Weight Gain and Treatment Interruptions With Second-Generation Oral Antipsychotics: Analysis of Real-World Data Among Patients With Schizophrenia or Bipolar I Disorder

Michael J. Doane,[1] Leona Bessonova,[1] Kathleen Mortimer,[2] Harry Cheng,[2] Gregory Donadio,[2] Thomas Brecht,[2] Amy K. O'Sullivan,[1] Hannah Cummings,[1] David McDonnell,[3] Jonathan M. Meyer[4]

[1]Alkermes, Inc., Waltham, MA, USA; [2]OM1, Inc., Boston, MA, USA; [3]Alkermes Pharma Ireland Ltd., Dublin, Ireland; [4]University of California San Diego School of Medicine, La Jolla, CA, USA

BACKGROUND

- Several second-generation antipsychotic (SGA) medications are approved for acute and maintenance treatment of schizophrenia (SZ) and bipolar I disorder (BD-I)[1,2]; however, many are associated with weight gain and long-term adverse effects, such as diabetes and cardiovascular disease[3]
- Up to 50% of patients treated with SGAs experience clinically significant weight gain (CSWG) of ≥7% of their baseline weight; furthermore, CSWG is even more common in patients who are beginning an SGA for the first time (observed in up to ~70% of patients)[4]
  - The proportion of patients experiencing CSWG increases with time on treatment[4]
- Antipsychotic-associated weight gain is a main reason for discontinuation of oral SGAs,[5] which, in turn, may increase patients' risk of relapse and subsequent hospitalizations[6,7]
- Most prior data on weight gain with antipsychotics have come from clinical trials, and there is a lack of real-world data on longitudinal patterns of weight gain after initiating treatment with SGAs
- This retrospective analysis describes real-world patterns of antipsychotic-associated weight gain, as well as treatment interruptions (i.e., switching or discontinuation), among patients with SZ or BD-I following initiation of select oral SGAs associated with a moderate to high (M-H) risk of weight gain (**Table 1**)[8] using claims and electronic medical record (EMR) data
  - Patients were considered as being treated with SGAs with M-H risk of weight gain if they remained on their initiated SGA with M-H risk of weight gain or switched to other SGAs with M-H risk of weight gain within allowable windows of time, as described in Methods below

OBJECTIVES

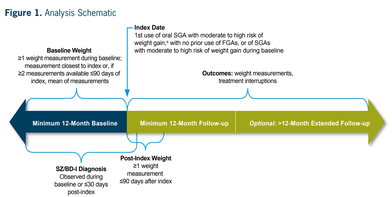
- To evaluate the following for patients diagnosed with SZ or BD-I:
  - The proportion of patients with CSWG of ≥7% and ≥10% from baseline weight and the median time to CSWG
  - The proportion of patients with treatment interruptions and the median time to interruptions
  - The proportion of patients with CSWG who return to baseline weight after interrupting treatment

METHODS

Data Source and Methods

- Data for this retrospective analysis were from the OM1 Real-World Data Cloud (OM1, Inc.; Boston, MA), which includes de-identified patient-level health care claims and EMRs linked for >50 million patients using patient-specific identifiers
- Claims and EMR data are updated at least quarterly and, for this analysis, covered data from January 2013 to February 2020
- This analysis (**Figure 1**) included patients who initiated oral SGAs with M-H risk of weight gain; these SGAs were determined based on a comprehensive review of antipsychotic-related side effects from clinical studies[3]
  - Oral M-H risk of weight gain SGAs evaluated in this analysis are listed in **Table 1** by indication
  - Patients had no observed use of these SGAs with M-H risk of weight gain or of any first-generation antipsychotics (FGAs) during the baseline period (≥12 months prior to treatment initiation)

Figure 1. Analysis Schematic



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

Table 1. Oral SGAs With Moderate to High Risk of Weight Gain Included in the Analysis, by Indication[a]

SZ	BD-I
Clozapine	Olanzapine/fluoxetine
Iloperidone	
Paliperidone	
Olanzapine	
Risperidone	
Quetiapine	

BD-I, bipolar I disorder; SGA, second-generation antipsychotic; SZ, schizophrenia.
[a]Indications for each SGA are available in the US Food and Drug Administration FDA Label Databases. https://nctr-crs.fda.gov/fdalabel/ui/spl-summaries/criteria/57988.

Inclusion Criteria

- Eligible patients were required to meet the following inclusion criteria:
  - Diagnosis of SZ or BD-I prior to or within 30 days of SGA initiation
    - Patients with both SZ and BD-I 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 new prescription/fill of indicated M-H risk of weight gain SGAs, with no observed prior use of any M-H risk of weight gain SGAs 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

- Body weight, including proportion of patients with CSWG ≥7% and ≥10% from baseline body weight
- Treatment interruptions (defined as switches or discontinuations)
  - Switches were defined as any new prescription/fill for oral SGAs not in the M-H risk of weight gain SGAs group, or any long-acting injectables (LAIs), during treatment with M-H risk of weight gain SGAs or within 30 days of the end of treatment with M-H risk of weight gain SGAs
    - The switch date was based on the prescription/fill date for the new antipsychotic
  - Use of another M-H risk of weight gain SGA indicated for the same condition was not categorized as a switch, and patients were defined as remaining on treatment with M-H risk of weight gain SGAs if the switch occurred within 30 days (otherwise, defined as having discontinued treatment with SGAs)

Analytic Methods

- Baseline characteristics were summarized by mental health condition
- Descriptive analyses included proportions of patients with CSWG and treatment interruptions, as well as median time to each outcome
- Categorical variables were presented as a number and a percentage; continuous variables were presented as means, SDs, medians, and 25th (Q1) and 75th (Q3) percentiles

RESULTS

Patient Characteristics

- A total of 8,174 patients with SZ and 9,142 patients with BD-I who initiated M-H risk of weight gain SGAs were included in the analysis
- For the SZ and BD-I groups, median length of follow-up was 153.4 and 159.4 weeks, respectively
- In the SZ and BD-I groups, respectively, the 3 most common psychotropic medications other than SGAs used at baseline were antidepressants (62.8% and 69.7%), anti-anxiety medications (38% and 46.4%), and mood stabilizers (16.8% and 23.1%)
- Most patients were female (SZ, 61.6%; BD-I, 72.2%), and mean patient age was 57.4 years in the SZ group and 48.2 years in the BD-I group; commercial insurance was the most common source of insurance coverage (SZ, 40.4%; BD-I, 51.1%) among those with known insurance (**Table 2**)

Table 2. Baseline Patient Characteristics

Parameter	SZ Group (n=8,174)	BD-I Group (n=9,142)
Sex, n (%)		
Female	5,037 (61.6)	6,604 (72.2)
Race, n (%)[a]		
White	5,554 (80.9)	7,036 (89.7)
Black	1,235 (18.0)	770 (9.8)
Other	75 (1.1)	37 (0.5)
Age at index date, years		
Mean (SD)	57.4 (17.7)	48.2 (15.3)
Median (Q1–Q3)	58 (46–71)	49 (36–59)
Age category at index date, years, n (%)		
18–24	354 (4.3)	634 (6.9)
24–34	656 (8.0)	1,359 (14.9)
35–44	908 (11.1)	1,680 (18.4)
45–54	1,515 (18.5)	2,111 (23.1)
55–64	1,788 (21.9)	1,942 (21.2)
≥65	2,953 (36.1)	1,416 (15.5)
Insurance type, n (%)[b]		
Commercial	2,781 (40.4)	3,677 (51.1)
Medicaid	773 (11.2)	939 (13.1)
Medicare	2,392 (34.7)	1,742 (24.2)
Multiple	909 (13.2)	775 (10.8)
Other	31 (0.5)	59 (0.8)
Select comorbidities, n (%)[c]		
Depression	4,208 (51.5)	4,883 (53.4)
Anxiety disorders	3,988 (48.8)	5,142 (56.2)
Chronic pulmonary disease	3,597 (44.0)	3,943 (43.1)
Diabetes without chronic complications	2,253 (27.6)	1,787 (19.5)
Cerebrovascular disease	1,884 (23.0)	1,093 (12.0)
Congestive heart failure	1,132 (13.8)	615 (6.7)
Peripheral vascular disease	1,048 (12.8)	623 (6.8)
Myocardial infarction	592 (7.2)	389 (4.3)

[a]Total n=6,864 for SZ, n=7,843 for BD-I.
[b]Total n=6,886 for SZ, n=7,192 for BD-I.
[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.
BD-I, bipolar I disorder; Q1, quartile 1; Q3, quartile 3; SZ, schizophrenia.

- Mean baseline weights were 187.1 lbs (SZ) and 192.6 lbs (BD-I); 45.5% and 50.7% of patients with SZ and BD-I, respectively, were classified as obese at baseline (**Table 3**)

Table 3. Weight and BMI Measurements

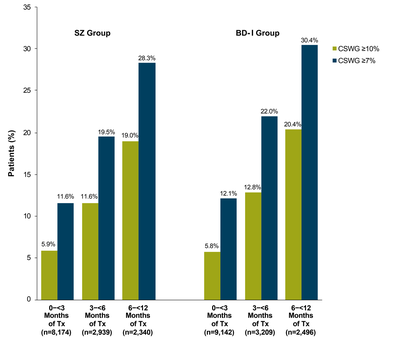
Parameter	SZ Group (n=8,174)	BD-I Group (n=9,142)
Number of weight measures prior to or on index date,[a] mean (SD)	6.3 (5.1)	6.3 (5.1)
Time from baseline weight measure to index date, mean (SD), weeks	6.0 (10.0)	5.2 (9.5)
Number of weight measures after index date,[b] mean (SD)	14.7 (13.5)	15.4 (13.5)
Baseline weight, mean (SD), lbs	187.1 (51.7)	192.6 (53.1)
BMI closest before or on index date, mean (SD), kg/m^2	30.3 (7.6)	31.3 (8.0)
BMI category, n (%)[c]		
<18.5 kg/m^2	168 (2.1)	142 (1.6)
18.5–24.9 kg/m^2	1,968 (24.3)	1,924 (21.1)
25–29.9 kg/m^2	2,277 (28.1)	2,425 (26.6)
≥30.0 kg/m^2	3,690 (45.5)	4,619 (50.7)

[a]Includes all observed time prior to and including index date (all patients had data for ≥12 months prior to index date).
[b]Includes all observed time after index date (all patients had data for ≥12 months after index date).
[c]Total n=8,103 for SZ, n=9,110 for BD-I.
BD-I, bipolar I disorder; BMI, body mass index; SZ, schizophrenia.

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

- Mean change in weight from baseline at 0 to <3, 3 to <6, and 6 to <12 months after initiation of M-H risk of weight gain SGAs was 2.2, 3.5, and 6.0 lbs, respectively, in the SZ group, and 3.1, 4.6, and 6.7 lbs, respectively, in the BD-I group
- Proportions of patients with CSWG of ≥7% or ≥10% within the first 3 months to ≥6 months after initiation of M-H risk of weight gain SGAs are shown in **Figure 2**

Figure 2. Proportion of Patients With Clinically Significant Weight Gain Among Patients Remaining on SGAs of Moderate to High Risk of Weight Gain at the Start of the Follow-up Interval[a]



BD-I, bipolar I disorder; CSWG, clinically significant weight gain; SZ, schizophrenia; Tx, treatment.
[a]Number of patients still using SGAs of moderate to high risk of weight gain at the start of the follow-up interval who had weight measure(s) in the interval.

- Median time to CSWG of ≥7% was 14 weeks for both the SZ and BD-I groups; median time to CSWG of ≥10% was 19 weeks for the SZ group and 20 weeks for the BD-I group (**Table 4**)

Table 4. Time to CSWG in Patients Using SGAs of Moderate to High Risk of Weight Gain

Parameter	SZ Group	BD-I Group
Patients with CSWG ≥7%, n (%)[a]	1,350 (21.1)	1,657 (22.3)
Time to CSWG ≥7%, weeks		
Mean (SD)	22.2 (24.3)	23.9 (28.3)
Median (Q1–Q3)	14 (5–31)	14 (6–32)
Patients with CSWG ≥10%, n (%)[a]	857 (13.4)	1,012 (13.6)
Time to CSWG ≥10%, weeks		
Mean (SD)	27.8 (28.3)	30.6 (31.9)
Median (Q1–Q3)	19 (8–39)	20.0 (9.0–42.5)

[a]Total number of patients with weight measurements that occurred with while on treatment to assess change from baseline: n=6,384 for SZ and n=7,429 for BD-I.
BD-I, bipolar I disorder; CSWG, clinically significant weight gain; SGA, second-generation antipsychotic; SZ, schizophrenia.

Treatment Interruptions With Oral SGAs With M-H Risk of Weight Gain

- Median (Q1–Q3) duration of treatment was 13 (4–41) weeks and 13 (4–39) weeks, respectively, for the SZ and BD-I groups
- Over 96% of patients in both groups discontinued or switched treatment (i.e., had a treatment interruption) during follow-up (**Table 5**)

Table 5. Treatment Interruption Patterns and Time to Interruption in Patients Using SGAs of Moderate to High Risk of Weight Gain

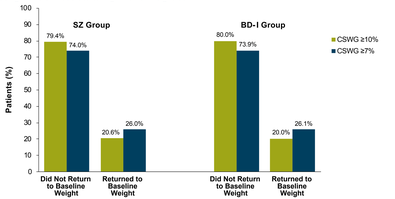
Parameter	Interruptions, n (%)	Time to Interruption, Weeks	
		Mean (SD)	Median (Q1–Q3)
SZ group (n=8,174)			
Discontinued or switched treatment	7,920 (96.9)[a]	27 (36)	12 (4–36)
Discontinued	7,512 (94.8)[b]	27 (36)	13 (4–36)
Switched	408 (5.2)[b]	24 (33)	9 (2–34.5)
Switched to LAI	110 (27.0)[c]	19 (30)	5 (0–22)
Switched to oral SGA with low risk of weight gain	298 (73.0)[c]	25 (34)	10 (2–38)
BD-I group (n=9,142 in cohort)			
Discontinued or switched treatment	8,915 (97.5)[a]	27 (37)	13 (4–35)
Discontinued	8,419 (94.4)[b]	27 (37)	13 (4–35)
Switched	496 (5.6)[b]	28 (39)	12 (4–36)
Switched to LAI	18 (3.6)[c]	24 (40)	2 (0–40)
Switched to oral SGA with low risk of weight gain	478 (96.4)[c]	28 (39)	12 (4–36)

[a]Denominator is the total number of patients in the SZ group or BD-I group.
[b]Denominator is the total number of patients who discontinued or switched.
[c]Denominator is the total number of patients who switched.
BD-I, bipolar I disorder; LAI, long-acting injectable; Q1, quartile 1; Q3, quartile 3; SGA, second-generation antipsychotic; SZ, schizophrenia.

Weight Gain and Treatment Interruptions With Oral SGAs With M-H Risk of Weight Gain

- In patients in the SZ group with a treatment interruption (n=7,920/8,174 [96.9%]), 20.2% and 12.7% experienced CSWG of ≥7% and ≥10%, respectively, before treatment interruption; the median (Q1–Q3) times to CSWG of ≥7% and ≥10% were 12 (5–28) weeks and 18 (7–37) weeks, respectively
  - In the small cohort of patients with SZ who did not experience a treatment interruption (n=254/8,174 [3.1%]), 44.5% and 30.7% experienced a CSWG of ≥7% and ≥10%, respectively, during follow-up; the median (Q1–Q3) time to a CSWG of ≥7% and ≥10% was 35 (16–59) weeks and 36.5 (15–59) weeks
- In patients in the BD-I group with a treatment disruption (n=8,915/9,142 [97.5%]), 21.5% and 12.9% of patients experienced a CSWG of ≥7% and ≥10% before treatment interruption; the median (Q1–Q3) times to CSWG of ≥7% and ≥10% were 13 (5–30) weeks and 19 (8–40) weeks, respectively
  - In the small cohort of patients with BD-I who did not experience a treatment interruption (n=227/9,142 [2.5%]), 48.5% and 36.6% experienced a CSWG of ≥7% and ≥10%, respectively, during follow-up; the median (Q1–Q3) time to CSWG of ≥7% and ≥10% [2.5%] were 30 (12–70) weeks and 39 (19–69) weeks
- Most patients with CSWG who experienced treatment interruptions (including those who switched to SGAs with low risk of weight gain) did not return to their baseline weight during the follow-up period (**Figure 3**), and for those who did, it took ~9 months or longer
  - In the SZ group with available follow-up weight measures, 26.0% of the 818 patients with a CSWG of ≥7% and 20.6% of the 505 patients with a CSWG of ≥10% returned to their baseline weight in a median time of 38 and 39 weeks, respectively
  - In the BD-I group with available follow-up weight measures, 26.1% of the 1,008 patients with a CSWG of ≥7% and 20.0% of the 599 patients with a CSWG of ≥10% returned to baseline weight in a median time of 39 and 47 weeks, respectively

Figure 3. Proportion of Patients[a] Returning to Baseline Weight After Treatment Interruption in Patients Using SGAs of Moderate to High Risk of Weight Gain



BD-I, bipolar I disorder; CSWG, clinically significant weight gain; Q1, quartile 1; Q3, quartile 3; SGA, second-generation antipsychotic; SZ, schizophrenia.
[a]Includes patients with CSWG before treatment interruption who also had a subsequent weight measurement.

LIMITATIONS

- General limitations of conducting research using a secondary database, including the following, apply to this analysis:
  - Measurements of outcomes, including patients' weights and treatment interruptions, were not assessed at regular intervals across patients
  - Medications ordered (EMR data) and prescriptions filled (claims data) were proxies for patients' use of these medications
- Lower baseline weight has been established as a risk factor of weight gain following treatment with antipsychotics,[9] and analysis of this relatively older population with SZ (mean age, 57.4 years) and BD-I (48.2 years) with relatively high baseline weight (approximately half were obese upon treatment initiation) may underestimate weight gain associated with oral SGAs, particularly relative to what might be expected in younger patients and in those with lower starting weight
- The analysis reflected a patient population who had some interaction with the healthcare system, based on inclusion criteria of data spanning ≥12 months before and ≥12 months after index date; therefore, this population and may not be representative of all patients with SZ or BD-I

CONCLUSIONS

- In this retrospective analysis, patterns of weight gain and treatment interruptions were similar across SZ and BD-I patients
- Both CSWG and treatment interruptions occurred quickly after initiating SGAs with M-H risk of weight gain (~2–3 months for ≥7% CSWG; ~2–3 months for treatment switches or discontinuations)
- Treatment discontinuations were far more common than switches to SGAs of low risk of weight gain or LAIs, and those who did switch did so after a median of ~2 to 3 months
- Among patients who experienced CSWG, most (~75%) did not return to their baseline weight after interrupting treatment; for those who did return to baseline weight or lower, it took a median time of ~9 to 11 months to do so
- These real-world data suggest that CSWG and treatment interruptions occur quickly in patients with SZ and BD-I, and that, despite changes to the treatment regimen (including switches to SGAs with low risk of weight gain), most patients fail to return back to their baseline weight, highlighting the importance of effective antipsychotic therapies that have limited antipsychotic-associated weight gain

REFERENCES

1. Yatham LN, et al. *Bipolar Disord.* 2018;20(2):97-170. **2.** American Psychiatric Association. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. 2019. Available at: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. **3.** Solmi M, et al. *Ther Clin Risk Manag.* 2017;13:757-77. **4.** Bak M, et al. *PLoS One.* 2014;9(4):e94112. **5.** Lieberman JA, et al. *N Engl J Med.* 2005;353(12):1209-23. **6.** Weiden PJ, et al. *Schizophr Res.* 2004;66(1):51-7. **7.** Weiden PJ, et al. *Psychiatr Serv.* 2004;55(8):886-91. **8.** Bushe CJ, et al. *J Psychopharmacol.* 2013;27(4):358-65.

DISCLOSURES

M.J. Doane, L. Bessonova, A.K. O'Sullivan, and **H. Cummings** are employees of Alkermes, Inc. **K. Mortimer, H. Cheng, G. Donadio,** and **T. Brecht** are employees of OM1, Inc., which contracted with Alkermes, Inc. to access these data and complete analyses. **D. McDonnell** is an employee of Alkermes Pharma Ireland Ltd. **J.M. Meyer** has served as a speaker or advisor for Acadia Pharmaceuticals, Alkermes, Inc., Allergan (AbbVie), Intra-Cellular Therapies, Neurocrine, Otsuka America, Inc., Sunovion Pharmaceuticals, and Teva Pharmaceutical Industries Ltd.

ACKNOWLEDGMENTS

This study was sponsored by Alkermes, Inc. Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc.

Copies of this poster obtained through this QR (Quick Response) code are for personal use only and may not be reproduced without permission of Alkermes. For permission, contact USMedInfo@Alkermes.com.

Supported by funding from Alkermes, Inc.