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An Open Pilot Study of the Combination of Escitalopram and Bupropion-SR for Outpatients With Major Depressive Disorder

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Abstract

Objective—Monotherapy with a selective serotonin reuptake inhibitor (SSRI) is the most common initial treatment for major depressive disorder (MDD), but this monotherapy leads to remission in fewer than a third of patients. The combination of the SSRI escitalopram and bupropion-SR is commonly used for treating patients with MDD who have had an inadequate response to antidepressant monotherapy. This pilot study was conducted to evaluate this combination in the treatment of MDD in patients with chronic or recurrent MDD to estimate safety, tolerability, and remission rates.

Method—In this study, 51 outpatients with chronic or recurrent non-psychotic MDD were treated with a combination of escitalopram and bupropion-SR for up to 12 weeks. Participants were started on escitalopram at 10 mg/day, and bupropion-SR was then added at week 1, starting at 150 mg/day. The maximum dose of escitalopram was 20 mg/day and the maximum dose of bupropion-SR was 400 mg/day.

Results—Rates of response (62%) and remission (50%) at study exit (based on participants for whom at least one post-baseline measure was collected) were significantly higher than is typical for SSRI monotherapy. The level of treatment emergent events was low, and only 3 participants (6%) discontinued treatment due to side effects. The mean maximum dose of escitalopram was 18 mg/day, which was achieved by week 6, and the mean dose at study exit was also 18 mg/day. The mean maximum dose of bupropion-SR was 329 mg/day, which was achieved by week 8, and the mean dose at study exit was 327 mg/day.

Conclusions—These results suggest that the combination of escitalopram and bupropion-SR is effective and well tolerated. Further controlled trials comparing this combination with monotherapy are needed.

Keywords

major depressive disorder; bupropion; escitalopram; medication combinations; adverse events

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are the medications most commonly used as first-line treatment for major depressive disorder (MDD). SSRIs, which are typically well tolerated and safe, usually lead to improvement in depressive symptoms; however, full remission does not occur in most patients. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study assessed response and remission rates in 2,876 patients with MDD following initial treatment with a highly selective SSRI, citalopram. After up to 14 weeks of treatment with citalopram at doses up to 60 mg/day, only 28.6% of patients had remission of depression based on scores on the 17-item Hamilton Rating Scale for Depression (HRSD₁₇)¹ in the modified intent-to-treat sample (i.e., participants with at least one post-baseline visit).² Patients in the STAR*D study who did not achieve remission with citalopram treatment could move on to one of several alternative treatments, one of which was a combination of citalopram with bupropion-SR (Wellbutrin SR). Trivedi and colleagues³ reported that 29.7% of the patients in the group who received adjunctive bupropion-SR in doses up to 400 mg/day for an additional 12 weeks (based on the full intent-to-treat sample) achieved remission.

Because the great majority of patients with MDD do not remit with initial SSRI monotherapy, it is appropriate to evaluate alternative approaches to antidepressant therapy. The current practice of first using antidepressant monotherapy for 8--12 weeks does not lead to remission in most patients; in the STAR*D study, most patients did not remit until their treatment either was changed to a second antidepressant or they received an antidepressant combination treatment. The current paradigm that specifies first using a full course of antidepressant monotherapy may, therefore, contribute to protracted treatment from which many patients will fail to benefit, and there may be significant attrition.⁴ In order to shorten the time to remission, one possible option is to use a combination of antidepressant medications early in the course of the illness. Theoretically, use of two medications with complementary mechanisms of action as an early treatment option could lead to remission and a shorter course of illness for many patients.⁵ Before such a treatment strategy could be considered for widespread use, however, it would be necessary to show that it was safe and well-tolerated for a range of subjects with MDD.

The combination of bupropion-SR and an SSRI is a treatment strategy that is commonly used for treatment-resistant MDD.⁶ The two medications have disparate (and possibly complementary) mechanisms of action.⁷ This combination is also popular because open-label studies have suggested that it is safe, effective, and may help reverse some of the sexual dysfunction seen with SSRI monotherapy.⁸ Nevertheless, systematic data are limited regarding the safety, tolerability, and effectiveness of combinations of an SSRI plus bupropion-SR in the treatment of a range of patients with MDD. Given the low remission rates achieved using optimal dosing and duration of treatment with single SSRIs, combining an SSRI and bupropion-SR early in the course of treatment may be useful in achieving higher rates of response and remission, especially for those with chronic or recurrent depression.

The purpose of this study was to examine the safety, tolerability, and efficacy of the combination of the SSRI escitalopram (the s-isomer of citalopram) and bupropion-SR in an open label trial involving outpatients with nonpsychotic chronic and/or recurrent MDD. Escitalopram was selected as the SSRI because it is one of the most commonly used medications for MDD, is well tolerated, and has a low risk of drug-drug interactions.

MATERIALS AND METHODS

This pilot study was performed as part of the Depression Trials Network, a national infrastructure for research in depression funded by the National Institute of Mental Health (NIMH). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The project was overseen by the network's National Coordinating Center at the University of Texas Southwestern Medical School and the Data Coordinating Center at the University of Pittsburgh. A Data Safety and Monitoring Board oversaw safety issues, the adequacy and integrity of data, and the study's capabilities to meet its objectives. The study was conducted at four sites: the Department of Psychiatry and Biobehavioral Sciences at the David Geffen School of Medicine at the University of California Los Angeles (UCLA), the Department of Psychiatry at Harbor-UCLA Medical Center, the Clinical Research Institute at the University of Kansas School of Medicine, and the Department of Psychiatry at the Columbia University College of Physicians and Surgeons.

Participants

The study enrolled outpatients, 18--65 years of age, who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)⁹ criteria for chronic and/or recurrent non-psychotic MDD as documented by a DSM-IV checklist and confirmed by the Mini-International Neuropsychiatric Interview Plus (MINI Plus).¹⁰ Participants were recruited through their treating physician or clinic staff using confidential procedures approved by local Institutional Review Boards, or via flyers and/or posters in the community. Participants had to be fluent in English, since non-English-speaking personnel were not available for the study. Participants also had to be able to understand the nature of the study and sign written informed consent. After consent was obtained, a physician determined eligibility for participation based on a diagnostic interview. To be enrolled in the study, participants had to have a baseline score ≥ 14 on the 17-item Hamilton Rating Scale for Depression (HRSD₁₇).¹ In addition, to participate in the study, patients were required to have clinician approval indicating that treatment with antidepressant medications in combination was appropriate and safe based on the patients' symptoms and medical condition, especially for participants who were taking other non-excluded concomitant medications. Participants in the study received \$80 as compensation for their time.

Patients were excluded if they had a lifetime history of bipolar I or II disorder or bipolar disorder not otherwise specified (NOS), schizophrenia, schizoaffective disorder, psychosis NOS, anorexia nervosa or bulimia nervosa, or a current primary diagnosis of obsessive-compulsive

disorder. Patients were excluded if they had a clear-cut intolerance for either escitalopram or bupropion-SR or a lack of response to an adequate trial of the combination in the current episode of MDD (patients who had failed to respond to monotherapy with one of the drugs were eligible to participate). The study also excluded patients who had received and did not respond to seven or more sessions of electroconvulsive therapy during the current episode of MDD. Women who were sexually active and were not using adequate contraception, or who were pregnant or breast-feeding were also excluded from the study. Additional exclusion criteria included any general medical condition or concomitant medication(s) that contraindicated use of the medication combination used in the study; the need for immediate hospitalization for substance/alcohol detoxification or treatment, or immediate hospitalization for a psychiatric disorder; or the use of exclusionary medications (antipsychotic or anticonvulsant medications, mood stabilizers, central nervous system stimulants, or antidepressant medication used for the treatment of depression or other purposes such as smoking cessation). Patients taking thyroid medication for hypothyroidism could be included if they had been stable on the medication for 3 months, as could patients who were participating in a modality of psychotherapy that was not targeting depressive symptoms (e.g., supportive therapy, marital therapy). Patients who were receiving therapy that was depression-specific, such as cognitive therapy or interpersonal psychotherapy of depression, were excluded. Patients were also excluded if they had current alcohol dependence or abuse (i.e., during the previous 6 months), significant liver disease for which the use of the study medication was contraindicated, a known hypersensitivity to either study medication, uncontrolled narrow-angle glaucoma, or if they were taking monoamine oxidase inhibitors.

Measures

Participants were seen for eight clinic visits, including evaluation at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12. The baseline visit lasted about 1 hour and each follow-up visit lasted approximately 30 minutes. The Quick Inventory of Depressive Symptomatology--Self-Rated (QIDS-SR₁₆)^{11,12} was collected at baseline and at each clinic visit as a primary outcome measure of remission and response and of severity of depression. Self-reports have often been used in effectiveness trials (e.g., the IMPACT¹³ and PATHWAYS¹⁴ studies). In addition, the QIDS-SR₁₆ is highly reflective of results obtained with the HRSD₁₇. It reduces patient burden, provides a cost-efficient and reliable measure of outcome that abrogates the need for independent clinician ratings, is as sensitive to symptom change as clinician ratings,¹⁵ and has been proven to be as reliable and valid as the Quick Inventory of Depressive Symptomatology--Clinician Rating (QIDS-C₁₆).^{11,12} Severity of depressive symptoms was also assessed at baseline and at each subsequent visit by clinicians using the QIDS-C₁₆. Clinicians also assessed side effects and possible adverse events during the course of treatment using the self-report Frequency, Intensity, and Burden of Side Effects Rating (FIBSER),¹⁶ the 55-item, self-report Systematic Assessment for Treatment Emergent Events--Systematic Inquiry (SAFTEE-SI),¹⁷ the 4-item, clinician-rated Barnes Akathisia Rating Scale (BARS),¹⁸ and the 5-item, clinician-rated Abnormal Involuntary Movement Scale (AIMS).¹⁹ These measures provided consistent information regarding medication side effects and tolerability. Data on side effects and adverse events were collected at each visit, along with measures of blood pressure, pulse, and weight. Study physicians used the General Principles for Treatment Implementation²⁰ and symptom severity and tolerability information to make dose adjustments as needed. These measures and procedures (i.e., a measurement-based approach to care) were successfully used in the STAR*D study and resulted in high-quality care with vigorous but tolerable dosing in both primary care and psychiatric settings.

Intervention

Participants were started on escitalopram 10 mg/day, and bupropion-SR 150 mg/day was added at week 1. Participants were eligible to receive an increased dose of escitalopram (an additional

10 mg/day) starting at week 4, or of bupropion-SR (up to an additional 300 mg/day at week 4 or 400 mg/day at weeks 6--10) if they did not respond to the medication combination (score on QIDS-C₁₆ 11¹² ≥ 9) or had a partial response (QIDS-C₁₆ = 6--8). Medications were maintained at the same dosage if participants achieved remission (QIDS-C₁₆ ≤ 5). Dosage of the medications could be decreased or the participant could exit the study if significant side effects could not be managed within the protocol.

Data Analysis

The goals of this study were to determine the proportion of participants who achieved remission and to evaluate the side effects experienced by the participants. Remission was defined as a QIDS-SR₁₆ score ≤ 5 at the last clinic visit. Response was defined as an improvement of $\geq 50\%$ on the QIDS-SR₁₆ score relative to baseline. Intolerable side effects were defined as attrition due to side effects or an indication of at least severe impairment due to side effects as rated on the FIBSER. A 90% confidence interval was used to estimate the variability of each proportion.

Descriptive statistics are presented as means (standard deviations) for continuous variables and percentages for discrete variables. Kaplan-Meier methods were used to estimate the cumulative proportion with first remission, first response, and study discontinuation.

RESULTS

Of the 53 participants who were screened for the study, 2 were determined to be ineligible, none refused to participate, and 51 were enrolled in the protocol. Sociodemographic and clinical characteristics of the sample are shown in Table 1. Participants were predominantly female and Caucasian, with multiple past episodes of depression. The average duration of the current episode was more than 5 years (mean = 67 ± 103 months). Approximately two-thirds of participants met criteria for chronic depression and three-quarters met criteria for recurrent depression. Of the 51 participants, 21 (41%) participants had had no prior antidepressant trials, 20 (39%) had had one failed prior antidepressant trial, and 10 (20%) had had two prior failed antidepressant trials. More than half had some degree of suicidal ideation. Further details on comorbid diagnoses are presented in Table 1.

The mean maximum dose of escitalopram was 18 mg/day and of bupropion-SR was 329 mg/day; these doses were achieved by treatment weeks 6 and 8, respectively (Table 2). The mean doses at week 12 were 16 mg/day of escitalopram and 328 mg/day of bupropion-SR. Of the 51 participants who entered the protocol, 10 discontinued before completion, 3 due to medication side effects and 7 due to reasons unrelated to medication (e.g., time commitments). Two of the three participants who withdrew due to side effects discontinued during the first week of the protocol. The highest frequency, intensity, and burden of side effects were reported between weeks 2 and 8 of treatment. One serious adverse event was reported, a hospitalization for worsening depression and the development of suicidal ideation after medication was discontinued.

Of the 46 patients for whom data from at least one post-baseline visit were available, 24 patients (52%) reported at least a moderate side-effect burden (defined by a FIBSER score > 2) at some point during the study, although only 7 patients (15%) reported this level of burden at their last visit (Table 3). A variety of specific somatic complaints were reported on the SAFTEE-SI prior to treatment (Table 4), the most prevalent being "trouble sleeping," "weakness and fatigue," "irritable," "trouble concentrating," and "feeling drowsy or sleepy." The most commonly reported treatment-emergent side effects at any point during the course of treatment were "feelings of drowsiness or sleepiness," "delayed, absent orgasm," "loss of sexual interest," "apathy," "nightmares," and "muscle twitching." (Table 4) Of those symptoms not present at

baseline, those with the highest incidence at the last study visits were “delayed, absent orgasm,” “sweating excessively,” “sexual arousal problems,” and “apathy.” Very few subjects reported sexual difficulties at the end of the study that were worse than at baseline: there was one report of “loss of sexual interest” and one of “delayed, absent orgasm” that were worse than at study entry. Of the participants who presented with a specific somatic symptom, most reported an improvement in the severity of the symptom at study exit, except for those with “numbness or tingling” in whom the severity of the complaint improved in only half of the participants. Weight gain and akathisia were uncommon. The side-effect burden was lower among participants who remitted than in those who did not, but rates of hypertension, weight change, and akathisia were not different among remitters and nonremitters (Table 5).

Of the 49 patients for whom post-baseline data on blood pressure were available, 8 patients (16%) had clinical hypertension defined as systolic blood pressure > 140 and diastolic blood pressure > 90 at some point during the study, but none of the patients had hypertension at the last visit (Table 3). However, up to 38% (17/45) of participants reported at least a 10% increase in systolic and/or diastolic blood pressure at some point during the study.

Of the 51 participants, more than 50% (27 patients) responded to combination drug treatment by week 8, 65% (33/51) responded by week 12, and 62% (28/45) had responded at study exit. Of the 51 participants, 59% (30 patients) had remitted by the end of week 12 and 50% (23/46) had remitted at study exit (Table 6). Of the 17 patients who had had no prior failed treatment trials and completed the study, 64% (11 patients) were in remission at exit, compared with 58% (11/19) of those who had had one failed trial, and 10% (1/9) of those who had had two prior failed treatment trials ($p = 0.017$), showing an inverse relationship between the remission rate and the number of prior unsuccessful treatment trials. The times to first remission, first response, and discontinuation are presented in Figure 1. For those participants who achieved remission, the percentage achieving first remission by week are shown in Figure 2. About 40% of those who ultimately remitted did so after 6 weeks.

DISCUSSION

The results of this study indicate that the combination of escitalopram and bupropion-SR is safe, well tolerated, and effective. The 12-week response and remission rates found for the combination were meaningfully higher than those that have been reported with SSRI monotherapy in most studies,^{3,21} and higher than those reported previously for combination therapy following unsuccessful monotherapy.³ Although the high remission rate reported in this study is encouraging, and could suggest that the combination of escitalopram and bupropion-SR is preferable to initial antidepressant monotherapy, this conclusion is not fully supported by the data presented here. There was no comparison of the medication combination with monotherapy using the individual agents within the same study. Such a comparison would be necessary in order to demonstrate superiority of the combination. Furthermore, the medications were administered in an open-label manner. Open-label designs have been reported to increase placebo response rates and, in the absence of a placebo control group, it is difficult to assess the specific effectiveness of the medications.

A primary goal of this study was to establish whether this medication combination would be safe and well-tolerated in well characterized patients typical of those seen in “real world” settings. A majority of patients in this study suffered from chronic and recurrent MDD and had failed to benefit from previous antidepressant medication treatment. For approximately 40% of subjects, the medication combination was the initial treatment in the current episode. In this broad range of subjects, few participants discontinued treatment due to emergent adverse events, and the rates of the most common treatment-emergent events (sexual dysfunction, sweating, apathy) were relatively low. Although this study did not compare SSRI monotherapy

with combined therapy, the rate of treatment-emergent sexual dysfunction with the escitalopram bupropion combination therapy was lower in this study than has been noted in many previous reports of SSRI monotherapy.²² The SAFTEE-SI data indicate that very few of the adverse events reported were actually worse at the end of treatment than at the beginning (i.e., apparent adverse events may not have been treatment-related). Although some participants experienced increases in blood pressure, no cases of sustained hypertension were noted at study exit. It is possible that using the combination of escitalopram and bupropion-SR as an initial therapy for the treatment of chronic and recurrent depression offers advantages over initial monotherapy.

Because of the low remission rates seen with antidepressant monotherapy, and the favorable outcomes, safety, and tolerability of the escitalopram and bupropion-SR combination reported here and elsewhere, clinicians may want to consider using this medication combination earlier in the course of antidepressant treatment. This approach is supported by previous prospective studies and retrospective reports regarding the effectiveness of the combination of bupropion-SR and an SSRI. DeBattista et al.²³ performed a prospective open-label 6-week study with 28 patients who were either partial- or non-responders to SSRI treatment. Bupropion-SR was added to these patients' preexisting medication regimen (primarily fluoxetine, sertraline, or paroxetine) in doses of 150--300 mg/day (mean dose 275 mg/day). The medication combination was well tolerated, with only one participant discontinuing due to a treatment-emergent adverse event, and 54% of participants responded by week 6. In a second open-label study, Lam et al.²⁴ treated 61 patients with treatment-resistant depression who had not achieved remission with either bupropion-SR or citalopram alone by initiating 6 weeks of treatment using one of two methods: switching to the other medication ($n = 29$) or combining the two medications ($n = 32$). The mean dose of bupropion-SR used in the combination was 248 mg/day. In this study, the combined medication therapy was superior to either monotherapy to which patients were switched in terms of final depression rating scores and remission rates (28% for the combination versus 7% for monotherapy), although there was no statistically significant difference in response rates between monotherapy and combination therapy. The adverse events with combined therapy were not significantly different from those with monotherapy and no participants discontinued treatment due to side effects. Finally, Ramasubbu²⁵ treated six patients who were partially responsive to a combination of an SSRI and lithium by adding either desipramine or bupropion-SR. He reported that both medications yielded good symptomatic improvement and that the addition of bupropion-SR was better tolerated.

In a retrospective study of 27 patients who received combination treatment with bupropion-SR and an SSRI (primarily fluoxetine or sertraline),²⁶ combination therapy was associated with greater symptomatic improvement than monotherapy, yet rates of adverse events were similar in those receiving combination therapy compared with those receiving monotherapy. Spier²⁷ reported on 15 patients who had achieved an inadequate treatment response with monotherapy and who were then treated with bupropion-SR in addition to either an SSRI or venlafaxine. He found that combination therapy was well tolerated, and that 80% of the patients responded. Finally, in a posthoc analysis of data from 53 geriatric patients who had not responded to paroxetine plus interpersonal psychotherapy, Whyte et al.²⁸ compared a number of different switching strategies: switching to venlafaxine-XR monotherapy versus switching to a variety of different combination strategies involving bupropion-SR, nortriptyline, or lithium. They reported that all of the medication combinations produced response rates comparable to the monotherapy strategy, and that all of the combinations were associated with higher rates of treatment-emergent adverse events that led to discontinuation than was monotherapy. The lower reported efficacy and higher reported rates of discontinuation due to side effects may reflect the fact that the participants were geriatric patients, and this may limit generalizability of the findings.

The results of this pilot study must be interpreted with caution as there were several study limitations. This was an open-label medication study and such studies commonly yield higher rates of clinical improvement than do blinded studies. Furthermore, because this study had no monotherapy or placebo comparison groups, it is impossible to know how participants might have fared on monotherapy under similar clinical conditions. Participants in the study did receive more individualized attention (e.g., more frequent visits, more diligent management) than is typical in routine clinical practice, which may have contributed to higher than usual remission and response rates. Finally, although we did document symptom improvement with this medication combination, we did not document improvement in overall functional status.

Despite these limitations, the results presented here are encouraging and indicate that pharmacotherapy with the combination of escitalopram and bupropion-SR merits consideration as an early treatment option in MDD. However, this study does not help identify which patients are likely to benefit more from combination treatment than monotherapy. Most clinicians use combination treatment after an initial SSRI fails to benefit a patient. The present results indicate that, on the basis of safety and tolerability concerns, there is little reason to reserve this medication combination for the later stages of treatment. This study included both patients who had received unsuccessful treatment during the current episode and patients for whom this was the initial treatment. Patients in general reported treatment-emergent adverse events that were limited in frequency and severity, and seldom led to discontinuation. Future controlled studies should compare monotherapy with this combination treatment in patients with a range of severity of depression to help elucidate a possible role for this combination as an initial treatment for MDD.

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N at risk									
Discontinuation	51	46	46	46	45	43	42	41	
Remission	—	46	40	38	29	23	21	17	
Response	—	45	39	35	27	19	16	12	

Figure 1.
Cumulative probability of discontinuation, remission, and response by week

Figure 2.
Percentage distribution of week of first remission ($\text{QIDS-SR}_{16} \leq 5$) for participants in remission at exit

Table 1

Sociodemographic and clinical characteristics

Characteristic	N ⁴	Mean±SD n (%)
Age, yr	51	45 ± 14
Male gender	51	14 (27)
Race		
Caucasian	51	46 (90)
African-American	51	2 (4)
Other	51	3 (6)
Illness onset age, yr	51	24 ± 14
Number of lifetime episodes	51	5 ± 5
Current episode duration, months	51	67 ± 103
Received psychotropics, current episode	51	18 (35)
Number of prior failed trials		
0	51	21 (41)
1	51	20 (39)
2	51	10 (20)
MINI ¹ diagnoses (current)		
Major depressive episode	51	51 (100)
Mood disorder related to GMC ²	51	1 (2)
Substance-induced mood disorder	51	0 (0)
Chronic depression	51	33 (65)
Recurrent depression	51	38 (75)
Melancholic depression	51	21 (41)
Dysthymia ³	38	2 (5)
Suicide risk	51	28 (55)
Agoraphobia	51	2 (4)
Panic disorder without agoraphobia	51	1 (2)
Panic disorder with agoraphobia	51	1 (2)
Agoraphobia without panic history	51	0 (0)
Agoraphobia with panic history	51	1 (2)
Agoraphobia without history of limited symptom attacks	51	0 (0)
Social phobia	51	6 (12)
Specific phobia	51	4 (8)
Obsessive-compulsive disorder (OCD)	51	3 (6)
GMC-related OCD	51	0 (0)
Substance-induced OCD	51	0 (0)
Posttraumatic stress disorder	51	1 (2)
Alcohol dependence	51	0 (0)
Alcohol abuse	51	0 (0)
Substance dependence	51	0 (0)
Substance abuse	51	0 (0)
Generalized anxiety disorder	51	17 (33)
Premenstrual dysphoric disorder	36	4 (11)

¹ Mini international neuropsychiatric interview

² General medical condition

³ 13 subjects received a "not applicable" response

⁴ Although there were 51 total subjects, not all data were available for all subjects, resulting in a smaller sample size for some measures

Table 2

Dosage, discontinuation, and adverse events by week

Characteristic	Week 0		Week 1		Week 2		Week 4		Week 6		Week 8		Week 10		Week 12	
	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)
Bupropion-SR, mg			39	150±0	46	157±33	45	267±63	42	295±85	38	329±85	40	328±80	41	328±85
Escitalopram, mg	50	10±0	40	10±1	46	10±2	45	17±5	42	18±4	38	18±4	40	18±4	41	16±5
Side effects (FIBSER ¹)																
≥ 50% of the time			40	9 (23)	46	17 (37)	45	17 (38)	41	11 (27)	38	14 (37)	39	14 (36)	41	10 (24)
≥ Moderate intensity			40	12 (30)	46	17 (37)	45	16 (36)	41	16 (39)	38	14 (37)	39	13 (33)	41	11 (27)
≥ Moderate burden			40	7 (18)	46	8 (17)	45	11 (24)	41	9 (22)	38	8 (21)	39	7 (18)	41	6 (15)
Cumulative discontinuation																
Any reason	51	5 (10)	51	5 (10)	51	5 (10)	51	6 (12)	51	8 (16)	51	9 (18)	51	10 (20)	51	10 (20)
Side effects	51	2 (4)	51	2 (4)	51	2 (4)	51	2 (4)	51	3 (6)	51	3 (6)	51	3 (6)	51	3 (6)
Hypertension ²	47	2 (4)	38	1 (3)	45	3 (7)	45	3 (7)	41	0 (0)	38	2 (5)	38	0 (0)	39	0 (0)
≥ 10% systolic increase			38	4 (11)	44	3 (7)	44	2 (5)	41	5 (12)	37	6 (16)	37	2 (5)	38	5 (13)
≥ 10% diastolic increase			38	6 (16)	44	8 (18)	44	11 (25)	41	6 (15)	37	7 (19)	37	7 (19)	38	8 (21)
Pulse	47	76±10	38	76±10	45	77±11	44	76±10	41	76±10	38	77±10	37	77±13	39	77±11
≥ 10% pulse increase			38	9 (24)	44	10 (23)	43	12 (28)	41	15 (37)	37	11 (30)	37	12 (32)	38	14 (37)
Weight, lb	48	190±61	38	188±61	43	190±62	43	192±62	41	191±64	36	192±67	37	192±64	38	188±67
≥ 7% weight increase			37	0 (0)	43	0 (0)	43	0 (0)	41	0 (0)	35	0 (0)	37	0 (0)	38	1 (3)
AIMS ³ total score ≥ 2	51	1 (2)	39	1 (3)	45	2 (4)	45	1 (2)	41	1 (2)	38	0 (0)	38	1 (3)	40	1 (3)
≥ Moderate akathisia ⁴	50	1 (2)	39	0 (0)	45	0 (0)	45	1 (2)	41	0 (0)	38	0 (0)	38	0 (0)	40	0 (0)

¹ Frequency, intensity, and burden of side effects rating scale

² Systolic blood pressure >140 and diastolic blood pressure >90

³ Abnormal involuntary movement scale

⁴ Barnes akathisia rating scale

NOTE: Although there were 51 total subjects, not all data were available for all subjects, resulting in a smaller sample size for some measures

Table 3

Treatment-emergent adverse events, remission, and response¹

Characteristic	Baseline		Ever		Exit	
	N	n (%N±.5CI ²)	N	n (%N±.5CI ²)	N	n (%N±.5CI ²)
≥Moderate side effect burden ³			46	24 (52±14)	46	7 (15±10)
Hypertension ⁴			49	8 (16±10)	49	0 (0±0)
≥10% systolic increase	47	2 (4±5)	45	12 (27±13)	45	7 (16±11)
≥10% diastolic increase			45	17 (38±14)	45	9 (20±12)
≥7% weight increase			45	1 (2±3)	45	1 (2±3)
AIMS ⁵ total score ≥2	51	1 (2±3)	51	5 (10±8)	51	1 (2±3)
≥Moderate akathisia ⁶	50	1 (2±3)	51	2 (4±5)	51	0 (0±0)
Remission ⁷			46	30 (65±14)	46	23 (50±14)
Response ⁸			45	33 (73±13)	45	28 (62±14)

¹ Baseline visit may be counted at all three time points

² Difference between the upper and lower 95% confidence limits multiplied by 0.5

³ Assessed by the Frequency, Intensity, and Burden of Side Effects Rating Scale

⁴ Systolic blood pressure > 140 and diastolic blood pressure > 90

⁵ Abnormal involuntary movement scale

⁶ Barnes Akathisia Rating Scale

⁷ 16-item Quick Inventory of Depressive Symptomatology--Self-rated ≤ 5

⁸ Percentage reduction in 16-item Quick Inventory of Depressive Symptomatology--Self-rated ≥ 50

NOTE: Although there were 51 total subjects, not all data were available for all subjects, resulting in a smaller sample size for some measures

Table 4

Systematic assessment for treatment emergent effects: percent present and percent change¹

Effect	All participants ²		Effects not present at baseline		Results at study exit for effects present at baseline		
	N ³	Baseline	Post-baseline ⁴	Exit ⁴	NWorse	Same	Better
Trouble sleeping	45	33 (73)	8 (18)	1 (2)	331 (3)	8 (24)	24 (73)
Nightmares	45	15 (33)	12 (27)	3 (7)	150 (0)	3 (20)	12 (80)
Feeling drowsy or sleepy	45	23 (51)	15 (33)	3 (7)	231 (4)	3 (13)	19 (83)
Feeling nervous or hyper	45	19 (42)	10 (22)	2 (4)	190 (0)	3 (16)	16 (84)
Weakness or fatigue	45	26 (58)	10 (22)	2 (4)	260 (0)	4 (15)	22 (85)
Irritable	45	26 (58)	5 (11)	0 (0)	260 (0)	5 (19)	21 (81)
Poor memory	45	16 (36)	7 (16)	0 (0)	160 (0)	5 (31)	11 (69)
Trouble concentrating	45	26 (58)	7 (16)	0 (0)	261 (4)	8 (31)	17 (65)
Feeling strange or unreal	45	11 (24)	2 (4)	0 (0)	110 (0)	1 (9)	10 (91)
Hearing or seeing things	45	0 (0)	2 (4)	0 (0)	00 (0)	0 (0)	0 (0)
Abnormal sensations	45	2 (4)	6 (13)	1 (2)	20 (0)	0 (0)	2 (100)
Numbness or tingling	45	6 (13)	3 (7)	0 (0)	60 (0)	3 (50)	3 (50)
Dizziness or faintness	45	6 (13)	6 (13)	0 (0)	60 (0)	1 (17)	5 (83)
Headache	45	18 (40)	6 (13)	0 (0)	180 (0)	5 (28)	13 (72)
Blurred Vision	45	7 (16)	6 (13)	3 (7)	70 (0)	1 (14)	6 (86)
ringing in ears	45	2 (4)	4 (9)	2 (4)	20 (0)	0 (0)	2 (100)
Stuffy nose	45	7 (16)	7 (16)	3 (7)	70 (0)	1 (14)	6 (86)
Dry mouth	45	11 (24)	10 (22)	2 (4)	110 (0)	3 (27)	8 (73)
Increased salivation	45	3 (7)	2 (4)	0 (0)	30 (0)	0 (0)	3 (100)
Muscle cramps, stiffness	45	11 (24)	8 (18)	1 (2)	110 (0)	2 (18)	9 (82)
Muscle twitching	45	4 (9)	12 (27)	3 (7)	40 (0)	0 (0)	4 (100)
Trouble sitting still	45	7 (16)	7 (16)	2 (4)	70 (0)	2 (29)	5 (71)
Tremor, shakiness	45	3 (7)	8 (18)	0 (0)	30 (0)	0 (0)	3 (100)
Poor coordination	45	2 (4)	7 (16)	1 (2)	20 (0)	0 (0)	2 (100)
Slurred speech	45	2 (4)	0 (0)	0 (0)	20 (0)	0 (0)	2 (100)
Heartbeat rapid, pounding	45	8 (18)	2 (4)	0 (0)	80 (0)	2 (25)	6 (75)
Trouble catching breath	44	4 (9)	5 (11)	3 (7)	40 (0)	0 (0)	4 (100)
Chest pain	45	2 (4)	2 (4)	0 (0)	20 (0)	0 (0)	2 (100)
Nausea, vomiting	45	1 (2)	7 (16)	3 (7)	10 (0)	0 (0)	1 (100)
Abdominal discomfort	45	11 (24)	10 (22)	0 (0)	110 (0)	0 (0)	11 (100)
Constipation	45	2 (4)	11 (24)	3 (7)	20 (0)	0 (0)	2 (100)
Diarrhea	45	2 (4)	5 (11)	2 (4)	20 (0)	0 (0)	2 (100)
Difficulty urinating	45	0 (0)	2 (4)	0 (0)	00 (0)	0 (0)	0 (0)
Frequent need to urinate	45	6 (13)	7 (16)	2 (4)	60 (0)	0 (0)	6 (100)
Menstrual irregularities	40	3 (8)	3 (8)	0 (0)	30 (0)	0 (0)	3 (100)
Loss of sexual interest	45	21 (47)	12 (27)	2 (4)	211 (5)	6 (29)	14 (67)
Sexual arousal problems	43	15 (35)	11 (26)	4 (9)	150 (0)	3 (20)	12 (80)
Delayed, absent orgasm	43	11 (26)	13 (30)	6 (14)	111 (9)	2 (18)	8 (73)
Sweating excessively	45	8 (18)	10 (22)	4 (9)	81 (13)	1 (13)	6 (75)
Fluid retention, swelling	45	5 (11)	2 (4)	0 (0)	50 (0)	1 (20)	4 (80)
Appetite decreased	45	5 (11)	9 (20)	3 (7)	50 (0)	1 (20)	4 (80)
Appetite increased	45	14 (31)	5 (11)	0 (0)	140 (0)	0 (0)	14 (100)
Weight gain	45	11 (24)	6 (13)	0 (0)	110 (0)	0 (0)	11 (100)
Weight loss	45	3 (7)	3 (7)	1 (2)	30 (0)	0 (0)	3 (100)
Skin rash, allergy	45	5 (11)	3 (7)	0 (0)	50 (0)	0 (0)	5 (100)
Diminished mental acuity	44	15 (34)	2 (5)	0 (0)	151 (7)	5 (33)	9 (60)
Difficulty finding words	45	13 (29)	4 (9)	1 (2)	132 (15)	1 (8)	10 (77)
Apathy	45	13 (29)	12 (27)	4 (9)	131 (8)	1 (8)	11 (85)
Dizziness	45	7 (16)	4 (9)	3 (7)	70 (0)	2 (29)	5 (71)
Bruising	44	2 (5)	2 (5)	1 (2)	20 (0)	0 (0)	2 (100)

Effect	All participants ²		Effects not present at baseline		Results at study exit for effects present at baseline		
	N ³	Baseline	Post-baseline ⁴	Exit ⁴	NWorse	Same	Better
Hair thinning/loss	45	3 (7)	2 (4)	1 (2)	30 (0)	1 (33)	2 (67)
Hot flashes	45	8 (18)	6 (13)	2 (4)	81 (13)	0 (0)	7 (88)
Clenching of teeth	45	13 (29)	1 (2)	0 (0)	130 (0)	3 (23)	10 (77)
Strange taste in mouth	45	3 (7)	11 (24)	3 (7)	30 (0)	0 (0)	3 (100)
Unable to sit still	45	5 (11)	6 (13)	2 (4)	50 (0)	1 (20)	4 (80)
Bothered by side effects	45	25 (56)	10 (22)	3 (7)	250 (0)	5 (20)	20 (80)

¹Data presented as n (%N)

²Effect rated moderate or severe

³Participants with baseline and at least 1 postbaseline rating

⁴Not present at baseline

NOTE: Although there were 51 total subjects, not all data were available for all subjects, resulting in a smaller sample size for some measures

Table 5Adverse events by remission at exit¹

Characteristic	Total (N=46) ³	Remission ²		p
		Yes (N=23)	No (N=23)	
Side effects (FIBSER ⁴)				
≥50% of the time	12 (26.1)	3 (13.0)	9 (39.1)	0.0439
≥Moderate intensity	13 (28.3)	4 (17.4)	9 (39.1)	0.1016
≥Moderate burden	8 (17.4)	1 (4.3)	7 (30.4)	0.0196
Hypertension ⁵	0 (0.0)	0 (0.0)	0 (0.0)	
≥10% systolic increase	7 (15.9)	4 (17.4)	3 (14.3)	0.7785
≥10% diastolic increase	9 (20.5)	5 (21.7)	4 (19.0)	0.8250
Pulse	77.0±10.4	76.3±9.0	77.8±11.9	0.8194
≥10% pulse increase	15 (34.1)	7 (30.4)	8 (38.1)	0.5923
Weight, percent change	-1.4±7.2	-2.6±9.0	-0.2±4.5	0.2086
≥7% weight increase	1 (2.3)	1 (4.3)	0 (0.0)	0.3338
AIMS ⁶ total score ≥2	1 (2.2)	0 (0.0)	1 (4.3)	0.3120
Moderate akathisia ⁷	0 (0.0)	0 (0.0)	0 (0.0)	

¹ Data presented as mean±SD and n (%N)

² 16-item Quick inventory of depressive symptomatology—self-rated ≤5

³ At least one postbaseline visit

⁴ Frequency, intensity, and burden of side effects rating scale

⁵ Systolic blood pressure >140 and diastolic blood pressure >90

⁶ Abnormal involuntary movement scale

⁷ Barnes akathisia rating scale

NOTE: Although there were 51 total subjects, not all data were available for all subjects, resulting in a smaller sample size for some measures

Table 6

Outcomes by week

Characteristic	Week 0		Week 1		Week 2		Week 4		Week 6		Week 8		Week 10		Week 12		Exit	
	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)	N	Mean±SD n (%N)
QIDS-C ₁₆ ¹	50	15±3	40	12±4	46	11±4	45	10±4	42	8±4	38	7±4	40	7±5	41	7±5	51	7±5
QIDS-SR ₁₆ ²	49	14±4	39	11±5	45	10±4	45	9±5	41	8±5	38	7±5	38	7±5	40	7±5	50	7±5
Cumulative remission ³		51		6 (12)	51	8 (16)	51	16 (31)	51	21 (41)	51	22 (43)	51	30 (59)	51	30 (59)	46	23 (50)
Cumulative response ⁴		51		6 (12)	51	10 (20)	51	18 (35)	51	25 (49)	51	27 (53)	51	33 (65)	51	33 (65)	45	28 (62)

¹ 16-item Quick inventory of depressive symptomatology—clinician-rated

² 16-item Quick inventory of depressive symptomatology—self-rated

³ First week in which QIDS-SR₁₆ ≤6 carried forward to Week 12

⁴ First week in which percentage reduction in baseline QIDS-SR₁₆ ≥50 carried forward to Week 12