Factors Associated with the Prescribing of Olanzapine, Quetiapine, and Risperidone in Patients with Bipolar and Related Affective Disorders

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Study Objective. To identify the factors associated with newly prescribed, first-line, second-generation antipsychotics (SGAs) associated with weight gain—olanzapine, risperidone, and quetiapine.

Design. Retrospective medical record review.

Setting. Outpatient and inpatient psychiatry services at a tertiary care, academic medical center.

Patients. Three hundred forty consecutive adults who had major depressive disorder with psychotic features, bipolar I, bipolar II, bipolar not otherwise specified, or schizoaffective disorder over two time periods (August 30–October 30, 2009, and April 1–May 31, 2010).

Measurements and Main Results. Clinical and sociodemographic variables associated with newly prescribed olanzapine, risperidone, and quetiapine were identified by using univariate and multivariate logistic regression. Several clinical factors were individually associated with initiation of these SGAs: mania (odds ratio [OR] 3.6, 95% confidence interval [CI] 1.2–10.8, p=0.02), psychosis (OR 3.3, 95% CI 1.5–6.9, p=0.002), and inpatient treatment (OR 3.8, 95% CI 1.8–7.9, p=0.0005). Prevalent use of lithium (OR 0.3, 95% CI 0.1–0.9, p=0.03) and being married (OR 0.3, 95% CI 0.1–0.8, p=0.02) were inversely associated with new use of an SGA. Mania, psychosis, married status, and lithium use remained independently associated on multivariate analysis. Factors related to metabolic or vascular risk were not associated with SGA initiation.

Conclusion. Psychiatric clinicians were influenced heavily by clinical features related to mental status and acuity when determining whether to prescribe SGAs. However, factors related to vascular risk were not associated. Future observational studies should consider current clinical status as an important factor in determining propensity to receive antipsychotics or other short-term treatments for bipolar and related disorders.

Key Words: antipsychotic agents, bipolar disorder, inpatients, logistic models, major depressive disorder, outpatients, propensity score, psychotic disorders.

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Second-generation antipsychotics (SGAs) are commonly prescribed for the treatment of bipolar disorders.[1, 2] Despite the reduced propensity for extrapyramidal symptoms compared with first-generation antipsychotics[3, 4]—especially high-potency first-generation antipsychotics[5]—SGAs have increasingly been associated with significant metabolic complications such as the metabolic

syndrome and its components of dyslipidemia, insulin resistance, and obesity.[6, 7] The SGAs produce variable weight gain, greatest for clozapine and olanzapine, followed by quetiapine and risperidone.[8] Clozapine tends to be reserved for treatment-refractory cases because of its adverse-effect profile and subsequent need for routine laboratory monitoring. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial found that change in Framingham-calculated 10-year coronary heart disease risk differed most among agents for participants who were at highest vascular disease risk at the outset of antipsychotic treatment.[9] Although not reflected in practice guidelines for bipolar disorder,[10] existing data support antipsychotic selection based on impact on vascular disease risk factors, and the American Diabetes Association and American Psychiatric Association consensus statement recommends "it may be preferable to initiate treatment with an SGA that appears to have a lower propensity for weight gain or glucose intolerance" for at-risk patients.[7]

With regard to vascular disease outcomes, a meta-analysis of clinical trials of antipsychotics in patients with dementia or related conditions found increased cerebrovascular events in those assigned antipsychotics.[11] Due to the infrequency of vascular events in younger populations, data linking antipsychotics to vascular outcomes are limited to large, pharmacoepidemiologic studies.[12–16] However, these studies are sensitive to confounding by indication, and key confounders, such as presenting clinical symptoms, health behaviors, and body mass index, may be unavailable in administrative claims databases. Unfortunately, there is a paucity of data regarding the determinants of antipsychotic prescribing in patients with bipolar and related disorders.[1, 2] Information about the clinical features associated with initiation of specific SGAs may be useful in the design and interpretation of such studies.

We sought to determine which patients from a clinical sample of outpatients and inpatients with diagnoses of a bipolar or related affective disorder are most likely to be prescribed the three first-line SGAs with greater propensity for causing weight gain: risperidone, olanzapine, and quetiapine. Our primary hypotheses were that patients prescribed these SGAs would be more likely to have manic or psychotic symptoms and less likely to have risk factors for vascular disease compared with the remainder of the sample not prescribed these drugs.

Methods

This retrospective medical record review was approved by the University of Iowa institutional review board. All consecutive patients aged 18 years or older with an encounter that included primary medical record diagnosis of a bipolar or related affective disorder including bipolar I, bipolar II, bipolar not otherwise specified, schizoaffective disorder (bipolar subtype), and major depressive disorder with psychotic features during August 30–October 30, 2009, and April 1–May 31, 2010, were included. These disorders have been considered to represent a spectrum of related conditions.[17–19] To maintain as representative a clinical sample as possible, no other inclusion or exclusion criteria were applied.

We identified individuals who were newly prescribed an SGA associated with weight gain—risperidone, olanzapine, or quetiapine—during a visit during these two time windows. New users could have been taking a different antipsychotic at the time the SGA was started. Based on the psychiatric clinician's written notes for the first visit at which one of these drugs was prescribed, we determined whether this was a new SGA user, which will be referred to throughout this article as a new user of risperidone, olanzapine, or quetiapine. The comparison (control) group was composed of all other individuals. In the case of multiple visits, only one visit was abstracted: the visit at which SGA was started or, for those who

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did not start SGAs, the last visit in the study period. Clinical and sociodemographic variables were abstracted to assess differences between new users of SGAs and all other individuals.

Age, sex, race or ethnicity, marital status, and insurance were obtained from the electronic hospital records. Type of insurance was classified as private, public, or none. Clinical features of the disorder were abstracted from the index visit narrative and mental status examination in the following categories: depressed, manic, psychotic, and suicidal. Active substance abuse was also noted. Measures of weight and body mass index were obtained from the records for each visit or the most recent prior visit when not available. Obesity was determined from a medical record diagnosis or body mass index of 30 or higher. The presence of hypertension or diabetes mellitus was determined by medical record diagnosis of or treatment for the respective condition. These diagnoses were not inferred from vital signs or laboratory values. Psychotropic drugs and any new prescriptions for SGAs were recorded. New use was noted irrespective of current or recent drugs.

Statistical Analysis

All statistical analyses were performed by using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). The study demonstrated 81% power to detect a medium effect size of 0.5 standard deviations for continuous variables. Descriptive statistics were generated. Univariate analyses assessed the association of new use of SGAs with the abstracted clinical and sociodemographic variables. Independent samples *t* tests and χ^2 tests were applied to identify associations between continuous and categoric variables, respectively, by new use of SGAs.

With new SGA use as the dependent outcome variable of interest, logistic regression models were explored to find the most useful multivariate model. The following independent variables were considered: age; sex; race (Caucasian or non-Caucasian); marital status (married or not married); insurance type; inpatient setting; prevalent use of lamotrigine, lithium, valproic acid, or antipsychotics; suicidal ideation; psychosis; depression; mania; active substance abuse; diagnosis or treatment of diabetes; diagnosis or treatment of hypertension; and obesity. Given the correlation of certain independent variables considered, stepwise procedures were deferred. Model selection began with significant variables from univariate analyses and sought a plausible model that minimized the Schwarz information criterion, which was selected over the Akaike information criterion to reduce the risk of overfitting by imposing a greater penalty for the number of model parameters.[20] Continuous variables were assessed for possible nonconformity to a linear gradient. Interactions were considered. Goodness of fit was assessed with use of the Hosmer-Lemeshow statistic.

Results

From a total of 735 inpatient and outpatient psychiatry visits for 340 patients, 36 (11%) new users of the three first-line SGAs associated with weight gain (risperidone, olanzapine, quetiapine) were identified in the two periods sampled. The remaining 304 patients served as the comparison (control) group. As shown in Table 1, the mean ± SD age of all participants was 46.4 ± 15.9 years. Approximately one third (34%) of diagnoses in this sample were for bipolar I. With regard to clinical features, 17% of the patients had some evidence of psychosis, 19% were depressed, 5% were manic, and 6% were suicidal. Nearly half of the patients (42%) were obese. Other clinical and sociodemographic characteristics of this sample are outlined in Table 1.

In univariate logistic regression, the presence of mania (odds ratio [OR] 3.6, 95% confidence interval [CI] 1.2–10.8, χ^2=5.28, *df*=1, p=0.02), psychotic symptoms (OR 3.3, 95% CI 1.5–6.9, χ^2=9.50, *df*=1, p=0.002), and treatment in an inpatient setting (OR 3.8, 95% CI 1.8–7.9, χ^2=12.22, *df*=1, p=0.0005) were associated with new use of an SGA. Prevalent use of lithium (OR 0.3, 95% CI 0.1–0.9, χ^2=4.80, *df*=1, p=0.03) and being married (OR 0.3, 95% CI 0.1–0.8, χ^2=5.22, *df*=1, p=0.02) were inversely associated with new use of an SGA. Other clinical and sociodemographic variables were not significantly associated with the initiation of SGAs, including obesity (OR 1.3, 95% CI 0.6–2.6, χ^2=0.40, *df*=1, p=0.52), hypertension (OR 0.5, 95% CI 0.2–1.4, χ^2=1.71, *df*=1, p=0.19), and diabetes (OR 0.6, 95% CI 0.2–2.2, χ^2=0.45, *df*=1, p=0.50).

The optimal multivariate model included prevalent lithium use, mania, married status, and psychosis, as shown in Table 2. The overall model was significant (likelihood ratio χ^2=25.92, *df*=4, p<0.0001) and demonstrated goodness-of-fit (Hosmer-Lemeshow χ^2=2.46, *df*=4, p=0.65) with an area under the curve of 0.77 (95% CI

Table 1. Sociodemographic and Clinical Characteristics of the 340 Patients

Characteristic	New Users of Second-Generation Antipsychotics Associated with Weight Gain (n=36)	Controls (n=304)	All Patients (n=340)
		No (%) of Patients	
Female	18 (50)	190 (63)	208 (61)
Race			
Caucasian	31 (86)	281 (92)	312 (92)
African-American	1 (3)	7 (2)	8 (2)
Asian	1 (3)	3 (1)	4 (1)
Unknown	2 (6)	7 (2)	9 (3)
Other	1 (3)	6 (2)	7 (2)
Ethnicity			
Hispanic or Latino	0 (0)	5 (2)	5 (1)
Primary psychiatric diagnosis			
Bipolar I	10 (28)	104 (34)	114 (34)
Bipolar II	5 (14)	55 (18)	60 (18)
Bipolar not otherwise specified	3 (8)	37 (12)	40 (12)
Major depressive disorder	8 (22)	28 (9)	36 (11)
Schizoaffective disorder	10 (28)	80 (26)	90 (26)
Psychotropic drugs			
Lithium[a]	3 (8)	79 (26)	82 (24)
Valproic acid derivatives	6 (17)	46 (15)	52 (15)
Lamotrigine	3 (8)	51 (17)	54 (16)
Carbamazepine	0 (0)	6 (2)	6 (2)
Antipsychotics			
First generation	10 (28)	46 (15)	56 (16)
Second generation	13 (36)	159 (52)	172 (51)
Antidepressants	17 (47)	177 (58)	194 (57)
Benzodiazepines	8 (22)	108 (36)	116 (34)
Clinical features			
Psychosis[b]	13 (36)	45 (15)	58 (17)
Mania[a]	5 (14)	13 (4)	18 (5)
Depression	9 (25)	57 (19)	66 (19)
Suicidal ideation	1 (3)	20 (7)	21 (6)
Active substance abuse	6 (17)	22 (7)	28 (8)
Inpatient setting[b]	14 (39)	44 (15)	58 (17)
Insurance			
Public	18 (50)	168 (55)	186 (55)
Private	18 (50)	131 (43)	149 (44)
None	0 (0)	5 (2)	5 (1)
Marital status			
Married[a]	4 (11)	92 (30)	96 (28)
Divorced or separated	9 (25)	51 (17)	60 (18)
Single	22 (61)	149 (49)	171 (50)
Widow	1 (3)	11 (4)	12 (4)
Unknown	0 (0)	1 (0.3)	1 (0.3)
Medical diagnosis or treatment			
Diabetes mellitus	3 (8)	37 (12)	40 (12)
Hypertension	5 (14)	72 (24)	77 (23)
Obesity	17 (47)	125 (41)	142 (42)
		Mean ± SD	
Age (yrs)	41.3 ± 15.5	47.0 ± 15.9	46.4 ± 15.9
Weight (kg)[c]	90.2 ± 25.5	88.5 ± 23.2	88.7 ± 23.5
Body mass index (kg/m^2)[d]	30.9 ± 7.5	30.8 ± 8.0	30.8 ± 7.9

[a]$p<0.05$ for comparison of new users versus controls.
[b]$p<0.01$ for comparison of new users versus controls.
[c]Data were missing for 8% of patients.
[d]Data were missing for 14% of patients.

Table 2. Multivariate Logistic Regression Model for Factors Associated with New Use of Second-Generation Antipsychotics Associated with Weight Gain in Bipolar Disorders

Factor	Odds Ratio (95% confidence interval)	χ^2	p Value
Lithium use	0.2 (0.06–0.8)	5.46	0.02
Manic state	5.7 (1.7–19.5)	7.86	0.005
Married status	0.3 (0.09–0.8)	5.08	0.02
Psychosis	2.5 (1.2–5.5)	5.59	0.02

The above variables were included in the selected multivariate regression model. Additional variables considered for the model included age, diagnosis, depression, suicidal ideation, active substance abuse, Caucasian, sex, insurance status, inpatient setting, valproic acid treatment, diagnosis or treatment for hypertension, diagnosis or treatment for diabetes mellitus, obesity, and weight or body mass index. The multivariate logistic regression equation was as follows: logit(p) = –2.026 – (1.570 • lithium) + (1.749 • mania) – (1.273 • married) + (0.935 • psychotic), where a value of 1 indicates the presence and 0 indicates the absence of the dichotomous variable.

0.70–0.85) on receiver operating characteristic analysis.

Discussion

The SGAs are a common treatment for bipolar and related disorders, although it is unclear how psychiatric clinicians select these drugs in practice, particularly those agents with a greater propensity for causing weight gain. In this analysis of clinical data from inpatient and outpatient psychiatric settings at a tertiary care center, risperidone, olanzapine, and quetiapine appeared to be more likely started in the presence of appropriate target symptoms—mania, or psychosis—especially in the higher acuity inpatient setting. These drugs were less likely to be prescribed to individuals who were married or taking lithium. Married status may reflect some marker of illness severity or function. Lithium may reduce risk through mania prophylaxis,[21, 22] although similar findings were not seen with valproic acid or lamotrigine. Those treated with lithium may be a select group, with lithium responders even considered a specific subtype,[23] and causal conclusions cannot be made from these data.

In an analysis of the National Ambulatory Medical Care Survey, prescription of SGAs was associated with a diagnosis of manic (OR 10.3, 95% CI 2.0–52.0) or mixed (OR 6.9, 95% CI 1.6–30.1) subtypes.[24] Our findings extend these results beyond a diagnostic subtype to a current clinical manifestation with mania or psychosis. In a sample of veterans with bipolar disorder, African-Americans were more likely than non–African-Americans to receive first-generation antipsychotics but not SGAs.[2] Our study found no racial differences, although our sample was predominantly Caucasian.

Limitations

Potential limitations included the use of medical record data and generalizability of our findings due to the tertiary care practice setting and homogeneous racial-ethnic composition of the study population. Medical record diagnoses for psychiatric conditions were made by faculty psychiatrists, but they could not be verified by structured interview. Presumably, prescribing patterns were based on the diagnosis made, mitigating the effect of any misclassification. Individual diagnoses did not appear to discriminate for new use of SGAs. If documentation did not include a diagnosis of or treatment for conditions such as hypertension or diabetes, these conditions were classified as not present. The potential to underestimate the prevalence of these conditions could reduce the ability to identify associations between the presence of these conditions and prescribing patterns. The prevalence of obesity was similarly underestimated due to missing data. Our data included current drugs but lacked a history of previous drug use.

Our sample, consistent with the population of Iowa, included a preponderance of Caucasian patients. This impeded our ability to assess racial-ethnic differences and may further limit the generalizability of our findings. Our sample also consisted only of those receiving treatment from psychiatric clinicians and may not reflect the practice of nonpsychiatric clinicians, who perhaps consider clinical data differently. The

results also may not generalize to prescribing of other antipsychotics or mood stabilizers. Nonetheless, this sample is a naturalistic reflection of psychiatric practice in a large, tertiary care hospital, allowing assessment of predictors for prescribing risperidone, olanzapine, and quetiapine in a real-world setting, in which the prevalence of antipsychotic use was consistent with prescribing data for other samples of patients with bipolar disorder.[2]

Our results indicate that clinical variables related to baseline mental status, many of which may not be readily available from administrative claims data, appear to be important predictors of antipsychotic prescribing akin to antidepressant prescribing.[25] Because of this unavailability, these predictors may not be incorporated into the propensity scores used for pharmacoepidemiologic studies of outcomes associated with SGAs.[12, 26] Future studies should be aware of this potential limitation and attempt to capture relevant clinical data when available or to calibrate propensity scores in a subsample in order to minimize the risk of residual confounding by indication. Clinical data related to metabolic and vascular risk were not significantly associated with new use of SGAs associated with weight gain, although diabetes was uncommon, and the study was underpowered to detect differences in variables of low prevalence. These results are nonetheless consistent with those from a larger sample not limited to bipolar disorders, suggesting that metabolic parameters are not considered in SGA selection[27] according to recommendations.[7] This is particularly concerning given that individuals with bipolar disorders remain at elevated risk for cardiovascular mortality.[28, 29]

Conclusion

Prescription of first-line SGAs that have been associated with weight gain in patients with bipolar and related affective disorders was appropriately largely driven by acuity of illness, as evidenced by inpatient setting, and the presence of psychotic or manic symptoms. These data are useful to understanding the determinants of prescribing and for those developing propensity score–based approaches to postmarketing surveillance studies, which should heed the role clinical presentation plays in influencing initiation of antipsychotics. Psychiatric clinicians seem to be especially influenced by clinical variables related to mental status. Future study could assess whether nonpsychiatric clinicians differentially consider these clinical variables.

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