The Effectiveness of Olanzapine, Risperidone, Quetiapine, and Ziprasidone as Augmentation Agents in Treatment-Resistant Major Depressive Disorder

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Background: Many questions remain regarding the use of atypical neuroleptics as antidepressant augmentation agents. To date, there have been no reports in the literature regarding the effectiveness of these drugs when trials of one or more of them have failed previously as antidepressant augmentation.

Method: This retrospective chart review was conducted to determine the effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone when given in a fee-for-service setting as antidepressant augmentation agents to patients with treatment-resistant, nonpsychotic major depressive disorder (DSM-IV). Prospective (Global Assessment of Functioning [GAF]) along with retrospective (Clinical Global Impressions-Improvement [CGI-I] and -Severity of Illness scales) ratings were completed for each patient. Analyses were conducted in an attempt to identify factors that appeared to correlate with response, including order of administration and Thase-Rush staging of treatment resistance.

Results: In this study of 76 medication trials in 49 patients, the overall response rate based on the CGI-I ratings was 65% (32/49). Individual rates of response were 57% (21/37) for olanzapine, 50% (7/14) for risperidone, 33% (6/18) for quetiapine, and 10% (1/10) for ziprasidone. None of the differences between neuroleptics in rates of response were significant. The difference between baseline and final GAF scores was statistically significant only in the olanzapine ($p < .001$) and risperidone ($p = .047$) groups. Rates of discontinuation did not vary significantly between agents, though trends were present. Crossover trials from one atypical neuroleptic to another in the event of nonresponse appeared to be effective.

Conclusions: Although limited by its design, this study suggests atypical neuroleptic augmentation of antidepressants may be a viable option in treatment-resistant major depressive disorder.

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The management of nonpsychotic, treatment-resistant major depressive disorder remains a significant clinical problem. As noted in a recent review,[1] there is accumulating evidence, though still limited, supporting the efficacy of atypical neuroleptics when added as antidepressant augmentation agents in this population. Thus far, case reports and a small number of published and unpublished clinical trials have suggested that olanzapine,[2–5] risperidone,[5–11] ziprasidone,[12] and possibly quetiapine[5] may be effective. However, the quality of clinical evidence available varies dramatically. The only published double-blind, placebo-controlled study in major depressive disorder to date is with olanzapine.[2]

Given the limited existing information, many questions remain about the use of the atypicals in depression. Are they all equally effective? Do they work only when added to one or all of the serotonin reuptake inhibitors, or might they work with other classes of antidepressants as well (as suggested in case reports with nefazodone,[5] tranylcypromine,[7] bupropion,[10] and mirtazapine[10])? Are there unique differences in tolerability among the atypicals in this patient population? Especially important to clinical practice is the question of crossing over between agents if a patient is unable to tolerate or does not respond to the first trial or subsequent crossover trials of an atypical neuroleptic. Thus far, there is only a single case report[5] documenting the effectiveness of such "crossover" treatments.

The previously cited studies suggest 2 very important characteristics of the atypicals that, if sustained, present a mandate for further study of their use in treatment-

resistant depression: (1) robust efficacy (60% of the subjects in the Shelton et al. study[2] were classified as responders) and (2) a rapid onset of response—often within the first week of treatment.[2,8] For these reasons, we present the largest open-label collection of systematically gathered cases to date on the effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as antidepressant augmentation agents in nonpsychotic major depressive disorder.

METHOD

A systematic review of over 2000 charts identified all patients treated with even a single dose of olanzapine, risperidone, quetiapine, or ziprasidone as augmentation for treatment-resistant, nonpsychotic major depressive disorder treated by the first author (J.G.B.) in a fee-for-service psychiatric outpatient clinic. Aripiprazole, yet another atypical neuroleptic, was not available in the United States at the time the chart review was conducted. All patients were evaluated at the time of initial assessment utilizing a semistructured diagnostic interview to screen for all major DSM-IV Axis I disorders, and any individual with a history of hypomania or mania, nonremitted substance abuse, psychosis, or dementia was excluded.

Detailed information on individual symptom status, adverse events, concomitant medications, and dosages was elicited and recorded at every visit. Return visits were scheduled as necessary according to the judgment of the treating clinician (J.G.B.). The response to atypical neuroleptic augmentation was evaluated utilizing the retrospectively rated Clinical Global Impressions-Improvement scale (CGI-I)[13] based on documented symptom severity. The Clinical Global Impressions-Severity of Illness scale (CGI-S)[13] was also used to retrospectively rate patients at baseline, prior to augmentation. Prospectively rated Global Assessment of Functioning (GAF)[14] scores were also available for most visits. All ratings were performed by the treating clinician, who has extensive experience with these scales and their use in clinical trials.

All patients included in this study were started on treatment with an atypical neuroleptic after being treated with an established antidepressant medication regimen for a minimum of 6 weeks. Antidepressant medication dosage was the highest dose tolerated by the patient, typically surpassing that considered a minimally effective dose as defined by Sackheim.[15] Patients who were started on treatment with additional antidepressant medications or had significant increases in their dosages were excluded to limit the confounding effect of such changes. In all cases, the maximum dose of the atypical neuroleptic was determined in a consistent manner—that is, the dosage was started at a dose likely to be tolerated by the patient and increased upward until the patient was either well or would not tolerate further dosage increases due to side effects.

Data Analysis

Demographic and disease-related variables were first analyzed using descriptive statistics on the following variables: age, sex, course of depression (recurrent/chronic), age at onset of depressive symptoms, duration of current episode, occurrence of breakthrough depression during treatment, number of prior antidepressants, Thase-Rush classifications[16] of treatment resistance for current and lifetime total episodes, maximum and maintenance doses of each neuroleptic agent, concomitant psychotherapy, order of neuroleptic administration, initial and final GAF ratings, initial CGI-S ratings, peak and final CGI-I ratings, and peak and final response status (with response defined as a CGI rating of much improved or very much improved). Bivariate correlations were performed between the above variables and GAF difference scores (final-initial) for each neuroleptic agent to explore potential predictors of response.

To assess the influence of order of administration on response, χ^2 tests of independence were performed on order of administration and peak and final response status for each agent. The potential influence of Thase-Rush staging on response was investigated using tests of independence between the Thase-Rush stage and final response status for each agent. The null hypothesis of no response to any atypical neuroleptic agent, as assumed for treatment-resistant patients, was tested using a χ^2 goodness-of-fit test between observed final response and zero-response rates. As a secondary outcome measure, initial and final GAF scores for each patient were compared using dependent-means t tests for each atypical neuroleptic agent.

Safety analyses of each agent were conducted by collecting frequencies of adverse events.

RESULTS

Of the 49 patients who met criteria for inclusion in the current study, 34 (69.4%) were women and 15 (30.6%) were men. Since individual patients were often crossed over from one agent to another due to a lack of efficacy or adverse event, our sample includes a total of 76 medication trials in 49 patients. All patients had primary Axis I diagnoses of major depressive disorder, with 12 diagnosed as chronic and 25 diagnosed as recurrent (unspecified for 12 patients). Durations of patients' current depressive episodes ranged from 0.1 to 41 years (mean ± SD = 4.71 ± 7.96 years). Prior to beginning atypical neuroleptic augmentation, patients had experienced treatment failure with a mean of 8.22 ± 5.05 antidepressants (range, 1–24).

Comorbid diagnoses, participation in concomitant psychotherapy, and presence of breakthrough depression at initiation of augmentation were recorded. Of the 49 patients included in this study, 23 had comorbid generalized

Table 1. Thase-Rush Classifications of Treatment Resistance for Current Depressive Episode in Patients With Treatment-Resistant Major Depressive Disorder

Stage	Description	Current Episode (N)
I	Failure of 1 adequate trial of an antidepressant	19
II	Failure of Stage I and 1 adequate trial of an alternative antidepressant from a different class	18
III	Failure of Stage II and an adequate trial of a tricyclic	8
IV	Failure of Stage III and an adequate trial of an MAOI	3
V	Failure of Stage IV and a trial of ECT	1

Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor.

Table 2. Concomitant Psychotropic Medications Used During Augmentation of Antidepressants With Atypical Neuroleptics, N

	Augmentation Agent			
Drug	Olanzapine	Risperidone	Quetiapine	Ziprasidone
SSRIs	24	8	10	5
TCAs	1	2	0	0
MAOIs	0	2	0	0
Atypical reuptake inhibitors (bupropion, venlafaxine)	12	6	9	5
Other antidepressants (nefazodone, trazodone, mirtazapine)	4	1	1	0
Benzodiazepines	5	5	6	4
Buspirone	1	0	0	0
Anticonvulsants	7	3	3	2
Lithium	3	2	1	1
Stimulants	6	4	2	4

Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

anxiety disorder, 12 had panic disorder, 9 had social phobia, 9 had attention-deficit/hyperactivity disorder, 6 had dysthymia, 4 had posttraumatic stress disorder, 4 had specific phobia, 2 had obsessive-compulsive disorder, and 1 each had alcohol abuse in remission, borderline personality disorder, and personality disorder not otherwise specified. Twenty-three patients were participating in concomitant psychotherapy. For 18 patients, antipsychotic augmentation was used for the treatment of breakthrough depression following a successful initial response to antidepressant treatment. Thase-Rush classifications for the current depressive episode are listed in Table 1. For more conservative estimates of response to augmentation, intent-to-treat analyses were performed using all patients who took each atypical neuroleptic agent.

While taking neuroleptics, patients were taking a variety of other psychotropic agents. Frequencies of treatment with concomitant psychotropic medications are indicated for each drug under study in Table 2.

The overall rate of response, based on CGI-I ratings, was 65.31% (32/49); 56.82% (25/44) of patients reached very much improved or much improved status following their first trial of an atypical, 27.27% (6/22) responded on their second trial, 30% (3/10) responded on their third trial, and 33.33% (1/3) responded on their fourth trial.

Olanzapine was the first atypical neuroleptic administered to 35 of the 37 patients in the study who took the drug, and 28 patients took the drug for at least 6 weeks. Patients were on treatment with the drug for a mean of 19.59 ± 21.66 weeks (range, 1–92 weeks). Patients were administered a mean maximum dose of 6.48 ± 4.25 mg (minimum = 1.25 mg, maximum = 20.00 mg) per day and a mean maintenance dose of 6.35 ± 4.22 mg (minimum = 1.25 mg, maximum = 20.00 mg) per day. The modal CGI-S rating was markedly ill, with 23 patients receiving this rating. Six patients were rated moderately ill, 5 were rated severely ill, and 1 patient each was rated borderline, mildly ill, and among the most extremely ill patients. A total of 23 patients showed response to olanzapine at their peak improvement, and 21 were still classified as responders at their last visit while taking olanzapine. Responders were on treatment with the drug for a mean of 2.27 ± 2.86 weeks (range, 0.43–12 weeks) before being rated as much improved or very much improved. Only 2 patients experienced breakthrough depression while taking olanzapine.

Among the 14 patients taking risperidone, 5 were administered the drug first, 3 took the drug as their second atypical neuroleptic augmentation attempt, and 6 took risperidone third. Twelve patients took this drug for 6 weeks or longer. Patients were on risperidone treatment for a mean of 35.86 ± 32.08 weeks (range, 4–94 weeks) and took a mean maximum daily dose of 0.85 ± 0.59 mg (minimum = 0.25 mg, maximum = 2.00 mg) and a mean maintenance daily dose of 0.65 ± 0.50 mg (minimum = 0.25 mg, maximum = 2.00 mg). Three patients were rated moderately ill at initiation of augmentation, 9 were rated markedly ill, and 2 were rated severely ill. The 7 patients rated as responders to risperidone at peak response maintained this improvement at their final risperidone visit, and only 2 patients experienced breakthrough depression while taking the drug. Responders were on treatment with the drug for a mean of 3.29 ± 2.50 weeks (range, 0.29–8 weeks) before attaining responder status.

Quetiapine was the first atypical neuroleptic administered to 4 of 18 patients taking the drug. It was the second agent for 11 patients, the third for 1, and the fourth for 2. Ten patients were treated with this drug for at least 6 weeks. Patients were treated with the drug for a mean of 17.94 ± 21.94 weeks (range, 2–74 weeks). The mean maximum daily dose of quetiapine was 166.67 ± 211.69 mg (minimum = 25 mg, maximum = 800 mg), and the mean maintenance daily dose was 155.21 ± 214.23 mg (minimum = 12.5 mg, maximum = 800 mg). Among pa-

Table 3. Rates of Response at the Last Visit to Augmentation of Antidepressants With Atypical Neuroleptics by Order of Administration[a]

Order of Administration	Augmentation Agent, % (N/N)			
	Olanzapine	Risperidone	Quetiapine	Ziprasidone
First	54 (19/35)	60 (3/5)	75 (3/4)	…
Second	100 (2/2)	33 (1/3)	18 (2/11)	17 (1/6)
Third	…	50 (3/6)	0 (0/1)	0 (0/3)
Fourth	…	…	50 (1/2)	0 (0/1)
Total	57 (21/37)	50 (7/14)	33 (6/18)	10 (1/10)

[a]Some patients responded to more than 1 drug. Ns for the first neuroleptic administered add up to 44 rather than 49 due to inadequate prior antipsychotic trials or missing data.

tients taking quetiapine, 1 had an initial CGI-S rating of mildly ill, 8 had ratings of moderately ill, 7 had ratings of markedly ill, and 2 had ratings of severely ill. Only 7 patients were classified as responders at peak improvement, and only 6 retained this response at their final quetiapine visits. Responders were on treatment with the drug for a mean of 4.00 ± 2.00 weeks (range, 2–7 weeks) before attaining responder status. Two patients experienced breakthrough depression while taking quetiapine.

Among the 10 patients taking ziprasidone, it was administered second to 6 patients, third to 3, and fourth to 1 patient. Only 5 patients took the drug for at least 6 weeks. Patients were on treatment with the drug for a mean of 9.40 ± 10.97 weeks (range, 1–28 weeks). The mean maximum daily dose was 57.78 ± 45.22 mg (minimum = 20.00 mg, maximum = 160.00 mg), and the mean maintenance daily dose was 53.33 ± 34.64 mg (minimum = 20.00 mg, maximum = 120.00 mg). Four patients had initial CGI-S ratings of severely ill, 2 patients had ratings of borderline, 2 were rated moderately ill, 1 was rated mildly ill, and 1 was rated among the most extremely ill patients. Only 1 patient was classified as a responder to ziprasidone, attaining a rating of very much improved after 3 weeks on treatment with the drug.

Frequencies of peak and final CGI-I ratings for patients treated with each atypical were obtained. Peak and final response status for patients receiving olanzapine was independent of order of administration: peak $\chi^2 = 1.29$, df = 1, p = .26 and final $\chi^2 = 1.61$, df = 1, p = .20. Responses to risperidone and ziprasidone were also independent of order of administration: peak $\chi^2 = 0.93$, df = 2, p = .63 and final $\chi^2 = 0.53$, df = 2, p = .77 for risperidone, and peak $\chi^2 = 0.53$, df = 2, p = .69 and final $\chi^2 = 0.74$, df = 2, p = .69 for ziprasidone. There was a slight trend toward dependence between peak response and order of quetiapine, $\chi^2 = 6.38$, df = 3, p = .09, but no dependence between final response and order, $\chi^2 = 5.01$, df = 3, p = .17. Response rates for order of administration of each agent are listed in Table 3.

No statistical relationship could be established between Thase-Rush stage and response rates for any agent. Partly influenced by small sample sizes, all tests of association between Thase-Rush stage and final response status were statistically nonsignificant for each agent (olanzapine $\chi^2 = 5.77$, df = 4; risperidone $\chi^2 = 0.67$, df = 3; quetiapine $\chi^2 = 1.52$, df = 4; and ziprasidone $\chi^2 = 1.41$, df = 3).

Frequencies of peak and final responses to augmentation revealed discrepancies between total numbers of peak responders and total final responders. Such discrepancies indicate loss of response. Among 23 patients initially responding to olanzapine, 2 lost response. All 7 patients initially responding to risperidone, all 6 patients responding to quetiapine, and the 1 patient responding to ziprasidone maintained their responses.

To explore whether response rates depended on the class of antidepressant being augmented, frequencies of responses were stratified by antidepressant class. Due to very small sample sizes in each group, as well as the fact that most patients took multiple antidepressants, these results were difficult to interpret and are not reported.

To determine whether the observed final response rates in the current study differed significantly from zero, which would be expected for treatment-resistant patients, the final response rates for each drug were compared with zero-response rates using χ^2 goodness-of-fit tests. For olanzapine, risperidone, and quetiapine, response rates were significantly different from zero: $\chi^2 = 852.01$, 87.63, and 62.23, respectively (df = 1), and $p < .001$ for all tests. The observed final response rate for ziprasidone was not significantly different from zero, $\chi^2 = 0.53$, df = 1, p = .47.

Global Assessment of Functioning scores were used as secondary outcome variables. Dependent-means t tests of differences between initial and final GAF scores for patients taking each drug revealed significant differences for olanzapine and risperidone, $t = 7.14$, df = 31, $p < .001$ and $t = 2.305$, df = 9, p = .047, respectively. However, the differences between initial and final GAF scores for patients on quetiapine and ziprasidone were nonsignificant, $t = –0.74$, df = 9, p = .48, and $t = 1.34$, df = 6, p = .23, respectively. Correlations between GAF difference scores and demographic, disease-related, and drug-related variables were also conducted for each agent. For the 32 patients treated with olanzapine for whom difference scores could be calculated, higher difference scores (greater improvement) were significantly correlated with having been on treatment with the drug for at least 6 weeks, r = 0.55, p = .001. Similarly, difference scores for the 10 patients using risperidone were significantly correlated with the number of weeks that patients used the drug, r = 0.72, p = .02. Difference scores for the 7 patients treated with ziprasidone were strongly negatively correlated with lifetime Thase-Rush classification, r = –0.95, p = .001, and for the 4 ziprasidone patients with complete disease-related information, difference scores were significantly positively correlated with depression recur-

Table 4. Discontinuations Due to Adverse Events (AEs) and Lack of Response, %[a]

Reason for Discontinuation	Augmentation Agent			
	Olanzapine (N = 37)	Risperidone (N = 14)	Quetiapine (N = 18)	Ziprasidone (N = 10)
Discontinued due to lack of response, no AE	14	28	28	10
Discontinued due to lack of response and AE	24	14	39	70
Discontinued due to AE following initial response	32	7	17	0
Total discontinuations due to AE[b]	56	21	56	70

[a]Numbers of patients shown in column headings are the total numbers who received each drug.
[b]Discontinuations due to lack of response and AE plus discontinuations due to AE following initial response.

Table 5. Adverse Events Leading to Discontinuation for Each Agent, %[a]

Adverse Event	Augmentation Agent			
	Olanzapine (N = 21)	Risperidone (N = 3)	Quetiapine (N = 10)	Ziprasidone (N = 7)
Weight gain	43	…	10	14
Increased appetite	10	…	…	…
Nausea	…	33	…	…
Sedation/drowsiness	14	…	40	29
Vivid dreams	5	…	…	…
Headache	10	…	…	14
Confusion	10	…	10	…
Fatigue	10	…	…	…
Irritability	…	…	10	14
Anxiety	…	33	…	…
Depression	…	33	…	…
Emotional numbing	…	…	…	14
Blurred vision	…	…	…	14
Twitching	…	…	…	14
Dizziness	…	…	…	14
Falls	…	…	10	…
Hypercholesterolemia	…	…	10	…
Galactorrhea	…	…	10	…

[a]All adverse events leading to discontinuation are summarized, including individual adverse events experienced by patients who discontinued ziprasidone due to multiple adverse events. Numbers of patients in column headings refer to the total numbers who discontinued each agent due to adverse events.

rence, r = 0.96, p = .04, and significantly negatively correlated with duration of current episode, r = –0.96, p = .04. GAF difference scores for patients on quetiapine were significantly negatively correlated with age, r = –0.82, p = .03, and positively correlated with occurrence of breakthrough depression during antidepressant treatment, r = 0.76, p = .01.

Patients experienced generally mild side effects with all atypical neuroleptics. Frequencies of individuals discontinuing each drug due to adverse events and lack of response are listed in Table 4. Overall, discontinuation rates due to adverse events were not significantly different among the 4 agents, $\chi^2 = 2.31$, df = 1, p = .13, although this result may have been influenced by small sample sizes. Specific adverse events leading to discontinuation of each agent are listed in Table 5, which includes all relevant adverse events reported by patients who discontinued due to multiple adverse events.

DISCUSSION

Evidence supporting the efficacy of the atypical neuroleptics as antidepressant augmentation agents is accruing in clinical trials, but we completed this study to assess the effectiveness of these agents in the real world of clinical practice, where patients often have far more options for treatment than do individuals who participate in clinical trials. In our experience, patients in clinical practice are far less willing to stay on treatment with a drug if they feel it is not effective or has unacceptable side effects.

Taken as a class, the atypical neuroleptics produced an overall response rate of 65.31%. The rate of response to the initial trial of augmentation was 56.82%. Regardless of order of administration, 2 of the drugs included, olanzapine and risperidone, demonstrated robust overall rates of response (57% and 50%, respectively) in this very difficult to treat sample of depressed patients. It was only in these 2 groups that the differences between prospectively determined baseline and end point GAF scores were statistically significant. The mean daily dosages that proved to be effective with olanzapine and risperidone were relatively low (6.48 mg and 0.85 mg, respectively)—far below those generally considered to be effective in other indications such as schizophrenia and even much lower than those reported in publications of antidepressant augmentation such as the Shelton et al. study,[2] in which patients were given a mean dose of olanzapine of 13.5 mg per day. Establishing the lowest effective dose is important, as this helps to improve tolerability. The initial response was relatively rapid (2.27 weeks for olanzapine and 3.29 weeks for risperidone) and generally sustained throughout the follow-up period, with relatively low rates of antidepressant breakthrough once a response was obtained. The response rate showed no significant relationship to Thase-Rush staging on the primary outcome measures, suggesting that patients may respond even if they have a history of failed trials from multiple classes of antidepressant agents.

Most of the patients in the study received olanzapine first because it remains the only atypical neuroleptic that has been shown to be effective in a published double-blind, placebo-controlled trial.[2] Therefore, we have limited data about the efficacy of olanzapine as a crossover agent and more information regarding the efficacy of the other atypicals in this role (see Table 3). Although the relatively small sample sizes and study limitations should be kept in mind, our findings support the efficacy of crossover trials from one atypical to another in the event

of failure of the first agent, particularly with risperidone, to which after 2 prior failed trials with other atypicals, 3 of 6 patients responded. Also, there were 2 patients who safely took risperidone with a monoamine oxidase inhibitor, which has been previously reported in the literature.[7] However, such combinations must be used with caution, as the first author (J.G.B.) is aware of one case in which a patient became comatose with severe vital sign instability after combining phenelzine and olanzapine.

Before discussing the relatively lower response rates seen with quetiapine (33%) and ziprasidone (10%) compared with the other drugs, it is worth noting that (1) none of the differences in response according to CGI-I ratings with any of the 4 drugs were statistically significantly different (although this may be due to the relatively small sample size in some of the cells), (2) all of the patients treated with ziprasidone were given the drug only after a failed trial of another atypical (although this did not seem to affect the response rate to risperidone, as described above), and (3) at least 1 patient responded well to all 4 agents, suggesting that each of the agents is worth trying before abandoning this strategy when managing treatment-resistant patients.

There are several possible reasons why quetiapine and ziprasidone showed relatively low rates of response in our study. The dosages given of both of these agents were relatively low due to the limitations imposed by side effects (although the dosages of olanzapine and risperidone were quite low as well). Drug half-life may be another possible reason for the low response rates. While olanzapine and risperidone have relatively long half-lives (20–70 hours and 6–24 hours, respectively), quetiapine and ziprasidone have quite short half-lives (4–10 hours and 3–10 hours, respectively),[17] and most of the patients took their medication on a once-daily basis. Finally, there may be unique neurochemical differences among the atypical neuroleptics that affect their efficacy in this patient population. One study, in rats, examining specific combinations of atypical neuroleptics and antidepressants revealed olanzapine combined with fluoxetine robustly increased dopamine and norepinephrine in the prefrontal cortex to a greater extent than olanzapine combined with sertraline or risperidone combined with fluoxetine.[18]

In addition to efficacy, the other major variable in the assessment of effectiveness is tolerability. As evidenced by the relatively long mean duration of drug trials for each of the agents (olanzapine 19.59 weeks, risperidone 35.86 weeks, quetiapine 17.94 weeks, and ziprasidone 9.40 weeks), the side effects that were present were relatively mild, although over time, patients did frequently choose to discontinue medications due to side effects. As for the specific reason cited by patients for discontinuation (as listed in Table 5), sedation was most commonly cited for quetiapine and ziprasidone and weight gain was most commonly cited for olanzapine (the adverse events cited for discontinuation with risperidone were evenly distributed, with 1 case each). As noted in Table 4, many of the patients who discontinued their medications did not do so until after they had obtained a response, particularly with olanzapine. The adverse event profiles of each of the atypical neuroleptics we have reported should be weighed against the profiles of traditional augmentation agents such as lithium and triiodothyronine.[19]

In summary, we believe we have shown the effectiveness of atypical neuroleptic augmentation of antidepressants in a relatively large sample of patients, but there are many limitations to this study. The fact that individuals were not assigned to treatment groups in a systematic fashion precludes any discussion of the relative efficacy of the 4 atypicals under study in this chart review, although there is no a priori reason to assume that the order of administration might affect adverse event reporting (most of the trials were conducted in serial fashion, and thus patients were typically continued on the same antidepressant regimen). Other limitations include the possibility of a retrospective bias on CGI ratings (however, prospective GAF scores presumably should not have been affected); the fact that patients were often on treatment with more than 1 antidepressant; the relatively small sample sizes for risperidone, quetiapine, and ziprasidone; and a lack of information on subjects who reached a full remission. Further studies seem clearly indicated.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), buspirone (BuSpar and others), fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), phenelzine (Nardil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor), ziprasidone (Geodon).

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