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Antipsychotic-Induced Weight Gain: Dose-Response Meta-Analysis of Randomized Controlled Trials

Hui Wu[1,2,7], Spyridon Siafis[1,7], Tasnim Hamza[3], Johannes Schneider-Thoma[1], John M Davis[4,5], Georgia Salanti[3,*], and Stefan Leucht[*,1,6,*]

[1]Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany; [2]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [4]Psychiatric Institute, University of Illinois at Chicago, Chicago, IL, USA; [5]Maryland Psychiatric Research Center, Baltimore, MD, USA; [6]Institute of Psychiatry, Psychology and Neuroscience, Department of Psychiatry, Department of Psychosis Studies, King's College London, London, UK
[7]These authors have contributed equally to this work.

*To whom correspondence should be addressed; tel: +49-89-4140-4249, fax: +49-89-4140-4888, e-mail: Stefan.Leucht@tum.de

Background: **Weight gain is among the most important side-effects of antipsychotics. It is, however, unclear whether it is associated with antipsychotic doses. We aimed to fill this gap with a dose-response meta-analysis.** ***Methods:*** **We searched multiple electronic databases (last update search June 2021) for all fixed-dose studies that investigated 16 second-generation antipsychotics and haloperidol in adults with acute exacerbation of schizophrenia or with negative symptoms. We estimated the dose-response curves by conducting random-effects dose-response meta-analyses. We used the restricted cubic spline to model the dose-response relationship. The primary outcome was mean weight gain in kg from baseline to endpoint, the secondary outcome was the number of patients with clinically important weight gain.** ***Findings:*** **Ninety-seven studies with 333 dose arms (36 326 participants) provided data for meta-analyses. Most studies were short-term with median duration of 6 weeks (range 4 to 26 weeks). In patients with acute exacerbation, amisulpride, aripiprazole, brexpiprazole, cariprazine, haloperidol, lumateperone, and lurasidone produced mild weight gain in comparison to placebo (mean difference at any dose≤1 kg), while more significant weight gain was observed by all other drugs. For most drugs, dose-response curves showed an initial dose-related increase in weight which plateaued at higher doses, while for others there was no plateau and some even had bell-shaped curves, meaning less weight gain to be associated with higher doses.** ***Interpretation:*** **Second-generation antipsychotics do not only differ in their propensity to produce weight gain, but also in the shapes of their dose-response curves. This information is important for dosing decisions in clinical practice.**

Key words: dose-response relationship/metabolic side-effects/olanzapine/risperidone/paliperidone/quetiapine

Introduction

Weight gain is one of the most important side-effects of antipsychotic drugs. It is associated with metabolic disturbances such as increase in glucose, cholesterol, and lipids and may thus contribute to the well-documented excess mortality of people with schizophrenia compared to the general population.[1] While it is well-known that antipsychotic drugs differ in their propensity to produce weight gain, little is known about the question of whether weight gain is dose-related. To know this would be important for various reasons. We have recently shown that the efficacy dose-response relationships of many antipsychotics have a hyperbolic shape and finally approach a plateau, i.e., beyond a certain threshold higher doses do not lead to more efficacy.[2] If in contrast higher doses were associated with more weight gain, this would be one more reason to avoid high doses for these drugs. But it is also possible that once the receptors that are responsible for weight gain are fully bound, higher doses of a given drug would not lead to more weight gain, i.e., the dose-response curves would again plateau. It is even conceivable that at higher doses, some antipsychotics have antihyperphagic effects that lead to less weight gain. Such a hypothesis has, for example, been put forward for 5-HT_{1A} receptor partial agonists such as lurasidone[3] and ziprasidone.[4]

We, therefore, conducted a meta-analysis of dose-response studies on weight gain, similar to our previous analysis on the efficacy of antipsychotic drugs.[5] With

this method we explored whether the dose-response relationships of the drugs are monotonic (higher doses are always associated with more weight gain), hyperbolic (weight gain increases with higher doses until a plateau is approached), or bell-shaped (weight gain increases up to certain doses beyond which less weight gain is produced than by lower doses).

Methods

Search Strategy and Selection Criteria

We followed the PRISMA guidelines (checklist in supplementary appendix 1) and registered a protocol in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020181467 (supplementary appendix 2).[6]

We included all fixed-dose studies that compared the following drugs with placebo or at least one different dose of the same drug in adult patients with schizophrenia or schizoaffective disorder: amisulpride, aripiprazole [oral and long-acting injectable (LAI)], asenapine (oral and transdermal patch), brexpiprazole, cariprazine, clozapine, haloperidol (oral and LAI), iloperidone, lumateperone, lurasidone, olanzapine (oral and LAI), paliperidone (oral and LAI), quetiapine [immediate-release (IR) and extended-release (ER)], risperidone (oral and LAI), sertindole, ziprasidone, and zotepine. We planned separate analyses for the following patient subgroups: (i) chronic with acute exacerbation (ii) first-episode, (iii) elderly, (iv) predominant negative symptoms, but there were only eligible studies for the first and last subgroup. We excluded maintenance studies in stable patients (relapse prevention studies). In these studies patients are all pretreated. Often there are even run-in phases during which patients are stabilized on the drug in question before they are randomized to staying on the drug or switching to placebo/another drug. This procedure would limit the additional weight gain in the randomized phase. The inclusion of such studies would thus lead to methodological and clinical heterogeneity.

We searched the Cochrane Schizophrenia Group's study-based register of trials for studies comparing at least two doses of SGAs or haloperidol until March 9, 2020 and ran a final PubMed search on June 14, 2021. We inspected the reference lists of our previous systematic reviews on the acute efficacy of antipsychotics.[2,7–10] For these reviews, we had undertaken exhaustive searches including multiple electronic databases, the medical reviews that pharmaceutical companies must submit to the FDA, the reference lists of other meta-analyses of second-generation antipsychotic drugs (SGA),[11–18] Cochrane reviews comparing SGAs and haloperidol versus placebo,[19–21] and Cochrane reviews on optimum SGA doses,[22,23] and we had sent requests to the manufacturers of the SGAs (Search strategy in supplementary appendix 3). There were no language restrictions except studies from mainland China for which major quality concerns have been raised.[24] Two reviewers (SL, HW) examined reports independently. Risk of bias was assessed with the Cochrane Risk of Bias tool 1.[25] All data were extracted in duplicate and independently by HW and SL.

Data Analysis

We conducted a one-stage dose-response meta-analysis[26] in a frequentist framework using restricted cubic splines with the R package "dosresmeta" developed by Crippa and Orsini.[27] We investigated the relationship between dose (independent variable) and weight gain (dependent variable or response). In pharmacology, such a relationship is usually called dose-response, although the term could be confusing, because we actually address whether weight gain is dose-related. The primary outcome was mean weight change from baseline to endpoint using mean differences (MD in kilogram, kg) as the effect size measure. The secondary outcome was the number of patients with weight gain, preferably defined as at least 7% increase from baseline, analyzed with odds ratios (OR). When the numbers of participants with weight gain were not reported, we imputed them from mean scores using a validated imputation method and a cut-off of 7% increase from baseline.[28] Considering that there was no clear difference between long-acting and oral formulations of antipsychotics regarding the risk of weight gain,[29] we pooled the available different formulations for each drug by converting them to oral equivalents (supplementary appendix 5). This allowed a more comprehensive synthesis of evidence and increased the precision of the results. Nevertheless, we conducted sensitivity analyses for the different formulations. As in our previous analyses,[2] knot locations at the 25th, 50th, and 75th percentiles were used. For asenapine and sertindole, knot locatons at the 10th, 50th, and 90th percentiles were used, because the former quantiles could not form three unique knot points for these two drugs. For drugs with enough data, we used the Wald test to assess overall dose-response association and reported the *P*-values. Alpha was set at two-sided 0.05.

Sensitivity analyses of the primary outcome were performed excluding studies that compared one single-dose of an antipsychotic with placebo and studies in treatment-resistant patients. *Posthoc* we also analyzed: different formulations of drugs separately; standardized mean difference (SMD) as effect size for risperidone LAIs and lurasidone (two studies[30,31] with Body Mass Index (BMI) data instead of weight change couldn't be analyzed otherwise); pooled data in the 2009 FDA sertindole clinical review from three individual studies[32–34] that included 8 mg/d data (not reported in the individual studies); dose-response relationship of weight gain rate (weight gain divided by study duration, kg/week). In a *posthoc* sensitivity analysis of the secondary outcome, we excluded studies with imputed number of patients with weight gain.

Heterogeneity in the dose-response meta-analysis was quantified with the variance partition coefficient (VPC) which is a multivariate extension of the I^2 value suggested by Crippa et al.[26] Small-study effect and possible publication bias were explored with contour-enhanced funnel plots of the pairwise comparison of an antipsychotic versus placebo when at least 10 studies were available.[25] Pairwise meta-analysis was conducted using the R package meta v4.12-0.[35] Data analysis was conducted in R statistical software v4.0.3.[36]

Results

We included 150 studies, from which 97 studies with 333 arms (n = 36 326 participants) provided usable data for meta-analysis. The PRISMA diagram of the search was provided (supplementary appendix 4). For the a priori defined analyses of specific patient-subgroups, data were only available for the chronic patients with acute exacerbations and patients with predominant negative symptoms (three studies on amisulpride, one of them also on olanzapine). The median study duration was 6 weeks, ranging from 4 to 26 weeks. Participants were already overweight at baseline with a median baseline weight of 79.4 kg, interquartile range IQR [73.8 kg, 84.8 kg] and BMI of 26.7 kg/m^2 IQR [25.6 kg/m^2, 28.5 kg/m^2]. Detailed description of included studies was provided (supplementary appendix 6). For overall risk of bias of included studies, 66 studies were rated as low, 25 moderate, and 6 high (supplementary appendix 7).

The dose-response curves of the primary outcome are presented in figure 1.

Subgroup of Chronic Patients With Acute Exacerbations

Amisulpride. A single 4-week dose-finding study (n = 241) compared amisulpride 400 mg/d, 800 mg/d and 1200 mg/d with 100mg/d.[37] Amisulpride produced negligible weight gain (maximum MD = 0.14 kg) and the dose response curve was in essence flat (P-value = 0.52, figure 1 Amisulpride).

Aripiprazole. Ten placebo-controlled studies (n = 2694) were included, eight studies examining aripiprazole oral,[38–44] one aripiprazole maintena[45], and one aripiprazole lauroxil.[46] Doses between 2 mg/d and 30 mg/d were examined. Study durations ranged from 4 to 12 weeks (median 4 weeks). The dose-response curve suggested a fairly linear relationship between dose and weight gain (P-value < .01). It increased up to 10mg/d and afterwards a slower increase, but even at 30 mg/d, the MD of weight gain was small (0.97 kg, figure 1 Aripiprazole).

Asenapine. Five studies (n = 1775) of six week duration examined asenapine doses between 5 mg/d and 20 mg/d with placebo, in which four were on asenapine oral[47–50] and one on asenapine maleate transdermal patch (HP3070).[51] The dose-response curve plateaued at approximately 10 mg/d and 1.5 kg MD of weight gain (P-value < .01, figure 1 Asenapine).

Brexpiprazole. Four studies (n = 2069) examined brexpiprazole doses between 0.25 mg/d and 5 mg/d with placebo.[52–55] Study durations were 6 weeks. The hyperbolic curve plateaued around 2 mg/d at 1.06 kg MD of weight gain (P-value < .01, figure 1 Brexpiprazole).

Cariprazine. Four studies (n = 1874) of six week duration examined doses between 1.5 mg/d and 9 mg/d with placebo.[42,56–58] The dose-response curve plateaued around 4 mg/d with a slight increase of weight (MD = 0.62 kg, P-value < .01, figure 1 Cariprazine).

Clozapine. A single small study of 16 weeks duration in treatment resistant patients (n = 43) was included.[59] It compared doses of 100 mg/d, 300 mg/d and 600 mg/d. The dose-reponse curve appeared to be linear, however, due to the small sample size and limited data, the confidence interval was extremely wide and no statistically significant dose-response relationship was detected (P-value = .25). The maximum MD of weight gain was 3.75 kg (figure 1 Clozapine).

Haloperidol. Twelve placebo-controlled studies (n = 2044) compared haloperidol doses between 4 mg/d and 20 mg/d,[32,34,39,44,47,60–66] from which eleven studies used single haloperidol doses as an active comparator in the evaluation of a second-generation antipsychotic, only one study was a dose-finding study for haloperidol.[32] Study durations ranged from 4 to 8 weeks (median 6 weeks). The dose-response curve plateaued at 8 mg/d (P-value < .01), and the MD of weight gain at the plateau was mild (0.73 kg, figure 1 Haloperidol).

Iloperidone. Four placebo-controlled dose-finding studies (n = 1905) examined iloperidone doses between 4 mg/d and 24 mg/d.[66,67] Study durations were 4 and 6 weeks. The dose-response curve had a relatively narrow confidence interval and reached a plateau at approximately 12 mg/d (P-value < .01) and a MD of weight gain of 2.26 kg (figure 1 Iloperidone).

Lumateperone. Three dose-finding studies (n = 1093) lasting between 4 and 6 weeks compared lumateperone doses between 20 mg/d and 120 mg/d with placebo.[68–70] There was obvious weight gain in the placebo groups, means from 0.83 kg to 1.82 kg, and the differences in weight gain between lumateperone arms and placebo were small. The maximum MD of weight gain was small (0.65 kg) and no overall dose-response relationship was detected (P-value = .27, figure 1 Lumateperone).

Lurasidone. Nine studies (n = 3124) of 6 weeks duration examined lurasidone doses between 20 mg/d and 160 mg/d.[65,71–78] The dose-response curve reached a plateau at 60 mg/d (maximum MD = 0.51 kg, P-value < .01, figure 1 Lurasidone).

Olanzapine. Sixteen studies (n = 3575) examined olanzapine doses between 1 mg/d and 40 mg/d, 15 of which examined olanzapine oral[48,61,76,79–90] and one olanzapine LAI.[91] In 11 out of 16 studies olanzapine was

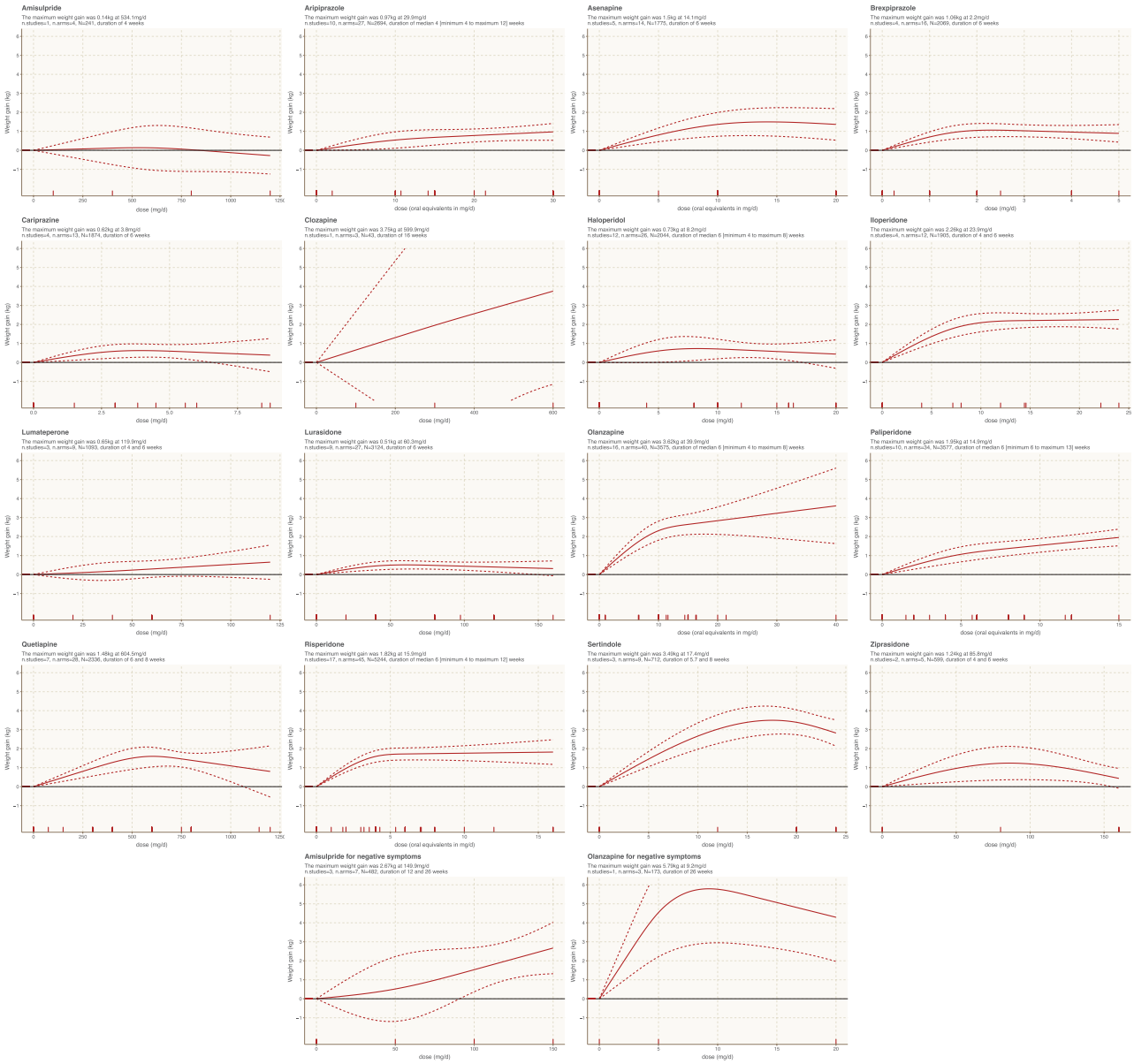

Fig. 1. Antipsychotics in patients with acute exacerbations of chronic symptoms and with predominant negative symptoms. Figure 1 shows the dose-response curves for individual antipsychotics. The dose-response curve represents the mean differences of weight gain (in kg) comparing a given dose of the drug to non-exposure (i.e., 0 mg/d or placebo). The dotted lines are 95% confidence intervals. We used knot locations at the 25th, 50th, and 75th percentiles to anchor the curves, except for asenapine and sertindole, knot locations at the 10th, 50th, and 90th percentiles were used. Y-axis represents mean differences of weight gain for the dose-response curve. X-axis represents doses. Marks along the X-axis indicate available dose data. Different formulations were pooled. Chouinard 1993 and Marder 1994 are the Canadian and the American part of the RIS-INT-3 study, only combined data were available. *n.* studies = number of studies; *n.* arms = number of arms; *N* = number of participants.

used as an active comparator for the evaluation of another second-generation antipsychotic. Study durations ranged between 4 and 8 weeks (median 6 weeks). The dose-response curve did not plateau at the highest examined dose (*P*-value < .01) (40mg/d with a corresponding MD = 3.62kg). Nevertheless, the slope of the curve was smaller beyond 10 mg/d and only one study[85] examined olanzapine dose of 40 mg/d (*n* = 195) explaining the wide confidence intervals beyond 20 mg/d (figure 1 Olanzapine).

Paliperidone. Ten studies (*n* = 3577) examined paliperidone doses between 1.5 mg/d and 15 mg/d, in which six were paliperidone oral studies[82–84,88,92,93] and four paliperidone LAI.[94–97] Study durations ranged between 6 and 13 weeks (median 6 weeks). The dose-response curve did not approach a clear plateau (*P*-value < .01) at the highest examined dose (MD = 1.95 kg at 15 mg/d) (figure 1 Paliperidone).

Quetiapine. Quetiapine IR and ER were pooled in the primary analysis. In seven studies (*n* = 2336) of 6 to 8

weeks duration, quetiapine oral doses between 75 mg/d and 1200 mg/d[60,77,98–102] were examined, where doses above 1000 mg/d came from two studies in treatment-resistant patients.[99,102] The dose-response curve was approximately bell-shaped (*P*-value < .01), peaking at MD of 1.48 kg at around 600 mg/d (figure 1 Quetiapine).

Risperidone. Seventeen studies (*n* = 5244) compared risperidone doses between 2 mg/d and 16 mg/d. Thirteen studies examined risperidone oral formulations,[43,50,56,62,63,66,69,70,103–108] 4 risperidone LAIs, including one study on risperidone RBP-7000, a sustained-release subcutaneous injection,[109] two risperidone consta, an intramuscular injection[30,110] and one risperidone ISM, a new intramuscular injection.[111] Study durations ranged between 4 and 12 weeks (median 6 weeks). The dose-response curve plateaued at approximately 5 mg/d and the maximum MD of weight gain was 1.82 kg (*P*-value < .01, figure 1 Risperidone).

Sertindole. Three studies (*n* = 712) compared sertindole doses between 12 mg/d and 24 mg/d with placebo.[32–34] Study durations were 6 and 8 weeks. The dose-response curve was approximately bell-shaped with a peak at 17 mg/d where the MD of weight gain was 3.49 kg (*P*-value < .01, figure 1 Sertindole).

Ziprasidone. Nine studies were eligible for inclusion, investigating a wide range of doses (4 mg, 10 mg, 40 mg, 60 mg, 120 mg, 200 mg, and 320 mg/day).[67,112–119] However, only two placebo-controlled studies (*n* = 599, 4 and 6 weeks) provided data for meta-analysis between 80 mg/d and 160 mg/d. The shape of the curve was estimated only by these two dose arms. The dose-response curve was bell-shaped with a peak of 1.24 kg MD in weight gain at around 80 mg/day (*P*-value = .02, figure 1 Ziprasidone).

Zotepine. Only one study with data was eligible from our search, which compared 300 mg/d zotepine (*n* = 53, mean dose = 240.57 mg/d) with placebo (*n* = 53) and chlorpromazine.[120] The MD of weight gain at 240.57 mg/d was 3.8 kg, but as there was only one dose arm a dose-response curve could not be estimated.

Subgroup of Patients With Predominant Negative Symptoms

Only three, comparably long studies (one 12 weeks and two 26 weeks, *n* = 482) were available in this subgroup.[121–123] All of them examined low doses of amisulpride which are sufficient for this indication (50–150 mg/d). There was a monotonic increasing dose-response relationship with no sign of plateau. The dose of 150mg/d has the largest MD of 2.67 kg (*P*-value < .01). Notably, all placebo arms in these studies were associated with weight loss, means ranging from 0.2 to 1.98 kg (figure 1 Amisulpride for negative symptoms).

One of the 26-week studies[121] (*n* = 173) also compared olanzapine oral 5 mg/d and 20 mg/d with placebo.[121] The dose-response curve plateaued at approximately 9 mg/d with considerable weight gain (MD = 5.8kg, *P*-value < .01, figure 1 Olanzapine for negative symptoms) and wide confidence intervals.

Secondary Outcome

Our secondary outcome was the number of patients with weight gain, usually reported as the number of patients with at least 7% increase from baseline (68 studies), other criteria used in studies were at least 5% increase (3 studies), 10 kg increase (1 study) or weight gain as an adverse event (16 studies). For the rest that didn't report this binary data, we used an imputation method to analyze.[28] Dose-response curves observed in the secondary outcome were comparable to the primary outcome (supplementary appendix 9).

Sensitivity Analyses

In the sensitivity analyses, results were largely unchanged (supplementary appendix 10).

One notable difference was that the dose-response curve of haloperidol became bell-shaped when the only true dose-finding study was analyzed.[32] The maximum mean difference of weight gain was 2.23 kg around 6 mg/d, which was a considerable weight increase in a short term (8 weeks).

Heterogeneity Assessments

For the primary outcome considerable heterogeneity (VPC ≥ 50%) across studies was observed for amisulpride, asenapine, cariprazine, olanzapine, and quetiapine, and lower levels of heterogeneity for the other antipsychotics (supplementary appendix 11).

Heterogeneity assessments of secondary outcome was also provided in supplementary appendix 11.

Small-Study Effect/Publication Bias

For the primary outcome, we investigated small-study effects for haloperidol, olanzapine, paliparidone, and risperidone, since there were at least ten studies available for these antipsychotics. We conducted pairwise meta-analyses comparing these antipsychotics with placebo. Visual assessments of the contour-enhanced funnel plots and the statistically results from the Egger's regression tests suggested small-study effects for olanzapine (*P*-value < .01) in a way that small studies reported more weight gain compared to large trials. Small-study effects were not detected in haloperidol (*P*-value = .44), paliperidone (*P*-value = .63) and risperidone (*P*-value = .72) studies. Detailed analyses are provided (supplementary appendix 12).

Discussion

We used dose-response meta-analysis to identify the possible relationships between weight gain and doses

of 17 antipsychotics. For most drugs, the dose-response curves showed an initial dose-related increase in weight which plateaued at higher doses, while for aripiprazole, olanzapine, and paliperidone, the curves did not reach a plateau. Notable bell-shaped curves were found for quetiapine and ziprasidone. The magnitudes of weight gain were generally consistent with the results of previous network meta-analyses, which excluded subtherapeutic doses and pooled not only fixed- but also flexible doses of the same compound.[7,124]

The pharmacological mechanisms of antipsychotic-induced weight gain are not entirely clear. Antipsychotics differ in their receptor-binding profiles, yet they all target $D_{2/3}$ receptors.[125] $D_{2/3}$ antagonism could interfere with reward signaling and lead to weight gain.[126] Above certain doses, dopamine receptors can be fully bound and the increasing dose-response curves could plateau, as it can be observed for antipsychotics that act primarily as dopamine antagonists, such as haloperidol. In addition to the dopaminergic antagonism, multiple and synergistic pathways have been suggested, such as antagonism of serotonin ($5\text{-}HT_{2C}$), histamine (H_1), and muscarinic receptors.[127,128] Therefore, it is conceivable that dose-response curves of antipsychotics involving these receptors, such as clozapine and olanzapine, don't reach a plateau, as observed in our results (limited data were available for clozapine). Some antipsychotics may also have anti-hyperphagic mechanisms. For example, antipsychotics that act as $5\text{-}HT_{1A}$ partial agonists could possibly induce less weight gain or even weight loss, when higher doses are used. Such hypothesis could be one of the underlying explanations for the dose-response curves that we found for lurasidone, quetiapine, and ziprasidone.[129] Finally, higher doses might be associated with more side-effects such as EPS and higher drop-out rates leading to less exposure to antipsychotic medications and potentially less weight gain.

Other rationales could also contribute to elucidating the dose-response curves. Characteristics of datasets, such as higher doses not examined, not enough distinguishable doses, weight gain imputed using last-observation-carried forward (LOCF) data could compromise the curves. Different subgroups of participants[130,131] could differ in their predisposition to gain weight. For example, we found sparse data in patients with predominant negative symptoms, who gained 2kg more than those did in the general group for both amisulpride and olanzapine.[121–123] This subgroup of patients might have lower body weight before initiation of antipsychotics, which could make them more vulnerable to antipsychotic-induced weight gain.[132,133] Furthermore, recovery of the negative symptoms may compensate the weight loss due to poor self-care and persistent disability.[134] In these comparably longer studies (one for 12 weeks, two 26 weeks), more weight gain happened after prolonged exposure to antipsychotics.[135]

In addition, a binary outcome (number of paticipants with significant weight gain) was investigated as a secondary outcome to test the robustness of the curves. Although dichotomous outcomes being more straighforward to clinical interpretation, ceiling effects when high cut-offs are applied make small changes less distinguishable. In our case, differences between continuous and dichotomous data were more obvious in antipsychotics with mild weight gain, such as aripiprazole and risperidone LAIs.

The one-stage approach allowed us to analyze a larger set of fixed-dose studies than a two-stage approach that excludes studies with less than three dose level groups,[26] which is more suitable for the complex weight gain question. However, our analysis has certain limitations. Fixed-dose studies with less than two dose levels of the same compound (or placebo) could not be analyzed using this approach. These non-dose-finding studies aimed to investigate head-to-head comparisons and could introduce heterogeneity. Nevertheless, a more comprehensive synthesis of evidence would require dose-response network meta-analysis, though their methods are still under development and not widely applied.[136,137] We were able to collate 150 eligible studies, from which 1/3 studies didn't provide usable data, otherwise, the precision of the curves could have been optimized. We also performed several sensitivity analyses to test the robustness of the results, however, not all heterogeneity was resolved and heterogeneity measures (i.e., VPC plots) should be interpreted with caution when only a few studies are available. Judgements of the curves rely on visual inspection, and due to the limited data, over-interpretation should be avoided. Antipsychotic-induced weight gain occurs quickly, often within the first weeks,[138] and more rapid than in the long-term.[139] However, almost all antipsychotics cause weight gain in the long-term,[135] and those with more weight gain in the short-term seem to cause more weight gain also in the long-term.[140] This work focused on short-term treatment from the point of early management/prevention of antipsychotic-induced weight gain.[141] We excluded maintenance studies to avoid methodological and clinical heterogeneity. In those studies, patients were all pre-treated which would limit the additional weight gain in the randomized phase. We found much fewer long-term data on this issue, moreover, some of which were not dose-finding studies. Only sparse data were available for individual antipsychotics. However, patients usually need to stay on the treatments for relapse prevention, which calls for urgency to investigate dose-response relationship for weight gain in longer durations.

Antipsychotic-induced weight gain is so far not clearly and completely understood.[142] Pillinger et al. found that increased baseline weight, male sex, and nonwhite race are more vulnerable to antipsychotic-induced metabolic dysregulation.[124] Moderators (e.g. demographics, baseline BMI, etc.) and mediators (e.g. adverse effects,

comedications, etc.) were not sufficiently investigated in our analysis. In this work, participants were already overweight at baseline, 69% were male and almost half were nonwhite race. We only had sparse data on two a priori defined patient-subgroups (chronic patients with acute exacerbations and patients with predominant negative symptoms). Studies rarely reported data of subgroups and meta-regressions analyzing study-level data of participant-level predictors have limited statistical power and are prone to ecological fallacy. This question could be better elucidated by an individual-participant-data meta-analysis.

Individual variability should be considered, by means such as using plasma concentration of antipsychotics[143] and genetic polymorphisms,[128] unfortunately, those were not commonly reported in trials and not adopted by us, yet they would be important to better understand pharmacologic modulation. Limitations of generalizability of clinical trial data to the real-life practice should not be omitted.[144,145]

Antipsychotic-induced weight gain is a complex question, and investigating its dose-response relationships helps clinicians to optimize treatment plans for patients. Second-generation antipsychotics differ not only in their propensities but also in the shape of the dose-response curves for weight gain. Early on monitoring of weight gain should always be kept in mind.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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