

Bupropion and Panic Disorder: Case Report and Review of the Literature

To the Editor: Whether bupropion is effective in the treatment of panic disorder is still a matter of debate. We report the case of a 47-year-old man with panic disorder initially treated with bupropion 150 mg daily. At 300 mg daily (because of the recurrence of anxiety symptoms) he had only a partial response to treatment, and he developed chest pain, severe agitation, increased anxiety, and cognitive impairment. Although the present data were limited by the nature of this case presentation, we suggest that bupropion may be a useful effective treatment option in patients with panic symptoms at only 150 mg daily.

About 1 in 20 people in the U.S. has a lifetime diagnosis of panic disorder. Recently, it was reported that in the U.S., the overall 12-month and lifetime prevalence rates for panic disorder (with or without agoraphobia) were, respectively, 2.1% and 5.1%, whereas the 12-month and lifetime prevalence rates for panic disorder with agoraphobia were, respectively, 0.6% and 1.1%.¹ Panic disorder with or without agoraphobia is more common in women, middle-aged people, people with low income, and in those who were widowed, separated, or divorced.¹ Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly used to treat both depressive and anxiety disorders.² Bupropion is the only antidepressant with a combined action on

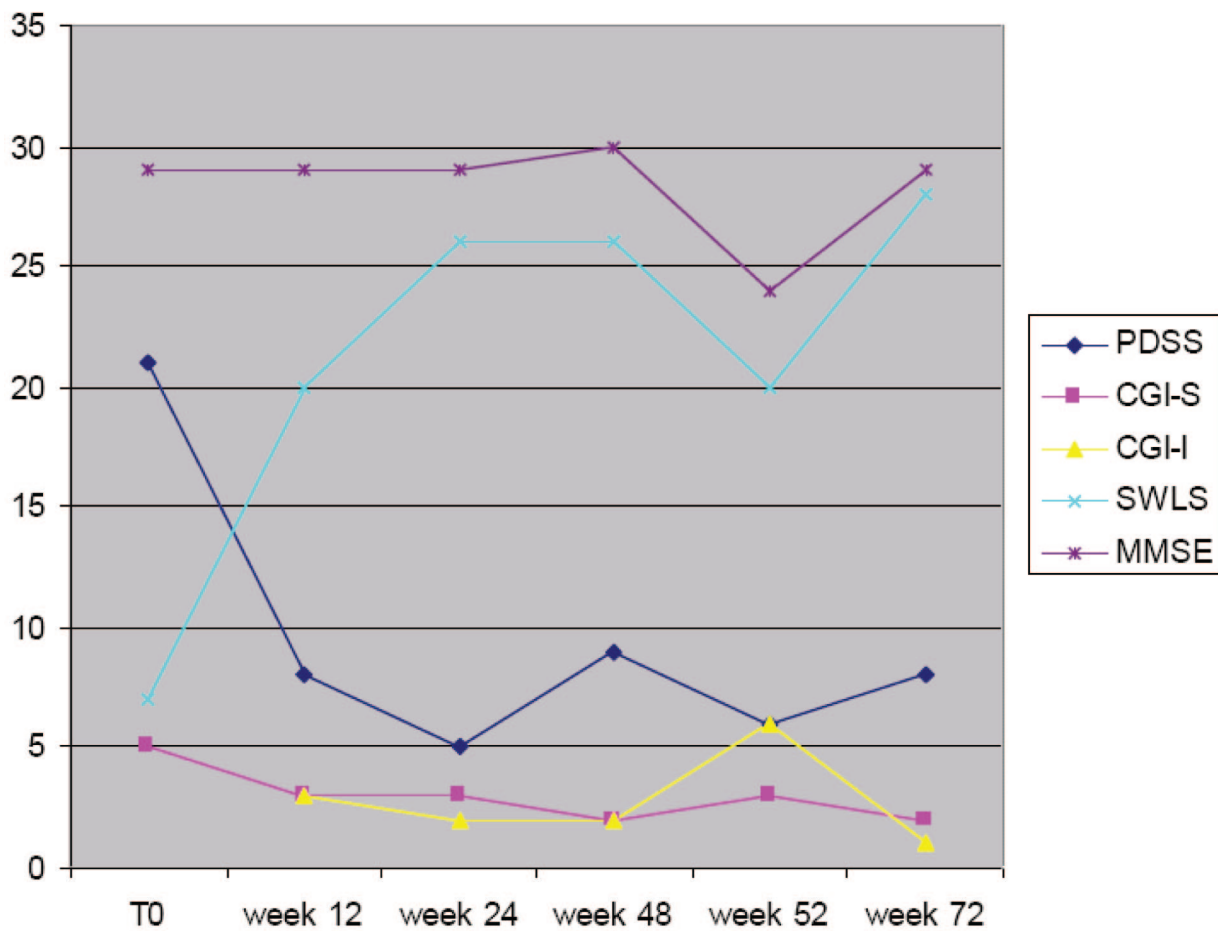
norepinephrine and dopamine neurotransmitter systems without any serotonergic activity,³ and it was initially developed to improve safety and tolerability of existing antidepressants.⁴ A recent survey revealed that this agent is mostly prescribed with the aim of ameliorating specific side effects, like sexual dysfunction, weight gain, and fatigue.⁵ Whether bupropion is effective in reducing anxiety symptoms is still not known, and only few reports have addressed efficacy of bupropion in patients with panic disorder.^{6,7} To our best knowledge, this is the first case report addressing this issue over a long follow-up period.

Case Report

A 47-year-old man with an 8-year history of panic disorder (with agoraphobia) previously treated with SSRIs antidepressants presented to the outpatient clinic with panic attacks (during the previous year, he suffered from more than two full panic attacks per week but less than one/day). Such attacks were characterized by shaking, trembling, tenseness, increased heart rate, breathlessness, dyspnea, fear of losing control and going crazy, and feelings of unreality. Such symptoms were associated with concerns regarding his negative social performance with agoraphobic behaviors (he becomes anxious in environments that are unfamiliar, and he feels that he may lose control when traveling even for short distances). He was diagnosed with DSM-IV panic disorder.⁸ At baseline, his Panic Disorder Severity Scale (PDSS)⁹ score was 21, the Clinical Global Impression, Severity of the illness (CGI-S)¹⁰ was 5. He was absolutely unsatisfied with life,

as assessed by the Satisfaction-With-Life Scale (SWLS)¹¹ score, which was 7, and he experienced a poor quality of life. He was treated with bupropion over a period of 72 weeks. Initial titration was 150 mg daily, with a subsequent improvement of panic symptoms over the following 12 weeks and 24 weeks of treatment (T1, T2) and a related improvement in his satisfaction and quality of life. However, at the following assessment (T3, after 48 weeks of treatment), he suffered from new panic attacks, characterized by feelings of unreality, dizziness, and agoraphobia, as assessed by the PDSS and CGI-S scores. No significant negative life-events were recorded at this time. He particularly described his symptoms as distressing and uncomfortable, described continued concerns regarding recurrence of the next panic attack, causing associated avoidance of social activities. Figure 1 summarizes in more detail the most relevant changes in all the clinical measures at the various time-points. Because of these problems, dosage of bupropion was increased to 300 mg daily, with a general improvement of agoraphobic avoidance; however, he later reported (T4, at 52-week follow-up) strong adverse effects, consisting of chest pain, severe agitation, increased daily anxiety, and cognitive impairment (e.g., short-term memory; altered ability to perform simple, relatively automatic, visual-motor tasks and maintain attention under timed conditions; and concentration- and attention-deficit), which were only clinically observed. His Mini-Mental State Exam (MMSE)¹² score was 24. At this time, he worked as a [broadcast employer] and described diffi-

FIGURE 1. Values (Scores) at Various Time-Points for All the Assessment Measures Applied



culties in taking phone messages and understanding new information. He also complained of motor problems with sports activities requiring rapid hand-eye coordination. After reduction to 150 mg bupropion per day, these adverse effects disappeared, and the clinical picture significantly improved, as showed in Figure 1. After 72 weeks of follow-up (T5) he gained more self-esteem; social-avoidance behaviors were reduced; and his level of life satisfaction significantly improved. At bupropion treatment of 150 mg daily, his MMSE score was 29. The study protocol was reviewed and approved by the local Public Health Department

IRB, and the patient provided written informed consent.

Discussion

We observed a substantial improvement in panic- and anxiety-related symptoms in a patient with a DSM-IV panic disorder diagnosis, hypertriglyceridemia, and hypercholesterolemia with bupropion at 150 mg daily and the onset of symptomatology characterized by chest pain, severe agitation, increased anxiety, and cognitive impairment at increased dosage (300 mg daily). This case report showed that bupropion was effective not only in reducing or eliminating panic attacks, avoidance

behavior, and anticipatory anxiety, but also in improving and normalizing psychosocial functioning and quality of life that represent the most relevant pharmacologic goal in the treatment of panic disorder.¹³ Only a few previous studies in the literature investigated the efficacy of bupropion in panic and anxiety disorders. Simon et al.⁶ have suggested in 20 outpatients meeting criteria for panic disorder with or without agoraphobia in an 8-week, two-center, open-label, flexible-dose trial, that bupropion SR may be meaningfully effective, resulting in clinically and statistically significant mean reduction of 1 to 2 points in the main outcome

measure (CGI Severity score), in both the intent-to-treat and completer samples. Gebhardt et al.¹⁴ most recently have reported that bupropion may be effective and well-tolerated in the case of a patient with Parkinson's disease who also suffered from panic disorder. However, previous evidence reported negative findings (e.g., increased panic and anxiety symptoms) with combined pharmacological strategies of the SSRI fluoxetine and bupropion,¹⁵ and a related lack of efficacy in the treatment of panic disorder with phobias.^{16,17} Also, we found that bupropion was effective and well tolerated only at 150 mg daily. When his dosage was increased to 300 mg daily, our patient experienced strong adverse effects; in particular, he was very fearful about the onset of chest pain. Effectively, the presence of cardiovascular risk factors such as hypertriglyceridemia, hypercholesterolemia, and hyperlipidemia, combined with the possible drug-induced coronary vasospasm, increased the risk of developing acute cardiovascular disease. de Graaf and Diemont¹⁸ have suggested that treatment with bupropion may be associated with chest pain, presumably exerting a direct action on the human myocardium by triggering catecholamine release.¹⁹ According with this evidence, Vidovich et al.²⁰ recently reported that bupropion presumably exacerbated a recent angina episode through coronary vasospasm in a patient suffering with depression, panic episodes, and recurrent coronary vasospasm, so bupropion treatment required a reduction of dosage in patients with cardiovascular disease. A further consideration must be relative to cognitive impairment, which was clinically observed with bupropion treatment at increased dosages. It was reported that bupro-

pion may suppress tumor-necrosis factor (TNF) synthesis by mediating increased signaling at beta-adrenoreceptors and D1 receptors, resulting in increased cAMP, which inhibits TNF synthesis.²¹ TNF is a pleiotropic cytokine deemed crucial in a broad range of biological activities, including inflammation, cell survival, and cell proliferation, but, also, cell death.²² TNF is also an important mediator of the β -amyloid (A β)-induced inflammatory response of the cognitive impairment in Alzheimer's disease,²³ so that TNF production seems to be determinant in synaptic plasticity and memory-formation in the healthy brain. However, the lack of an adequate check of cytokine levels and a direct relationship between increased cytokine levels and cognitive impairment do not allow us to hypothesize that bupropion treatment at higher dosages may be associated with synaptic loss and memory-consolidation disruption. Finally, bupropion may be effective only in some clinical aspects of anxiety disorders; in fact, although the features constituting the DSM-IV diagnostic definition of panic disorder form a coherent syndrome,²⁴ researchers have also documented only a partial independence of these symptom domains (e.g., panic frequency is not strongly associated with agoraphobic avoidance).²⁵ So, we believe, reviewing earlier evidence,²⁶ that bupropion at higher doses could be effective only in reducing symptoms like agoraphobic avoidance and less in reducing panic/anxiety symptomatology itself. We believe that physicians may benefit from this case presentation, which, although limited by the clinical nature of the study, adds relevant evidence of the efficacy of bupropion in panic disorder, also because results were sus-

tained over a long period of follow-up.

Conclusion

Only a few systematic prospective data studies and anecdotal reports have suggested that bupropion may be effective for panic/anxiety disorders. For patients suffering from a panic disorder, bupropion may be an effective and well-tolerated treatment strategy over a long follow-up period. However, we also found that bupropion was really effective and well-tolerated only when administered at mid-dosages. Further systematic longitudinal studies are required to test this hypothesis.

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