Effect of Concurrent Metformin on Adherence to and Persistence of Treatment With Second-Generation Antipsychotics in Nondiabetic Patients

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Abstract

Objective: Second-generation antipsychotic (SGA)-induced weight gain (AIWG) is a major factor contributing to SGA nonadherence. The aim of the study was to evaluate the effect of concurrent metformin treatment on SGA adherence and persistence.

Methods: A retrospective cohort study using MarketScan Commercial and Medicaid claims data included nondiabetic adults (≥18 years) with ≥30 days of overlapping prescriptions for SGAs and metformin. SGA-metformin concurrent users were 1:4 matched to SGA-only users and followed for 180 and 365 days to assess SGA adherence using proportion of days covered (PDC) and persistence (days until a 60-day gap). Additionally, concurrent users were classified into early (<30 days) and delayed (≥30 days) initiators based on the duration between SGA and metformin initiation. The differences between study groups were adjusted by propensity score using inverse probability of treatment weights (IPTW).

Results: In commercially insured patients, 575 concurrent users were matched to 2,300 SGA-only users, whereas Medicaid had 972 concurrent users matched to 3,888 SGA-only users. During the 180-day follow-up period, concurrent users demonstrated higher PDC and persistence to SGA than SGA-only users (PDC: commercial: 80.9% vs. 67.61%; Medicaid: 78.41% vs 68.27%; persistence: commercial: 139.0 vs 106.4 days; Medicaid: 149.1 vs 115.7 days). After IPTW adjustment, the differences in PDC between the study groups were 11.79% (commercial) and 9.64% (Medicaid), with corresponding differences in persistence of 32.14 (commercial) and 33.78 (Medicaid) days. The findings for the early and delayed initiators and the 365-day follow-up period were consistent with the main analysis.

Conclusion: The concurrent use of metformin with SGA drugs was associated with improved adherence and persistence to SGAs at both 180- and 365-day follow-up periods in adults with Medicaid and commercial insurance. Additionally, the observed improvement in SGA adherence among both early and delayed metformin initiators supports the effectiveness of metformin in enhancing adherence, whether used on a preventive basis or as a treatment for AIWG.

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Second-generation antipsychotics (SGAs) are widely used to treat psychotic disorders, particularly schizophrenia and bipolar disorders.[1] Developed to mitigate the limitations inherent to first-generation antipsychotics (FGAs), SGAs exhibit a diminished propensity for inducing extrapyramidal symptoms, such as tremors and muscular rigidity, by preferentially modulating serotonin (5-HT2A) and adrenergic receptors (α1 and α2), rather than exerting primary effects on dopamine D2 receptors.[1–3] Despite these advantages, SGA drugs are associated with a higher risk of metabolic side effects, including weight gain, insulin resistance, and dyslipidemia, which can increase the long-term risk of cardiovascular disease and type 2 diabetes mellitus (DM).[1–3]

Antipsychotic-induced weight gain (AIWG) remains a consistent concern among these patients, impacting them both physically and emotionally and often contributing to challenges in treatment adherence.[4] Just as extrapyramidal side effects lead to poor compliance with FGAs, many studies indicate weight gain as a cause for treatment noncompliance with SGAs.[4,5] A study by Weiden et al indicates that SGA recipients who are obese are twice as likely as those with a normal body mass index (BMI) to self-report missing their medication (odds ratio: 2.5; CI, 1.1 to 5.5).[6] The foremost finding of

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Clinical Points

- Previous studies have reported that the metformin is effective in causing weight loss in patients treated with second-generation antipsychotics (SGAs). However, there is no prior evidence to show that this can be translated into improved adherence to SGAs.
- In this study, individuals taking metformin along with an SGA had better adherence to SGA treatment compared to those not taking metformin, and these results may correspond to greater benefits in the long-term outcomes.

this survey is that weight gain emerges as a significant predictor of noncompliance with antipsychotic medication.[6] Results from a nationwide US survey of physicians and their patients with bipolar disorder indicate that weight gain was one of the factors significantly associated with nonadherence by patients who identified themselves as nonadherent.[7]

The role of antidiabetic drugs in the management of AIWG has been introduced in several studies. Metformin is one of the first-line antidiabetic treatments for type 2 DM with an added benefit of weight loss.[8] Metformin is well-tolerated and economical, making it suitable for long-term treatment.[9] The Diabetes Prevention Program (a randomized, double-blind trial of metformin vs placebo) found that weight loss while on metformin therapy was related to better adherence to metformin, an effect that was durable for at least 10 years of treatment.[10] Recent studies indicate that metformin can limit weight gain induced by SGA agents.[11,12] When metformin was combined with SGAs, there was a significant reduction in BMI and insulin resistance, according to a recent meta-analysis of 12 studies that included a total of 743 individuals.[14] The average weight reduction was 3.27 kg, and metformin significantly decreased BMI (−1.13 kg/m^2 [95% CI, −1.61 to −0.66]).[14] A retrospective chart review aimed at studying the effectiveness of adjuvant metformin in clozapine-induced weight gain concluded that at 6 and 12 months, metformin users had less weight gain compared to nonusers.[13]

A recent Cochrane review of pharmacologic interventions for the prevention of AIWG showed that metformin is one of the pharmacologic agents that may be effective for preventing AIWG.[15,16] The review showed that starting metformin along with antipsychotic treatment may reduce the extent of weight gain by 4.03 kg compared with controls. A new evidence-based guideline was developed recently and recommends prescribing metformin when initiating antipsychotic treatment to help mitigate weight gain in certain instances.[17]

However, a significant gap in literature exists if the concurrent use of metformin along with SGA impacts the adherence to SGA. In this study, we aim to evaluate the adherence to SGA in nondiabetic patients prescribed metformin and SGA concurrently.

METHODS

This study was approved by the Institutional Review Board at the University of Houston.

Study Data

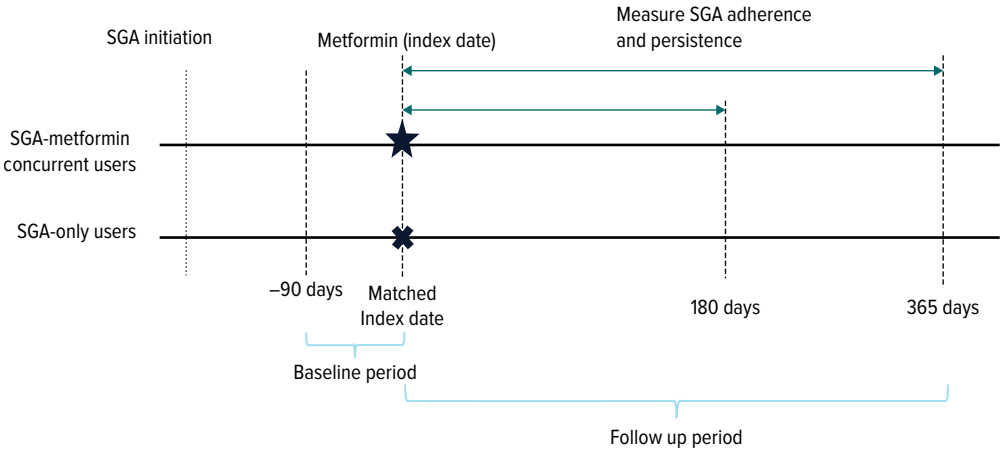
This retrospective cohort study utilized medical and pharmacy claims data from the IBM MarketScan databases, specifically the MarketScan Commercial database, and Medicaid between April 2017 and June 2019. The MarketScan Commercial database includes pharmacy and medical claims data for around 65 million individuals and their dependents in United States. This database provides comprehensive enrollee-specific information, including demographics, clinical details, inpatient and outpatient utilization, and expenditure data from over 350 payers—such as large employers, health plans, and various public and government organizations.

Study Cohort

This retrospective cohort study included nondiabetic patients 18 years or older who initiated SGA prescription between April 1, 2017, and June 30, 2019, after a 90-day washout period and continued the prescription for at least 60 days. Nondiabetic patients were defined as those who never received a diagnosis of type 1 or type 2 DM and did not fill any antidiabetic medication except for metformin. SGA-metformin concurrent users were identified as patients who had at least 1 metformin prescription filled after the SGA prescription and had a minimum of 30-day overlap between the two. The SGA-only users were those who had never filled a metformin prescription. According to the relative initiation time of SGA and metformin, the concurrent users were further categorized as early initiators, who initiated metformin within 30 days of SGA initiation, and delayed initiators, who initiated later than 30 days of SGA initiation.

Each SGA-metformin concurrent user was matched to 4 SGA-only users. To minimize the impact of potential immortal time bias that could occur when comparing concurrent users to SGA-only users, a technique known as prescription time-distribution matching was applied to establish the index date for the SGA-only group.[18,19] Immortal time bias could arise due to the requirement for the concurrent users to have continued SGA treatment for a certain duration (until the initiation of metformin) before being included in the cohort, which may inadvertently give the appearance of superior adherence and persistence outcomes for the concurrent users than the SGA-only users.[19] To address this, the "metformin

Figure 1.
Study Design



Abbreviation: SGA = second-generation antipsychotic.

initiation date" was set as the index date for the concurrent users. In parallel, an index date was assigned to SGA-only users based on the observed duration distribution between SGA initiation and concurrent metformin initiation among the concurrent metformin group. Other than the index date, we also matched the two study groups on age at the index date, gender, and continuous enrollment 90 days preceding the index date and 180 days postindex period (Figure 1).

Study Outcomes

Medication adherence was calculated during the 180-day follow-up period using the proportion of days covered and persistence. The *proportion of days covered* (PDC) was defined as the number of days in the follow-up period during which a patient had the SGA on hand, divided by the number of days until the end of supply. For all drugs, the days' supply, as reported on the prescription claim, was used to calculate the PDC. Overlapping days covered by 2 consecutive prescriptions of SGA were not counted twice in the PDC calculation. *Persistence* was calculated as the number of days of treatment from the index date to SGA discontinuation or the end of the follow-up period. *Discontinuation* was defined as a failure to refill SGA within the permissible gap period of 60 days between prescription fills.

Covariates

Differences in patient characteristics, comorbidities, and comedications may exist between concurrent users and SGA-only users. Such variations could hinder direct outcome comparisons between these groups. Factors associated with metformin prescription were controlled between the study groups to mitigate potential confounding from these disparities. These factors included patient characteristics like age, gender, region, race, and the specialty of the treating physician (psychiatrist or nonpsychiatrist). Comedications that could potentially affect the prescription of metformin in nondiabetic SGA users include the use of mood stabilizers, selective serotonin receptor inhibitors, serotonin and norepinephrine receptor inhibitors, atypical and tricyclic antidepressants, anxiolytics, antihypertensives, lipid-lowering agents, steroids, and weight loss medications.[20] Comorbid conditions included were schizophrenia, bipolar disorders, depression, anxiety, mood disorders, cardiovascular diseases, hypertension, polycystic ovarian syndrome (PCOS), obesity, and metabolic syndrome.[20] All of these covariates were identified during the 90-day baseline period preceding the index date.

Propensity Score Adjustment on Baseline Covariates

Individual patients' probability (propensity score) of receiving metformin treatment was estimated using the baseline covariates. Further, we used the inverse probability of treatment weights (IPTW) approach, which weighs the treatment groups based on their propensity scores. This approach creates a pseudopopulation in which the treatment groups are weighted with respect to confounding variables. Concurrent users received a weight of 1 divided by their propensity score (1/PS), while SGA-only users received a weight of 1 divided by the inverse of their propensity score (1/[1–PS]). To ensure that the weighted sample accurately represented the original population, these weights were then normalized by dividing each weight by the mean weight of the sample. This approach helped achieve a balanced

comparison between the concurrent users and SGA-only users by minimizing the influence of baseline differences on treatment outcomes.

Statistical Analysis

All baseline variables were analyzed, summarizing continuous variables using means (SD) and categorical variables using counts and percentages. *T* test was used for comparisons between continuous variables, and χ^2 test was used to compare categorical variables. Propensity score matching, using the IPTW analysis, was performed for the comparison of the study outcomes between

1. all SGA-metformin concurrent users and matched SGA-only users
2. SGA-metformin early initiators and matched SGA-only users
3. SGA-metformin delayed initiators and matched-SGA only users

All analyses used a significance criterion of $P<.05$, defined a priori. Statistical analysis was performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

Sensitivity Analysis

A series of sensitivity analyses were conducted to test the robustness of the study findings against the change in operational definitions applied in the main analysis:

1. Extending the follow-up period to 365 days to evaluate the robustness of the primary findings under different time horizons. The rationale for extending the follow-up period stems from the chronic nature of psychiatric conditions, as adherence and persistence patterns for SGA users vary over time. By analyzing a 365-day period, we aim to capture these potential shifts, offering a more comprehensive view of treatment adherence and persistence
2. Excluding patients with comorbid PCOS and/or comedications with a potential weight loss effect, namely, phentermine-topiramate, orlistat, naltrexone-bupropion, glucagon-like peptide-1 receptor agonists and metabolic syndrome.
3. Increasing the minimum overlap of metformin and SGA prescriptions to 90 days
4. Risperidone-metformin concurrent users and matched risperidone-only users
5. Aripiprazole-metformin concurrent users and matched aripiprazole-only users
6. Clozapine-metformin concurrent users and matched clozapine-only users
7. Olanzapine-metformin concurrent users and matched olanzapine-only users

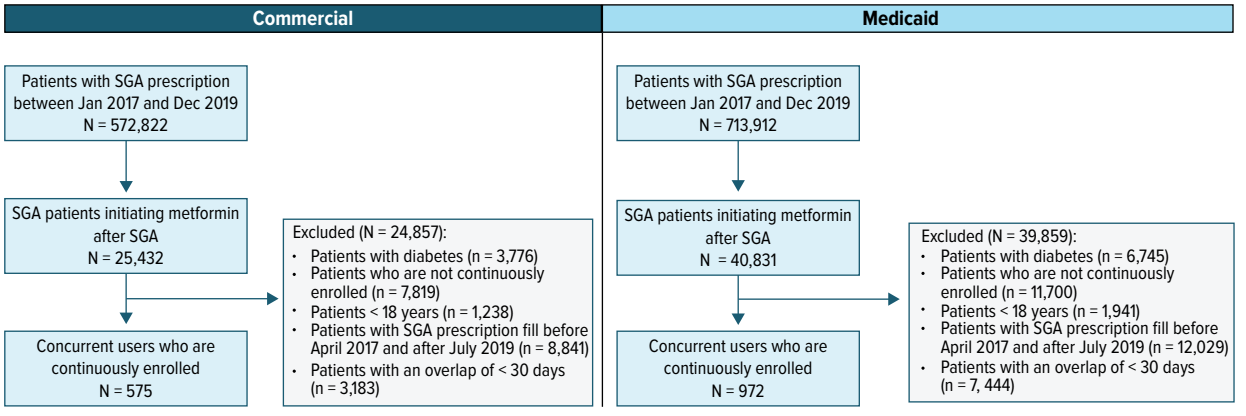
RESULTS

As presented in Figure 2, 575 SGA-metformin concurrent users were identified from the 2017 to 2019 MarketScan commercial claims data, and 972 SGA-metformin were identified from the Medicaid claims data. Out of 575 SGA-metformin concurrent users identified from commercial claims data, 154 patients were early initiators and 421 were delayed initiators, whereas in the Medicaid subgroup, 353 early initiators and 619 delayed initiators were identified.

Patient Characteristics

Table 1 shows the baseline characteristics of the SGA-metformin concurrent users and the SGA-only users. In commercial cohorts, SGA prescriber specialty was a psychiatrist in 52.17% of concurrent users compared to

Figure 2.
Sample Attrition



Abbreviation: SGA = second-generation antipsychotic.

Table 1.

Baseline Characteristics of Concurrent Users of SGA and Metformin and Their Matched SGA-Only Users

	Commercial subgroup			Medicaid subgroup		
	Concurrent users Frequency (%)	SGA-only users Frequency (%)		Concurrent users Frequency (%)	SGA-only users Frequency (%)	
Parameter	N = 575	N = 2,300	*P* value[a]	N = 972	N = 3,888	*P* value[a]
Age, mean (SD), y	38.85 (12.73)	39.64 (12.68)	<.0001	39.08 (12.98)	40.43 (12.69)	<.0001
Gender			.98			.87
Male	143 (24.87)	564 (25.16)		269 (27.88)	1,076 (28.14)	
Female	432 (75.13)	1,678 (74.84)		696 (72.12)	2,748 (71.86)	
Prescriber specialty			.002			.29
Psychiatrist	300 (52.17)	977 (42.48)		603 (62.49)	2,320 (60.65)	
Nonpsychiatrist	275 (47.83)	1,323 (57.52)		362 (37.51)	1,505 (39.35)	
Region			<.0001			
Northeast	124 (21.57)	458 (20.43)		–	–	
North central	127 (22.09)	482 (21.5)		–	–	
South	196 (34.09)	969 (43.22)		–	–	
West	124 (21.57)	332 (14.81)		–	–	
Race						.15
White	–	–		611 (70.47)	2,480 (73.21)	
Black	–	–		219 (25.26)	733 (21.71)	
Hispanic	–	–		17 (1.96)	74 (2.91)	
Other	–	–		20 (2.31)	91 (2.69)	
Comedications						
Mood stabilizers	286 (49.74)	797 (35.55)	<.0001	469 (48.6)	1749 (45.63)	.11
SSRI	224 (38.96)	966 (43.09)	.07	417 (43.21)	1,690 (44.18)	.58
Anxiolytics	233 (40.52)	853 (38.05)	.27	372 (38.55)	1,425 (37.25)	.46
Weight loss agents[b]	67 (11.65)	112 (5.0)	<.0001	139 (14.4)	315 (8.24)	<.0001
SNRI	120 (20.87)	423 (18.87)	.28	194 (20.10)	635 (16.6)	.01
Other antidepressants[c]	130 (22.61)	482 (21.50)	.56	222 (23.01)	939 (24.55)	.31
Antihypertensives	129 (22.43)	332 (14.81)	<.0001	284 (29.43)	801 (20.94)	<.0001
Lipid-lowering agents	62 (10.78)	160 (7.94)	.005	168 (17.41)	433 (11.32)	<.0001
Steroids	76 (13.22)	239 (10.66)	.08	290 (30.05)	959 (25.07)	.001
SGAs						
Clozapine	18 (3.13)	9 (0.4)	<.0001	31 (3.21)	52 (1.36)	<.0001
Olanzapine	97 (16.87)	286 (12.4)	<.0001	148 (15.34)	516 (13.49)	0.15
Risperidone	58 (10.09)	212 (9.50)	.67	147 (15.23)	538 (15.07)	.38
Quetiapine	152 (26.43)	821 (36.62)	<.0001	222 (23.01)	1,374 (35.92)	<.0001
Lurasidone	82 (14.26)	143 (6.38)	.76	143 (14.82)	423 (11.06)	.0001
Ziprasidone	27 (4.70)	75 (3.35)	.13	49 (5.08)	183 (4.78)	.71
Paliperidone	13 (2.26)	20 (0.89)	.08	71 (7.36)	253 (6.61)	.42
Aripiprazole	206 (35.83)	788 (34.26)	.04	228 (23.63)	986 (25.78)	.17
Comorbidities						
Schizophrenia[d]	75 (13.04)	164 (7.36)	<.0001	253 (26.22)	947 (24.76)	0.05
Bipolar disorder	219 (38.09)	583 (26.0)	<.0001	419 (43.42)	1,535 (40.13)	.05
Depression	234 (40.7)	940 (41.93)	.59	365 (37.82)	1,594 (41.67)	.03
Anxiety	263 (45.74)	1,074 (47.90)	.35	485 (50.26)	2054 (53.7)	.06
Other mood disorders	27 (4.70)	86 (3.84)	.35	40 (4.11)	129 (3.37)	.68
Cardiovascular disease	8 (1.39)	29 (1.29)	.85	63 (6.56)	203 (5.31)	.39
Hypertension	92 (16.0)	205 (9.14)	<.0001	248 (25.7)	796 (20.81)	.0001
PCOS	52 (9.04)	14 (0.62)	<.0001	86 (8.91)	33 (0.86)	<.0001
Obesity	105 (18.26)	119 (5.31)	<.0001	280 (29.02)	509 (13.31)	<.0001
Metabolic syndrome	97 (16.86)	102 (4.43)	>.0001	228 (23.45)	482 (12.39)	<.0001

[a]χ^2 test with a significance level of .05 (except age: *T* test).
[b]Includes phentermine-topiramate, orlistat, naltrexone-bupropion, glucagon-like peptide-1 receptor agonist drugs.
[c]Includes tricyclic and atypical antidepressants and Monoamine Oxidase Inhibitors.
[d]Includes schizophrenia, schizoaffective, and schizotypal disorders.
Abbreviations: PCOS = polycystic ovarian syndrome, SGA = second-generation antipsychotic, SNRI = serotonin and norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitor.

42.48% of SGA-only users (P =.002). Patients with a diagnosis of schizophrenia (commercial: 13.04% vs 7.36%, P <.0001; Medicaid: 26.22% vs 24.76%, P =.05), bipolar disorder (commercial: 38.09% vs 26.0%, P <.0001; Medicaid: 43.42% vs 40.13%, P =.05), hypertension (commercial: 16.0% vs 9.14%, P <.0001; Medicaid: 25.7% vs 20.81%, P =.0001), and obesity (commercial: 18.26% vs 5.31%, P <.0001; Medicaid: 29.02% vs 13.31%, P <.0001) were higher in SGA-metformin concurrent users compared to SGA-only users. A higher proportion of SGA-metformin concurrent users were on mood stabilizers (commercial only: 49.74% vs 35.55%, P <.0001), weight loss agents (commercial: 11.65% vs 5.0%, P <.0001; Medicaid: 14.4% vs 8.24%, P <.0001), antihypertensives (commercial: 22.43% vs 14.81%, P <.0001; Medicaid: 29.43% vs 20.94%, P <.0001), and lipid-lowering agents (commercial: 10.78% vs 7.94%, P =.005; Medicaid: 17.41% vs 11.32%, P <.0001). SGA-metformin concurrent users had a higher prescription of olanzapine (commercial only: 16.87% vs 12.4%, P <.0001) and clozapine (commercial: 3.13% vs 0.4%, P <.0001; Medicaid: 3.21% vs 1.36%, P <.0001); however, quetiapine prescription was lower in SGA-metformin concurrent userscompared to SGA-only users (commercial: 26.43% vs 36.62%, P <.0001; Medicaid: 23.01% vs 35.92%, P <.0001).

Adherence and Persistence to SGAs in SGA-Metformin Concurrent Users vs SGA-Only Users

Table 2 presents the unadjusted 180-day adherence and persistence of the two matched study groups. In both commercial and Medicaid cohorts, patients who concurrently initiated metformin had higher PDC to SGA compared to those who did not (commercial: 80.9% vs. 67.61%, P <.0001; Medicaid: 78.41% vs 68.27%; P <.0001). A similar trend was seen with persistence where the SGA-metformin concurrent users had higher persistence to SGA (commercial: 139.0 days vs 106.4 days, P<.0001; Medicaid: 149.1 days vs 115.7 days, P <.0001). Similarly, unadjusted PDC and persistence was higher in SGA-metformin concurrent users compared to SGA-only users among early initiators, delayed initiators, and patients with a 365-day follow-up period.

Table 3 presents the propensity score adjusted difference between SGA-metformin concurrent users and SGA-only users, using the IPTW method. SGA-metformin concurrent users had a PDC of 11.79% (P<.0001) and 9.64% (P<.0001) higher compared to SGA-only users in commercial and Medicaid cohorts, respectively. Similarly, persistence was 32.14 (P<.0001) and 33.78 (P<.0001) days longer in SGA-metformin concurrent users compared to SGA-only users in both study cohorts.

Sensitivity Analysis

Table 3 presents the results of the sensitivity analysis of extending the follow-up period to 365 days. The sample sizes of SGA-metformin concurrent users decreased to 317 in the commercial cohort and 535 in the Medicaid cohort. Consistent with the main analysis, superior adherence and persistence were observed in SGA-metformin concurrent users compared with SGA-only users. Additional sensitivity analyses—extending the overlap duration to 90 days and limiting the population to risperidone-metformin, aripiprazole-metformin, clozapine-metformin and olanzapine-metformin concurrent users—yielded results consistent with the main findings. Furthermore, excluding individuals with a diagnosis of PCOS or those prescribed comedications with potential weight loss and metabolic syndrome effect did not alter the observed trends.

Table 2.

Unadjusted PDC and Persistence of SGA During the 180-Day Follow-up Period

	Commercial subgroup			Medicaid subgroup		
	Concurrent users Mean (SD)	SGA-only users Mean (SD)	*P* value	Concurrent users Mean (SD)	SGA-only users Mean (SD)	*P* value
PDC	80.9 (18.51)	67.61 (25.54)	<.0001	78.41 (21.78)	68.27 (25.81)	<.0001
Persistence	139.0 (52.95)	106.4 (66.02)	<.0001	149.1 (47.87)	115.7 (65.16)	<.0001
Unadjusted PDC and persistence of SGA with 365-day follow-up period for SGA						
PDC	81.46 (12.10)	65.94 (30.01)	<.0001	79.12 (13.51)	66.70 (29.01)	<.0001
Persistence	304.69 (95.19)	237.19 (103.73)	<.0001	311.33 (98.71)	233.89 (11.05)	<.0001
Unadjusted PDC and persistence of SGA among early initiators during 180-day follow-up period						
PDC	78.73 (18.98)	62.95 (28.03)	<.0001	80.69 (23.96)	65.86 (27.85)	<.0001
Persistence	142.5 (54.71)	105.01 (65.31)	<.0001	144.90 (50.97)	106.7 (64.21)	<.0001
Unadjusted PDC and persistence of SGA among delayed initiators during 180-day follow-up period						
PDC	81.69 (18.28)	70.82 (25.07)	<.0001	79.53 (18.15)	69.35 (24.78)	<.0001
Persistence	139.4 (51.93)	104.1 (66.61)	<.0001	142 (25.79)	108.6 (65.24)	<.0001

Abbreviations: PDC = proportion of days covered, SGA = second-generation antipsychotic.

Table 3.

IPTW Model for PDC and Persistence With 180-Day Follow-Up Period for SGA and Sensitivity Analyses

		Commercial subgroup		Medicaid subgroup	
	Ref.	Estimate (SE)	*P* value	Estimate (SE)	*P* value
Main analysis with 180-day follow-up period					
PDC	SGA-only users	11.79 (1.41)	<.0001	9.64 (0.71)	<.0001
Persistence	SGA-only users	32.14 (3.72)	<.0001	33.78 (1.76)	<.0001
With 365-day follow-up period					
PDC	SGA-only users	14.71 (1.30)	<.0001	10.91 (1.14)	<.0001
Persistence	SGA-only users	62.12 (27.43)	<.0001	75.81 (5.31)	<.0001
Early initiators during 180-day follow-up period					
PDC	SGA-only users	13.31 (2.13)	<.0001	10.71 (1.68)	<.0001
Persistence	SGA-only users	34.31 (3.10)	<.0001	35.63 (4.98)	<.0001
Delayed initiators during 180-day follow-up period					
PDC	SGA-only users	9.61 (1.38)	<.0001	8.88 (1.61)	<.0001
Persistence	SGA-only users	32.75 (3.91)	<.0001	34.02 (2.85)	<.0001
With overlap duration of 90 days and 180-day follow-up period					
PDC	SGA-only users	14.91 (1.21)	<.0001	11.49 (1.90)	<.0001
Persistence	SGA-only users	60.69 (11.61)	<.0001	54.43(10.01)	<.0001
Excluding patients with PCOS and coprescribed other weight loss agents during 180-day follow-up period					
PDC	SGA-only users	11.61 (0.83)	<.0001	9.77 (1.24)	<.0001
Persistence	SGA-only users	30.91 (4.5)	<.0001	31.91 (8.61)	<.0001
Excluding patients with metabolic syndrome					
PDC	SGA-only users	11.64 (0.91)	<.0001	9.64 (1.91)	<.0001
Persistence	SGA-only users	31.92 (3.96)	<.0001	33.14 (1.14)	<.0001
Risperidone-metformin concurrent users during 180-day follow-up period					
PDC	Risperidone-only users	12.11 (1.39)	<.0001	10.40 (1.88)	<.0001
Persistence	Risperidone-only users	32.91 (6.17)	<.0001	37.12 (8.01)	<.0001
Aripiprazole-metformin concurrent users during 180-day follow-up period					
PDC	Aripiprazole-only users	12.51 (1.36)	<.0001	11.92 (2.49)	.001
Persistence	Aripiprazole-only users	38.75 (6.98)	<.0001	37.61 (8.91)	<.0001
Clozapine-metformin concurrent users during 180-day follow-up period					
PDC	Clozapine-only users	12.92 (2.04)	<.0001	11.61 (1.57)	<.0001
Persistence	Clozapine-only users	37.82 (4.48)	.001	38.42 (7.96)	<.0001
Olanzapine-metformin concurrent users during 180-day follow-up period					
PDC	Olanzapine-only users	12.84 (1.88)	<.0001	11.17 (2.98)	.001
Persistence	Olanzapine-only users	38.99 (5.46)	<.0001	38.19 (7.19)	<.0001

Abbreviations: IPTW = inverse probability of treatment weights, PDC = proportion of days covered, SE = standard error, SGA = second-generation antipsychotic.

DISCUSSION

Our study is the first to our knowledge to evaluate the impact of add-on metformin on adherence and persistence to treatment with SGAs. Our study findings show that SGA adherence is 10%–15% higher in commercially insured adults and 8%–10% higher in their Medicaid-covered counterparts during a 1-year follow-up period.

SGA drugs are the cornerstone for the management of severe mental disorders like schizophrenia, bipolar disorder, and major depressive disorder. Since these conditions often require long-term therapy, it is crucial to maintain consistent medication adherence over time. Weight gain may cause patients on SGAs to discontinue their medications because of concern about their appearance. This issue can be distressing on a physical and emotional level, potentially leading to challenges with adherence to the prescribed treatment.

SGA medication adherence is poor in general. A meta-analysis to evaluate the adherence to oral antipsychotics in patients with schizophrenia showed an adherence rate of 71.1%, lower than the 80% threshold used widely to define satisfactory adherence.[21] Another

systematic review showed that approximately 56% of patients living with schizophrenia and 44% of those living with bipolar disorder are nonadherent to their antipsychotics.[22] Our finding suggests that after excluding those patients who discontinued SGA treatment during the early phase of treatment (<60 days), the medication adherence in SGA-only users is still suboptimal (<70% in 6 months and 12 months).

Poor medication adherence often results in poor clinical outcomes. A study by Novick et al showed that nonadherence with antipsychotic medication in schizophrenia is common in the outpatient practice setting and influences long-term outcomes. Nonadherence is associated with an increased risk of relapses, hospitalization, and suicide. [23] Compliance rates of < 80% in adults with schizophrenia may increase the risk of hospitalization more than 2-fold and the risk of relapse.[24,25]

Our findings add to the existing literature and demonstrate that metformin, when used in SGA recipients without diabetes, promotes adherence and potentially enhances the effectiveness of mental health outcomes in patients. The effect is consistent in patients with different socioeconomic statuses (commercial and Medicaid enrolled individuals), and the slightly lower effect sizes associated with metformin observed in the Medicaid vs commercial cohorts may be explained away by the higher complexity of Medicaid patients' treatment regimens. We observed a higher prevalence of comorbidities among SGA-metformin concurrent users in Medicaid claims patients, along with greater use of comedications addressing both mental health disorders and metabolic syndrome. The combination of these factors, including higher comorbidity burden and increased polypharmacy, likely contributes to the reduced adherence to SGAs observed in Medicaid patients compared to those with commercial insurance.

Despite its strengths, this study had several limitations related to its design and data source. While insurance claims data are the gold standard for the measurement of medication adherence and persistence, there are inherent limitations. The lack of weight measurements leaves uncertainty about whether the observed improvement in adherence is mediated by the weight reduction associated with metformin. Future study is needed to confirm the causal pathway using linked electronic medical record and claims data. Additionally, the SGA-metformin concurrent users may have experienced more weight gain than the matched SGA-only users after controlling for obesity diagnosis. If present, this confounding by indication would likely bias the observed association toward the null. Therefore, the true effect of metformin may be underestimated, and adequately addressing this bias would likely have revealed an even stronger effect, further supporting our conclusions. Though we adjusted for severe mental health disorders at baseline, the severity of the disorders was not considered and stands as a potential limitation in estimating the true effect size. Further, we did not account for the SGA dose and mode of administration, which would be included in future studies. Though the study duration of 2017–2019 could be a potential limitation that the data are not very recent, we chose to use older data to avoid potential distortions in medication utilization behavior caused by the COVID-19 pandemic. However, there is no reason to believe that the effect estimates derived from pre-COVID data would not be generalized in the post-COVID period.

CONCLUSION

Concurrent use of metformin in SGA users offers benefit by improving adherence and persistence to SGA. Notably, higher adherence observed in both early and delayed metformin initiators suggests that metformin may be effective in improving SGA adherence when used for either the prevention or treatment of AIWG. Further research is needed to understand the extent to which this effect is mediated through metformin's weight loss effect on AIWG.

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