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Bupropion-induced psychosis: folklore or a fact? A systematic review of the literature

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Abstract

Objective: Bupropion is a substituted phenyl-ethylamine that is extensively utilized for the treatment of major depressive disorder and for smoking cessation. It is a reuptake inhibitor of dopamine and norepinephrine, and it also has some nicotinic antagonism. There are concerns that it may increase the risk of psychosis due to its dopaminergic effects. Our objective is to review the literature and analyze the risk of bupropion precipitating a psychotic illness in the general population as well as in the populations with a history of psychotic symptoms.
Methods: A Medline database search limited to human and English-language studies was conducted using the keywords "bupropion" and "psychosis." A total of 23 articles were selected based on the relevance of the articles and their references. The data from these articles were collated.
Results: Collated data show that there is some evidence to suggest that bupropion may cause or worsen psychosis in selected subpopulations. Higher doses of bupropion appear more likely to be associated with the outcome severity. Preexisting psychotic symptoms, substance abuse and drug interactions also seem to increase the risk. Concurrent use of antipsychotics at adequate doses appears to be protective.
Conclusions: The literature is incomplete and in some cases contradictory. In selected cases, bupropion appears to be associated with the induction of psychotic symptoms in addition to the precipitation or worsening of an existing psychotic syndrome. Further research including controlled studies is required to clarify the risk of bupropion precipitating a psychotic illness in vulnerable populations.

Keywords: Bupropion; Psychosis; Dopamine; Delirium; Catatonia

1. Introduction

Bupropion is a substituted phenyl-ethylamine antidepressant that was approved in 1989 by the Food and Drug Administration (FDA) in the United States for treatment of depression, with a recommended maximum daily dose of 450 mg. In 1997, it was also FDA approved for the indication of smoking cessation under the name Zyban, and in 2006, bupropion extended release was FDA approved for prophylaxis of seasonal depression. The original immediate-release formulation of bupropion was dosed three times daily. In an effort to improve tolerability and safety, a sustained-release (SR) formulation of bupropion, dosed twice daily, was subsequently introduced, and a once-daily extended-release formulation became available in 2003 [1]. Bupropion is a reuptake inhibitor of dopamine (DA) and norepinephrine (NE). It also acts as an antagonist at nicotinic acetylcholine receptors (nAchR), but it has no clinically significant effect on serotonin transporters [2–5]. It is reported to be more potent at the DA transporter as compared to the NE transporter, thereby increasing DA activity to a greater extent particularly in nucleus accumbens and in prefrontal cortex [4]. Bupropion undergoes extensive first-pass hepatic metabolism to multiple active metabolites that

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contribute to its psychotropic effects [4–6]. Bupropion is a substrate for cytochrome P450 (CYP) 2B6, and it is an inhibitor of CYP 2D6 [6]. Genetic polymorphisms and age-related variability in activity of CYP2B6 may have an impact on blood levels of bupropion and its metabolites in different people [5,7]. Inhibition of bupropion metabolism could also occur with drugs such as paroxetine, sertraline, fluoxetine, diazepam, clonazepam, ritonavir, efavirenz and others that may inhibit CYP2B6 by competitive or noncompetitive enzyme inhibition activity [6,8].

Bupropion has been found to have an efficacy comparable to the serotonin reuptake inhibitors (SSRIs) in major depression. In addition, it has been reported to augment the antidepressant effects of SSRIs in major depression and to have a beneficial effect in attention-deficit/hyperactivity disorder and seasonal affective disorder [4,5]. One significant advantage of bupropion is a reduced risk of sexual side effects when compared to SSRIs [4]. In addition, Post et al. found that it presented less risk of precipitating a manic switch in comparison to serotonin–norepinephrine reuptake inhibitors such as venlafaxine and that the risk might be comparable to SSRIs when used as an antidepressant in patients with bipolar disorder especially the rapid cycling type [9].

Due to its dopaminergic action, bupropion has a potential of precipitating psychosis in selected at-risk populations [10–12]. Excess DA is implicated in the pathogenesis of psychosis [13–15]. The potency of typical antipsychotics is directly correlated with their affinity for dopamine 2 receptors. It is also suggested that, at least in animal models, various types of injuries including stimulant exposure cause a preponderance of high-affinity states among DA receptors [13] that may be linked to the onset of psychotic symptoms. These observations support the view that even if the DA hypothesis does not fully explain the etiology of psychosis and schizophrenia, DA does play a significant role in the pathogenesis of psychosis. Therefore, as bupropion is a DA reuptake inhibitor and is related chemically to ethylamine stimulants, there is a question regarding the risk of bupropion precipitating psychosis de novo or initiating a recurrent psychotic episode in persons with a preexisting psychotic disorder.

2. Literature search

A literature search was conducted utilizing the Medline database. Keywords included “bupropion” and “psychosis.” The search was limited to human and English-language studies. A total of 43 results were retrieved. Out of these, 14 articles were selected based on their relevance to the topic at hand by reviewing the titles. Later, 9 more articles were included from the references of the original 14 chosen articles using the same methodology. The final results included 13 case reports, 1 case series, 7 controlled studies and 2 letters to editor on this subject (Tables 1, 2).

3. Results

Reports of perceptual alterations and psychotic symptoms associated with bupropion date back to as early as 1982 by Becker and Dufresne [16], before the drug received formal FDA approval. From the premarketing clinical trials, Johnston et al. reported an overall 2.8% incidence of hallucinations and 1.4% incidence of delusions in aggregate data from all trials. Consequently, they did not recommend using bupropion as a first-line drug for patients with a history of psychosis [17].

Cases continue to appear in literature, with the most recent one reported by Farooque et al. in 2010 [18]. A review of the selected literature revealed a variety of findings including data both suggesting and refuting the role of bupropion in precipitating psychosis in selected populations. The symptoms range from perceptual disturbances such as alteration of time sense, vivid dreaming [16], psychotic symptoms (e.g., paranoia, delirium, auditory and visual hallucinations) [19,20] and even catatonia [21]. Usage of these different terms deters delineation of the clinical response as it points towards precipitation of categorically different syndromes. The symptoms of psychosis induced by bupropion may be described as variants of catatonia according to the nosological system of Fink and Taylor [22,23]. These authors have proposed that catatonia should have a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* classification with three subtypes and four specifiers [23]. Thus, the existence of such states on a continuum seems to be more likely in this case, with the underlying mechanism being the hyperactivity of the dopaminergic system. This concept is not new and has been described in literature already, albeit in a different context [24]. Therefore, for the sake of simplicity, in this review, we have included all of these categories under an umbrella term of “psychotic symptoms,” although we have also striven to use the exact symptoms described by the authors.

In some of the studies and case reports in which bupropion was associated with psychotic symptoms and perceptual alterations warranting dose reduction or discontinuation of the medication, the patients received doses greater than 450 mg daily, which is above current recommendations [10,16,25,26]. In one of these cases, psychosis followed an overdose of bupropion SR 4200 mg [26]. Another study compared bupropion alone vs. bupropion in combination with haloperidol for the treatment of schizoaffective disorder in which bupropion doses ranged from 450 to 750 mg daily in three equally divided doses [10]. Out of nine patients in the bupropion group, three experienced psychosis warranting their withdrawal from the study, whereas no one in the bupropion plus haloperidol group experienced any psychosis [10]. All 12 patients studied by Becker and Dufresne experienced some type of perceptual alteration with bupropion, with the average dose being 561 ± 120 mg daily. According to the authors, “bupropion was associated with vivid dreaming and changes in attention, memory, and perception which may have contributed to its therapeutic effectiveness.” However, these