A Long-Term Trial of the Effectiveness and Safety of Atypical Antipsychotic Agents in Augmenting SSRI-Refractory Obsessive-Compulsive Disorder

Hisato Matsunaga, M.D., Ph.D.; Toshihiko Nagata, M.D., Ph.D.; Kazuhisa Hayashida, M.D.; Kenzo Ohya, M.D., Ph.D.; Nobuo Kiriike, M.D., Ph.D.; and Dan J. Stein, M.D., Ph.D.

Objective: Although atypical antipsychotic agents have been found effective in the augmentation of serotonin reuptake inhibitors (SRIs) for treatment-resistant obsessive-compulsive disorder (OCD) in short-term trials, there are few data on the effectiveness and safety of these agents in clinical settings over the long term.

Method: Subjects (N = 46) who responded to selective SRIs (SSRIs) in an initial 12-week trial were continued on SSRI monotherapy plus cognitive-behavioral therapy (CBT) for 1 year. Subjects (N = 44) who failed to respond to SSRIs were randomly assigned to 1 of 3 atypical antipsychotics—olanzapine, quetiapine, or risperidone—and were consecutively treated using SSRI + atypical antipsychotics combined with CBT for 1 year. This study was conducted from January 2006 to November 2007 at Osaka City University Graduate School of Medicine Hospital, Japan.

Results: Augmentation with atypical antipsychotics reduced mean ± SD Yale-Brown Obsessive Compulsive Scale (YBOCS) total scores in SSRI-refractory OCD patients (at initial assessment = 29.3 ± 9.9, after 1 year = 19.3 ± 6.8). However, compared to SSRI responders (at initial assessment = 25.8 ± 11.4, after 1 year = 13.7 ± 4.6), total YBOCS scores in those who required atypical antipsychotic augmentation were initially higher, and they remained at higher levels than those of SRI responders after 1 year of the treatments.

Conclusions: Our work does not sufficiently support the long-term effectiveness of the atypical antipsychotics in the augmentation of SSRIs for treatment-resistant OCD patients. Even though this approach seems useful for some types of OCD patients, such as those with symmetry/ordering and hoarding symptoms, these data emphasize the limitations of the current pharmacotherapeutic options in treatment-refractory OCD, and their chronic use raises a number of safety concerns.

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Received May 11, 2008; accepted July 15, 2008. *From the Department of Neuropsychiatry, Osaka City University Graduate School of Medicine, Osaka, Japan (Drs. Matsunaga, Nagata, Hayashida, Ohya, and Kiriike); and the Medical Research Council Unit on Anxiety Disorders, University of Cape Town, Cape Town, South Africa, and the Department of Psychiatry, Mt. Sinai Medical School, New York, N.Y. (Dr. Stein).*

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Corresponding author and reprints: Hisato Matsunaga, M.D., Ph.D., Department of Neuropsychiatry, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka, 545-8585, Japan (e-mail: hisato@msic.med.osaka-cu.ac.jp).

The effectiveness of serotonin reuptake inhibitors (SRIs) has been well established in the treatment of obsessive-compulsive disorder (OCD).[1–4] However, in practice, only about 60% of patients respond to SRI administration, and a minority experience symptom remission.[1–6] For such patients, additional pharmacologic treatment strategies such as administration of higher than standard therapeutic doses of selective SRIs (SSRIs) have been proposed,[1,7] and combination drug treatment strategies have also been investigated.[1–5,8] As for the combination drug treatments, 2 main strategies have currently been pursued: the first involves adding drugs, such as clomipramine or clonazepam, that may further enhance serotonin (5-HT) function, and the second is to add a dopamine (DA) receptor antagonist.[4] Early studies of the augmentation of SRIs with typical antipsychotics confirmed the efficacy of this strategy, especially for OCD patients with comorbid tic disorders.[9] More recently, second-generation atypical antipsychotic agents that modulate both 5-HT and DA function, such as risperidone, olanzapine, and quetiapine, have been found effective in the augmentation of SRIs for treatment-resistant OCD.[1,3–6,8,10–15]

Nevertheless, the atypical antipsychotics have been associated with common and serious adverse effects, such as body weight gain and metabolic dysregulation.[16–21] Metabolic dysregulation includes glucoregulatory dysfunction and dyslipidemia.[16,18,19] Indeed, studies of some atypical antipsychotics in SSRI-refractory OCD patients have similarly reported significant body weight gain.[10–13] Atypical antipsychotic-induced body weight gain may influence patients' adherence to medication, and it places them at risk for a broad range of medical problems.[16,18,19,20,22]

Most work on atypical antipsychotics in treatment-refractory OCD has been conducted in the form of short-term efficacy studies. There have been fewer studies of the effectiveness, safety, and tolerability of these agents in the context of a clinic where CBT is also provided, and where treatment is continued for a significant period of time. In the current effectiveness study, we sought to examine the response of SSRI-refractory patients to augmentation with atypical antipsychotics, comparing adverse events in those patients to a control group of SSRI responders.

METHOD

Subjects and Assessment

Subjects were 137 consecutive outpatients who met DSM-IV[23] criteria for OCD and had received standardized treatment for at least 1 year at the OCD clinic at Osaka City University Graduate School of Medicine Hospital. Each subject was diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient version (SCID-I/P)[24] and gave informed consent to take part after receiving a complete description of this study. This study was approved by the Institutional Review Board of Osaka City University Graduate School of Medicine and conducted between January 2006 and November 2007. All subjects were free of medical illness based on results of physical examination and screening tests of blood and urine, and no subjects received any lipid-lowering or hypoglycemic agent during the 1-year study period. Information was obtained regarding demographic profile, family and medical history, and clinical features and course. Global functioning was assessed using the DSM-IV Axis V Global Assessment of Functioning Scale (GAFS).[23] OCD symptom content and severity were assessed using the Japanese version of the Yale-Brown Obsessive Compulsive Scale (YBOCS)[25,26]

After the pretreatment assessments, each subject was initially treated with SSRIs (fluvoxamine or paroxetine). This treatment was usually initiated with low daily dosages (fluvoxamine, 50 mg or paroxetine, 10 mg) and the assignment to any particular SSRI was random. If the medication was tolerated, dosage was gradually increased over 4 weeks to a maximum of fluvoxamine, 250 mg/day, or paroxetine, 50 mg/day. After at least 12 weeks from treatment initiation, cognitive-behavioral therapy (CBT) using exposure and response prevention was added, with psychoeducational interventions and behavioral analysis.

After a 12-week SSRI trial, subjects were divided into 2 groups; SSRI responders were defined as patients who showed a decrease of 25% or more in their YBOCS total score and were also rated as "much improved" (2) or "very much improved" (1) on the Clinical Global Impressions-Improvement (CGI-I) scale. Forty-six subjects were assigned to this group, and they subsequently continued SSRI monotherapy and had CBT initiated. Forty-four subjects who showed a less than 10% decrease in symptoms on YBOCS with a CGI-I scale score of 3 or 4 were considered SSRI-refractory. These subjects were randomly assigned to 1 of 3 atypical antipsychotics—risperidone, 1 to 5 mg/day (N = 7), quetiapine, 25 to 100 mg/day, (N = 19), or olanzapine, 1 to 10 mg/day (N = 18)—and continued SSRI + atypical antipsychotics for at least one half year (mean = 228 days); all of these subjects also had CBT initiated. However, the combination of paroxetine and risperidone was prohibited because of paroxetine's robust inhibition of the cytochrome P-450 (CYP450) enzymes, particularly 2D6, which elevates the serum levels of risperidone.[27] Finally, 47 subjects who exhibited a 10% to 25% reduction on YBOCS were excluded from further analysis.

For each subject in both the SSRI responders and the SSRI + atypical antipsychotics groups, 1-year treatment response was evaluated using change in YBOCS total score. Additionally, body weight changes during the 1-year treatments were estimated using the body mass index (BMI). Fasting blood sugar and serum lipid profiles (total cholesterol and triglycerides) were measured for each subject at both the time of initial assessment and approximately 1 year after the beginning of the treatment. Blood samples were taken in the hospital laboratory between 9:00 a.m. and 10:00 a.m. after the patients had fasted for at least 10 hours.

Analysis

For the main between-group comparisons, 2-tailed group t tests or 1-way and 2-way analysis of variance were used. For categorical data, χ^2 tests with Yates correction for discontinuity or Fisher exact test (if the minimum expected cell size ≤ 5) were used. In the SSRI + atypical antipsychotic group, Pearson correlation coefficients were also analyzed to examine the relation of variables associated with body weight or serum lipid profiles. Significance levels were set for $p < .01$ in view of multiple testing.

RESULTS

Sociodemographic variables (age, sex) and clinical history (age at onset, duration of illness, comorbid depression) did not differ significantly across the 2 groups

Table 1. Demographic Profiles, Clinical Features, and Metabolic-Related Profiles at Initial Assessment of 90 Subjects With Obsessive-Compulsive Disorder[a,b]

	SSRI Responders, N = 46	SSRI + Atypical Antipsychotics, N = 44
Sex, male/female	17/29	14/30
Age, mean ± SD, y	28.5 ± 7.3	29.8 ± 8.5
Age at onset, mean ± SD, y	21.7 ± 5.6	21.6 ± 6.7
Duration of illness, mean ± SD, y	6.7 ± 5.5	8.2 ± 5.1
Education, mean ± SD, y	13.7 ± 2.1	12.7 ± 2.3
Married, %	45.70	36.30
GAFS score, mean ± SD	53.3 ± 6.2	46.5 ± 6.1*
Comorbidity of major depression, %	39.10	31.80
YBOCS total score, mean ± SD	25.8 ± 11.4	29.3 ± 9.9*
Body mass index, mean ± SD, kg/m^2	20.5 ± 2.2	20.3 ± 2.4
Fasting blood sugar, mean ± SD, mg/dL	78.6 ± 9.5	80.6 ± 9.9
Triglycerides, mean ± SD, mg/dL	101.5 ± 39.0	98.7 ± 38.3
Total cholesterol, mean ± SD, mg/dL	152.5 ± 30.6	145.6 ± 29.6

[a]Group means of parametric variables were compared by 2-tailed t tests.
[b]Comparisons of non-parametric variables were made by χ^2 tests with Yates correction for discontinuity.
*p < .01 compared to the SSRI responders group.
Abbreviations: GAFS = Global Assessment of Functioning Scale, SSRI = selective serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 2. Group Comparisons of Clinical Variables After 1-Year Treatment[a,b]

	SSRI Responders, N = 46	SSRI + Atypical Antipsychotics, N = 44
YBOCS		
Total score, mean ± SD	13.7 ± 4.6	19.3 ± 6.8*
Improvement rate, mean ± SD	50.0 ± 14.3	40.4 ± 17.9*
Percentage of subjects with YBOCS reduction >50%	50.00	31.80
Body mass index (BMI)		
BMI, mean ± SD, kg/m^2	21.2 ± 2.6	23.3 ± 3.1*
Rate of increased BMI, mean ± SD	4.2 ± 5.0	13.5 ± 9.9*
Percentage of subjects with BMI increase > 10%	15.20	50.00*
Fasting blood sugar and serum lipid profiles		
Fasting blood sugar, mean ± SD, mg/dL	80.9 ± 9.3	88.6 ± 7.3*
Triglycerides, mean ± SD, mg/dL	115.9 ± 44.8	165.0 ± 68.6
Total cholesterol, mean ± SD, mg/dL	172.8 ± 32.1	188.2 ± 32.6

[a]Group means of parametric variables were compared by 2-tailed t tests.
[b]Comparisons of non-parametric variables were made by χ^2 tests with Yates correction for discontinuity.
*p < .01 compared to the SSRI responders group.
Abbreviations: SSRI = selective serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.

(Table 1). At initial assessments, the mean BMI, fasting blood sugar, triglyceride, and total cholesterol values were also similar in both groups. These laboratory data for each subject were in the normal range. However, subjects in the SSRI + atypical antipsychotics group were significantly more likely than those in the SSRI responders group to have a lower mean score on the GAFS ($t = 5.26$, $df = 88$, $p < .01$) and a higher mean total score on the YBOCS ($t = 4.40$, $df = 88$, $p < .01$). Subjects in the SSRI + atypical antipsychotics group showed a significantly elevated prevalence of symmetry obsessions ($\chi^2 = 10.5$, $df = 1$, $p < .01$), ordering ($\chi^2 = 8.5$, $df = 1$, $p < .01$), repeating rituals ($\chi^2 = 6.8$, $df = 1$, $p < .01$), and hoarding symptoms ($p < .01$; Fisher exact test) than those in the SSRI responders group.

At 1 year, there were no significant differences in the distributions of SSRIs in the SSRI responders and the treatment-refractory groups (fluvoxamine/paroxetine; SSRI responders: 30/16, SSRI + atypical antipsychotics: 23/21). The mean ± SD maximum dosage of paroxetine was similar across the groups (SSRI responders, 36.3 ± 6.5 mg/day, SSRI + atypical antipsychotic, 42.2 ± 4.3 mg/day), but the mean ± SD dose of fluvoxamine in the SSRI + atypical antipsychotics group (203 ± 63.4 mg/day) was significantly higher than that in the SSRI responders group (175.9 ± 58.0 mg/day). In the SSRI + atypical antipsychotics group, mean ± SD doses of risperidone were 3.1 ± 1.9 mg/day, of olanzapine were 5.1 ± 3.2 mg/day, and of quetiapine were 60.0 ± 37.3 mg/day.

Table 2 demonstrates the results of the group comparisons of clinical variables after the 1-year treatment. Although the mean reduction ($t < 2.95$, $df = 88$, $p < .01$) in total YBOCS score in the SSRI responders group was significantly higher than that in the SSRI + atypical antipsychotics group, there was no significant difference in the percentage of subjects whose improvement rate on the YBOCS was more than 50%.

While no patients discontinued the 1-year treatment because of side effects, patients in the SSRI + atypical antipsychotics group complained of increased appetite (34%), increased body weight (27%), and sleepiness (12%) or sedation (7%). Both increased appetite ($\chi^2 = 4.8$, $df = 1$, $p < .01$) and increased body weight ($\chi^2 = 6.1$, $df = 1$, $p < .01$) were significantly more frequent in this group than in the SSRI responders group. Indeed, after 1-year treatment, both the mean BMI and the mean rate of increase in BMI were significantly higher in the SSRI + atypical antipsychotics group than in the SSRI responders group (BMI; $t = 3.56$, $df = 88$, $p < .01$, increased in BMI; $t = 5.67$, $df = 88$, $p < .01$). Subjects in the SSRI + atypical antipsychotics group were more likely to have more than a 10% increase in BMI ($\chi^2 = 10.9$, $df = 1$, $p < .01$), had a significantly higher mean fasting blood sugar, and showed a trend towards increased triglyceride and total cholesterol levels. In the SSRI + atypical antipsychotics group, additionally, BMI at the follow-up

exhibited significant correlations with BMI at the initial assessments (3.44, $p < .0001$) and with fasting blood sugar at endpoint (2.59, $p < .01$).

Comparisons across individual atypical antipsychotics found no significant group differences in the fluvoxamine/paroxetine ratio, mean reduction on YBOCS total score, or follow-up BMI, fasting blood sugar, triglyceride, or total cholesterol levels. However, subjects treated with olanzapine or quetiapine showed significantly higher mean ± SD rate of increased BMI compared to those treated with risperidone (olanzapine; 15.4 ± 8.8, quetiapine; 13.8 ± 9.4, risperidone; 6.5 ± 4.4; $F = 11.9$, $df = 2,87$; $p < .01$).

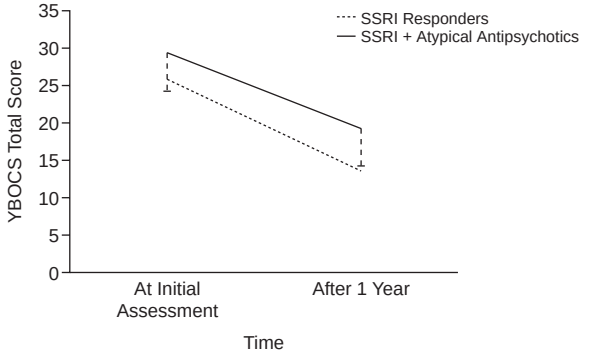
DISCUSSION

The main findings of this study were (1) that although SSRI-refractory OCD patients responded to augmentation with atypical antipsychotics, they had higher YBOCS scores both before and after treatment compared with those who showed good responses to SSRI monotherapy, and (2) that although SSRI + atypical antipsychotics patients were highly adherent to atypical antipsychotics, they demonstrated significant increases in BMI.

Even though the patients in the SSRI + atypical antipsychotics group were a clinically more severe group at baseline, no significant group differences existed in the rate of the subjects who showed a 1-year treatment response of a more than 50% reduction in YBOCS total score. (A YBOCS total score reduction of more than 35% is generally seen as an indicator of full response.)[5] However, our findings did not sufficiently support the effectiveness of the atypical antipsychotics in the augmentation of SSRIs for treatment-refractory OCD patients. It is notable that, even after the 1-year treatment, YBOCS scores in the SSRI + atypical antipsychotics group remained higher than in those who had initially responded to SSRIs (Figure 1). Whereas all of the subjects received augmentation with CBT in the extension phase of the treatment, the mean 1-year improvement rate obtained from the SSRI + atypical antipsychotics group was similar or inferior to the acute or long-term outcome of subjects treated by CBT alone.[28–30] Indeed, CBT has been proven effective even for the patients who do not respond to pharmacotherapy.[31]

However, it should be noted that patients in the SSRI + atypical antipsychotics group were significantly more likely than the SSRI responders group to have symmetry/ordering and repeating rituals or hoarding symptoms, which is consistent with recent studies suggesting that these OCD symptom dimensions are associated with refractoriness to SSRIs,[32,33] CBT,[34,35] or both.[36] It has been suggested that the symmetry/hoarding dimension correlates with comorbid Tourette's syndrome or chronic tic disorder, in which case this subgroup would benefit from the direct effects of neuroleptic medication.[33] It has also been suggested that patients with checking and cleaning symptoms may respond best to exposure methods, but other subtypes, such as patients with ordering compulsions and hoarding, have rarely been included in trials of CBT.[34] In addition, patients with high scores on the hoarding dimension may be more likely to drop out prematurely from CBT and tend to improve less.[35] Thus, it is possible that this augmentation strategy may be useful in supporting the combination treatments, especially CBT, for at least some types of OCD patients refractory to SSRI alone.

Figure 1. Change in YBOCS Total Scores in Patients With Obsessive-Compulsive Disorder Who Responded to Treatment With SSRIs (N = 46) and Nonresponders Who Had SSRI Treatment Augmented With Atypical Antipsychotics (N = 44)



Abbreviations: SSRI = selective serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Although no patients discontinued the treatments due to side effects, subjects in the SSRI + atypical antipsychotics group demonstrated a significantly higher rate of BMI, as well as a significantly higher level of fasting blood sugar, than those in the SSRI responders group. Additionally, the SSRI + atypical antipsychotics group was relatively more likely to show elevated levels of triglycerides and total cholesterol. The adverse metabolic consequences of atypical antipsychotics are increasingly recognized,[16–22] and the data here are consistent with previous findings from the short-term efficacy trials.[10–13,16–22]

In this study, however, subjects in the SSRI responders group also showed a considerable mean ± SD rate of increased BMI (4.2 ± 5.0) during the 1-year study period. This finding is consistent with body weight gain observed during long-term treatment with SSRIs; a significant increase in body weight (≥ 7%) was observed in 14.5% of OCD patients who had consecutively received SSRI treatment for 2.5 years.[37] Whereas the mechanisms responsible for it remain uncertain, SSRI-induced body weight gain may be due to pharmacologic effects on 5-HT_{2C} receptor activity of SSRIs.[37] In addition, women are considered

more likely than men to experience increased body weight during the extended administration of SSRIs,[37,38] suggesting that female predominance of subjects in this study may also be associated with the body weight gain found in the SSRI responders group.

In the SSRI + atypical antipsychotics group, the 1-year rate of increased BMI was significantly correlated with BMI before treatment initiation, which may be reflective of some vulnerability factors related to susceptibility to atypical antipsychotic–induced body weight gain. It has been speculated that gene variants in receptors such as the 5-HT_{2C} receptor may play a role in determining individuals' responses to atypical antipsychotics, as well as their side effect profiles, including body weight gain liability.[16,20,27,39] Indeed, interindividual variations in body weight gain responses to atypical antipsychotics have been suggested.[16,21,22] Age, sex, and/or ethnic differences in atypical antipsychotic-related body weight gain liability may also occur,[16,22,39] and medications may differ in their propensity for body weight gain.[14–19,22] Not all prior work is consistent; some previous studies have suggested an inverse correlation between BMI gain associated with atypical antipsychotics and BMI at baseline.[21,40,41] Previous work has suggested that subjects treated with olanzapine showed the most elevated BMI rate, along with a trend towards higher lipid levels compared to levels in the subjects who received other types of atypical antipsychotics such as risperidone. Indeed, clozapine and olanzapine are generally considered as producing the most body weight gain, and quetiapine and risperidone produce intermediate body weight gain, and the differences in body weight gain associated with the agents may reflect their order of risk for insulin resistance, glucoregulatory dysfunction, and dyslipidemia.[18] As for quetiapine, however, a wider variation in extent of body weight gain has been reported (body weight gain ≥ 7%) occurring in 11% to 25% of patients treated with quetiapine for 6 to 8 weeks), and, as in this study, quetiapine-induced body weight gain equivalent to that induced by olanzapine has also been reported elsewhere.[21]

Another possible factor contributing to the significant body weight gain in the SSRI + atypical antipsychotics group may be a drug-drug interaction between SSRIs and atypical antipsychotics; for the drug-drug interaction of many psychotropics, the CYP450 metabolizing enzyme plays a major role. For instance, paroxetine, a potent inhibitor of CYP2D6 may elevate plasma concentrations of co-administered risperidone, and severe body weight gain was reported during the combined administration.[42] It has been suggested that fluvoxamine, a potent inhibitor of CYP1A2, one of the major isoforms responsible for olanzapine metabolism, elevates plasma olanzapine concentrations.[43] Conversely, the effectiveness of the atypical antipsychotic augmentation may also be affected by the type of SSRIs.[44]

Although the mechanism for the effect of atypical antipsychotics is not fully understood, there were no correlations between treatment response and side effects of the augmentation with atypical antipsychotics in this study. On the other hand, the significant association between BMI at the follow-up and fasting blood sugar levels at endpoint found here suggests the possibility that elevated levels of fasting blood sugar might be induced by the same mechanisms as atypical antipsychotic-related diabetes type II, although some patients taking atypical antipsychotics experience new-onset diabetes without changes in adiposity.[18] Additionally, antipsychotic affinity at both histamine and muscarinic acetylcholine receptors may also correlate with body weight gain and metabolic liability.[16,17,21,45] Thus a range of mechanisms may have contributed to both the body weight gain and metabolic disturbances seen in our sample.

To summarize, this is one of first studies regarding the long-term effectiveness and safety of atypical antipsychotics in the augmentation of SSRIs for SSRI-refractory OCD patients. Even though our work cannot sufficiently support the effectiveness of the atypical antipsychotics in the augmentation of SSRIs for treatment-resistant OCD patients, atypical antipsychotics seem useful for some types of OCD patients, such as those with symmetry/ordering and hoarding symptoms. Nevertheless, these data emphasize the limitations of the current pharmacotherapeutic options in treatment-refractory OCD, which raise a number of safety concerns when used chronically. In particular, our results are consistent with previous comparisons of body weight and/or metabolic changes associated with each atypical antipsychotic. However, these results should be interpreted with caution because of the open-label and uncontrolled design of this study. Given that atypical antipsychotics may show differences in their effects on body weight gain and lipid and glucose metabolism, along with possible differences in pharmacodynamic and/or pharmacokinetic drug interactions with SSRIs,[12,19,22,27,44] larger controlled and adequately powered studies of SSRI-refractory OCD patients are required to further examine the differential risk of body weight gain and metabolic disturbances with various atypical antipsychotics. In the interim, however, it seems clear that alternative strategies to the treatment of refractory OCD urgently need to be developed.

Drug names: clomipramine (Anafranil and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), fluvoxamine (Luvox and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others).

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