Citalopram and Bupropion-SR: Combining Versus Switching in Patients With Treatment-Resistant Depression

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Objective: There are limited data comparing medication strategies in patients with treatment-resistant depression. In this study, we compared the effects of combining citalopram and bupropion-SR versus switching to the other monotherapy in treatment-resistant depression.

Method: This was a naturalistic, open-label cohort study. Patients with DSM-IV major depressive disorder who had not responded to at least 1 previous antidepressant and at least 6 weeks of treatment with citalopram or bupropion-SR were treated in a standard clinical protocol. In alternate months, eligible consecutive patients were treated by adding citalopram or bupropion-SR, or by switching to the other medication. Patients were assessed at baseline and after 6 weeks of treatment with the 29-item version of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD).

Results: A total of 61 patients completed the study: 32 in the combination condition and 29 in the monotherapy switch condition. The combination condition was superior to the monotherapy switch in the SIGH-SAD change score (–14.8 vs. –10.1, respectively, $p < .04$) and the proportion of patients in clinical remission (28% vs. 7%, $p < .05$). There were no differences in the proportion of patients who had side effects or in the severity of the side effects experienced.

Conclusion: The results of this cohort study suggest that combining citalopram and bupropion-SR is more effective than switching to a monotherapy. Combination treatment was well tolerated with no greater side effect burden than monotherapy. Limitations of this study include the nonrandomized design, open-label treatment, and small sample size.

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Despite the many effective medications that are available for patients with major depressive disorder, up to 40% of patients will have minimal or partial response to an antidepressant.[1,2] Treatment-resistant depression (TRD) is a significant public health burden because it is associated with poor quality of life, increased health services utilization and costs, and increased morbidity and mortality.[2–6]

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, but there is only limited evidence available to advise on strategies when patients do not respond optimally to an SSRI.[7] These strategies include switching (stopping the antidepressant and starting another), augmenting (adding a medication that by itself is not an antidepressant), and combining (adding another antidepressant medication).[8–10] Augmentation strategies have the best-documented evidence for efficacy in TRD, but these studies are limited by small numbers and primarily involve patients resistant to tricyclic antidepressants. For example, there are very few studies of lithium and triiodothyronine augmentation in SSRI nonresponders.[4,7]

There is also increasing use of combination antidepressant strategies in clinical practice.[11,12] There are several potential advantages of combining antidepressants. Given the novel neurochemical effects of newer antidepressants,[13] combining medications provides the possibility of enlisting additional synergistic mechanisms of action in

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TRD. Adding a second agent may build on partial responses to the first medication without losing any benefits gained from the first agent. It may be possible to target specific residual symptoms with a second agent or to treat side effects associated with the first medication. It may also be possible to use lower doses of each agent when combining them, as opposed to larger doses of a single agent, and, hence, reduce the overall side effect burden.

There are also potential disadvantages, however, to a combination strategy. There may be additive side effects when adding a second medication. Taking 2 medications may be more difficult than taking 1, leading to problems with compliance and adherence. Depending on the cost of each drug, it may be more expensive to take 2 medications. There is also the potential for drug-drug interactions. Perhaps the most important disadvantage of combining medications is that one can never be sure that both medications are necessary, since it is possible that any response is related only to the action of the second medication.

Despite the fact that combination strategies appear to be commonly used in clinical practice, there is very little evidence to support the efficacy of this approach. Most combination studies have had open-label designs, which limit the validity and generalizability of results.[14] One strategy examined in a series of studies was adding bupropion-SR to SSRI antidepressants. Bupropion-SR affects both noradrenaline and dopamine,[15] making it a rational choice to add to an SSRI for TRD. Open-label studies in which bupropion-IR or bupropion-SR was added to SSRIs, including fluoxetine, paroxetine, sertraline, and venlafaxine,[16–19] found overall clinical response rates of 76% (35 out of 46 patients).[14]

In all of these studies,[16–19] bupropion-SR was added to the treatment of patients who were partially responsive or nonresponsive to the SSRI alone. This design does not address the question of whether the combination strategy works better than a switch strategy. The objective of our study was to examine whether such a combination approach is superior to a monotherapy switch.

METHOD

Patients were seen at an outpatient mood disorders clinic at a tertiary university hospital medical center. This was a naturalistic, nonrandomized, open-label cohort study. Consecutive patients with DSM-IV major depressive disorder, as determined by an unstructured clinical interview supplemented with diagnostic checklists, in whom treatment with at least 1 antidepressant had failed (defined as at least 6 weeks at a therapeutic dose and a Clinical Global Impressions scale [CGI][20] score of "minimally improved" or worse) were treated with citalopram or bupropion-SR (selected by physician choice) for at least 6 weeks. Patients who were then rated on the CGI as minimally improved or worse were subsequently treated in 1 of 2 protocols for 6 weeks: either they were switched to the other agent (e.g., if they were taking citalopram, they were switched to bupropion-SR monotherapy, and vice versa), or the other antidepressant was added (e.g., if they were taking citalopram, bupropion-SR was added, and vice versa). The clinic psychiatrists alternated use of these clinical protocols for new patients every 2 months.

Patients switched to the other monotherapy were tapered off the initial medication to reduce discontinuation symptoms, but the tapering schedule was left to the discretion of the clinician. Patients were treated in an open-label manner, and the medications could be increased every 2 to 3 weeks, depending on clinical response and tolerance. The alternating clinical protocol method used open-label standard treatments and was approved by the Human Ethics Committee at the University of British Columbia. Patients gave written informed consent for use of anonymous clinical data for chart reviews.

Patients were rated before and after 6 weeks of treatment with the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD), which comprises the 21-item depression scale and an 8-item addendum for atypical symptoms (hypersomnia, hyperphagia, carbohydrate craving, weight gain, fatigue, social activity, reverse diurnal variation, and afternoon slump).[21] Side effects were monitored with global clinician ratings of none, mild, moderate, and marked.

All data are reported as mean ± SD. Unpaired t tests were used to analyze parametric data, while Mann-Whitney and chi-square tests were used for nonparametric data.

RESULTS

There were 32 patients treated with combination citalopram and bupropion-SR (22 started on citalopram and 10 started on bupropion-SR) and 29 patients treated with the monotherapy switch (17 patients started on citalopram and switched to bupropion-SR, and 12 patients started on bupropion-SR and switched to citalopram). There were no dropouts during treatment. Table 1 lists patient demographic and clinical information. None of the variables listed were significantly different among groups. The mean daily doses of medications used for combination therapy were citalopram, 33.1 ± 9.7 mg, and bupropion-SR, 248.4 ± 72.4 mg/day. For the monotherapy switch, the mean daily doses were citalopram, 38.8 ± 13.2 mg, and bupropion-SR, 283.3 ± 68.5 mg.

The clinical results are shown in Figures 1 and 2. The combination group showed significantly greater improvement in change scores on the SIGH-SAD compared with the monotherapy switch group (–14.8 ± 10.1 vs. –10.1 ± 6.8, respectively; $t = 2.1$, $df = 59$, $p < .04$). There were no differences in SIGH-SAD change scores in the

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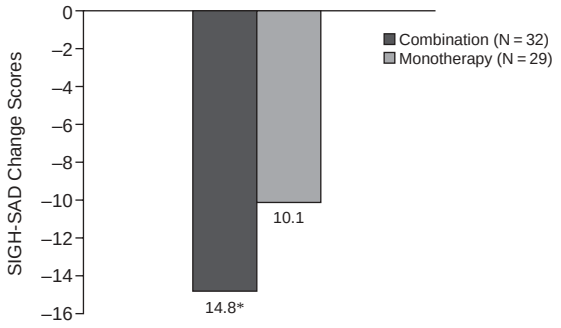
Table 1. Demographic and Clinical Information for Patients Treated With Combination Therapy (citalopram plus bupropion-SR) vs. Monotherapy Switch[a]

Variable	Combination (N = 32)	Monotherapy (N = 29)
Gender, N		
Female	22	20
Male	10	9
Age, y, mean ± SD	37.5 ± 10.0	36.4 ± 9.3
Duration of episode, mo, mean ± SD	12.0 ± 10.7	13.4 ± 12.6
No. of previous antidepressants, mean ± SD	2.3 ± 1.0 (range: 1–4)	2.5 ± 1.2 (range: 1–5)
Baseline SIGH-SAD score, mean ± SD	30.0 ± 5.7	31.2 ± 7.8

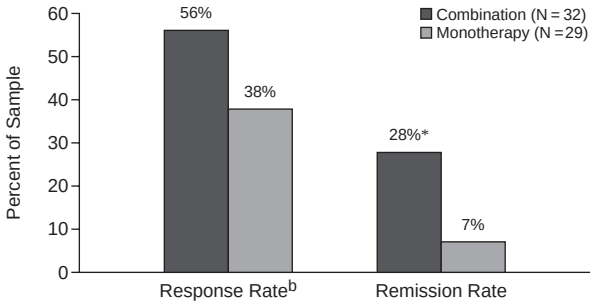
[a]None of the comparisons are statistically significant.
Abbreviation: SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version.

Figure 1. Change in SIGH-SAD Scores for Combination Treatment (citalopram plus bupropion-SR) vs. Monotherapy Switch Treatment



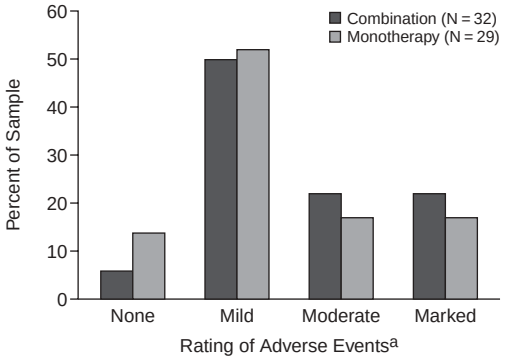
*p < .04.
Abbreviation: SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version.

Figure 2. Response and Remission Rates[a] for Combination Treatment (citalopram plus bupropion-SR) vs. Monotherapy Switch Treatment



[a]Response rate defined as 50% or greater improvement in SIGH-SAD ratings at posttreatment. Remission rate defined as 50% or greater improvement in SIGH-SAD ratings and a posttreatment SIGH-SAD score of 10 or less.
[b]p > .15, not significant.
*p < .05.
Abbreviation: SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version.

Figure 3. Adverse Events Ratings for Combination Treatment (citalopram plus bupropion-SR) vs. Monotherapy Switch Treatment



[a]p > .35, not significant.

monotherapy switch group among patients switched to citalopram versus those switched to bupropion-SR (t = 1.04, df = 27, p = .31). The response rates (defined as 50% or greater improvement in SIGH-SAD score at posttreatment), while numerically higher in the combination group compared with the monotherapy group, did not significantly differ among groups (56% vs. 38%, respectively; $\chi^2 = 2.0$, df = 1, p > .15). The remission rates (defined as 50% or greater improvement in SIGH-SAD score and a posttreatment SIGH-SAD score of 10 or less), however, were significantly superior for the combination group (28% vs. 7%, respectively; $\chi^2 = 4.6$, df = 1, p < .05).

Figure 3 shows the percentage of patients for each global severity category of adverse events. There were no significant differences in the global severity of adverse events among the combination and monotherapy groups (Mann-Whitney U = 404, p > .35). None of the patients had to discontinue treatment due to adverse events. Of patients rated as having marked adverse events, the combination group reported insomnia (N = 4, 12%), sexual dysfunction (N = 2, 6%), and headache (N = 1, 3%), while the monotherapy switch group reported sexual dysfunction (N = 3, 10%) and insomnia (N = 2, 7%).

DISCUSSION

In this study, the combination of citalopram and bupropion-SR was superior to a strategy of switching to monotherapy in patients with TRD. Despite the chronicity (mean episode duration greater than 1 year) and treatment resistance (mean number of antidepressants received prior to study greater than 2, prospective failure to

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respond to another) of the illness, the combination treatment produced substantial clinical response within 6 weeks. Although the remission rate at 28% was lower than in some antidepressant studies, this likely reflects the short duration of treatment for this chronically ill TRD group. Longer treatment durations are required to determine if the remission rate rises with time.

Additionally, the combination strategy was well tolerated by patients with no significant differences in adverse events between the combination treatment and monotherapy groups. Discontinuation symptoms may have inflated side effect scores in the monotherapy switch group, but the initial medication was tapered off to minimize this occurrence. The mean doses used for monotherapy were higher, most likely because patients who were not responding were increased to higher doses. The side effect burden is of particular importance when using combination treatment. In this regard, citalopram and bupropion-SR are each rated among the least likely to have liability for side effects among the newer antidepressants.[22] Another advantage of this combination is that citalopram has few clinically relevant interactions with the cytochrome P450 isoenzyme system,[8] while bupropion-SR may have mild to moderate inhibitory effects on the 2D6 isoenzyme.[19,23,24]

There are limitations to this study that may qualify these findings. There was no randomization of patients, and medications were used in an open-label design, which may result in systematic bias in patient characteristics and/or clinical ratings. We tried to minimize bias by using consecutive patients, alternating protocols, and standardized rating scales, but placebo response cannot be ruled out. The open-label treatment and flexible dosing, however, may make the results more generalizable to "real world" clinical care.

In summary, the combination of citalopram and bupropion-SR was superior to a monotherapy switch strategy for acute treatment of TRD, and the combination strategy was well tolerated by patients. Future randomized controlled trials will be required to confirm the efficacy of this approach. Future studies will be enhanced by using structured assessments and operational definitions of treatment resistance, and by determining the optimal duration of maintenance for combination treatment.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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