Olanzapine in the Treatment of Apathy in Previously Depressed Participants Maintained With Selective Serotonin Reuptake Inhibitors: An Open-Label, Flexible-Dose Study

Lauren B. Marangell, M.D.; Christopher R. Johnson, M.D.; Barbara Kertz, M.S.; Holly A. Zboyan, B.A.; and James M. Martinez, M.D.

Background: We report a clinical trial of olanzapine in the treatment of prominent apathy in the absence of depression in patients on long-term treatment with selective serotonin reuptake inhibitors (SSRIs) for nonpsychotic major depression.

Method: Participants were 21 men and women who met DSM-IV criteria for major depressive disorder in full remission (Montgomery-Asberg Depression Rating Scale [MADRS] score ≤ 12) who had been taking an SSRI for at least 3 months. Data are presented (last observation carried forward) based on 20 enrolled participants who completed at least 1 follow-up visit. Participants had significant symptoms of apathy, defined as a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 3, an Apathy Evaluation Scale (AES) score > 30, and a MADRS item 8 (inability to feel) score ≥ 2. Participants with a personal or family history of psychosis were excluded. Olanzapine was titrated in 2.5-mg increments at weekly intervals, until CGI-S score improved ≥ 2 points from baseline or ≥ 1 point with dose-limiting side effects, and participants continued in the protocol for 8 weeks at a stable dose following this improvement.

Results: Improvement was clinically evident and demonstrable on all symptom assessments: AES (mean ± SD change in score = –21.3 ± 8.7; $p < .0001$), CGI-S (–2.7 ± 0.9; $p < .0001$), MADRS (–5.6 ± 5.9; $p = .001$), and MADRS item 8 (–2.2 ± 1.4; $p < .0001$). The mean dose of olanzapine was 5.4 ± 2.8 mg/day.

Conclusion: These preliminary data suggest that olanzapine may be effective in treating apathy syndrome in nonpsychotic patients taking SSRIs.

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Corresponding author and reprints: Lauren B. Marangell, M.D., Department of Psychiatry, One Baylor Plaza BCM 350, Houston, TX 77030 (e-mail: laurenm@bcm.tmc.edu).

There is an expanding literature regarding an apathy syndrome that arises weeks or months into otherwise effective treatment with selective serotonin reuptake inhibitors (SSRIs) in several disorders. Hoehn-Saric et al.[1,2] initially reported an apathy syndrome characterized by symptoms of indifference, loss of initiative, poor attention, and disinhibition related to SSRIs in a case report and case series of patients with depression and panic disorder. George and Trimble[3] later reported a similar syndrome in a patient with Gilles de la Tourette's syndrome and obsessive-compulsive disorder treated with fluvoxamine. Garland and Baerg[4] recently described an amotivational syndrome in a case series of 1 child and 4 adolescents who were taking SSRIs for the treatment of depression, obsessive-compulsive disorder, or anxiety disorder not otherwise specified.

We report a clinical trial of olanzapine in the treatment of prominent apathy in the absence of depression in patients on long-term antidepressant treatment with SSRIs for nonpsychotic major depression. We will refer to this

phenomenon of apathy in the absence of depression as antidepressant apathy syndrome (AAS). To our knowledge, no studies looking at specific treatment interventions for AAS have been published to date.

Further definition of this syndrome is critical. Levy et al.,[5] in a study of dementia patients, and Marin et al.,[6] in depressed patients, have concluded that an apathy syndrome can be distinguished from concomitant depression. This differentiation has been aided by the development of operational criteria to define and specifically characterize apathy as a primary loss of motivation not attributable to emotional distress, intellectual impairment, diminished level of consciousness, or as a symptom of another illness.[6–8] We propose that AAS is a unique neuropsychiatric syndrome distinct from depression and characterized by loss of motivation and blunted emotional responsivity, but further study is required to validate this hypothesis.

The term "poop-out" has been used nonspecifically to describe both tachyphylaxis and what we refer to as AAS. However, a distinction between these 2 phenomena is clinically meaningful. *Tachyphylaxis* refers to a recurrence of depressive symptoms despite continued treatment with an initially effective antidepressant, and its management typically involves increasing the antidepressant dose. In contrast, *antidepressant apathy syndrome* refers to apathy symptoms in the absence of core depressive symptoms. Anecdotal evidence suggests that the management of AAS may involve reducing or stopping the SSRI[1–4] (which increases the risk of relapse into depression) or trying another medication intervention.

We undertook the current study to determine if the addition of olanzapine to ongoing SSRI treatment would attenuate symptoms of AAS in nonpsychotic outpatients who were not acutely depressed. The rationale for using olanzapine in apathy syndrome is 2-fold. First, apathy associated with frontal lobe injury has been reported to respond to medications that theoretically increase dopamine in frontal lobes.[9,10] Preliminary experience with patients who are experiencing antidepressant-associated apathy suggests that they, too, may exhibit short-term therapeutic response to the addition of a stimulant or dopamine agonist.[1] Olanzapine has been shown to enhance frontal dopamine by blocking the tonic serotonin-induced inhibition of dopamine release.[11,12] Second, the apathy syndrome that we describe bears some resemblance to the negative symptoms of schizophrenia. Such negative symptoms preferentially respond to atypical antipsychotic medications, such as olanzapine.[13]

METHOD

Participants were recruited through local advertisement. All participants provided oral or written informed consent after an explanation of study procedures and possible adverse effects. Participants were evaluated clinically and with standard rating scales for eligibility. Participants were required to have received treatment with an SSRI for major depressive disorder (DSM-IV criteria) for a minimum of 3 months prior to enrollment. Additionally, participants were required to have significant symptoms of apathy, characterized by meeting all of the following criteria: a score > 3 on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[14] a score > 2 on item 8 (inability to feel) of the Montgomery-Asberg Depression Rating Scale (MADRS),[15] and a total score > 30 on the Apathy Evaluation Scale (AES).[16] Volunteers with a MADRS score > 12, those with concomitant illnesses, and those with a family history of a psychotic disorder were excluded.

Participants

Of the 21 participants enrolled, 8 failed to complete the study (2 participants withdrew consent, 1 experienced recurrence of depression, 1 developed diverticulitis, and 4 discontinued due to side effects, including sedation, weight gain, decreased concentration, and agitation). Thirteen participants completed all study visits. Data are presented (last observation carried forward) based on 20 enrolled participants who completed at least 1 follow-up visit.

Medication

Participants began treatment with olanzapine, 2.5 mg q.h.s., and continued their current SSRI medication in accordance with the standard dosage guidelines. No changes in SSRI dose were made from at least 3 months prior to the study through study termination. The dose of olanzapine was titrated on a weekly basis in 2.5-mg increments until patients' CGI-S score improved 2 or more points from baseline or 1 or more points with dose-limiting side effects. The total possible dose range of olanzapine was 2.5 to 20 mg. Participants continued in the protocol for a total of 8 weeks at a stable dose following improvement on the CGI-S, as noted above. Olanzapine titration and duration of follow-up were defined a priori.

Measures

Participants were assessed every week with the following standard rating scales: the CGI-S,[14] the MADRS,[15] the AES,[16] the Scale for the Assessment of Negative Symptoms (SANS),[17] the Arizona Sexual Experience Scale (ASEX),[18] the Simpson-Angus Scale,[19] and report of treatment-emergent adverse effects. Response was defined, a priori, as an improvement of 2 or more points on the CGI-S, because in the absence of data, we were not certain that the AES, SANS, or MADRS would adequately characterize this syndrome. The primary and secondary efficacy measures include scores on the CGI-S, MADRS item 8 (inability to feel), total MADRS, AES, ASEX, and SANS. Primary and secondary safety measures include

Table 1. Baseline Clinical and Demographic Features (N = 20)[a]

Variable	Mean	SD	Median	Range
Age, y	50.5	10.8	49.0	21–68
Length of SSRI treatment, mo	30.6	28.8	23.5	3–119
MADRS	10.2	2.3	11.0	6–12
AES	44.1	9.4	43.5	31–61
CGI-S	4.1	0.8	4.0	3–5

[a]Abbreviations: AES = Apathy Evaluation Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

Table 2. Clinical Outcomes (N = 20)[a]

	Baseline		Final		
Measure	Mean	SD	Mean	SD	p Value
CGI-S	4.1	0.8	1.4	0.6	< .0001
AES	44.1	9.4	22.8	5.0	< .0001
MADRS (item 8)	2.6	1.0	0.5	0.9	< .0001
MADRS (total)	10.2	2.3	4.6	5.8	.001
MADRS (except item 8)	7.6	2.4	4.2	5.0	.010
ASEX	21.5	6.4	19.1	6.2	.1360
SANS	30.6	8.7	10.2	9.8	< .0001
Simpson-Angus Scale	1.8	2.1	0.9	1.2	.0710

[a]Abbreviations: AES = Apathy Evaluation Scale, ASEX = Arizona Sexual Experience Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, SANS = Scale for the Assessment of Negative Symptoms.

ratings from the treatment-emergent adverse events scale and the Simpson-Angus Scale.

Statistics

The primary analyses examined change in the efficacy measures from baseline to endpoint. Specifically, pretreatment to posttreatment comparisons were made using paired t tests and repeated-measures analysis of variance (ANOVA) of primary and secondary efficacy measures. Statistical analysis was performed using Minitab Release 10.2 (Minitab Inc, State College, Pa.). Wilcoxon signed rank t tests were conducted comparing baseline and final scores on the AES, MADRS (total), MADRS (item 8), MADRS total (excluding item 8), SANS, CGI-S, Simpson-Angus Scale, and ASEX. The CGI-S was the a priori primary outcome measure.

RESULTS

Baseline and final mean rating scale scores and statistical results are presented in Tables 1 and 2. All primary (rated on CGI-S) and secondary (rated on AES, MADRS item 8, and SANS) apathy efficacy rating scale scores showed significant improvement from baseline to study endpoint. In addition, improvement was clinically meaningful.

In this sample of 20 participants, the mean age was 50.5 ± 10.8 years. Participants included 7 men and 13 women; 17 subjects were white, 2 were Hispanic, and 1 was African American. The mean length of SSRI treatment was 30.6 ± 28.8 months. SSRIs used to treat the participants included citalopram (N = 1, dose = 30 mg), fluoxetine (N = 7, mean dose = 30 ± 15.3 mg), paroxetine (N = 5, mean dose = 26 ± 8.9 mg), and sertraline (N = 7, mean dose = 79 ± 26.7 mg). There was no significant difference in an ANOVA comparison of baseline symptom ratings among the participants when grouped by which SSRIs they were taking during the study.

The mean number of weeks that the 20 participants remained in the study was 7.4 ± 2.6. The completers (N = 13) remained in the study for a mean of 8.8 ± 1.9 weeks, and the noncompleters (N = 7) remained in the study for a mean of 4.9 ± 1.9 weeks.

Sixteen participants reached "improved" status, defined as an improvement of 2 or more points on the CGI-S from baseline, on 1 or more ratings. Twelve of these 16 patients sustained the improved status throughout the remainder of their study participation, and 4 remained at least 1 point improved on the CGI-S by the end of their study participation. The mean number of weeks from treatment to first "improved" status in these 16 participants was 2.6 ± 1.3.

Seven of the 20 enrolled participants for whom data are presented, 3 of which achieved "improved" status, did not complete the study. Five of the 7 discontinued due to side effects, including sedation (N = 1), weight gain (N = 1), tremor and agitation (N = 1), sedation and decreased concentration (N = 1), and constipation and exacerbation of preexisting diverticulitis (N = 1). One participant did not complete the study due to a depressive episode. One participant did not complete the study due to unrelated psychosocial issues.

The mean final dose of olanzapine was 5.4 ± 2.8 mg. The mean baseline weight was 185.8 ± 36.9 lb (84.3 ± 16.7 kg), and the mean final weight was 192.4 ± 38.5 lb (87.3 ± 17.5 kg). The mean weight change during the study was an increase of 6.6 ± 5.3 lb (3.0 ± 2.4 kg).

Common side effects (self-reported in ≥ 7% of patients) included sedation (N = 12), increased appetite (N = 8), stiffness (N = 7), edema (N = 6), dry mouth (N = 5), insomnia (N = 4), agitation (N = 3), headache (N = 3), tremor (N = 3), weight gain (N = 3), constipation (N = 2), dizziness (N = 2), dry eyes (N = 2), and night sweats (N = 2). All were judged to be mild or moderate by the investigator. Only 3 participants subjectively reported weight gain as a possible side effect, despite a mean weight gain of 6.6 lb (3.0 kg) in the study group.

DISCUSSION

A statistically significant improvement from baseline to study completion was observed on the means of the primary and secondary apathy outcome measures (CGI-S,

AES, MADRS item 8, and SANS). The responses all occurred between 1 to 6 weeks (mean = 2.6 ± 1.4 weeks) following initiation of olanzapine, and all participants maintained their initial response during 8 weeks of fixed-dose follow-up.

Since no generally accepted measure of apathy exists, change in CGI-S score was used as the a priori primary outcome measure. This measure also ensured that participants experienced a significant level of impairment due to apathy at baseline. The AES, MADRS, MADRS item 8, SANS, and ASEX were used as additional measures. The AES, developed by Marin et al.,[16] appears to be a valid and reliable measure of apathy, although it was not used as the primary outcome measure in the study because it had not been utilized previously in this population (AAS patients). The total MADRS score was used as a measure of depressive symptoms. Symptoms of depression sufficient for a MADRS score > 12 were an exclusion criterion. The MADRS item 8 rates "inability to feel," which is consistent with our definition of apathy. We included the SANS, a measure typically used to assess the negative symptoms of schizophrenia, because of the similarities between negative symptoms and apathy. We hypothesized that we could capture a change in apathy on the SANS because of this overlap. This overlap also implies that treatments effective for the negative symptoms of schizophrenia may be effective in treating AAS. We used the ASEX, a measure of sexual function, to determine the impact of the addition of olanzapine on sexual function. Both antipsychotics and SSRIs are known to adversely affect sexual function. However, lack of sexual desire may be an important component of an apathy syndrome. As such, it would have been an interesting finding to see an improvement in the ASEX along with improvement in apathy. While a numerical improvement in the ASEX was observed, this change was not statistically significant. Furthermore, improvement in sexual function was not clinically reported.

The results of this study suggest that olanzapine may be an effective treatment for AAS in patients on long-term treatment with SSRIs for nonpsychotic depression. However, several limitations of the study warrant discussion. First, the study consists of a small sample size, which limits our ability to interpret these findings and apply them to a larger population. Second, this study was not randomized and lacked a control group. This prevents us from determining how olanzapine would have compared with another agent or placebo. Spontaneous improvement, or a placebo response, cannot be excluded. Third, this study was done in an open-label fashion, which might introduce both rater and subject bias. A blinded study with a treatment group and a control group would decrease the potential for such types of bias. Fourth, this study looked specifically at subjects with the apathy syndrome on long-term treatment with SSRIs. We cannot conclude whether this intervention would prove effective in non–SSRI-related cases of apathy in the context of antidepressant treatment. Finally, there was variance in this population in terms of different SSRI agents, dosing schedules, and durations of treatment. We were not able to determine whether some individuals are more likely to develop AAS on treatment with certain SSRIs, whether the phenomenon of apathy is related to SSRI dose, or whether response to olanzapine is dependent on unknown interactions with specific SSRIs. Other limitations of the study may also exist.

The exact etiology of AAS is unknown. However, some evidence suggests that serotonergic action on dopamine in the frontal cortex may play a central role in certain apathy syndromes. Disruption of catecholamine systems by brain injury,[20] especially in the frontal lobes,[21,22] has long been implicated in causing symptoms of depression and apathy. There is speculation that chronic stimulation of central serotonin neurons may attenuate dopamine functioning in the frontal cortex.[23] Millan and colleagues[24] recently reported data suggesting that 5-HT_{2C} receptors exert tonic, inhibitory effects on dopaminergic and noradrenergic neurotransmission in the frontal cortex. A possible mechanism of action of olanzapine in the treatment of AAS is the reversal of inhibited dopamine release in the frontal lobe through blockade of chronic serotonergic stimulation by SSRIs. Of note, a recent preclinical study reported significant increase in rat prefrontal cortex dopamine in response to fluoxetine in combination with olanzapine; this response was not seen with either agent alone or with olanzapine in combination with sertraline.[12] Other animal studies have shown a complex interaction of neurotransmitter release among serotonin, norepinephrine, and dopamine neurons in the frontal lobe.[25]

In addition to olanzapine, other promising treatments for AAS may exist. Apathy symptoms commonly seen in Alzheimer's patients improve after treatment with anticholinergic medications.[26] A variety of agents, including stimulants,[27,28] modafinil,[29] bupropion,[30] and olanzapine,[31] have been used to augment antidepressants, although studies to date have not specifically addressed apathy in the absence of depression. However, dopaminergic agents, such as amantadine[32] and bromocriptine,[33] have been used successfully to treat apathy in other neuropsychiatric conditions.

As noted above, the findings of this study are preliminary. Double-blind, controlled studies with larger sample sizes and less variation in treatment variables are needed to provide more definitive conclusions. In addition, further study is needed to characterize the etiology and epidemiology of this problem.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), modafinil (Provigil), olanzapine (Zyprexa), paroxetine (Paxil), sertraline (Zoloft).

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