Schizophrenia Bulletin vol. 47 no. 4 pp. 948–958, 2021
doi:10.1093/schbul/sbaa191
Advance Access publication 6 February 2021

Does Switching Antipsychotics Ameliorate Weight Gain in Patients With Severe Mental Illness? A Systematic Review and Meta-analysis

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Objective: **Obesity and adverse metabolic outcomes in patients with severe mental illness are clinically significant but potentially preventable. Importantly, the evidence for switching to antipsychotics to reduce cardiometabolic burden is unclear.*Method:* PubMED, Embase, PsycINFO, and Cochrane were searched from inception to March 8, 2020. Articles reporting weight and metabolic changes after antipsychotic switching vs staying on the previous antipsychotic were meta-analyzed both across and within group.*Results:* Of 61 identified studies, 59 were meta-analyzed (40% rated high quality). In the switch-vs-stay pairwise meta-analyses, only aripiprazole significantly reduced weight (−5.52 kg, 95% CI −10.63, −0.42, *P* = .03), while olanzapine significantly increased weight (2.46 kg, 95% CI 0.34, 4.57, *P* = .02). Switching to aripiprazole also significantly improved fasting glucose (−3.99 mg/dl, 95% CI −7.34, −0.64, *P* = .02) and triglycerides (−31.03 mg/dl, 95% CI −48.73, −13.34, *P* = .0001). Dropout and psychosis ratings did not differ between switch and stay groups for aripiprazole and olanzapine. In before-to-after switch meta-analyses, aripiprazole (−1.96 kg, 95% CI −3.07, −0.85, *P* < .001) and ziprasidone (−2.22 kg, 95% CI −3.84, −0.60, *P* = .007) were associated with weight loss, whereas olanzapine (2.71 kg, 95% CI 1.87, 3.55, *P* < .001), and clozapine (2.80 kg, 95% CI 0.26, 5.34, *P* = .03) were associated with weight gain. No significant weight or other cardiometabolic changes were observed when switching to amisulpride, paliperidone/risperidone, quetiapine, or lurasidone.*Conclusions:* Switching antipsychotics to agents with lower weight gain potential, notably to aripiprazole and ziprasidone, can improve weight profile and other cardiometabolic outcomes. When choosing switch agents, both the weight gain potential of the pre- and post-switch antipsychotic must be considered. Antipsychotic switching in psychiatrically stable patients must be weighed against the risk of psychiatric worsening.**

Key words: obesity/schizophrenia/bipolar disorder/antipsychotics/switching

Introduction

The prevalence of obesity in patients with severe mental illness (SMI) is up to 60%, twice the rate of the general population.[1,2] In turn, obesity and dyslipidaemia, along with hypertension, and smoking, are major risk factors for cardiovascular disease, type 2 diabetes mellitus (T2DM) and cancer.[3,4] These physical comorbidities contribute to the 3-fold increase in standardized mortality rate[5] and a 15-year reduction in life expectancy[6] compared to the general population. Being overweight or obese also increases the risk of all-cause mortality.[7,8]

Second-generation antipsychotics (SGA) are important contributors to weight gain.[9,10] The resulting obesity can influence a patient's perception of their treatment, resulting in poor adherence and subsequent exacerbation of symptoms, reduction in quality of life, and readmission to hospital.[11–13]

Strategies to counteract weight gain[14] include lifestyle interventions[15] and augmentation with metformin[16] or glucagon-like peptide 1 receptor agonists (eg, exenatide, liraglutide).[17] Given the challenges associated with people with SMI engaging in lifestyle interventions[18] or the risks of polypharmacy,[9] switching to an antipsychotic

with a lower propensity to induce weight gain may be preferable.[19]

Although antipsychotic switching has been recommended as strategy to mitigate metabolic disorders among people with severe mental illness,[2,9] the efficacy of switching and the most appropriate choice of agent are unclear. To our knowledge, only one preliminary meta-analysis (studies = 4, n = 636), published a decade ago, investigated the cardiometabolic effects of antipsychotic switching.[20] We updated this review and included secondary outcomes, ie, other cardiometabolic measures, dropouts, and psychotic symptoms.

Method

Protocol

This systematic review followed a prespecified PROSPERO (International Prospective Register of Systematic Reviews) protocol (CRD42018114907) and we followed the PRISMA guidelines.[21]

Search Strategy

We searched PubMED, Embase, PsycINFO, and the Cochrane Library from inception to March 8, 2020. The basic search terms included "Switch* OR Substitut* OR Comparative AND Diabetes OR Obesity OR Weight OR BMI OR Obese OR Cholesterol OR Triglyceride* OR Blood Pressure OR "Metabolic Syndrome" AND (list of predefined antipsychotics) OR Antipsychotic*" (supplementary table 1.1). Two authors (W.M. and E.G.) screened at title abstract and full text levels. We hand searched included studies for relevant references and contacted experts regarding potential unpublished data.

Selection Criteria

We included randomized controlled trials or observational studies of people with SMI), such as schizophrenia and related psychoses, bipolar disorder, and major depressive disorder, that investigated a switch from any single or combination of antipsychotics to a different antipsychotic monotherapy for ≥4 weeks. Studies had to report endpoint and or mean change for cardiometabolic parameters, such as weight, body mass index (BMI), waist circumference, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, total cholesterol, triglycerides, systolic and or diastolic blood pressure, blood glucose levels, glycated hemoglobin (HbA1c), insulin, or presence of metabolic syndrome. We included comparisons of switching antipsychotics ("switch") vs remaining on the same agent ("stay"), as well as studies without such controls. We excluded case reports, review articles, editorials, conference abstracts, articles using overlapping datasets to included studies, and studies solely switching from paliperidone to risperidone, or vice versa, as these SGAs were not considered sufficiently different. A switch to either paliperidone or risperidone was analyzed together.

Data Extraction

One author extracted data on study characteristics, participant details, clinical outcomes, efficacy measures, and metabolic parameters, which was validated by a second author (W.M. and E.G.). The primary outcome was change in weight when switching from one to another antipsychotic compared to staying in the same agent. We also examined before-to-after switch data on weight on commencing an antipsychotic agent. Secondary outcomes were pair-wise or before-to-after analyses of other cardiometabolic outcomes, including BMI, waist circumference, total, HDL and LDL cholesterol, triglycerides, fasting blood glucose, HbA1c, and insulin. Data were extracted on the antipsychotic used prior to the switch. Where switches from specific single antipsychotics were not available, we categorized prior antipsychotics as either mixed SGAs, mixed first-generation antipsychotics (FGAs), or mixed FGA/SGAs. Finally, we extracted data on drop-outs and changes in the scores of 2 total psychosis symptoms scales; the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS).

Risk of Bias Within Studies

We assessed studies, which compared switching to a new antipsychotic vs staying on a previous antipsychotic using the following criteria adapted from the Cochrane Collaboration guidelines[22]: (1) adequate generation of allocation sequence; (2) adequate random sequence generation; (3) blinding of allocation to conditions to participants; (4) blinding of allocation to conditions to assessor; (5) appropriate reporting on missing data; (6) reporting aligns with prespecified primary outcome measures; and (7) other sources of potential bias including pharmaceutical company funding. Studies were deemed to be of high quality if they had at least 4 domains with low risk of bias. To clarify selective outcome reporting, clinical trial registries were searched, and registered trials compared against the published studies.

For studies that only had data before-to-after switching, we used the modified Newcastle-Ottawa Quality Assessment Scale (supplementary table 4.3).[23] A high-quality study has a score of 4 or more (maximum 5). We assessed 5 domains: representativeness of the sample; sample size (low bias if study size >200); loss to follow up; ascertainment of diagnosis of severe mental illness; and quality of descriptive statistics.

Statistical Analyses

We performed a pairwise meta-analyses using Comprehensive Meta-Analysis version 3.3 and Review Manager version 5.3.5 for comparisons of switching to a specific antipsychotic vs remaining on the previous agent. We also conducted a meta-analysis of before-to-after data of switching to a different antipsychotic. Meta-analyses were only included if at least 2 studies had useable data for the outcome of interest. The primary outcome of interest was the pairwise comparison of change in weight, with secondary outcomes of pairwise differences in other cardiometabolic symptoms, dropouts, and psychosis scores, and before-to-after changes in weight, plus other cardiometabolic outcomes, dropouts, and psychosis symptoms. Where possible, outcomes were presented as mean difference but we used the standardized mean difference (SMD) when primary data required conversion to effect size for combination in a meta-analysis, notably different psychosis scores. We used random effects models as we were unable to assume homogeneity among studies.

We conducted sensitivity analyses on prior antipsychotic, study setting (hospital or community), diagnosis, whether or not the study had weight loss as a primary outcome, age group of participants (child and youth or adult), and country of study. We undertook a meta-regression on dropouts, study duration, mean baseline BMI, mean age of participants, and mean duration of illness. We explored heterogeneity using the I^2 statistic, with an I^2 >50% indicating significant heterogeneity. We investigated publication bias, using Kendal's Tau and Egger's test,[24] when meta-analyses included ≥10 studies.

Results

Included Studies

We identified 5,767 unique studies, of which 5,435 were excluded at title and abstract level. An additional 270 were excluded at full text review (supplementary table 3.1). We included 61 articles in the systematic review; 59 articles contributed to the meta-analyses (supplementary appendix 2). There were 8,554 participants with a mean age of 39.2 ± 9.9 years and 56.9% males. Mean study duration was 26.3 ± 19.7 weeks. Studies came from North America (n = 21), South America (n = 1), Europe (n = 8), Asia (n = 22), the Middle East (n = 2); and multiple countries (n = 7). The antipsychotics switched to included aripiprazole (n = 16), amisulpride (n = 2), blonanserin (n = 1), clozapine (n = 3), Iloperidone (n = 1), lurasidone (n = 2), olanzapine (n = 14), paliperidone/risperidone (n = 9), quetiapine (n = 8), and ziprasidone (n = 11). Five studies assigned patients to 2 or more different antipsychotics for comparison. Twenty-four studies provided data on a switch from a specific single antipsychotic, including risperidone (n = 5), clozapine (n = 1), amisulpride (n = 1), fluphenazine (n = 1), quetiapine (n = 1), olanzapine (n = 10), aripiprazole (n = 2), perphenazine (n = 1), and haloperidol (n = 2). Seven studies had data on switching from mixed FGAs, 10 from mixed SGAs, and 26 from mixed FGA/SGAs (supplementary table 7).

Thirty-three studies (54.1%) included people with schizophrenia, 17 studies (27.3%) people with schizophrenia or schizoaffective disorder, 2 studies (3.3%) people with bipolar disorder and 9 studies (14.8%) people with a mix of mental disorders. Most studies included community samples (n = 26, 43.3%) with the remainder from hospitals with or without community samples (supplementary table 7).

The overall study quality was low; only 4 of the 10 studies with data on switch-vs-stay were rated to be of high quality using the Cochrane tool, and only 20 of 51 before-to-after studies were rated to be of high quality using the Newcastle-Ottawa scale (supplementary appendix 4). Lack of blinding was the most common issue in the RCTs while in the before-to-after studies the main issues were small sample sizes and high attrition.

Ten studies (16.3%) had data on switching to a new antipsychotic vs staying on the previous agent.[25–34] Of these, 4 were switches to aripiprazole,[25,27,33,34] 4 switched to olanzapine,[29–32] 1 switched to risperidone,[26] and 1 switched to quetiapine.[28] Fifty-one studies (83.6%) provided observational data on the outcomes of interest before-to-after a switch to a specific antipsychotic.[35–84] Pairwise meta-analyses of switch-vs-stay were only possible for 2 antipsychotics, aripiprazole and olanzapine. By contrast, we conducted before-to-after meta-analyses for 9 antipsychotics: aripiprazole; amisulpride; clozapine; lurasidone; olanzapine; paliperidone/risperidone; quetiapine; and ziprasidone. Only qualitative results were available for blonanserin and iloperidone (supplementary table 7).

Pairwise Meta-Analyses of Switch-vs-Stay

Change in Body Weight

Aripiprazole Four studies (2 high quality[25,33] and 2 low quality[27,34]) contributed data for switching to aripiprazole (n = 182) vs staying on the previous antipsychotics (n = 214). Previous antipsychotics included a mix of SGAs. Three studies (2 high quality,[25,33] 1 low quality,[27] n = 333) contributed data for the primary outcome of body weight.[25,27,33] Compared to staying on the previous antipsychotics, a switch to aripiprazole was associated with a 5.52 kg weight loss (figure 1 and supplementary table 5.1). The results remained significant when the low-quality study was omitted. It was not possible to disaggregate the results by prior antipsychotic.

Olanzapine Four studies (1 high quality,[31] 3 low quality[29,30,32]) contributed data on switching to olanzapine compared to staying on previous agents. Previous antipsychotics included risperidone,[29] amisulpride,[31] long-acting injectable FGAs,[30] and a mix of risperidone

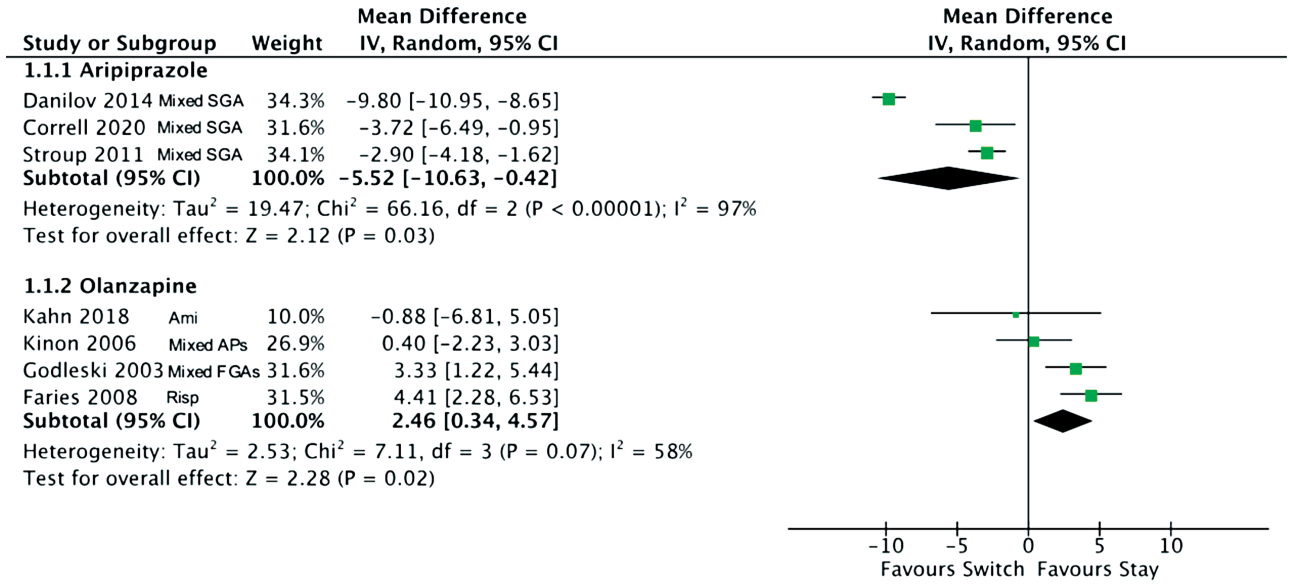

Fig. 1. Pairwise meta-analysis of switching to an antipsychotic for weight change. Mixed SGA = Prior antipsychotics were a mix of second generation antipsychotics; Ami = Prior antipsychotic was amisulpride; Mixed FGAs = Prior antipsychotics were a mix of first generation antipsychotics; Risp = Prior antipsychotic was risperidone.

Table 1. Pairwise meta-analyses of metabolic and safety outcomes for switching to an antipsychotic

	Studies	Participants	Statistic	Mean	95% CI	*P* value	I^2
Switch to Aripiprazole							
Weight (kg)	3	305	MD	−5.52 kg	−10.63 kg to −0.42 kg	.03	97%
Fasting glucose (mg/dl)	2	239	MD	−3.99	−7.34 to −0.64	.02	0%
Triglycerides (mg/dl)	2	239	MD	−31.03	−48.73 to −13.34	.001	0%
HDL cholesterol (mg/dl)	2	239	MD	+2.90	−2.11 to 7.92	.26	70%
Psychotic symptoms	3	301	SMD	−0.44	−1.20 to 0.32	.26	88%
Drop outs	3	334	OR	+1.67	0.59 to 4.73	.33	48%
Switch to Olanzapine							
Weight (kg)	4	353	MD	+2.46 kg	0.34 kg to 4.57 kg	.02	58%
Psychotic symptoms	3	252	SMD	+0.06	−0.23 to 0.35	.70	75%
Drop outs	2	147	OR	+0.86	0.19 to 3.95	.85	69%

Note: CI, confidence interval; HDL, high-density liposome; MD, mean difference; OR, odds ratio; SMD, standardized mean difference.

and FGAs.[32] Compared to staying on previous antipsychotics, switching to olanzapine was associated with a 2.46 kg weight gain (figure 1 and supplementary table 5.2). The results were no longer significant when data were restricted to the one high-quality study or when the analysis was restricted to studies switching only from SGAs.

Other Cardiometabolic Outcomes

Aripiprazole

Two studies (1 high quality[33] and 1 low quality,[27] n = 239) contributed data for other metabolic outcomes. Aripiprazole was associated with a reduction in fasting glucose triglycerides, but not HDL cholesterol (table 1 and supplementary table 5.1). When restricted to the one high-quality study, only triglycerides were significantly lower in the aripiprazole group. There was insufficient data to undertake meta-analyses of other cardiometabolic components.

Olanzapine

Data were not available for meta-analyses of other cardiometabolic outcomes for a switch to olanzapine.

Safety

Aripiprazole There was no significant difference between switching to aripiprazole or staying on previous antipsychotic for psychotic symptoms (1 high quality[33] and 2 low quality,[27,34] n = 301) or dropouts (2 high quality,[25,33] 1 low quality,[34] n = 334) (table 1). The result remained nonsignificant with sensitivity analysis by study quality. There were insufficient data to explore other adverse drug reactions.

Olanzapine There was no statistically significant difference between switching to olanzapine or staying on previous antipsychotic for psychotic symptoms (3 low-quality studies,[29,30,32] n = 252), or dropouts (1 high-quality,[31] 1 low-quality[32] study, n = 147) (table 1). There were insufficient data to explore other adverse drug reactions.

Before-to-After Meta-analyses

Change in Body Weight

Aripiprazole Fourteen studies (n = 488) contributed data for weight for aripiprazole.[25,27,33,36,39,42,46,47,51,54,67,78,79,83] After switching to aripiprazole, participants had a mean weight loss of 1.96 kg (figure 2 and Supplementary table 6.1). When restricted to the 7 high-quality studies, there was no significant change in weight. Sensitivity analysis by recruitment site remained significant for mixed inpatient and community, but not for community alone. Weight loss remained statistically significant when prior antipsychotic was restricted to SGAs, but not for a mix of SGAs or FGAs. Weight loss remained significant irrespective of diagnosis, or whether weight loss was the primary outcome of the study. Sensitivity analysis of age group showed significant weight loss in the 13 adult studies but not in the one child and youth study. Studies from North America (n = 5) and Asia (n = 7) reported significant weight loss but not the 2 studies from Europe (supplementary table 6.2). Meta-regression by drop out proportion, study duration, baseline BMI, and mean sample age significantly impacted the overall result for weight change (supplementary table 6.3). There were insufficient data for meta-regression by duration of illness. There was no evidence of publication bias (Eggers regression = 8.48, SE = 4.92, 2-sided P = .11, Kendall's Tau −0.20 P = .32; supplementary table 6.4).

Amisulpride

One high-quality[55] and one low-quality[62] study contributed data on weight before-to-after switch to amisulpride from mixed SGAs (figure 2). There was no difference in weight after switching to amisulpride. There were insufficient data to undertake sensitivity analyses or meta-regression (supplementary table 6.5). There were no data for other metabolic outcomes.

Clozapine

One high-quality[74] and one low-quality[49] study contributed data on weight before-to-after switch to clozapine from a mix of FGA/SGAs. Patients switched to clozapine gained 2.8 kg (figure 2). There were insufficient data to undertake sensitivity analyses or meta-regression (supplementary table 6.6).

Lurasidone

Data from 2 high-quality studies of switch to lurasidone (1 from olanzapine[75] and 1 from a mix of FGA/SGAs[66]) showed no difference in weight (figure 2). There were insufficient data to undertake sensitivity analyses or meta-regression (supplementary table 6.7).

Olanzapine

Thirteen studies (3 high quality[59,64,74] and 10 low quality,[29,30,32,35,38,49,70,77,80,85] n = 1,426) contributed data on the effect of switching to olanzapine with a 2.7 kg weight gain (figure 2 and supplementary table 6.8). Sensitivity analyses by study quality, prior antipsychotic (mixed FGA/SGAs, mixed FGA, haloperidol, perphenazine, or risperidone), diagnosis, age group, or recruitment region had no impact on the weight gain. A hospital sample was not associated with weight gain whereas community

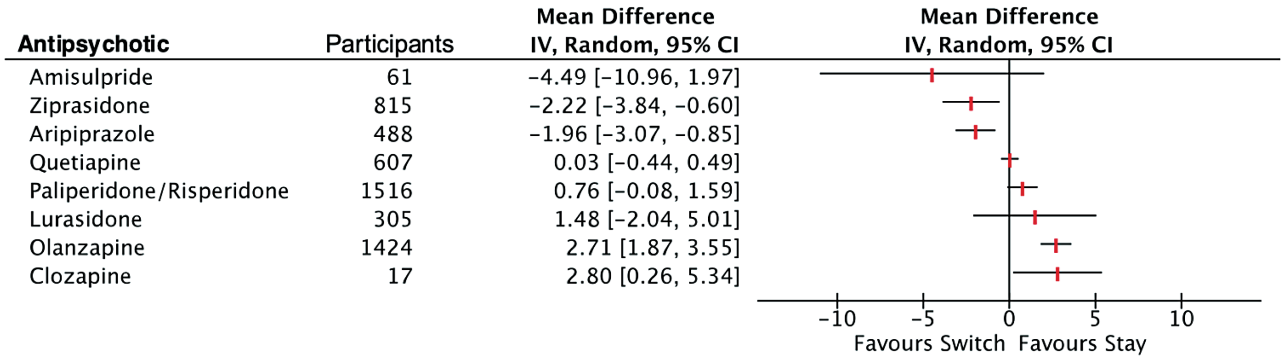

Fig. 2. Before-to-after meta-analysis of switching to an antipsychotic for weight change (in kg).

or mixed setting samples were both associated with significant weight gain following a switch to olanzapine. Studies with weight as a primary outcome did not show any change in weight (supplementary table 6.9). Meta-regression by dropout proportion, study duration, mean sample age, and duration of illness showed these factors did not influence results (supplementary table 6.10). There was no evidence of publication bias with Kendall's tau or Eggers regression (supplementary table 6.11).

Paliperidone/Risperidone

Four high-quality[37,41,52,71] and 5 low-quality[50,57,73,80,85] studies (n = 1,516) of paliperidone/risperidone showed no change in weight (figure 2 and supplementary table 6.12). When restricted to high-quality studies, there was significant weight gain. There was significantly greater weight gain with a change from mixed APs and mixed FGAs, but not olanzapine or perphenazine. One low-quality study of children switching from olanzapine reported >5 kg weight loss with switch to risperidone.[73] This was the only study that reported weight loss with switch to paliperidone/risperidone. Studies in mixed settings reported significant weight gain, but not studies in community settings. Analyses restricted to studies from Europe or the United States reported significant weight gain (supplementary table 6.13). Meta-regression by increasing age was associated with significantly greater weight gain but this was no longer significant when the child and youth study was excluded. Study duration or dropout proportion did not influence weight change in meta-regressions (supplementary table 6.14).

Quetiapine

There were 1 high-quality[44] and 6 low-quality[41,43,58,65,68,85] studies of quetiapine (n = 607, all adults). There was no change in weight when switching to quetiapine (figure 2 and supplementary table 6.15). Sensitivity analyses by study quality, setting, diagnosis, and country did not affect the results. Two low-quality studies[43,58] of switching from olanzapine reported significant weight loss, while one low-quality study[58] of switching from haloperidol was associated with significant weight gain (supplementary table 6.16). There was no difference in weight when switching from risperidone, perphenazine, mixed FGA/SGAs, or mixed SGAs. Meta regression by dropout proportion, study duration, and mean sample age did not influence results (supplementary table 6.17).

Ziprasidone

Nine studies (3 high quality[40,48,72] and 6 low quality,[36,53,60,63,69,82] all adult, n = 815) of switching to ziprasidone showed a significant weight loss (figure 2 and supplementary table 6.18). This significant weight loss remained in sensitivity analyses for quality, setting, previous antipsychotics (aripiprazole, quetiapine, olanzapine, and mixed FGA/SGAs), diagnosis, weight as primary study outcome, and country (supplementary table 6.19). Meta-regression by dropout proportion, study duration, mean sample age, and duration of illness did not influence the results. Higher baseline BMI was associated with greater weight gain (supplementary table 6.20).

Other Metabolic Outcomes

Switching to aripiprazole, lurasidone, or ziprasidone was generally associated with improvements in most other cardiometabolic outcomes (supplementary appendix 5). By contrast, clozapine was associated with an increase in BMI. Olanzapine, quetiapine, and paliperidone/risperidone were neutral in terms of change in other cardiometabolic outcomes.

Safety

Switching to aripiprazole, paliperidone/risperidone, quetiapine, or ziprasidone was associated with a reduction in psychotic symptoms, while switching to olanzapine did not change psychotic symptoms (supplementary appendix 5).

Qualitative Analysis

Other Antipsychotics One high-quality study (n = 52) examined switching to blonanserin from a mix of FGA and SGAs. They reported no change in weight or other metabolic outcome besides a small improvement in HbA1c.[83] Another low-quality study (n = 500) investigated a switch to iloperidone from risperidone, olanzapine, or aripiprazole and reported significant weight gain (0.84 kg, 95% CI 0.50 kg, 1.19 kg, $P < .001$).[81]

Discussion

This systematic review is the most comprehensive synthesis of the impact of switching antipsychotics on metabolic outcomes; a previous meta-analysis only included 4 small trials.[20] We included data from 61 studies and 8,554 participants on switching to 11 different antipsychotic medications and conducted meta-analyses for 9 antipsychotics.

Aripiprazole had the best evidence for weight loss upon antipsychotic switching; 5.5 kg in the pairwise and 2.0 kg in the before-to-after analysis. Switching to ziprasidone was also associated with weight loss but based on only before-to-after data. These findings are consistent with existing data on their lower propensity for weight gain.[9] Switching to olanzapine was associated with 2.5–2.7 kg weight gain in switch-vs-stay and before-to-after meta-analyses. Switching to clozapine-induced weight gain in before-to-after studies. This finding reflects the adverse cardiometabolic profile of these agents.[9] Switching to

amisulpride, paliperidone/risperidone, quetiapine, or lurasidone had no effect on weight.

Switching from risperidone to olanzapine led to weight gain. Switching from olanzapine to lurasidone or quetiapine led to weight loss, but switching from olanzapine to paliperidone/risperidone had no effect. Switching from haloperidol to quetiapine or olanzapine led to weight gain but switching from aripiprazole or quetiapine to ziprasidone led to weight loss; there was no effect when switching from paliperidone/risperidone to quetiapine. Switching from perphenazine to olanzapine, was associated with weight gain while switching from perphenazine to quetiapine or paliperidone/risperidone was weight neutral.

Switching to aripiprazole improved triglycerides (both types of analyses) and total, LDL and HDL cholesterol (before-to-after analysis). Switching to ziprasidone improved metabolic outcomes (before-to-after analyses) but switching to clozapine or olanzapine (before-to-after analyses) worsened outcomes. Switching to aripiprazole, risperidone/paliperidone, quetiapine, or ziprasidone improved psychotic symptoms (before-to-after analysis).

This is the first study to comprehensively assess the effects of switching antipsychotics. We further explored the effects of potential confounders and effect modifiers, such as study duration, study quality, recruitment setting, prior antipsychotic, diagnoses, weight as a primary outcome, country of recruitment, dropouts, baseline BMI, mean sample age, and duration of illness. For the most part, these factors did not influence the overall results for weight changes with antipsychotic switching.

This study has several limitations. Although we were able to conduct pairwise switch-vs-stay meta-analyses for both aripiprazole and olanzapine, there were only usable data for before-to-after analyses for the other antipsychotics. These analyses are subject to regression to the mean and may therefore overstate changes in weight and other metabolic syndrome components associated with switching; results need to be interpreted with caution. By contrast, there might have been insufficient power to demonstrate a significant change with some comparisons, such as weight loss on switching to lurasidone, or weight gain when switching from risperidone to quetiapine, despite their known cardiometabolic profile.[86,87] Thus, lack of demonstrated overall weight gain for the switch to quetiapine may have been due to lack of power and/or opposing/neutralizing results of significant weight gain when switching from haloperidol to quetiapine and significant weight loss when switching from olanzapine to quetiapine. This finding indicates the importance of considering the cardiometabolic profile of both the pre- and post-switch antipsychotic in the clinical decision-making process.

For the antipsychotics where both analyses types were conducted (ie, before-to-after and switch-vs-stay) there was consistency in weight changes across the analysis types, so observations of weight change from before-to-after studies may be broadly reflective of switch-vs-stay studies. While studies often reported whether participants as a group were on FGAs and/or SGAs, most studies did not specify the antipsychotic agent prior to switching. This lack of detail constrained our ability to conduct sensitivity analyses of switching from specific antipsychotics. The studies also lacked data on the duration of the previous antipsychotic and of the cardiometabolic impact of switching antipsychotics in specific disorders, such as bipolar disorder and depression. Most studies only considered people aged 18–64 years hence limiting generalizability to nonelderly adults. Overall study quality was low, with only 40% rated as being of high quality. Overall, heterogeneity was high in many of the meta-analyses, and as such, our results should be treated with caution. We explored heterogeneity in sensitivity analyses, but it remained high in most analyses.

Switching antipsychotics is only one strategy in managing obesity and metabolic syndrome among people with SMI.[14,19] Switching to aripiprazole, with an SMD of −1.93 (95% CI −3.70 to −0.16, $P = .03$, supplementary table 5.2) in our pairwise meta-analyses of switch-vs-stay, compared favorably to other published weight loss interventions among people with schizophrenia. Lifestyle interventions including individual lifestyle counseling (SMD −0.98, 95% CI −1.15 to −0.81, $P < .001$) and physical activity (SMD −0.96, 95% CI −1.27 to −0.66, $P < .001$) can reduce weight and improve components of metabolic syndrome.[14] Uptake remains a major challenge for their effectiveness.[9] Moreover, the clinical relevance of lifestyle intervention associated weight loss has been challenged given that trials often recruit more motivated participants compared to observational studies with participants who may be more generalizable to real-world populations of people with SMI.[18] Augmentation with pharmacological agents is also effective in reducing weight.[14] For instance, augmentation with aripiprazole (SMD −0.73, 95% CI −0.97 to −0.48, $P < .001$) or topiramate (SMD −0.72, 95% CI −1.56 to −0.33, $P < .001$) can lead to weight loss.[14] However, aripiprazole may only work when added to high-risk antipsychotics, such as olanzapine and clozapine.[88] Topiramate augmentation has been associated with cognitive adverse drug reactions hence limiting its tolerability.[14] The most promising nonpsychotropic agents include metformin (SMD −0.53, 95% CI −0.69 to −0.38, $P < .001$)[14,16] and glucagon-like peptide receptor agonists (GLP1-RAs) (SMD −0.44, 95% CI −0.60 to −0.28, $P < .001$).[14,17]

Although switching to a different antipsychotic, notably aripiprazole and ziprasidone, may lead to weight loss, these benefits must be weighed against any potential risks of adverse drug reactions or deterioration in psychotic symptoms. Reassuringly, we found no change in psychotic symptoms in the switch to aripiprazole (switch-vs-stay). Indeed, aripiprazole and ziprasidone

improved psychotic symptoms in the before-to-after analyses, but this finding may be confounded by regression to the mean. Nevertheless, switching antipsychotics in psychiatrically stable patients may risk relapse and detrimental consequences for at least some patients.[89] Given clozapine is the most effective[90] and efficacious[91] medication for treatment refractory schizophrenia (TRS), it may not be feasible to switch from clozapine for patients with TRS. In these instances, consideration should be given to augmentation with metformin[16] or a GLP1-RA.[92] Despite clozapine's association with poorer metabolic outcomes,[93] it remains the most effective antipsychotic for reducing all-cause mortality.[94]

Managing obesity and metabolic syndrome therefore requires a combination of lifestyle and pharmacological strategies.[19] The priority should be primary prevention of weight gain given the challenges of reversing weight gain and the potential for relapse in symptoms. This goal cannot be achieved solely by starting patients on an agent with a lower propensity for weight gain. All antipsychotics seem to induce weight gain in antipsychotic-naive patients[95,96] and so patients will require early concomitant lifestyle treatments to manage this risk.[19]

In summary, switching to aripiprazole or ziprasidone is an evidence-based approach to improving cardiometabolic risk in people with SMI, while switching to olanzapine or clozapine can significantly worsen cardiometabolic status. These results need to be considered when weighing efficacy and safety of specific antipsychotics. However, there is a need for further, adequately powered, high-quality, randomized controlled trials, examining the effects of switching to antipsychotics with a lower propensity for weight gain, notably ziprasidone and aripiprazole and, possibly, lurasidone and the newly FDA-approved lumateperone that appears to have a low cardiometabolic risk profile,[97] with data disaggregated for the pre-switch antipsychotic. Finally, further data on the impact of switching antipsychotics on other cardiometabolic parameters, including lipids, blood glucose levels, and blood pressure, as well as on psychopathology and patient-reported outcomes, like quality of life, treatment satisfaction, and adherence are needed.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

Funding

D.S. was supported in part by an NHMRC ECF GNT1111136. W.M., E.G., K.W., C.C., S.K., and S.H. have no relevant funding to declare.

Conflict of Interest

D.S., W.M., E.G., K.W., and S.H. have no conflicts of interest to declare. C.C. has been a consultant and/or advisor to or have received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma. S.K. been a consultant and/or advisor to Lundbeck and Janssen

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