Weight Gain and Comorbidities Associated With Oral Second-Generation Antipsychotics: Analysis of Real-World Data for Patients With Bipolar I Disorder or Schizophrenia

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BACKGROUND

- Antipsychotic medications are effective pharmacotherapies for the treatment of bipolar I disorder (BD-I) and schizophrenia (SZ)[1,2]
- Although second-generation antipsychotics (SGAs) have lower extrapyramidal symptom liability than first-generation antipsychotics (FGAs),[3] most SGAs are associated with clinically significant weight gain (CSWG) and the emergence of metabolic effects, including diabetes and cardiovascular (CV) disease[4]
  - Antipsychotic-associated weight gain can occur within the first few weeks after initiating therapy and may continue over long-term treatment[5]; the emergence of weight gain or metabolic effects are commonly cited reasons for oral SGA discontinuation[6]
  - Weight gain and metabolic effects occurring as a consequence of SGA treatment are among the most common and bothersome side effects for patients with BD-I or SZ[7,8]; the resulting distress caused by these effects may increase the risk for suboptimal adherence and subsequent hospitalization[9-11]

OBJECTIVE

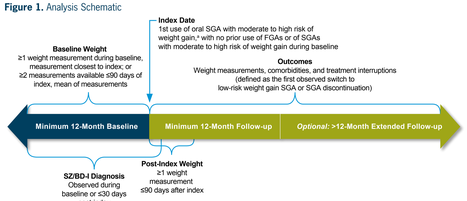
- This analysis of real-world data describes CSWG and cardiometabolic comorbidities observed in patients with BD-I and SZ after initiating select SGAs

METHODS

Data Source and Methods

- This retrospective analysis used the OM1 Real-World Data Cloud (OM1, Inc.; Boston, MA), which included de-identified patient-level health care claims and electronic medical record (EMR) data for >50 million patients in the United States. The analysis time period was from January 2013 to February 2020
- Based on a comprehensive review of antipsychotic-associated side effects from clinical studies,[4] patients who initiated an oral SGA associated with moderate to high (M-H) risk of weight gain (index) were included, and were followed for a minimum of 12 months (**Figure 1**)
  - The SGAs analyzed, along with their respective indications, were as follows:
    - Olanzapine/fluoxetine: BD-I only
    - Olanzapine, risperidone, and quetiapine: BD-I and SZ
    - Clozapine, iloperidone, and paliperidone: SZ only
- Use of another SGA with M-H risk of weight gain indicated for the same condition within 30 days of ending the index treatment was not categorized as a switch, and patients were defined as remaining on treatment with an SGA with M-H risk of weight gain (otherwise, they were defined as having interrupted treatment)

Figure 1. Analysis Schematic



*Included olanzapine/fluoxetine (BD-I only); olanzapine, risperidone, quetiapine (BD-I or SZ); and clozapine, iloperidone, and paliperidone (SZ only).
BD-I, bipolar I disorder; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; SZ, schizophrenia.

Inclusion Criteria

- Diagnosis of BD-I or SZ prior to or within 30 days of SGA initiation
  - Patients with both BD-I and SZ diagnoses were categorized in the SZ cohort
- Linked EMR and claims data for ≥12 months before and ≥12 months after index date
  - Index date: date of first prescription/fill of indicated SGA with M-H risk of weight gain with no observed prior use of any SGA with M-H risk of weight gain or any FGA in ≥12 previous months
- ≥18 years of age on index date
- ≥1 weight measurement in the 12 months prior to or including index date and ≥1 weight measurement in the 3 months following index date

Outcomes

- Percent change in body weight, including the proportion of patients with CSWG of ≥7% and ≥10% from baseline
- Development of new comorbidities after index date
  - Incident CV conditions of interest
    - Coronary artery disease
    - Type 2 diabetes mellitus
    - Dyslipidemia
    - Hypertension
  - Incident "other" CV conditions
    - Acute events
    - Congestive heart failure
    - Others not captured in CV conditions of interest
  - Increased CV burden, defined as patients with a prevalent CV condition at baseline who developed a new CV condition during follow-up

Analytic Methods

- Baseline characteristics were summarized separately for the BD-I and SZ cohorts
- Descriptive analyses included overall percent change in weight, proportion of patients with CSWG, and proportion of patients with new comorbidities during follow-up
  - Overall percent change in weight was also stratified by baseline body mass index (BMI)
  - Development of comorbidities was also stratified by baseline BMI and by CSWG during follow-up
- Categorical variables were presented as number and percentage; continuous variables were presented as means, standard deviations (SDs), medians, and 25th (Q1) and 75th (Q3) percentiles

RESULTS

Patient Characteristics

- A total of 9,142 patients with BD-I and 8,174 patients with SZ initiated an SGA with an M-H risk of weight gain and were included in the analysis (**Table 1**)
- For the BD-I and SZ groups, median length of follow-up was 159.4 and 153.4 weeks, respectively (ie, ≈3 years of follow-up)
- Across both cohorts, most patients were female, and commercial insurance was the most common type of health care coverage used
- At baseline, antidepressants (69.7% and 62.8%), anti-anxiety medications (46.4% and 38.2%), and mood stabilizers (23.1% and 16.8%) were the most common psychotropic medications taken in the BD-I and SZ cohorts, respectively
- On average, patients with BD-I were ≈9 years younger but weighed ≈2.5 kg more at baseline than those in the SZ cohort; more than 70% of each cohort was overweight or obese at baseline

Table 1. Baseline Patient Characteristics

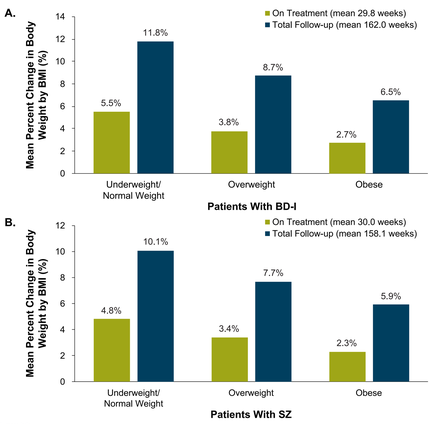
Parameter	Patients With BD-I (n=9,142)	Patients With SZ (n=8,174)
Sex, n (%)		
Female	6,604 (72.2)	5,037 (61.6)
Race, n (%)[a]		
White	7,036 (89.7)	5,554 (80.9)
Black	770 (9.8)	1235 (18.0)
Other	37 (0.5)	75 (1.1)
Age at index date, years		
Mean (SD)	48.2 (15.3)	57.4 (17.7)
Median (Q1–Q3)	49 (36–59)	58 (46–71)
Age category at index date, n (%), years		
18–24	634 (6.9)	354 (4.3)
25–34	1,359 (14.9)	656 (8.0)
35–44	1,680 (18.4)	908 (11.1)
45–54	2,111 (23.1)	1,515 (18.5)
55–64	1,942 (21.2)	1,788 (21.9)
≥65	1,416 (15.5)	2,953 (36.1)
Insurance type, n (%)[b]		
Commercial	3,677 (51.1)	2,781 (40.4)
Medicaid	939 (13.1)	773 (11.2)
Medicare	1,742 (24.2)	2,392 (34.7)
Multiple	775 (10.8)	909 (13.2)
Other	59 (0.8)	31 (0.5)
Select comorbidities, n (%)[c]		
Depression	4,883 (53.4)	4,208 (51.5)
Anxiety disorders	5,142 (56.2)	3,988 (48.8)
Chronic pulmonary disease	3,943 (43.1)	3,597 (44.0)
Diabetes without chronic complications	1,787 (19.5)	2,253 (27.6)
Cerebrovascular disease	1,093 (12.0)	1,884 (23.0)
Congestive heart failure	615 (6.7)	1,132 (13.8)
Peripheral vascular disease	623 (6.8)	1,048 (12.8)
Myocardial infarction	389 (4.3)	592 (7.2)
Baseline weight, mean (SD), kg	87.4 (24.1)	84.9 (23.5)
BMI category, n (%)[d]		
<18.5 kg/m^2	142 (1.6)	168 (2.1)
18.5–24.9 kg/m^2	1,924 (21.1)	1,968 (24.3)
25.0–29.9 kg/m^2	2,425 (26.6)	2,277 (28.1)
≥30.0 kg/m^2	4,619 (50.7)	3,690 (45.5)

[a]Total n=7,843 for BD-I; n=6,864 for SZ.
[b]Total n=7,192 for BD-I; n=6,886 for SZ.
[c]The 3 comorbidities with the highest prevalence for each patient group (depression, anxiety disorders, and chronic pulmonary disease) are shown, in addition to select cardiovascular and diabetes comorbidities.
[d]Total, n=9,110 for BD-I; n=8,103 for SZ.
BD-I, bipolar I disorder; BMI, body mass index; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; SZ, schizophrenia.

Weight Gain After Initiation of Oral SGAs Associated With Moderate to High Risk of Weight Gain

- The mean (SD) percent increase in weight during treatment (mean treatment duration, 30 weeks in each cohort) was 3.7% (7.0) and 3.3% (7.2) in patients with BD-I and SZ, respectively
- Mean (SD) percent weight gain during treatment was highest for underweight/normal weight patients (BD-I: 5.5% [8.7]; SZ: 4.8% [8.1]) compared with those who were overweight (BD-I: 3.8% [6.8]; SZ: 3.4% [7.6]) or obese (BD-I: 2.7% [5.9]; SZ: 2.3% [6.0]) (**Figure 2A and 2B**)
  - Time on index treatment represented approximately 20% of patients' total follow-up time, however approximately 40% of the observed weight gain occurred during time on treatment

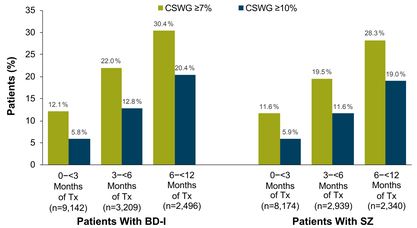
Figure 2. Mean Percent Change in Weight From Baseline by Body Mass Index Category in (A) Patients With Bipolar I Disorder and (B) Patients With Schizophrenia



BMI, body mass index.

- The proportion of patients with ≥7% or ≥10% weight gain increased over the course of the study in both BD-I and SZ cohorts, as shown in **Figure 3**

Figure 3. Proportion of Patients With Clinically Significant Weight Gain While On Treatment With Oral SGAs With Moderate to High Risk of Weight Gain, by Follow-up Interval



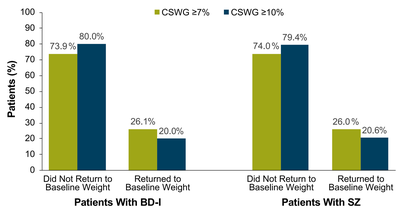
BD-I, bipolar I disorder; CSWG, clinically significant weight gain; SGA, second-generation antipsychotic; SZ, schizophrenia; Tx, treatment.

- The median time to CSWG of ≥7% was 14 weeks for both the BD-I and SZ groups; median time to CSWG of ≥10% was 20 weeks for the BD-I group and 19 weeks for the SZ group

Weight Gain and Treatment Interruptions During Use of Oral SGAs With Moderate to High Risk of Weight Gain

- More than 96% of patients in each group switched to a low weight risk SGA, a long-acting injectable antipsychotic, or discontinued SGA treatment during follow-up (8,915/9,142 [97.5%] in the BD-I cohort and 7,920/8,174 [96.9%] in the SZ cohort)
  - Median (Q1–Q3) duration of treatment was 13 (4–39) weeks and 13 (4–41) weeks, respectively, for the BD-I and SZ groups
- Among patients with CSWG who experienced treatment interruptions, ≈75% to 80% failed to return to their baseline weight during the follow-up period (**Figure 4**)

Figure 4. Proportion of Patients[a] Using SGAs With Moderate to High Risk of Weight Gain and Return to Baseline Weight After Treatment Interruption



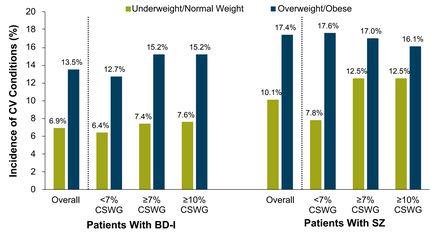
[a]Includes patients with CSWG before treatment interruption who also had a subsequent weight measurement.
BD-I, bipolar I disorder; CSWG, clinically significant weight gain; SGA, second-generation antipsychotic; SZ, schizophrenia.

- In the minority of patients who returned to their baseline weight across both cohorts (<26.1%; **Figure 4**), it took a median of 38 weeks or longer to do so

Incidence of CV Conditions Over 12 Months Following Antipsychotic Treatment Initiation

- At baseline in the BD-I cohort, 38.7% had no CV condition of interest (ie, coronary artery disease, type 2 diabetes mellitus, dyslipidemia, or hypertension) and 39.5% had no "other" CV condition
- Baseline prevalence of CV conditions was higher in overweight/obese patients with BD-I compared with underweight/normal weight patients with BD-I
  - In patients with BD-I who had no CV conditions at baseline, there was an 11.3% incidence of CV conditions of interest and a 12.0% incidence of "other" CV conditions over the 12-month follow-up period
  - 33.6% and 56.2% of the overweight/obese and underweight/normal weight patients with BD-I, respectively, had no chronic CV condition of interest at baseline; of these, 13.5% and 6.9%, respectively, went on to develop CV condition(s) of interest in the 12-month follow-up period (**Figure 5**)
  - Overweight/obese patients with BD-I had a higher incidence of CV conditions in follow-up compared with underweight/normal weight patients
- At baseline in the SZ cohort, 24.3% had no CV condition of interest (ie, coronary artery disease, type 2 diabetes mellitus, dyslipidemia, or hypertension), and 24.0% had no "other" CV condition
- Baseline prevalence of CV conditions was higher in overweight/obese patients with SZ compared with underweight/normal weight patients with SZ
  - In patients with SZ who had no CV conditions at baseline, there was a 14.7% incidence of CV conditions of interest and a 15.8% incidence of "other" CV conditions over the 12-month follow-up period
  - 20.7% and 34.3% of the overweight/obese and underweight/normal weight patients with SZ, respectively, had no chronic CV condition at baseline; of these, 17.4% and 10.1%, respectively, went on to develop CV condition(s) of interest in the 12-month post-index period (**Figure 5**)

Figure 5. Incidence of Cardiovascular Conditions of Interest[a] in Patients With Bipolar I Disorder and Schizophrenia, by BMI and CSWG Status Over 12 Months of Follow-up

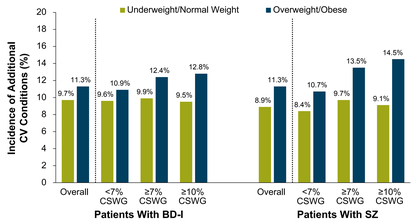


[a]Includes coronary artery disease, type 2 diabetes mellitus, dyslipidemia, and hypertension.
BD-I, bipolar I disorder; CSWG, clinically significant weight gain; SZ, schizophrenia.

Added CV Condition Burden in the 12-Month Follow-up Period After Antipsychotic Treatment Initiation in Patients With a CV Condition at Baseline

- In total, 6,323 (69.2%) of the BD-I cohort and 6,742 (82.5%) of the SZ cohort had 1 or more of the 4 chronic CV conditions of interest (coronary artery disease, type 2 diabetes mellitus, dyslipidemia, or hypertension) at baseline
  - In patients with 1 or more CV conditions at baseline, 11.0% of patients in the BD-I cohort and 10.7% of patients in the SZ cohort developed a new CV condition during the 12-month follow-up period
    - The proportion of patients who developed new CV conditions was numerically greater among patients who were overweight/obese compared with those who were underweight/normal weight at baseline, respectively, in both the BD-I (11.3% vs 9.7%) and SZ (11.3% vs 8.9%) cohorts
    - The proportion of patients who developed new CV conditions was numerically greater in those with ≥10% CSWG compared with those with ≥7% CSWG in obese patients across both cohorts; this was not the case, however, among patients with BD-I or SZ who were underweight or normal weight at baseline (**Figure 6**)

Figure 6. Development of Additional Cardiovascular Conditions in Overweight/Obese vs Underweight/Normal Weight Patients Who Had ≥1 Cardiovascular Condition at Baseline, by CSWG Status Over 12 Months of Follow-up



BD-I, bipolar I disorder; CSWG, clinically significant weight gain; SZ, schizophrenia.

LIMITATIONS

- This study included a relatively high proportion of commercially insured patients, which may reflect a more stable population and may not be representative of all patients living with BD-I and SZ
- The current findings from the BD-I and SZ cohorts in this analysis were derived from patients who were relatively old and, thus, may not be generalizable to younger patients with BD-I or SZ
- The long-term impact of CSWG on cardiometabolic conditions cannot be assessed, and this analysis examined the development of CV conditions within 12 months of treatment initiation only

CONCLUSIONS

- In this retrospective analysis, patterns of weight gain and development of CV comorbidities were similar across patients with BD-I and SZ; these data support previous findings that weight gain associated with SGAs of M-H risk of weight gain is independent of disease state
- CSWG occurred quickly after initiating SGAs associated with M-H risk of weight gain (eg, ≈3–4 months for ≥7% CSWG)
- Among patients who experienced CSWG on treatment, most (≈75%) did not return to their baseline weight after interrupting treatment; for those who did return to baseline weight, it took a median time of ≈9–10 months to do so
  - These results highlight the persistence of weight gain that patients may experience with SGAs of M-H risk of weight gain
- Development of new CV comorbidities within 12 months of initiation of these SGAs was highest in patients who were overweight or obese at baseline, and generally increased for patients with ≥7% or ≥10% CSWG in both the BD-I and SZ cohorts after initiating treatment
  - Patients with BD-I or SZ are already at risk for CV conditions because of their underlying disease state, and weight gained during treatment with SGAs may further exacerbate these health risks
  - This is the first study of which we are aware that suggests that emergent CV conditions may be observed in some patients within 12 months of treatment initiation with SGAs of M-H weight gain risk
- The patient's overall health should be considered when treating those living with BD-I or SZ, including various chronic and costly comorbidities associated with weight gain

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AUTHOR DISCLOSURES

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Alkermes Patient Inspired

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