

# Patient choice as a driver of medication-switching in non-adherent individuals with bipolar disorder

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**Objective:** Psychotropic-related weight gain is a common concern among patients with bipolar disorder (BD). This concern affects satisfaction with treatment and may lead to non-adherence and relapse. This was a 12-week, uncontrolled prospective trial of patient-choice-facilitated ziprasidone switching among non-adherent BD patients with weight concerns. This study was conducted from January 2011 to July 2012.

**Method:** Patients were asked to identify the “offending” BD medication which they believed was causing weight problems, and this agent was replaced with ziprasidone. The primary outcome was change in adherence as measured with the Tablets Routine Questionnaire (TRQ). Secondary outcomes included medication attitudes, BD symptoms, global psychopathology, social functioning, and quality of life.

**Results:** The most common agents causing weight concerns were quetiapine (N=7, 23%), aripiprazole (N=4, 13%), olanzapine, lithium, and divalproex (all N=3, 10%). Adherence improved from a baseline of missing 48.6% of prescribed BD medication in the past week (44.9% in the past month) to missing 25.3% ( $P=0.002$ ) of prescribed BD medication in the past week ( $P<0.001$ , in the past month) at endpoint. Medication attitudes, symptoms, functioning, and quality of life improved but there were no differences in body weight.

**Conclusion:** While findings must be tempered by methodological limitations such as small sample and uncontrolled design, patient-facilitated medication-switching appeared to improve adherence and BD outcomes in these non-adherent individuals. Additional studies involving patient-facilitated medication-switching and shared decision-making in BD are needed.

**Keywords:** bipolar disorder, ziprasidone, antipsychotic, adherence, weight gain, shared decision-making

## Introduction

Medication-related weight gain is common among patients with bipolar disorder (BD). This affects treatment satisfaction and may lead to reduced adherence. Patient-centered care, as defined by the Institute of Medicine (IOM), is “care that is respectful of and responsive to individual patient preferences, needs, and values”.<sup>1</sup> Ideally, care that is both patient-centered and evidence-based can lead to active patient engagement and good outcomes.

Ziprasidone is a second-generation antipsychotic medication<sup>2</sup> approved by the US Food and Drug Administration (FDA) for acute treatment of BD manic and mixed episodes and for BD maintenance as an adjunct treatment. Ziprasidone may have a minimal potential for weight gain and dyslipidemia.<sup>3-5</sup>

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This was a 12-week, uncontrolled prospective trial of patient-facilitated medication-switching among poorly adherent BD patients who self-identified medication-related weight concerns as their reason for non-adherence. Patients were asked to self-select the BD medication which they believed was causing weight problems. We anticipated that patient-choice-driven switching would lead to improved adherence. We also evaluated effects of patient-choice-driven switching on medication attitudes and clinical outcomes.

## Methods

### Setting and population

We enrolled individuals  $\geq 18$  years of age with type I or II BD confirmed with the Mini International Neuropsychiatric Inventory (MINI).<sup>6</sup> The study was approved by the institutional review board, all participants provided informed consent, and oversight included an external Data and Safety Monitoring Board (DSMB).

All individuals were on maintenance BD medication (lithium, antipsychotic, anticonvulsant), had medication weight gain concerns, and poor adherence defined as missing  $\geq 20\%$  of prescribed BD medications as measured by the Tablet Routines Questionnaire (TRQ),<sup>7,8</sup> which was related to weight concerns. Individuals were excluded if they had a contraindication to ziprasidone, eating disorder, substance dependence, clozapine treatment, financial reasons for non-adherence, medical conditions that could interfere with protocol participation, or were at risk of harm to themselves or others. Pregnant and breastfeeding women were excluded. The study was conducted from January 2011 to July 2012.

### Study assessments

Participants completed assessments at baseline and at 2-, 4-, 8-, and 12-week follow-up. Treatment satisfaction was assessed at study endpoint, and post-study at 16 weeks.

### Primary outcome

Adherence behavior was assessed with the Tablets Routine Questionnaire (TRQ).<sup>7,8</sup>

### Secondary outcomes

Secondary measures included the Morisky Rating Scale,<sup>9</sup> an additional brief self-reported adherence assessment, and adherence attitudes measured with the Drug Attitude Inventory (DAI) scale.<sup>10</sup> Depressive symptoms were measured with the Montgomery-Åsberg Depression Rating Scale (MADRS)<sup>11</sup> and manic symptoms were measured with the Young Mania Rating Scale (YMRS).<sup>12</sup> Global

psychopathology was measured with the Clinical Global Impressions (CGI) scale.<sup>13</sup> Functioning was measured with the Social and Occupational Functioning Scale (SOFAS),<sup>14</sup> and the Global Assessment of Functioning (GAF) scale.<sup>15</sup> Quality of life was measured with the 12-item Short Form Health Survey (SF-12).<sup>16</sup>

Biological and safety outcomes included body mass index (BMI), vital signs, laboratory testing (electrolytes, renal, thyroid and liver functions, total cholesterol, triglycerides, complete blood count), and electrocardiography. Involuntary movements were evaluated with the Abnormal Involuntary Movement Scale (AIMS),<sup>17</sup> Simpson-Angus Scale (SAS),<sup>18</sup> and Barnes Akathisia Scale (BARS).<sup>19</sup> Reported side effects were assessed at every study visit.

### Intervention

#### Ziprasidone

During screening, the study research psychiatrist evaluated the feasibility of switching from the maintenance BD medication that the individual identified as causing weight-related non-adherence. Only a single drug was permitted to be identified as the “offending” agent. If an individual was not able to identify which medication caused the most weight gain concerns, the most recently initiated medication was selected. Ziprasidone was titrated up to a maximum of 160 mg/day with dose reductions as clinically indicated. Offending agents were discontinued.

### Concomitant treatments

Stable psychotropic drugs prescribed prior to baseline (except for the patient-identified offending agent) were continued. New psychotropic medications were prohibited.

### Data analysis

Descriptive statistics were calculated for baseline characteristics. We conducted a modified intent-to-treat analysis for subjects who received at least one dose of study medication. Separate longitudinal mixed models were fit with first-order autoregressive, AR (1) covariance matrix, for the primary adherence and for the symptom measures with TRQ weekly and monthly, with YMRS, and with MADRS as the dependent variable.

## Results

### Screened and enrolled samples

Fifty-five individuals were screened, 32 fit eligibility criteria and consented, and 30 were eventually enrolled. Age, sex, and race did not differ significantly between screened and enrolled patients. One consented individual did not complete baseline

assessments and another had elevated liver function tests that were a contraindication to ziprasidone. Table 1 illustrates baseline demographic and clinical variables.

## Ziprasidone treatment

The mean endpoint dose of ziprasidone was 61.3 mg/day (standard deviation [SD]: 31.9, range: 20–120 mg/day).

## BD agents identified by patients as causing weight gain concerns

Table 1 illustrates BD agents replaced in patient-choice–driven switching. The most common weight concern agents were quetiapine (N=7, 23%), aripiprazole (N=4, 13%), and olanzapine, lithium, and divalproex (all N=3, 10%). Nearly all (29/30) individuals readily identified the medication they perceived as most problematic for weight gain.

## Concomitant medication

In addition to ziprasidone, individuals were on other BD treatments including antidepressants (22/30, 73%), anticonvulsants (10/30, 33%), lithium (2/30, 7%), stimulants (1/30, 3%), and one individual on long-acting injectable risperidone (3%). Including ziprasidone, there was a mean of 2.2 BD medications (SD: 0.889, mode: 2, range: 1–4). Seven individuals (23%) received ziprasidone monotherapy.

**Table 1** Characteristics of 30 non-adherent individuals with BD who received patient-choice–driven medication-switching

Variable	Value
Mean age in years (SD, range)	44.2 (10.2, 23–69)
Female N (%)	15 (50)
Race N (%)	
White	13 (43)
Black	16 (53)
Other	1 (3)
Hispanic ethnicity N (%)	4 (13)
Mean education in years (SD, range)	11.7 (2.6, 6–18)
Marital status N (%)	
Single, never married	14 (47)
Type of bipolarity N (%)	
Type I	28 (93)
Type II	2 (7)
Mean age at onset of illness in years (SD, range, median)	23.9 (12.1, 10–65, 20)
Past suicide attempt N (%)	22 (73)
Offending BD agent N (%)	
Lithium	3 (10)
Anticonvulsant	4 (13)
Antipsychotic	18 (60)
Antidepressant	5 (17)

**Abbreviations:** BD, bipolar disorder; SD, standard deviation.

## Drop-outs

Six subjects (20%) terminated the study prematurely. Four (13%) were lost to follow up, one (3%) dropped out due to hospitalization, and one (3%) due to ziprasidone side effects (gastrointestinal [GI] distress).

## Primary outcome

Table 2 includes univariate analysis of TRQ change. Adherence improved from missing 48.6% of medication in the past week to missing 25.3%. Table 3A and B illustrate estimated TRQ weekly and monthly means with respect to time period using longitudinal mixed models. Time periods and sex were viewed as factor levels, and age was included as a covariate. Subject-level random intercepts were fitted as well. Time period factor *P*-values for both TRQ weekly and monthly were <0.001, indicating that TRQ was significantly changed while sex and age were not significant.

**Table 2** Change from baseline in adherence, treatment attitudes, BD symptoms, functioning, and biological parameters among individuals in patient-choice–driven medication-switching

Variable	Baseline*	12 weeks*	Statistic: <i>t</i> , <i>df</i> , <i>P</i> -value
TRQ			
Past week	48.6 (20.1)	25.3 (26.9)	–3.425, 23, 0.002
Past month	44.9 (19.1)	19.4 (18.4)	–5.226, 23, <0.001
Morisky scale	2.4 (0.9)	0.8 (1.0)	–6.652, 22, <0.001
DAI	7.2 (2.1)	8.6 (1.4)	3.058, 23, 0.006
CGI	4.1 (0.9)	2.5 (1.1)	–5.619, 23, <0.001
MADRS	19.5 (11.4)	8.5 (7.0)	–5.042, 23, <0.001
YMRS	9.5 (6.5)	4.4 (4.6)	–3.426, 23, 0.002
AIMS	1.3 (2.4)	1.8 (3.1)	0.406, 22, 0.688
SAS	0.4 (0.7)	0.2 (0.4)	–1.283, 22, 0.213
BAS	0.03 (0.19)	0.13 (0.45)	1.367, 22, 0.186
SF-12			
Mental score	37.1 (9.6)	45.2 (10.3)	3.550, 22, 0.002
Physical score	39.8 (14.5)	42.9 (12.5)	1.178, 22, 0.252
SOFAS	51.0 (8.9)	57.4 (12.2)	2.710, 23, 0.012
Physical parameters			
BMI	33.6 (8.9)	34.0 (9.1)	–0.988, 23, 0.334
Total cholesterol (mg/dL)	174.2 (44.5)	181.6 (48.6)	1.227, 22, 0.233
Triglycerides (mg/dL)	137.1 (90.3)	139.0 (71.1)	–0.388, 22, 0.702
QTC interval on EKG (ms)	420.7 (24.4)	413.4 (23.0)	–1.325, 18, 0.202

**Note:** \*All values reported as mean (SD) using univariate analysis.

**Abbreviations:** AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; BD, bipolar disorder; BMI, Body Mass Index; CGI, Clinical Global Impression; DAI, Drug Attitudes Inventory; EKG, electrocardiography; MADRS, Montgomery Asberg Rating Scale; SAS, Simpson Angus Scale; SD, standard deviation; SF-12, Medical Outcomes Study Short Form General Health Survey; SOFAS, Social and Occupational Functioning Scale; TRQ, Tablet Routines Questionnaire; YMRS, Young Mania Rating Scale; QTC, corrected QT interval; *df*, degrees of freedom.

**Table 3** Estimated means of TRQ in the past week/past month with respect to time period

Time period	Past week					Past month				
	Mean	SE	df	95% confidence interval		Mean	SE	df	95% confidence interval	
				Lower bound	Upper bound				Lower bound	Upper bound
<b>TRQ estimates<sup>a</sup></b>										
Base	43.74 <sup>b</sup>	4.28	66.46	35.19	52.29	43.05 <sup>c</sup>	4.13	55.4	34.78	51.32
Week 1	44.63 <sup>b</sup>	4.34	69.18	35.98	53.28	42.28 <sup>c</sup>	4.17	57.3	33.93	50.63
Week 2	14.23 <sup>b</sup>	4.35	69.13	5.56	22.91	22.48 <sup>c</sup>	4.73	79.69	13.07	31.89
Week 4	11.48 <sup>b</sup>	4.65	81.96	2.23	20.72	9.24 <sup>c</sup>	4.46	67.93	0.35	18.13
Week 8	21.90 <sup>b</sup>	5.12	101.92	11.76	32.05	14.84 <sup>c</sup>	4.82	83.07	5.24	24.43
Week 12	26.84 <sup>b</sup>	4.41	71.68	18.06	35.62	20.59 <sup>c</sup>	4.23	59.42	12.13	29.05
Week 16	20.01 <sup>b</sup>	5.1	93.78	9.88	30.14	16.24 <sup>c</sup>	4.81	79.93	6.68	25.81

**Notes:** <sup>a</sup>Computed average; proportion of doses missed over the time period; <sup>b</sup>covariates appearing in the model are evaluated at the following values: age =45.71 years; <sup>c</sup>covariates appearing in the model are evaluated at the following values: age =45.73 years.

**Abbreviations:** SE, standard error; TRQ, Tablet Routines Questionnaire; df, degrees of freedom.

## Secondary outcomes

Table 2 illustrates univariate analyses that show improvement in symptoms, attitudes, global psychopathology, mental component of the SF-12, and functioning. The physical component of the SF-12 was unchanged. Both depressive and manic symptoms improved. Time periods and sex were viewed as factor levels, and age was included as a covariate. Subject-level random intercepts were fit as well. Time period factor was significant for YMRS ( $P=0.010$ ) and MADRS ( $P<0.001$ ), while sex and age were not significant.

## Tolerability and adverse effects

As noted in Table 2, there were no changes in physical parameters, including BMI. Side effects that occurred in more than 5% of patients were sedation (N=20, 67%), GI disturbance (N=11, 37%), mild-to-moderate muscle twitching or contraction (N=6, 20%), restless/akathisia (N=3, 10%), and sexual dysfunction (N=2, 7%). There were six serious adverse events (SAEs), none of which were deemed by the DSMB to be study related. Four of the SAEs were hospitalizations due to suicidal thinking or suicide attempts in which ziprasidone was continued in three cases and stopped in one case. One SAE was a non-related car accident and one SAE was an emergency room visit for acute bronchitis.

## Patient satisfaction and post-study continuation on ziprasidone

Treatment satisfaction information was available for 26 individuals. Of these, 24 (92%) strongly agreed or agreed that they were satisfied with ziprasidone, and 22 (81%) strongly agreed or agreed that they had less weight concerns compared to the previous offending agent. Twenty-three individuals (89%) agreed or strongly agreed that the benefits of ziprasidone outweighed the side effects. Among

17 individuals for whom post-study status was available, 16 individuals (94%) were still on ziprasidone.

## Discussion

This open-label, uncontrolled trial of patient-driven medication-switching suggested that BD patients with poor adherence and medication-related weight gain concerns had improvements in adherence, medication attitudes, symptoms, and functioning. In spite of less weight concern, there were no differences in body weight.

More than half of people with BD are poorly adherent and poor adherence is related to negative outcomes.<sup>20</sup> Patient-driven medication-switching may help in engaging individuals to a greater extent in their own care. This is consistent with the importance of shared decision-making in psychiatric practice.<sup>21</sup> In this study we allowed patients to make the choice as to which of their medications should be replaced. Atypical antipsychotics, lithium, and antidepressants were all sources of weight concerns. Patients welcomed the opportunity to provide input on pharmacotherapy decision-making and valued the consideration of relative burdens and benefits of their therapeutic regimen. Perhaps adherence and attitude improvement were related to individuals feeling that they had an active involvement in treatment. Symptom and functional status improvement may have been due to better adherence. Most individuals were satisfied with patient-facilitated drug-switching.

In contrast to our initial expectation, we did not find a change in BMI. It is possible that because patients were poorly adherent to begin with, any weight change related to formally discontinuing a drug causing weight gain was obscured. Alternatively, since BMI is a difficult factor to change in people with serious mental illness,<sup>22</sup> and our study did not include a diet or exercise component, it is perhaps not surprising that BMI was unchanged.

In conclusion, actively involving BD patients with medication-related weight concerns in prescribing decisions improved adherence and weight concerns, but did not change actual body weight. The interpretation of the study findings must be tempered with the methodological limitations, including small sample and the uncontrolled open-label design. Additional studies involving patient-driven medication-switching in BD are needed.

## Disclosure

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The study has been registered on ClinicalTrials.gov with ID Number: NCT01293825. Portions of this data have been presented at the 9th International Conference on Bipolar Disorder; Pittsburgh, PA, USA; June 10, 2011, and 10th International Conference on Bipolar Disorder; Miami, FL, USA; June 15, 2013.

The authors report no other conflicts of interest in this work.

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