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From Smoking Cessation to Recreational Misuse: The Unexpected Journey of Bupropion

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Abstract **Case Report**

Bupropion is an atypical antidepressant that inhibits the reuptake of norepinephrine and dopamine and is approved for the treatment of major depressive disorder and smoking cessation. Its unique pharmacological profile has led to growing interest in other indications, including attention-deficit/hyperactivity disorder (ADHD). However, its dopaminergic activity may also be associated with misuse and dose-related toxicity, particularly in individuals with substance use disorders. We report the case of a 34-year-old man with polysubstance use disorder, ADHD, recurrent depressive disorder, and social anxiety disorder who was admitted for benzodiazepine, pregabalin, and tobacco withdrawal. Treatment with bupropion, venlafaxine, quetiapine, and tapering lorazepam resulted in significant improvement in mood and attentional functioning. Following discharge, however, the patient independently increased his bupropion dosage from 300 mg/day to 600 mg/day and repeatedly requested further dose escalation, raising concerns regarding potential misuse in a context of addictive vulnerability. This case highlights the complex balance between the therapeutic benefits and risks of bupropion in patients with psychiatric and addictive comorbidities. While the drug may improve depressive symptoms, cognitive functioning, and smoking cessation outcomes, its dopaminergic properties may contribute to misuse behaviors in susceptible individuals. Furthermore, doses exceeding recommended therapeutic limits are associated with an increased risk of severe adverse effects, particularly seizures. Careful patient selection, close clinical monitoring, and regular reassessment of the benefit–risk balance are therefore essential when prescribing bupropion to high-risk populations.

Keywords: Bupropion; Misuse; Substance Use Disorder; ADHD; Depression; Toxicity; Seizures.

I. INTRODUCTION

Bupropion is an atypical antidepressant belonging to the class of norepinephrine–dopamine reuptake inhibitors (NDRIs). Its unique mechanism of action distinguishes it from conventional antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) [1].

Initially developed and marketed for the treatment of major depressive disorder, its distinctive pharmacological profile including the relative absence of sedation, sexual dysfunction, and significant weight gain, as well as its dopaminergic activity has led to a progressive expansion of its therapeutic indications.

Today, bupropion is also widely used for smoking cessation and has attracted growing interest in other areas, including attention-deficit/hyperactivity disorder (ADHD) in adults, weight management (particularly in combination with naltrexone), and the treatment of stimulant use disorders. While this diversification reflects its therapeutic versatility, it also raises important concerns regarding safety and appropriate use.

Two major issues currently surround the use of bupropion. First, increasing reports of misuse have emerged, particularly among individuals with psychiatric vulnerabilities or substance use disorders, due to its dopaminergic effects, which may induce feelings of euphoria at high doses. This raises concerns regarding misuse and, in some cases, the development of a substance use disorder involving bupropion itself. Second, bupropion has a relatively narrow therapeutic margin, meaning that toxic doses are not far above recommended therapeutic doses. Consequently,

intentional or accidental overdose may result in serious adverse effects, including seizures, cardiovascular complications, and neuropsychiatric manifestations.

II. CASE REPORT

We report the case of Mr. Z.Y., a 34-year-old unemployed single man admitted to our department for detoxification from benzodiazepines, pregabalin, and tobacco, with the goal of maintaining abstinence.

His psychiatric history included untreated childhood attention-deficit/hyperactivity disorder, marked social anxiety, several major depressive episodes, and a medication overdose suicide attempt in 2015 during a depressive episode. He had also undergone eight previous hospitalizations in addiction treatment units.

Regarding substance use, the patient reported regular consumption of:

- Tobacco: approximately 10 cigarettes per day;
- Benzodiazepines: approximately 6 tablets per day;
- Pregabalin: approximately 15 tablets per day.

The following diagnoses were retained:

- Substance use disorder;
- Attention-deficit/hyperactivity disorder (ADHD);
- Recurrent depressive disorder;
- Social anxiety disorder.

A combined psychotherapeutic and pharmacological treatment approach was initiated, including:

- Bupropion 300 mg/day;
- Venlafaxine 150 mg/day;
- Quetiapine 300 mg/day;
- Lorazepam 7.5 mg/day with gradual tapering.

The patient rapidly reported significant improvement in mood and attentional abilities, likely related to the synergistic effects of bupropion and venlafaxine. However, following discharge, he independently increased the bupropion dose to 600 mg/day and repeatedly requested further dose escalation. This situation raised two major clinical concerns: potential misuse of bupropion for psychostimulant or euphoric effects and the risk of toxicity associated with overdose.

III. DISCUSSION

This case illustrates the complexity of bupropion use in patients with psychiatric and addictive comorbidities. The patient presented several factors likely to influence both treatment efficacy and risk profile, including substance use disorder, adult ADHD, recurrent depressive disorder, and social anxiety disorder.

Therapeutic Value of Bupropion in Addiction and ADHD

Bupropion exerts its pharmacological effects through inhibition of dopamine and norepinephrine reuptake. Unlike serotonergic antidepressants, it directly targets neural circuits involved in motivation, reward processing, and executive functioning.

This mechanism is particularly relevant in patients with addiction, among whom mesocorticolimbic dopaminergic hypoactivity has frequently been described. Several studies have demonstrated that bupropion reduces tobacco craving and alleviates nicotine withdrawal symptoms. Its efficacy in smoking cessation is now well established and represents one of its main approved indications.

In addition, evidence suggests that bupropion may provide benefit in adult ADHD. Although generally less effective than psychostimulants, it represents a valuable alternative for patients with contraindications to stimulants or a high risk of substance misuse. The rapid improvement in attentional functioning observed in our patient is consistent with published findings regarding the effects of bupropion on executive functions and attention regulation.

The frequent coexistence of ADHD and substance use disorders deserves particular attention. Epidemiological studies indicate that individuals with ADHD are significantly more likely to develop substance use disorders during their lifetime. In this context, bupropion may represent a particularly relevant therapeutic option because it simultaneously targets multiple psychopathological dimensions.

Misuse Potential and Addictive Properties

Although bupropion is not classified as a controlled substance in most countries, increasing numbers of misuse cases have been reported, particularly in North America.

Its misuse potential is believed to result from its dopaminergic activity. Although considerably weaker than cocaine or amphetamines, dopamine transporter inhibition may produce stimulant-like effects at high doses, including increased energy, enhanced well-being, reduced fatigue, and mild euphoria.

Cases involving supratherapeutic doses exceeding 1,500 mg and even 3,000 mg per day have been described. Some individuals report subjective effects resembling those produced by amphetamines. Various routes of misuse have been documented, including intranasal administration, intravenous injection following tablet dissolution, and repeated ingestion of high oral doses.

Risk factors associated with misuse include:

- History of substance use disorders;

- Personality disorders;
- History of incarceration;
- Seeking psychostimulant effects;
- Poorly controlled ADHD.

Several of these risk factors were present in our patient. His repeated requests for dose escalation despite objective clinical improvement may be considered a warning sign suggestive of non-therapeutic use. Although a formal diagnosis of bupropion use disorder cannot be established, this case underscores the importance of carefully monitoring medication-related behaviors in individuals with addictive vulnerabilities.

Toxicity and Consequences of Overdose

The toxicological profile of bupropion represents another important aspect of its clinical use. Among currently available antidepressants, bupropion is recognized as one of the most epileptogenic agents.

At recommended therapeutic doses, seizure incidence is estimated to range between 0.1% and 0.4%. However, this risk increases substantially when daily doses exceed 450 mg. Extended-release formulations pose additional challenges because delayed absorption may postpone symptom onset for several hours.

Although the precise mechanisms remain incompletely understood, bupropion and its active metabolites appear to increase neuronal excitability through modulation of catecholaminergic pathways, thereby facilitating seizure occurrence.

Clinical manifestations of intoxication may include:

- Psychomotor agitation ;
- Tremor;
- Hallucinations ;
- Confusion ;
- Sinus tachycardia;
- QRS and QT prolongation ;
- Ventricular arrhythmias;
- Seizures;
- Status epilepticus.

Seizures may occur up to 24 hours after ingestion of extended-release formulations, warranting prolonged observation of asymptomatic patients following significant overdose.

In the present case, several factors likely lowered the seizure threshold, including a history of heavy substance use, recent benzodiazepine withdrawal, and unsupervised dose escalation.

ADHD, Addiction, and Misuse of Dopaminergic Treatments

The presence of ADHD constitutes a key element in understanding this patient's clinical course. Numerous studies have demonstrated that adults with ADHD are at significantly increased risk of developing substance use disorders compared with the general population.

This association may be explained by shared neurobiological mechanisms involving mesocortical and mesolimbic dopaminergic pathways responsible for attention regulation, motivation, and reward processing. Impulsivity, sensation seeking, difficulties delaying gratification, and executive dysfunction may contribute to the initiation and maintenance of addictive behaviors.

Some authors have proposed the self-medication hypothesis, suggesting that psychoactive substances or psychotropic medications may be used to compensate for attentional deficits, motivational difficulties, or emotional dysregulation associated with ADHD.

In this context, the rapid improvement in attention and cognitive functioning observed after initiation of bupropion may have increased the patient's subjective valuation of the medication. Consequently, his repeated requests for dose escalation may reflect not only a search for euphoric effects but also a desire to enhance or maintain perceived cognitive and motivational benefits.

This distinction is clinically important. In patients with co-occurring ADHD and substance use disorders, requests for higher doses do not necessarily indicate recreational intentions. They may also reflect persistent ADHD symptoms, unrealistic treatment expectations, or confusion between cognitive enhancement and psychostimulant effects.

Nevertheless, the coexistence of severe polysubstance use, addictive behaviors, and unsupervised dose escalation constitutes a significant warning signal requiring close monitoring.

IV. CONCLUSION

Bupropion represents an effective therapeutic option for patients with substance use disorders, particularly when comorbid ADHD, depression, or social anxiety disorder are present. However, its potential for misuse, although relatively uncommon, requires particular vigilance among individuals with addictive vulnerabilities. Furthermore, its narrow therapeutic margin entails a significant risk of toxicity, especially seizure-related toxicity, which must be anticipated and promptly managed in cases of overdose. Careful monitoring, patient education, and multidisciplinary follow-up are essential to maximize therapeutic benefits while minimizing associated risks.

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