Brief Report

THE COMBINATION OF DULOXETINE AND BUPROPION FOR TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER

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Our objective was to assess the effectiveness and safety of the combination of duloxetine and bupropion for treatment-resistant major depressive disorder (TRD). A retrospective chart review was conducted to identify patients with major depressive disorder (MDD) who had not experienced full remission of symptoms following an adequate trial of either duloxetine (n = 3) or bupropion (n = 7), and who then received the combination of these two antidepressants for TRD. Ten patients [37.2 ± 11.3 years of age, five women, baseline Clinical Global Impressions (CGI) scale score 4.4 ± 1.1], seven of whom had not remitted following treatment with bupropion (330 ± 67 mg, 20.5 ± 12.2 weeks), and three of whom had not remitted following treatment with duloxetine (90 ± 30 mg, 18 ± 2 weeks) received at least 4 weeks of combination treatment. The CGI was administered when the combination was first prescribed, and following 8.8 ± 4.0 (range, 4–16) weeks of treatment. There was a significant decrease in CGI-S (Severity) scores (4.4 ± 1.1 to 2.1 ± 0.9, P < .0001) following combination treatment. Three (30%) patients were remitters at follow-up, and six (60%) were responders who did not achieve full symptom remission. The mean maximum adjunctive duloxetine and bupropion doses were 60.0 ± 17.3 mg and 175.0 ± 114.5 mg, respectively. Side effects reported during combination treatment were nausea (n = 2), dry mouth (n = 2), jitteriness/agitation (n = 2), fatigue/drowsiness (n = 2), increased blood pressure (n = 1), increased sweating (n = 1), insomnia (n = 1), pruritus (n = 1), headache (n = 1), sexual dysfunction (n = 1), and weight gain (n = 1). Although preliminary, these results suggest a possible role for the combination of duloxetine and bupropion for TRD. Depression and Anxiety 23:178–181, 2006.

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INTRODUCTION

A growing number of reports suggest that treatment of major depressive disorder (MDD) with antidepressants which simultaneously inhibit the reuptake of serotonin and norepinephrine (SSRIs and SNRIs, respectively), including venlafaxine [Thase et al., 2001] and duloxetine [Goldstein et al., 2004], may

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result in greater remission rates than treatment with the SSRIs. Unfortunately, however, there is a paucity of studies that exclusively focus on the augmentation or combination of agents with the SNRIs. A number of published reports [Bodkin et al., 1997; DeBattista et al., 2003; Kennedy et al., 2002] suggest that combining the SSRIs or venlafaxine with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion, reported to be the most popular adjunctive strategy among a large survey of clinicians [Mischoulon et al., 2000], can often be effective in the treatment of resistant or refractory depression. However, to date, there are no reports focusing on the combination of the SNRI duloxetine with bupropion. Our goal in this study is to assess the efficacy and safety of combining the SNRI duloxetine with the NDRI bupropion for treatment-resistant MDD (TRD).

METHODS

Our retrospective chart review was conducted as follows: Charts of patients with MDD that we treated from August 2004 to the present (duloxetine was approved by the Food and Drug Administration on August 3, 2004) were reviewed confidentially by the treating clinician. Institutional Review Board approval was specifically obtained for treating clinicians to review charts of their patients for possible inclusion in this report. Only patients who had not experienced full symptom remission (i.e. those with CGI = S [Clinical Global Impression = Severity] >1) following treatment of adequate dose (60 mg of duloxetine, 150 mg of bupropion) and duration (minimum of 8 weeks) with either duloxetine or bupropion, who were prescribed combination treatment with the alternate agent (bupropion or duloxetine) for the treatment of depression were included in this report. Only charts that included the CGI scale [Guy, 1976] as a measure of symptom severity (CGI-S) and improvement (CGI-I) were selected. During the case reviews we collected age, gender, age of onset of MDD (years), duration of current MDD episode (months), number of lifetime major depressive episodes (MDEs), conventional antidepressants utilized and doses, and CGI scores during visits immediately before and during the prescription of the adjunctive agent (duloxetine or bupropion) for depression. As this was not a clinical trial, the frequency of follow-up is not uniform but biased in favor of treatment failure (for example, on average, partial and nonresponders had to return to the clinic multiple times, for medication adjustments than treatment remitters). Therefore, we had to take care to define time points of interest a priori to avoid introducing bias. For this reason, the time points of interest with regard to depression severity were defined as "baseline" (severity immediately before the combination treatment) and end point (last available visit or last visit on the combination for patients who stopped treatment). Side effects following the prescription of the adjunctive agent, as well as reasons for discontinuing adjunctive treatment, however, were collected during all visits available. Remission was defined as a CGI-S score of 1 (equivalent to *not currently depressed*). Response was defined as a CGI-I score less than 3 (equivalent to *much better* or *very much better*) and a CGI-S score greater than 1. We used paired *t*-tests to compare CGI-S scores before and following combination treatment.

RESULTS

Ten patients' charts (5/10 women; mean age, 37.2 ± 11.3 years) were identified and reviewed, and none were found ineligible for inclusion in this report. Baseline clinical variables of this sample were as follows: age of onset of MDD, 18.2 ± 4.4 years; duration of current MDE, 33.6 ± 64.6 months; number of lifetime episodes, 3.7 ± 2.2; number of failed trials (current episode), 3.1 ± 0.9; baseline CGI-S scores, 4.4 ± 1.1. For two patients, the most recent MDE was melancholic; for four patients it was atypical, and for four patients it was neither melancholic nor atypical. Seven patients had not remitted following treatment with bupropion (mean maximum dose, 330 ± 67 mg, 20.5 ± 12.2 weeks—with all but one patient treated with doses greater than 150 mg) and received adjunctive duloxetine (mean maximum dose, 60.0 ± 17.3 mg), and three patients had not remitted following treatment with duloxetine (mean maximum dose, 90 ± 30 mg, 18 ± 2 weeks—with all but one patient treated with doses greater than 60 mg) and received adjunctive bupropion (mean maximum dose, 175.0 ± 114.5 mg). All 10 patients received at least 4 weeks (mean duration, 8.8 ± 4.0 weeks; range, 4–16 weeks) of combination treatment. All but one patient received more than the minimum duration of combination treatment (4 weeks). There was a significant decrease in CGI-S scores (4.4 ± 1.1 to 2.1 ± 0.9, $P<.0001$) following combination treatment. In addition, 3/10 (30%) patients achieved remission (CGI-S = 1), six patients (60%) responded but did not achieve remission (CGI-I <3 but CGI-S >1), and one (10%) patient experienced a partial response (CGI-I = 3 but CGI-S >1) following combination treatment. There were no significant differences in baseline CGI-S scores (4.2 ± 1.3 vs. 4.6 ± 0.5, respectively; $P>.05$) or in the degree of change in CGI-S scores (2.4 ± 0.7 vs. 2.0 ± 1.0, respectively; $P>.05$) between patients who received adjunctive duloxetine or bupropion. One patient decided to discontinue adjunctive treatment due to lack of efficacy, and two patients discontinued adjunctive treatment (one patient taking bupropion, one taking duloxetine) at end point due to severe side effects (sweating in the case of duloxetine, and headache in the case of bupropion). New or preexisting but worsening side effects reported during combination treatment were nausea ($n=2$; both new), dry mouth ($n=2$; both new), jitteriness/agitation ($n=2$; both

preexisting and worsening), fatigue/drowsiness ($n = 2$; both new, one noted as severe), increased blood pressure ($n = 1$; new), increased sweating ($n = 1$; new and noted as severe), insomnia ($n = 1$; preexisting and worsening), pruritus ($n = 1$; new), headache ($n = 1$; preexisting and worsening, and noted as severe), sexual dysfunction ($n = 1$; new), and weight gain ($n = 1$; new).

DISCUSSION

Our findings in this study suggest the potential usefulness of combining the SNRI duloxetine and the DNRI bupropion for the treatment of resistant or refractory MDD. Specifically, a significant decrease in depressive symptoms following combination treatment was reported among 10 outpatients with MDD who had not achieved full symptom remission following several treatments including either bupropion or duloxetine monotherapy. In addition, almost 33% of all patients treated with the combination experienced a full remission of symptoms, while another 60% experienced significant symptom improvement that was short of full remission of symptoms. Although preliminary and speculative, our findings suggest that simultaneously enhancing dopaminergic, noradrenergic, and serotonergic neurotransmission may represent a promising pharmacotherapeutic strategy for patients who have not experienced remission of their depression despite initial treatment with standard antidepressants that do not directly influence all three monoamine neurotransmitter systems. Side effects reported during the combination treatment were nausea, dry mouth, jitteriness/agitation, and fatigue/drowsiness, followed by increased blood pressure, sweating, insomnia, pruritus, headache, sexual dysfunction, and weight gain.

One limitation of this study is its relatively small sample size, making it possible that the present encouraging findings are due to chance. Several other limitations of our study also deserve mention. First, the chart review method we utilized for data collection carries with it the possibility of inaccurate documentation of treatments, because it is often a challenge to document treatments provided and clinical response in clinical practice as accurately as in clinical trials. In addition, in this study, we only relied on a single rating to assess clinical improvement (CGI) and could not replicate our findings with other, more accurate clinician or patient-rated scales. In addition, the rating used to assess clinical improvement (CGI) provides only limited information, because it is a one-dimensional, categorical rating that does not give any specific information regarding symptom pattern response. Furthermore, the minimal duration of combination treatment for inclusion of a case in the present report was only 4 weeks, whereas the minimal effective doses of bupropion and duloxetine were defined as 150 mg and 40 mg, respectively. It is quite possible that setting more stringent criteria for inclusion in this study (i.e., optimal doses of bupropion or duloxetine, as well as a longer duration of combination treatment with these two agents) would have yielded different results. However, the majority of cases pooled had failed to experience significant symptom improvement despite initial treatment with much higher doses of bupropion and duloxetine. Similarly, all but one patient received combination treatment with bupropion and duloxetine for more than 4 weeks. With respect to diagnosis, clinicians did not uniformly and consistently utilize structured interview instruments to make the diagnosis of MDD. Rather, the diagnosis was most often assigned based on clinical judgment with DSM-IV criteria as the reference point. Although this could be viewed as a limitation of our study, investigators who participated in this study are highly experienced clinicians who have each conducted hundreds of structured diagnostic interviews and work in specialized depression research programs located in hospital-based academic centers. Furthermore, patients' available clinical history for this study was limited. In particular, structured interviews were not consistently conducted to determine psychiatric comorbidity. Therefore, the extent to which chronicity and comorbidity impacted response to treatment is difficult to accurately assess. Finally, patients were not routinely assessed for increases in blood pressure or for the presence tachycardia in this report. Clinical trials involving the regular measurement of vital signs, as well as the use of electocardiograms, would be necessary to shed further light on the safety of this combination treatment.

CONCLUSION

A significant decrease in depressive symptomatology was reported among 10 outpatients with MDD who had failed to experience full symptom remission following treatment with either duloxetine or bupropion, who then went on to receive the combination of the two antidepressants for at least 4 weeks. Although preliminary, these results suggest a possible role for the combination of duloxetine and bupropion for treatment-resistant or refractory MDD. Prospective, randomized, double-blind, controlled studies are necessary to explore further the role of the combination of duloxetine and bupropion for TRD.

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