THE ANTIDEPRESSANT EFFECTS OF RISPERIDONE AND OLANZAPINE IN BIPOLAR DISORDER

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ABSTRACT

Objective
To describe the antidepressant effectiveness of olanzapine and risperidone and compare their tolerability when employed adjunctively in bipolar I/II disorder.

Method
In an observational study, twenty-one ambulatory subjects with DSM-IV defined bipolar I/II disorder, in any phase of the illness, openly received adjunctive risperidone or olanzapine. The primary efficacy parameters were the Hamilton Depression Rating Scale (HDRS-17) and the Maier and Philips Severity Subscale. Secondary efficacy parameters included the Young Mania Rating Scale (YMRS) along with the Clinical Global Impressions Scale (CGI). Response was defined as a significant change from baseline to endpoint in the total mean HDRS-17 score. The primary tolerability parameters were the Abnormal Involuntary Movement Scale (AIMS) along with changes in weight and body mass index (BMI-kg/m^2). Patients were evaluated prospectively with repeated monthly assessments for up to 6 months.

Results
Eleven patients openly received risperidone; 10 received olanzapine adjunctive to either lithium or divalproex. Total mean HDRS-17 scores significantly decreased from baseline to endpoint in both groups (p=0.001), with the mean HDRS-17 total scores falling from 17(SD=3.2) to 5(SD=1.5) by 6 months in the risperidone-treated group and from 18 (SD=1.9) to 7 (SD=2.0) in the olanzapine-treated group. Differences between the risperidone-treated group and the olanzapine-treated group were not significant at 6 months (p=0.754). The mean doses of study medication were 2.88 (SD=1.6) mg/day for the risperidone-treated group and 12.69 (SD=2.3) mg/day for the olanzapine-treated group. Both risperidone and olanzapine were generally well tolerated. No patients developed tardive dyskinesia. Significant weight gain was experienced by patients in both groups [mean weight gain at endpoint was 5.9 kg in risperidone (p=0.023) and 11.3 kg in olanzapine (p=0.001)]. There was a significant difference in weight gain between the risperidone-treated group and the olanzapine-treated group (p=0.001).

Conclusions
These pilot data, from the first prospective comparison study of risperidone and olanzapine in bipolar disorder, suggest that adjunctive administration of either agent may reduce depressive symptom severity. No subjects receiving risperidone or olanzapine developed tardive dyskinesia. Both compounds imparted substantial weight gain with significantly more weight gain accrual with olanzapine. As this was an observational study, the antidepressant effect and tolerability profile of these compounds requires validation via double-blind placebo controlled investigations.

Key Words: Bipolar disorder, risperidone, olanzapine, adjunct therapy, cohort study

Bipolar disorders are prevalent episodic heterogeneous disorders, which affect approximately 2% of the general population.[1] Prolonged periods of recovery are unusual and pervasive functional impairment is common in affected persons.[2, 3] The substantive illness burden attributable to bipolar disorder[4] creates substantial humanistic and economic costs.[5]

An expanding body of controlled-trial data suggests both risperidone and olanzapine are effective against the manic and mixed phase of bipolar disorders.[6,7] There remains however, a dearth of data evaluating the antidepressant effects of these compounds in this patient population. Depressive symptoms are often the index presentation of bipolar disorder[8], and subsyndromal symptoms are omnipresent during the maintenance phase.[10]

Depressive symptoms powerfully and prospectively predict relapse of illness[9], represent a principal quality of life detractor[10], and presage suicidal behavior in bipolar disorder.[11] There exists a pressing need for novel therapeutic avenues to alleviate depressive symptoms. Confirmation of an antidepressant effect (e.g. bi-directional efficacy) may support the notion that some atypical antipsychotics are mood stabilizers in bipolar disorder.[12] More recently, published evidence suggests both adjunctive risperidone and olanzapine may offer an antidepressant effect in bipolar disorder.[13, 14]

We are however, unaware of any published evidence that has attempted to directly evaluate and compare the antidepressant and tolerability profiles of these two agents within the same study in bipolar disorder. This pilot study sought to provide prospective data describing the antidepressant efficacy and tolerability of risperidone and olanzapine in ambulatory bipolar disorder. Tardive dyskinesia and weight gain liability were the adverse events of primary interest.

METHODS

This pilot study was carried out with the approval of the Ethics Committee of the Medical Faculty, Centre for Addiction and Mental Health (CAMH), University of Toronto, and informed consent was obtained from all subjects.

Between September 1999 and December 2000, 21 males and females between the ages of 18 and 50 years with bipolar I/II in any syndromal phase of the disorder according to DSM-IV criterion were enrolled.[15] Subjects were judged to be eligible for enrollment if in the opinion of the clinician the intensity of affective symptoms required pharmacological intervention. Patients were consecutively recruited from the bipolar clinic (CAMH) assessment service.

The subjects were judged by the investigator to be in generally good health and could be safely treated with anticonvulsants, antidepressants or benzodiazepines. Subjects receiving divalproex sodium or lithium must have been receiving the medication for a period of at least 2 weeks (plasma levels within therapeutic range: Lithium 0.50-1.50 nmol/L; divalproex sodium 350-700 μmol/L). Patients were permitted to have had prior (but not concomitant) exposure to other antipsychotic agents.

Subjects were excluded from the study if they had prior exposure to risperidone or olanzapine, were diagnosed with substance dependence within the past 30 days, had a course of electroconvulsive therapy (ECT) in the preceding 4 weeks prior to visit 1 or during the protocol, were assessed to be a suicide risk, had active neurological or medical problems, or were incapable of providing informed consent. In women, a urine test was carried out in order to exclude pregnancy. After informed consent was obtained, relevant demographics, diagnoses, and other clinical data were collected. All patients received a physical exam; concomitant medications, vital signs, weight change and laboratory tests (which included clinical chemistry, leptin, haematology, electrolyte group, thyroid function test and mood stabilizer plasma levels) were recorded. Weight, BMI (kg/m^2), random blood glucose, lipid profiles and leptin were assessed at each visit and endpoint. Waist to hip ratio was not measured. Differential effects on glucose, lipids and leptin are reported in a companion paper.

Treatments with risperidone or olanzapine were openly assigned by patient preference after extensive review of the relative merits and liabilities of each agent by the treating clinician. Dosing for both antipsychotics was determined clinically on the basis of effectiveness.

tolerability. Patients did not switch their mood stabilizers during the 6-month observation period.

Patients were assessed prospectively on a monthly basis by either the treating clinician and/or the clinical research coordinator. Satisfactory inter-rater reliability between the treating clinician and the research coordinator has been previously established. The following assessments were the primary efficacy parameters completed at each visit: the Hamilton Depression Rating Scale (HDRS-17)[16] and the Maier and Philip Severity Subscale.[17] The Young Mania Rating Scale (YMRS)[18] and Global Impression for Severity (CGI-S) and Improvement (CGI-I)[19] were secondary efficacy parameters. Response was based on a significant change from baseline to endpoint in the HDRS-17 total score. The primary safety parameters were the Abnormal Involuntary Movement Scale (AIMS) and changes from baseline in weight (kg) and body mass index (BMI-kg/m^2). Independent t-tests and analysis of variance (ANOVA) using repeated measures design were used to analyze the data.

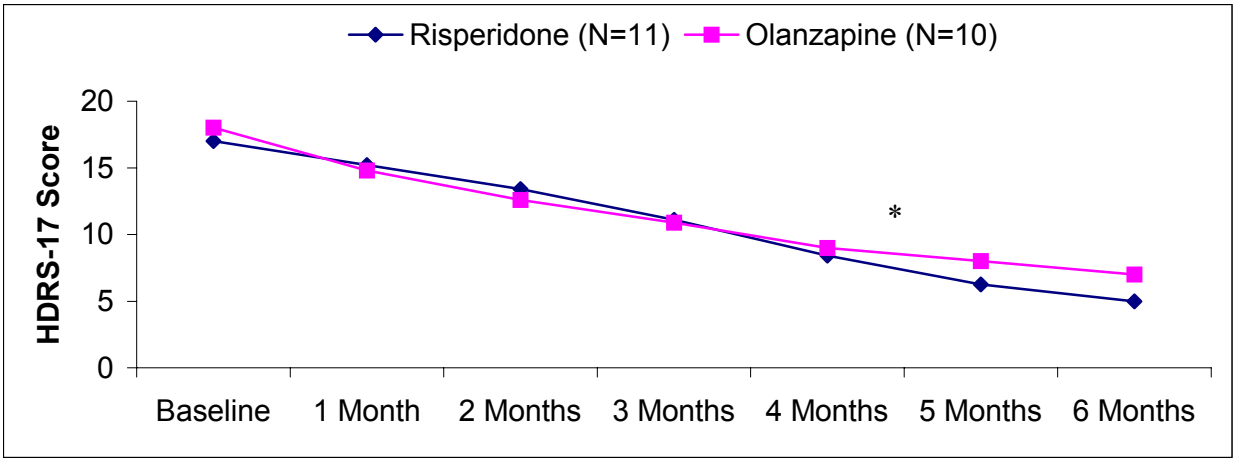
RESULTS

Baseline demographics and clinical characteristics were comparable between both groups (Table 1). Benzodiazepines were used in 5 (46%) patients in the risperidone-treated group and 4(40%) patients in the olanzapine-treated group.

At baseline, patients were in various phases of the illness including depression (n=13), mixed states (n=6), and hypomanic (n=2). No patients exhibited psychotic symptoms. The mean doses of study medication were 2.88 (SD=1.6) mg/day for the risperidone-treated group and 12.69 (SD=2.3) mg/day for the olanzapine-treated group. Five patients were receiving lithium (mean dose=970 mg/day, SD= 375.3 mg/day, mean duration=6.1 years) and 16 patients were receiving divalproex sodium (mean dose=1126.31 mg/day, SD=414.36 mg/day, mean duration=5.7 years). The mean plasma levels for lithium and divalproex sodium were 1.09 meq/l and 485.4 umol/l, respectively. There were no significant changes in lithium and divalproex sodium levels from baseline to endpoint between the two study groups (p=0.231).

Total mean HDRS-17 scores significantly decreased from baseline to endpoint in both groups (p=0.001), with the mean HDRS-17 total scores falling from 17 (SD=3.2) to 5 (SD=1.5) by 6 months in the risperidone-treated group and from 18 (SD=1.9) to 7 (SD=2.0) in the olanzapine-treated group (Fig.1).

FIG. 1 HDRS-17 Scores



Total mean HDRS-17 scores significantly decreased from baseline to endpoint in both groups (*p=0.001) however, differences between the groups were not significant (p=0.754).

TABLE 1 Clinical Demographics

Patient	Treatment	Age	Gender F:Female M:Male	Diagnosis	Age of Onset	Number of Prior Episodes	Co-morbidity	Past Suicide Attempts	Prior Hospitalizations
1	Risperidone	27	F	BPI	22	3	Anxiety Disorder	1	2
2	Risperidone	55	F	BPI	24	6	Anxiety Disorder	2	4
3	Olanzapine	36	M	BPII	28	4	Personality Disorder	0	2
4	Risperidone	36	F	BPII	26	5	None	1	3
5	Olanzapine	21	M	BPI	30	4	Anxiety Disorder	0	3
6	Olanzapine	23	M	BPI	32	6	None	0	5
7	Olanzapine	32	F	BPI	23	3	Anxiety Disorder	0	1
8	Risperidone	37	F	BPI	20	5	Anxiety Disorder	1	2
9	Risperidone	38	F	BPI	28	6	Anxiety Disorder	2	3
10	Risperidone	53	M	BPII	25	8	Personality Disorder	0	4
11	Olanzapine	36	F	BPII	27	3	Anxiety Disorder	0	1
12	Olanzapine	56	M	BPII	31	10	Past Alcohol Abuse	1	5
13	Risperidone	25	F	BPI	20	2	Anxiety Disorder	0	0
14	Risperidone	34	F	BPI	23	4	Personality Disorder	1	1
15	Olanzapine	59	M	BPI	21	9	Past Substance Abuse	2	5
16	Olanzapine	44	M	BPI	23	9	None	1	6
17	Risperidone	54	F	BPII	28	7	Anxiety Disorder	2	3
18	Olanzapine	52	F	BPI	26	8	Personality Disorder	2	3
19	Olanzapine	26	F	BPI	24	2	Anxiety Disorder	0	0
20	Risperidone	31	M	BPII	22	4	Past Alcohol Abuse/Anxiety Disorder	0	1
21	Risperidone	33	M	BPI	27	4	Past Substance Abuse	0	1

Differences between the risperidone- treated group and the olanzapine-treated group were not significant (p=0.754). Statistically significant reductions in the CGI-I scores (p=0.001) were observed at 6 months compared with baseline for both treatment groups.

Statistically significant reductions in YMRS scores were also observed at 6 months compared with baseline for both treatment groups (p=0.001), with the mean YMRS total scores falling from 14 (SD=2.2) to 5 (SD=4.7) by 6 months in the risperidone-treated group and from 16 (SD=3.8) to 6 (SD=1.7) in the olanzapine-treated group. Differences between the two treatment groups were not significant (p=0.672). All patients met full symptomatic remission (mean total YMRS score<12, mean total HDRS <7) at endpoint.[3,20] All patients entering the study in any phase of the illness exhibited antidepressant effects (decrease in their HDRS-17 total score and the Maier and Philip Severity Subscale total score) with novel antipsychotics. A subsequent analysis revealed that the antidepressant effects noted in the sample were significant for the core depressive symptoms (as assessed by Maier and Philip Severity Subscale) at endpoint for both treatment groups with the mean Maier and Philip Severity Subscale total scores falling from 15 (SD=4.8) to 2 (SD=1.4) by 6 months in the risperidone- treated group (p=0.001) and from 16 (SD=3.6) to 2 (SD=1.1) in the olanzapine-treated group (p=0.001).

Five (45%) patients in the risperidone-treated group and 5(50%) patients in the olanzapine-treated group reported adverse events (p=0.745). The most commonly reported adverse events were dizziness (n=2) and somnolence (n=2), for risperidone and olanzapine, respectively. Patients did not exhibit any evidence of tardive dyskinesia at the end of the observation period. There were no dropouts in this study.

Weight gain was recorded in both treatment groups; the mean weight gain was 5.9kg for the risperidone-treated group (p=0.023) and 11.3kg for the olanzapine-treated group (p=0.001). The mean weight gain was significantly greater among the olanzapine-treated patients (p=0.001). The percentage change in weight for the risperidone-treated group was 8.6 (p=0.05), and 18.3 (p=0.001) in the olanzapine-treated group.

DISCUSSION

This observational study is the first attempt to describe the antidepressant effectiveness of olanzapine and risperidone and prospectively compare their tolerability and safety when employed adjunctively in bipolar disorder. Moreover, patients presenting with manic symptoms also demonstrated significant within-treatment group improvement. Both agents appeared effective in this sample of non-psychotic, mildly symptomatic outpatients with bipolar disorders. These results converge with the existing data suggesting an antidepressant effect with novel antipsychotics.[21, 25] Dwight et al., noted significant antidepressant effects in 8 patients (6 schizoaffective bipolar and 2 schizoaffective depressed) receiving high dose risperidone monotherapy.[26] Hillert et al., reported a 70% response rate in persons with psychotic depression receiving risperidone.[27]

Keck et al., noted that patients who displayed a moderate to marked response to risperidone were more likely to be younger, receive a diagnosis of bipolar disorder or schizoaffective disorder-depressed type and manifest a shorter duration of illness.[28] Ostroff and Nelson, noted an antidepressant effect of adjunctive risperidone 0.5-1.5 mg/day in 8 patients with DSM-IV defined MDD without psychotic features.[25] All subjects in this study exhibited insufficient response to index SSRI treatment and all achieved full remission within one week of risperidone administration. A recently completed Canadian study evaluating the spectrum of effectiveness and tolerability of adjunctive risperidone in bipolar disorder noted significant changes in depressive symptom severity under naturalistic conditions.[25]

Significant antidepressant effects have also been described with olanzapine in diagnostically heterogeneous patient populations from disparate settings.[22] It has been previously noted that olanzapine offers a significantly greater antidepressant effect than haloperidol in persons with psychotic disorders.[22] In a study of unipolar psychotic depression (N=30) combination treatment with olanzapine and antidepressants was superior to conventional antipsychotic-antidepressant treatment (p=0.04).[29] These data were extended and corroborated by Ghaemi et al., who retrospectively evaluated the antidepressant

effectiveness of olanzapine in 10 diagnostically diverse patients.[24]

Data from the first double-blind placebo controlled trial evaluating the efficacy of novel antipsychotics in refractory major depressive disorder was recently published.[21] Twenty-eight persons with non-psychotic DSM-IV Major depressive disorder refractory to SSRI and non-SSRI antidepressants (some of which also had TCA and ECT treatment) were assigned to either fluoxetine-placebo, olanzapine-placebo or fluoxetine-olanzapine treatment for 8 weeks, with a subsequent 8-week open label extension.[30]

There were significant differences in the mean change from baseline on the MADRS observed at week 1 that was sustained to the end of the study and throughout the open label extension. Depressive symptom reduction with the olanzapine-fluoxetine combination was significantly greater than the monotherapy groups.[21]

The antidepressant effects of olanzapine in bipolar disorder have been recently evaluated in persons with acute mania. It was demonstrated that persons with bipolar disorder receiving the combination of olanzapine and mood stabilizer (lithium or valproic acid) exhibit significant reductions in depressive symptoms when compared to mood stabilizers alone .[3]

Antidepressant effects for quetiapine are also described in both psychotic and mood disorder populations.[31,32] Furthermore, clozapine's antimortality effect in persons with schizophrenia/schizoaffective disorder has been hypothesized to be mediated in part by an antidepressant effect.[33] A small body of data hints clozapine may be a promising adjunctive alternative treatment in some patients with refractory bipolar disorder.[33,34] Conventional antipsychotic are effective anti-manics however, their antidepressants and prophylactic effects are unproven in bipolar disorder.[34,35] Their frequent administration in bipolar disorder is juxtaposed to concerns surrounding the possibility of depressive symptoms worsening[36], rapid cycling induction[37], and neurological side effects.[34] The atypical antipsychotics appear to offer an improved therapeutic index over the older agents.[38] No patient in our study developed tardive dyskinesia.

The biochemical rationale for novel antipsychotics offering an antidepressant effect is speculative. High affinity for the 5-HT_2 receptor is noted with all available atypical antipsychotics.[39] 5-HT_2 antagonism is shared amongst several antidepressants (mirtazapine, nefazadone, trazadone, fluoxetine). Interestingly, it has been previously noted that other $5HT_2$ antagonists (e.g. ritanserin, seratepine) are potentially effective in generalized anxiety disorder.[40] It is further noted that α-2 adrenoreceptor antagonism (noted with mirtazapine) is capable of enhancing serotonin neurotransmission.[41] Risperidone appears to exhibit high affinity for the alpha-2 receptor.

Many available and candidate antidepressants in early phase development recruit and engage classical monamines as a primary step in the cascade of events leading to depressive symptom relief. Olanzapine has been demonstrated by in vivo microdialysis technique to increase extra cellular concentrations of norepinephrine and dopamine in the prefrontal cortex (PFC).[42] Moreover, the combined administration of olanzapine with fluoxetine results in synergetic increases in catecholamine concentrations .[43]

Most of the patients in our study gained weight. Significant weight gain has been previously described with atypical antipsychotics.[44] There are also recent data describing glucose regulation disturbances and dyslipidemia with several of these agents.[45,46] The mechanisms of antipsychotic-induced weight gain and attendant metabolic morbidity awaits further delineation.[47] It is not known at this time if some diagnostic groups are more at risk of weight gain.[48] It has been previously suggested that bipolar patients may be at a higher risk for developing significant weight gain with some novel antipsychotics.[6,36,49]

Importantly, bipolar disorder patients are likely to receive concomitant medications, which also impart substantial weight gain. Weight gain liability with these agents should be incorporated into psychoeducational information provided to patients and weight, blood glucose, and lipid parameters should be routinely monitored in treated patients.[47]

The results of this study need to be interpreted with caution. These data are open, uncontrolled, prospective data with non-blinded symptom and tolerability assessments in a heterogeneous group of patients. This clearly introduces several limitations to the validity of the

findings. Both risperidone and olanzapine were selected and dosed to maximize efficacy and tolerability, which could have artifactually affected the results obtained. The information provided on risperidone and olanzapine were standardized to include a review of the efficacy in the various phases of the illness and common side effects with each agent. Furthermore, the naturalistic design introduces many confounds that may have contributed to the effects observed (e.g. concomitant medications, supportive interaction).

Moreover, we don't have the details on the type of prior antipsychotic treatment and reasons for discontinuation. This study was not powered to detect efficacy differences between risperidone and olanzapine. Our failure to find a difference between the two treatments however does not tacitly imply that a difference does not exist. Moreover, it was curious that there were no dropouts or medication changes in this study. Bipolar studies are notoriously limited by high dropout rates.

This could imply a myriad of uncontrolled factors influenced results (e.g. milder illness, patient motivation and expectancy etc.). Notwithstanding the limitations of naturalistic studies, the patients enrolled are reflective of typical patients and treatment setting which, adds to the generalizability of the results. These data are intended to be hypothesis generating for future work.

CONCLUSION

In summary, this pilot data suggest both adjunctive risperidone and olanzapine may offer an antidepressant effect in bipolar disorder. Both agents were generally well tolerated although both imparted substantial weight gain. Controlled multi-site comparative studies in bipolar depression would be illuminating to the field. In the interim, clinicians are encouraged to monitor weight in persons receiving these agents.

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