Bupropion for Patients With Obsessive-Compulsive Disorder: An Open-Label, Fixed-Dose Study

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Objective: In the present study, we examined the efficacy of bupropion for patients with obsessive-compulsive disorder (OCD).

Method: Twelve patients with OCD according to DSM-IV criteria were included in an open trial with bupropion, maximum dosage 300 mg per day, during 8 weeks. The primary efficacy parameter was the Yale-Brown Obsessive Compulsive Scale (YBOCS). A responder was defined by a reduction in score on the YBOCS of ≥ 25%. Data were collected from February 2003 to July 2003.

Results: An intent-to-treat analysis using the last observation carried forward demonstrated that bupropion had no mean effect on OCD symptoms (mean YBOCS decrease was 1.1 ± 9.6). Four patients improved, with a mean decrease on the YBOCS of 31%, and 2 of them met responder rate criteria. Eight patients experienced an exacerbation of OCD symptoms, with a mean increase on the YBOCS of 21%.

Conclusion: Bupropion is not an effective treatment for OCD, but the bimodal distribution of the effect supports the notion that dopamine might be involved in the pathophysiology of OCD.

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Serotonin reuptake inhibitors (SRIs) are the drugs of choice for the treatment of obsessive-compulsive disorder (OCD).[1] Improvement of treatment is, however, an unmet need in OCD, because 40% to 60% of the patients fail to respond to SRIs,[2] and a substantial number of patients who do respond are left with residual symptoms.

Unlike SRIs, bupropion is a preferential dopamine and norepinephrine reuptake inhibitor.[3] It has shown to be effective in patients with depression and social phobia,[4,5] but data on its efficacy in OCD are lacking. In view of the high comorbidity of OCD with social phobia and major depression, bupropion might also be effective in patients with OCD.[6–9] Moreover, recent studies from our group have implicated dopamine in the pathophysiology of OCD.[10,11] In addition, atypical antipsychotics have been shown to augment the effects of SRIs in OCD patients who fail to respond to SRIs alone.[12–14] These data all point to a possible role of dopamine in OCD.[15–19] These findings prompted us to study the efficacy and tolerability of bupropion in patients with OCD.

METHOD

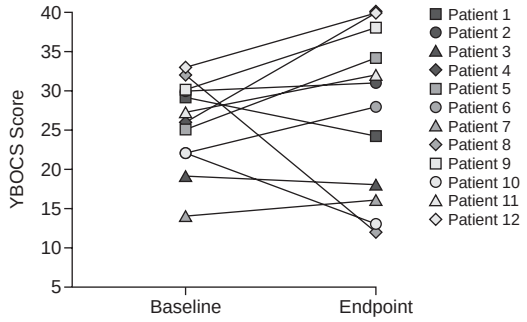
Subjects

Twelve outpatients (6 women and 6 men) gave written informed consent for participation in this study. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht, Utrecht, the Netherlands. The mean ± SD age of the patients was 32.5 ± 9.0 years. Patients were diagnosed with primary OCD according to DSM-IV criteria,[20] ascertained with the Mini-International Neuropsychiatric Interview (MINI).[21] The MINI is a short, structured diagnostic psychiatric interview for DSM-IV disorders. Inclusion criteria were at least 1 year's duration of OCD symptoms together with a score on the Yale-Brown Obsessive Compulsive Scale (YBOCS)[22] of at least 18, or 12 if the patient exhibited only obsessions or compulsions. The subjects' mean score on the YBOCS was 25.8 ± 6.0, and the mean duration of illness was 16.6 ± 8.0 years.

Three patients had a comorbid diagnosis of dysthymia following the DSM-IV criteria with a Hamilton Rating Scale for Depression (HAM-D)[23] score (17 items) of less than 17. One patient met DSM-IV criteria for a social phobia. A concomitant obsessive-compulsive personality disorder was present in 2 subjects.

Patients were excluded if they received a current codiagnosis of dementia, delirium, or amnestic or other cognitive disorders; schizophrenia or other psychotic disorders; bipolar disorder; or substance use disorder. Patients with major depressive disorder (MDD) were also excluded.[23] The mean HAM-D score of the subjects included in this study was 5.8 ± 3.0. Six of 12 patients were

Figure 1. YBOCS Score Changes in 12 OCD Patients in an 8-Week Trial of Bupropion



Abbreviations: OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

medication naive, and those who had been using psychotropic medication were drug free for at least 2 weeks. None of the patients had been using fluoxetine. All patients were healthy based on the results of physical examination.

Study Design

In an 8-week trial, patients started with bupropion extended release (XR) at a dosage of 150 mg/day, which was increased to a maximum of 300 mg/day after 2 weeks. No other psychotropic drugs were administered, and behavioral therapy was not administered. Behavioral ratings administered every 2 weeks included the YBOCS, the global improvement item of the Clinical Global Impressions scale (CGI),[24] the 17-item HAM-D, and the Hamilton Rating Scale for Anxiety (HAM-A).[25] Blood pressure, pulse, and side effects were recorded at each visit. Data were collected from February 2003 to July 2003.

Statistical Analysis

The primary efficacy parameter, the YBOCS score, was analyzed for all patients with at least 1 assessment after baseline, following an intent-to-treat (ITT), last-observation-carried-forward procedure with 1-way analysis of variance. Response to treatment was defined as a $\geq$ 25% decrease in YBOCS score compared with baseline. Baseline-to-endpoint changes in the outcome measures were examined for significance with 2-tailed Student t tests, with $p \leq .05$.

RESULTS

The ITT analysis showed a nonsignificant mean decrease in YBOCS score of 1.1 ± 9.6. Four patients improved (mean decrease 31%), of whom 2 could be qualified as responders, and 8 patients deteriorated (mean increase 21%) (Figure 1), resulting in an early discontinuation of 5 patients. Similar data were obtained on the CGI. Patients whose conditions were exacerbated were predominantly women (N = 5), with a higher number of previous pharmacologic treatments and a higher baseline score of compulsions on the YBOCS. Other characteristics like age, age at onset, duration of illness, and subtypes of OCD symptoms could not distinguish responders from nonresponders.

At baseline, the mean ± SD HAM-D and HAM-A scores were 5.8 ± 3.4 and 2.7 ± 2.1, respectively. In the entire sample, mean HAM-D scores increased nonsignificantly (3.2 ± 6.8), and the mean HAM-A scores increased significantly (4.7 ± 5.0, $p < .01$). In the 5 dropouts, the mean HAM-D scores (7.8 ± 6.3, $p < .05$) and mean HAM-A scores (8.4 ± 5.6, $p = .05$) increased significantly. Subanalyses on the HAM-D anxiety and depression items did not show a predominant increase in either item.[26]

Side effects included sleeplessness (N = 6), dry mouth (N = 5), nausea (N = 5), obstipation (N = 2), nervousness (N = 3), and palpitations (N = 1). Patients 2 and 9 stopped smoking as a side effect, and patient 2 started smoking again after he stopped bupropion because of exacerbation of OCD symptoms. Patient 3 experienced a small improvement of his social phobia.

DISCUSSION

The data show that bupropion is not an effective treatment for patients with OCD, which contrasts to findings in patients with MDD and social phobia.[4,5] Placebo-controlled trials in depression reveal that SRIs and bupropion are equally effective in this condition.[5] In an open-label study in patients with social phobia, bupropion has also shown promising results in that 50% of the patients who completed the study were considered responders to treatment.[4] The present findings therefore confirm that OCD stands out as a psychiatric condition that responds to all antidepressants uniquely related to the serotonin system.

The finding that some patients experienced a substantial deterioration is intriguing in view of the purported role of dopamine in the pathophysiology of OCD. It is tempting to speculate that the deterioration is accounted for by the increased availability of dopamine elicited by bupropion.[27] Several lines of evidence have implicated dopamine in the pathophysiology of OCD. First, amphetamine, a dopamine releaser, has been reported to induce compulsive behavior in hyperactive children.[28,29] Second, animal studies have shown that quinpirole, a dopamine D_2 receptor agonist, induces compulsive checking behavior in rodents.[30,31] Third, addition of an atypical antipsychotic to ongoing therapy with an SRI has been shown to reduce the severity of obsessive-compulsive symptoms in therapy-refractory patients.[12–14]

To date, 2 studies have directly addressed the role of dopamine in OCD. Using [^{123}I]iodobenzamide (IBZM)

single-photon emission computed tomography (SPECT) imaging, we recently found a decreased D_2 receptor binding in the basal ganglia of patients with OCD.[10] In another SPECT study conducted by our group with $^{[123]}$I-beta CIT SPECT imaging, a higher dopamine transporter binding (DAT) ratio was found in the basal ganglia of patients with OCD as compared with age- and sex-matched controls.[11] Similar findings using another SPECT ligand were recently also reported by Kim et al.[32] Since bupropion blocks the DAT, resulting in elevated levels of extracellular dopamine, one would expect an improvement of OCD symptoms if the elevated DAT binding is the primary cause of the symptoms. However, if the observed increased DAT binding is secondary to, e.g., an elevated dopaminergic output in the basal ganglia of OCD patients, and the lower D_2 binding also points in this direction, one would expect blockade of the DAT by bupropion to increase OCD symptoms.

Limitations of this study are the small sample size and the open-label design of the study. Whether the direction of the response was related to availability of bupropion is also unknown, as no blood drug levels were available. Due to the risk of epileptic insults, a known side effect at higher dosages, the maximum dosage of bupropion in this study was limited to 300 mg daily. In conclusion, although bupropion is not effective for OCD, the results of our study support the notion that dopamine might be implicated in the pathophysiology of OCD.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), norepinephrine (Levophed and others).

REFERENCES

1. Greist JH, Jefferson JW, Kobak KA, et al. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: a meta-analysis. Arch Gen Psychiatry 1995;52:53–60
2. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder: a double-blind comparison with placebo. Arch Gen Psychiatry 1989;46:36–44
3. Li SX, Perry KW, Wong DT. Influence of fluoxetine on the ability of bupropion to modulate extracellular dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. Neuropharmacology 2002;42:181–190
4. Emmanuel NP, Brawman-Mintzer O, Morton WA, et al. Bupropion-SR in treatment of social phobia. Depress Anxiety 2000;12:111–113
5. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. Ann Pharmacother 2001; 35:1608–1613
6. Grabe HJ, Meyer C, Hapke U, et al. Lifetime-comorbidity of obsessive-compulsive disorder and subclinical obsessive-compulsive disorder in Northern Germany. Eur Arch Psychiatry Clin Neurosci 2001;251: 130–135
7. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychol Med 2001; 31:481–487
8. Overbeek T, Schruers K, Vermetten E, et al. Comorbidity of obsessive-compulsive disorder and depression: prevalence, symptom severity, and treatment effect. J Clin Psychiatry 2002;63:1106–1112
9. Welkowitz LA, Struening EL, Pittman J, et al. Obsessive-compulsive disorder and comorbid anxiety problems in a national anxiety screening sample. J Anxiety Disord 2000;14:471–482
10. Denys D, van der Wee N, Janssen J, et al. Low-level of dopaminergic D_2 receptor binding in obsessive-compulsive disorder. Biol Psychiatry 2004; 55:1041–1045
11. van der Wee NJ, Stevens H, Hardeman JA, et al. Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by [123I][beta]-CIT SPECT. Am J Psychiatry. In press
12. Denys D, van Megen H, Westenberg H. Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive-compulsive disorder: an open-label study. J Clin Psychiatry 2002;63:700–703
13. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57:794–801
14. Hollander E, Rossi NB, Sood E, et al. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. Int J Neuropsychopharmacol 2003;6:397–401
15. Goodman WK, McDougle CJ, Price LH, et al. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? J Clin Psychiatry 1990;51(suppl 8):36–43
16. Brambilla F, Perna G, Bussi R, et al. Dopamine function in obsessive compulsive disorder: cortisol response to acute apomorphine stimulation. Psychoneuroendocrinology 2000;25:301–310
17. Campbell KM, McGrath MJ, Burton FH. Behavioral effects of cocaine on a transgenic mouse model of cortical-limbic compulsion. Brain Res 1999;833:216–224
18. Insel TR, Hamilton JA, Guttmacher LB, et al. D-amphetamine in obsessive-compulsive disorder. Psychopharmacology (Berl) 1983;80: 231–235
19. Satel SL, McDougle CJ. Obsessions and compulsions associated with cocaine abuse [letter]. Am J Psychiatry 1991;148:947
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
21. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
22. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–1011
23. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
24. Guy W. Clinical Global Impressions. ECDEU Assessment Manual for Psychopharmacology [Revision]. US Dept Health, Education, and Welfare Publication (ADM) 91-338. Rockville, Md: National Institute of Mental Health; 1976
25. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
26. Moritz S, Meier B, Schick M, et al. Dimensional structure of the Hamilton Depression Rating Scale in patients with obsessive-compulsive disorder. Psychiatry Res 2004;125:171–180
27. Ascher JA, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56: 395–401
28. Borcherding BG, Keysor CS, Rapoport JL, et al. Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability? Psychiatry Res 1990;33:83–94
29. Campbell KM, McGrath MJ, Burton FH. Behavioral effects of cocaine on a transgenic mouse model of cortical-limbic compulsion. Brain Res 1999;833:216–224
30. Szechtman H, Sulis W, Eilam D. Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive-compulsive disorder (OCD). Behav Neurosci 1998;112:1475–1485
31. Szechtman H, Culver K, Eilam D. Role of dopamine systems in obsessive-compulsive disorder (OCD): implications from a novel psychostimulant-induced animal model. Pol J Pharmacol 1999;51:55–61
32. Kim CH, Koo MS, Cheon KA, et al. Dopamine transporter density of basal ganglia assessed with [(123)I]IPT SPET in obsessive-compulsive disorder. Eur J Nucl Med Mol Imaging 2003;30:1637–1643