disorder was higher in the stimulant cohort compared to the bupropion cohort. Specifically, the risk difference between the two cohorts was calculated to be 0.9% with a 95% confidence interval (CI) ranging from 0.008 to 0.010, which was statistically significant (z = 20.867, P < 0.001).

	Patients in Cohort	Patients with Outcome	Risk
Stimulants	349 586	6 706	1.92%
Bupropion	123 592	624	1.03%

Table 3. Risk of Developing CD in ADHD Patients Treated with Stimulants or Bupropion

The stimulant cohort (n=349 586) had 6,706 patients who developed the outcome, resulting in a risk of 1.92%. In contrast, the bupropion cohort (n=123 592) had 624 patients with the outcome, translating to a risk of 1.03%.

The Risk Ratio (RR) was 1.864 (95% CI: 1.756 to 1.978), indicating that patients in the stimulant cohort were 1.864 times more likely to develop Conduct Disorder compared to those in the bupropion cohort. The Odds Ratio (OR) was similarly elevated at 1.881 (95% CI: 1.771 to 1.998), further confirming the increased risk associated with stimulant use. Figure 1 below summarizes these values.

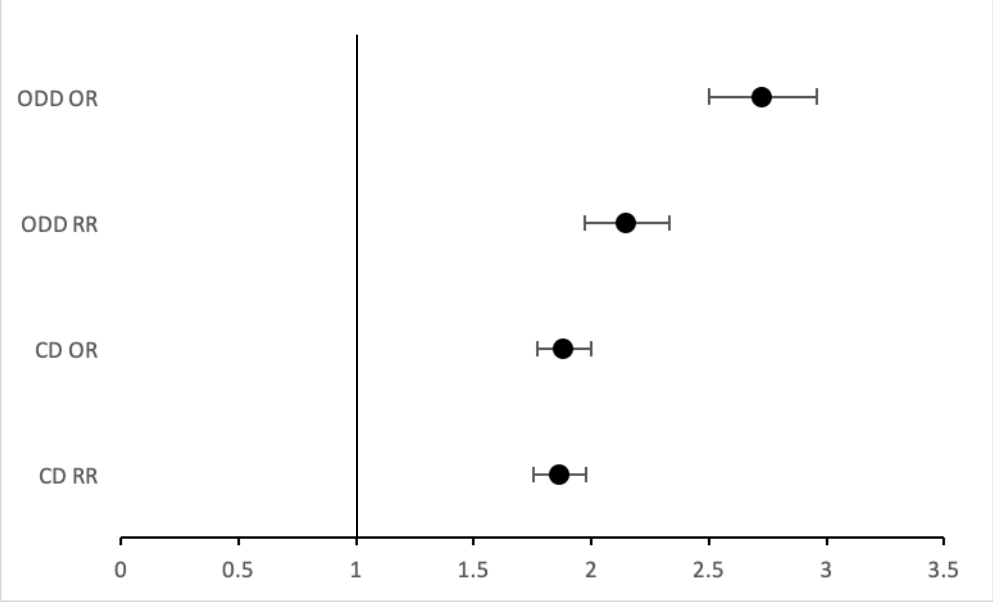

Figure 3. Odds ratios and Risk Ratios of Developing ODD or CD in ADHD Patients Treated with Stimulants vs. Bupropion
ODD OR: 2.722 (95% CI: 2.503-2.960); ODD RR: 2.7 (95% CI: 2.484-2.934); CD OR: 1.881 (95% CI: 1.771 to 1.998); CD RR: 1.864 (95% CI: 1.756 to 1.978).

Kaplan-Meier Survival Analysis
Kaplan-Meier survival analysis demonstrated that the survival probability at the end of the time window was 94.14% for the stimulant cohort, compared to 96.81% for the bupropion cohort. The difference in survival probabilities between the two cohorts was statistically significant, as indicated by the log-rank test ($\chi^2 = 179.694$, df = 1, $P < 0.001$).
The hazard ratio for the stimulant cohort relative to the bupropion cohort was calculated to be 1.504 (95% CI: 1.416 to 1.597), indicating that the risk of developing Conduct Disorder over time was 50.4% higher in the stimulant cohort. This difference was statistically significant, with a chi-square value of 31.967 (df = 1, $P < 0.001$).

Number of Instances
For CD, the mean number of instances in the stimulant cohort was 4.666 (SD: 12.845) with a median of 2, whereas in the bupropion cohort, the mean was 3.550 (SD: 10.148) with a median of 1. The t-test for this comparison was significant, with a t-value of 2.929 (df=7976) and a p-value of 0.003.

4. DISCUSSION

Main Findings

Our study's findings suggest that bupropion, an atypical antidepressant primarily used for depression and smoking cessation, may be associated with a reduced risk of developing Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) in patients with Attention-Deficit/Hyperactivity Disorder (ADHD). This finding is noteworthy as it contrasts with the commonly observed risks associated with stimulant medications.

Bupropion's pharmacological profile, which involves the modulation of norepinephrine and dopamine reuptake, could contribute to its differential impact on behavior and psychiatric comorbidities. The pharmacological effects on the dopaminergic and noradrenergic systems are crucial for behavioral regulation, which may explain its ability to mitigate the risk of CD and ODD. Studies have shown that the behavioral effects of bupropion are more prominent than its cognitive effects (Turgay, 2009). Unlike stimulants, which can exacerbate impulsive and aggressive behaviors, bupropion's effects on mood and impulse control might help mitigate the risk of developing disruptive behavioral disorders. The dopaminergic and noradrenergic systems play crucial roles in behavioral regulation, and bupropion's action on these systems could be beneficial in reducing the incidence of ODD and CD (Wilens et al., 2001).

There is a high comorbidity of anxiety disorders in individuals with ADHD, which ranges from 25% to 50% (Shear et al., 2006). Therefore, the potential for stimulants to exacerbate anxiety symptoms is a significant concern (Mancini et al., 1999). This has led to an increased interest in alternative pharmacological treatments that might offer better tolerability and reduced anxiety. Several studies have suggested that bupropion may effectively reduce ADHD symptoms in both adults and adolescents (Kuperman et al., 2001; Barrickman et al., 1995), with some evidence indicating a lower risk of anxiety compared to stimulant medications (Verbeeck et al., 2017; Wilens et al., 2001; Wilens et al., 2005). Bupropion's efficacy in managing ADHD symptoms, particularly in patients with comorbid anxiety or depression, highlights its potential as a more tolerable alternative to stimulant medications. One randomized, double blind study found no statistically significant difference in anxiety levels between bupropion and methylphenidate, although those on methylphenidate reported more frequent headaches (Jafarinia et al., 2012). Bupropion has also been shown to be effective in treating ADHD with comorbid depression (Daviss et al., 2001). However, comprehensive, large-scale comparisons between bupropion and stimulants specifically focusing on anxiety levels in ADHD patients are limited.

Furthermore, the existing literature underscores the importance of comprehensive ADHD treatment in improving long-term outcomes, including reductions in oppositional and aggressive behaviors. These findings suggest that bupropion could play a key role in a broader treatment strategy aimed at preventing the development of CD and ODD by not only addressing core ADHD symptoms but also mitigating the potential for comorbid psychiatric disorders that are often exacerbated by traditional stimulant treatments. Shaw et al. conducted a systematic review to assess whether ADHD treatment has a preventive effect on delinquent behavior and other long-term outcomes. They found that individuals with treated ADHD generally had better outcomes compared to those untreated, particularly in areas like driving, obesity, self-esteem, and social and academic functioning. However, the impact on antisocial behaviors, such as delinquency and crime, was inconsistent, with only half of the studies showing a positive effect (Shaw et al., 2012). The review highlights the need for more research to identify factors that make ADHD treatment effective in preventing delinquent behavior.

In a study by the MTA Cooperative Group (1999), 579 children with ADHD Combined Type were assigned to four different treatments over 14 months: medication management, intensive behavioral treatment, combined treatment, or standard community care. All groups

showed symptom improvement, but the combined treatment and medication management groups had the most significant reductions in ADHD symptoms. Notably, combined treatment was particularly effective in improving oppositional/aggressive symptoms, internalizing symptoms, and social skills, while medication strategies were generally more effective than community care (MTA Cooperative Group, 1999).

5. CONCLUSION

Bupropion, as an atypical antidepressant, may offer significant benefits in reducing the incidence of Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) among patients with ADHD due to its unique mechanism of action. Unlike stimulants, which primarily act on dopamine reuptake and can exacerbate impulsive and aggressive behaviors, bupropion modulates both norepinephrine and dopamine reuptake. This dual action likely contributes to its positive effects on mood and impulse control, thereby reducing the risk of developing disruptive behavioral disorders.

Our study suggests that bupropion may be associated with a lower risk of developing Oppositional Defiant Disorder and Conduct Disorder in patients with ADHD compared to stimulant medications. The use of the TriNetX database provided a robust platform for analyzing a large, diverse cohort, enhancing the validity of our findings. These results have significant implications for clinical practice, particularly for patients at high risk for comorbid behavioral disorders. The potential for bupropion to manage ADHD symptoms while mitigating the risk of comorbid disorders underscores its value as an alternative treatment option. However, further research is needed to confirm these results, explore underlying mechanisms, and refine treatment strategies for ADHD and its associated comorbidities.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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