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The role of weight gain in explaining the effects of antipsychotic drugs on positive and negative symptoms: An analysis of the CATIE schizophrenia trial

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ABSTRACT

Second-generation antipsychotics are associated with moderate benefits in terms of improved schizophrenia symptoms, but also with higher rates of side-effects such as excessive weight gain (WG); a consensus on their efficacy has not been reached. To date, no study has evaluated the interplay of treatments and side-effects in a single framework, which is a critical step to clarify the role of side-effects in explaining the efficacy of these antipsychotics. We used recent methods for mediation and interaction to clarify the role of WG in explaining the effects of second-generation drugs on schizophrenia symptoms. We used data from 1460 participants in the CATIE trial, assigned to either perphenazine (first-generation comparison drug), olanzapine, quetiapine, risperidone, or ziprasidone. The primary outcome was an individual's score on the Positive and Negative Syndrome Scale (PANSS) for symptoms of schizophrenia after 9 months, separately evaluated as positive (PANSS+), negative (PANSS−), and total PANSS score. WG after 6 months was investigated as a potential mediator and effect modifier. Results showed that, by limiting WG, patients would benefit of a considerably better improvement in terms of PANSS symptoms. In the scenario of weight change being controlled between −2% and 1% for all participants, patients assigned to olanzapine would experience the highest significant improvements in both PANSS+ (−2.66 points; 95% CI: −4.98, −0.35), PANSS− (−1.59; 95% CI: −4.31, 1.14), and total PANSS (−6.11; 95% CI: −13.13, 0.92). In conclusion, occurrence of excessive WG hampers the potentially beneficial effects of second-generation antipsychotics, thus suggesting future directions for treatment and interventions.

1. Introduction

Antipsychotic drugs are a key treatment for patients with schizophrenia. The first generation of medications has been largely replaced by second-generation drugs, developed and approved in the '90s. Investigating the relative efficacy, safety, and effectiveness of these new-generation drugs has been the focus of several clinical trials and observational studies over the last decades (Leucht et al., 2013).

An important indicator to assess the efficacy of antipsychotic drugs is the improvement in positive and negative schizophrenia symptoms, commonly measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Improved scores on the PANSS scale have been associated with beneficial effects such as higher quality of life (Karow et al., 2005), and lower risk of hospitalization (Glick et al., 2015). However, these second-generation drugs are very heterogeneous both in terms of mechanisms, side-effects, and targeted outcomes. Despite most of the second-generation antipsychotics are designed to directly target and improve PANSS positive symptoms, studies have provided contrasting results with regards to these symptoms (Fusar-Poli et al., 2015; Lieberman et al., 2005; Rosenheck et al., 2006). In addition, second-generation antipsychotics have been subjected to critiques because of the high rate of side-effects, such as the potential higher rate of development of excessive weight gain (Lieberman et al., 2005; Meyer et al., 2008). Thus far, a consensus on

Abbreviations: CATIE, clinical antipsychotic trials of intervention effectiveness; CDE, controlled direct effect; PANSS, positive and negative syndrome scale; WG, weight gain.

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the relative efficacy and effectiveness of first and second-generation antipsychotics has not been reached (Leucht et al., 2013; Lieberman and Stroup, 2011).

The occurrence of metabolic side-effects such as excessive weight gain may hamper the performances of the drugs on their targeted outcomes. Excessive WG may interfere with the potentially positive effects of the treatments as it increases the risk of treatment discontinuation as a result of intolerability (Allison et al., 1999; Davis et al., 2009). As such, it is critical to evaluate the interplay of treatments and side-effects in a single framework, to clarify the role of these side-effects in explaining the observed efficacy of the treatments and potentially improving the care of the patients. To the best of our knowledge, no studies have attempted to quantify the efficacy of second-generation drugs in terms of improved PANSS score while simultaneously taking into account their effect on weight gain. Excessive weight gain may act both as a modifier, possibly antagonistically, of the treatment effects on PANSS score (i.e. symptoms improvement is different depending on the level of weight gain), and as a mediator of the treatment effect (i.e. weight gain is involved in the mechanism through which the drugs affect PANSS).

The aim of this paper is to apply recently developed methods in causal mediation and interaction analysis on data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) to clarify and quantify the role of weight gain in explaining the relative efficacy on PANSS score of second-generation drugs for the treatment of schizophrenia.

2. Methods

2.1. Study population

The CATIE Project Schizophrenia Trial was conducted between January 2001 and December 2004 at 57 clinical sites in the United States to compare the effectiveness of antipsychotic drugs. Details on rationale, design, and methods, have been largely described by previous publications (Stroup et al., 2003). In brief, participating patients were randomly assigned, under double-blind conditions, to receive perphenazine (first-generation comparison drug), olanzapine, quetiapine, or risperidone, and followed-up for up to 18 months or until treatment was discontinued for any reason. Ziprasidone was also added to the study, after one year, following its approval by the Food and Drug Administration (FDA). Patients whose assigned treatment was discontinued could receive other treatments in following phases. This study focuses on the first phase of the CATIE trial, which assumes an intent-to-treat analysis.

Inclusion criteria to the CATIE trial required participants to be 18 to 65 years of age; having received a diagnosis of schizophrenia, as determined on the basis of the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition; being able to take oral antipsychotic medication, as determined by the study doctor. Exclusion criteria included diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; history of serious adverse reactions to the proposed treatments; only one schizophrenic episode; history of treatment resistance; pregnant or breastfeeding; serious and unstable medical condition. In total, 1460 participants were included in the phase 1 of the CATIE study and were considered for the current analyses (Lieberman et al., 2005).

The study was approved by the institutional review board at each site, and written informed consent was obtained from the patients or their legal guardians.

2.2. Treatments

Patients were randomized into five groups: olanzapine (Zyprexa, Eli Lilly) (7.5 mg), quetiapine (Seroquel, AstraZeneca) (200 mg), risperidone (Risperdal, Janssen Pharmaceutica) (1.5 mg), perphenazine (Trilafon, Schering-Plough, at the time of the study) (8 mg), or (after January 2002) ziprasidone (Geodon, Pfizer) (40 mg). Randomization was stratified on diagnosis of tardive diskenesia and availability of ziprasidone. For this reason, the population we are here considering does not include patients with tardive diskenesia. All analyses evaluated in this paper assume an intent-to-treat analysis. For additional details on doses and administration procedures we refer to previous publications (Stroup et al., 2003).

2.3. Outcomes definitions

The primary outcome of this study was the individual PANSS score. This was evaluated as a total PANSS score, as well as a score in positive symptoms (PANSS+) and negative symptoms (PANSS−). Individual scores were assessed according to the standard criteria (Kay et al., 1987), with 7 items to detect excess or distortion of normal functions (PANSS+), and 7 items to detect diminution or loss of normal functions (PANSS−). Each item was scored from 1 to 7, thus yielding a total score ranging from 7 to 49, for both PANSS+ and PANSS−. The total PANSS score included 16 additional items summarizing general psychopathology behaviors, thus ranging from 30 to 210. For all three scales, higher score indicates more severe pathology. Weight gain, the secondary outcome that we considered in this study, was assessed at each study visit by the examining physician and is reported and evaluated as percent change from weight at baseline to weight at 6 months.

Both PANSS symptoms and weight data were collected at baseline and every three months into the study. For these analyses we used the performance in PANSS scores after 9 months, and percent weight gain after 6 months. This was done to ensure that weight gain (the mediator) temporally preceded PANSS scores (the outcomes) which would be required to causally interpret results from a mediation analysis.

2.4. Confounders

Potential baseline confounders evaluated in this study included: age (continuous, years); gender; race (categorical: white, black, others); marital status (yes vs no); employment status (yes vs no); education (continuous, years); systolic blood pressure (continuous); diastolic blood pressure (continuous); waist-hip circumference (continuous); total PANSS score at baseline (continuous); baseline weight (continuous, *lb*); number of previous hospitalization (continuous); previous use of antipsychotic (yes vs no).

Treatment randomization is expected to balance the treatment groups on most of the potential confounders. Nevertheless, when performing mediation analysis, randomization on the treatment does not assure that the same randomization will hold for the mediator (i.e. the association between the mediator and outcome will likely be confounded), even in expectation (Valeri and Vanderweele, 2013). For this reason, all statistical analyses we present are adjusted for the confounders listed above.

2.5. Statistical analysis

All analyses in this study were performed by pairwise comparison of each second-generation drug and perphenazine, a first-generation drug chosen as referent group in the CATIE study (Lieberman et al., 2005). To maximize efficiency and avoid bias, treatment comparisons were conducted on an analytic subsample of the population ($n = 1229$), described elsewhere (Stroup and Lieberman, 2010), which was obtained by only including subjects who had an equal chance of randomization to the treatments under comparison. We first estimated multivariable-adjusted treatment effects on PANSS+, PANSS−, and total PANSS score, using linear regressions. Multivariable-adjusted linear regression models were also used to estimate changes in percent weight gain between new-generation drugs and perphenazine. This main analysis was replicated in a sensitivity analysis by further adjusting for time under previous treatments.

We next investigated weight gain both as a possible effect modifier and as a mediator of treatment effects on PANSS scores. Effect modification occurs when the treatment effect on a given outcome varies over levels of a third variable, and it is commonly assessed by including an interaction term between the treatment and the third covariate in the statistical model (VanderWeele, 2009). Despite effect modifiers are generally identified among pre-treatment covariates (Kraemer et al., 2002), recent literature has discussed the interpretation and evaluation of post-treatment factors as potential effect modifiers of the exposure-outcome association (VanderWeele, 2014). In this paper we tested for effect modification of weight gain (i.e. whether antipsychotics effects on PANSS vary according to the amount of 6-months weight gain) by including interaction terms between second-generation treatments and weight gain in predicting PANSS scores.

While effect modification investigates the specific subgroups of participants for whom an effect is observed, mediation analysis evaluates the mechanisms explaining how these effects are produced. Specifically, mediation analysis was used to investigate the contribution of weight gain in the mechanism through which antipsychotic treatments affect PANSS score (Fig. 1). The underlying assumption of mediation analysis is that a certain proportion of the treatment effects on the outcome acts through an effect that is operated on weight gain, which in turn causes a change in the outcome (indirect effect); the remaining proportion is the treatment effect due to pathways independent of weight gain (direct effect) (Baron and Kenny, 1986). Several authors have suggested that mediation and effect modification can occur simultaneously, situation that can be taken into account be conducting mediation and interaction analysis within the counterfactual framework (Valeri and VanderWeele, 2013). Counterfactual effects are defined in terms of hypothetical interventions, as they estimate what the outcome would be had the exposure being set to a different value (Hernán, 2004). In mediation analysis, the interpretation of counterfactual direct and indirect effects requires this hypothetical intervention to be hypothesized on both the exposure and the mediator (Vanderweele, 2011). Moreover, by using a counterfactual approach it is possible to detect antagonistic effects of treatments and mediators (i.e. one prevents the outcome while the other causes it). Under this framework for causal inference, the total effect of the treatment on the outcome can be decomposed in a natural direct and natural indirect effect thorough the hypothesized mediator, accounting for treatment mediator interaction. An additional causal contrast of particular interest in our study is the controlled direct effect (CDE). Although the CDE cannot be used in general to decompose the total effect, it can provide information on treatment effects on the outcome, had the mediator been fixed to a specific value. In the presence of treatment mediator interaction, the controlled direct effect takes different values depending on the level at which the mediator is fixed. We estimated the CDEs of each second-generation drug on PANSS scores over quartiles of weight gain, that is, what the treatment effects on PANSS+, PANSS−, and total PANSS would be had hypothetical interventions been designed to fix weight gain at specific levels.

All analyses were performed with Stata (version 14; StataCorp), and all tests were two tailed.

3. Results

Table 1 presents the baseline characteristics of the study population stratified by levels of percent weight gain at 6 months from the beginning of the trial (quartiles of the weight gain distribution). An additional column is also displayed including those study participants with missing value on weight gain, that is, patients who dropped out the study within the first 6 months. The proportion of men was higher among those experiencing heavy weight loss or gain. Black or African American, participants with higher PANSS total score at baseline, and those with lower baseline weight, were more likely to experience weight gain. No substantial differences over quartiles of weight gain were observed for other covariates, nor between participants who dropped out and those who were still under treatment after 6 months. Baseline characteristics were also calculated by assigned treatment and are included as a Supplementary Table (Table S1).

3.1. PANSS scores

The average PANSS+, PANSS-, and total PANSS score, calculated after 9 months from the beginning of the study were, respectively, 15.4 ($sd = 5.27$), 18.6 ($sd = 6.0$), and 66.9 ($sd = 17.1$). Differences in PANSS score between second-generation drugs and perphenazine are shown in Table 2. Patients treated with olanzapine had lower PANSS score, but differences were moderate and non-significant (PANSS+: $\beta = -0.85$; 95% CI: −1.83, 0.12. PANSS−: $\beta = -0.67$; 95% CI: −1.78, 0.45. PANSS total: $\beta = -2.81$; 95% CI: −5.70, 0.09). Higher PANSS scores were only observed in patients assigned to the risperidone group (PANSS+: $\beta = 0.30$; 95% CI: −0.09, 0.69. PANSS−: $\beta = 0.10$; 95% CI: −0.29, 0.50. PANSS total: $\beta = 1.17$; 95% CI: 0.07, 2.26). No significant differences were observed when comparing perphenazine with quetiapine or ziprasidone. Changes were negligible when further adjusting these models for time under previous treatment (data not shown).

3.2. Weight gain

The average percent weight gain among patients in the perphenazine group was negligible (0.5%). Compared to this referent group, significantly higher percent weight gain was observed among participants assigned to olanzapine ($\beta = 3.65\%$, 95% CI: 2.42, 4.87), quetiapine ($\beta = 1.03\%$, 95% CI: 0.44, 1.62), and risperidone ($\beta = 0.58\%$, 95% CI: 0.22, 0.94) (Table 3). No differences in percent weight gain were observed between perphenazine and ziprasidone.

3.3. Effect modification and mediation

Results from the interaction analysis are presented in the Supplementary Material (Table S2), as no significant results were observed possibly due to a limited power of our sample. Coefficients associated with the interaction terms were positive in all statistical models, suggesting that weight gain may operate as an antagonist in the association between antipsychotic drugs and PANSS scores.

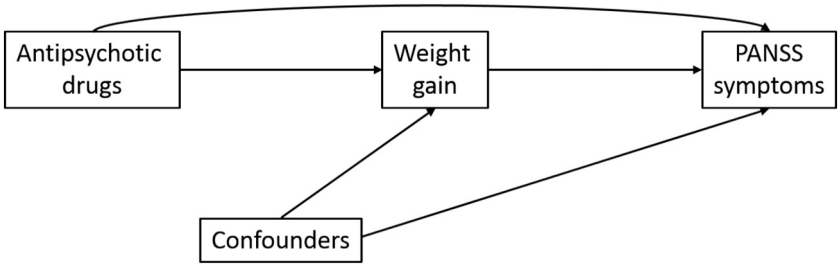

Fig. 1. Direct acyclic graph representing the potential role of weight gain as a mediator of the causal pathway through which antipsychotic drugs affect PANSS scores. Despite the randomization at the treatment level, this model requires taking into account potential confounders of the mediator-outcome association.

Table 1
Baseline characteristics of the study population by quartiles of percent weight gain after 6 months from the beginning of the study.

	Quartiles of percent weight gain after 6 months, % (median)					
	−18 to −2 (−4)	−2 to 1 (0)	1 to 4 (2)	4 to 19 (7)	Missing[a]	*p*-Value[b]
N	238	237	237	237	511	
Age, years (sd)	40.0 (10.9)	41.9 (10.3)	40.8 (10.5)	38.6 (11.3)	38.7 (11.0)	0.1
Female, n (%)	56 (24)	65 (27)	69 (29)	59 (25)	130 (25)	0.5
Race/ethnicity						0.2
White, n (%)	150 (63)	148 (63)	147 (62)	138 (58)	290 (57)	
Black or African American, n (%)	71 (30)	76 (32)	78 (33)	92 (39)	185 (95)	
Other, n (%)	17 (7)	12 (5)	11 (5)	7 (3)	25 (5)	
Educational years, mean (sd)	11.7 (3.5)	11.1 (3.9)	11.9 (2.9)	11.6 (3.6)	11.3 (3.6)	0.8
Married, n (%)	25 (11)	23 (10)	26 (11)	25 (11)	67 (13)	0.9
Employed, n(%)	17 (7)	15 (6)	15 (6)	12 (5)	38 (8)	0.8
Use of previous medication, n (%)	182 (76)	175 (74)	169 (71)	173 (73)	346 (68)	0.6
Systolic blood pressure, mmHg (sd)	125.4 (14.9)	125.5 (17.2)	124.0 (16.7)	124.3 (15.7)	124.2 (16.1)	0.2
Diastolic blood pressure, mmHg (sd)	80.2 (10.6)	78.7 (11.3)	78.4 (10.9)	78.9 (11.7)	78.5 (10.4)	0.1
Waist-hip ratio, mean (sd)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.1
N of previous hospitalization, mean (sd)	0.6 (1.1)	0.5 (0.8)	0.5 (0.9)	0.7 (0.9)	0.8 (1.1)	0.03
Total PANSS score, mean (sd)	72.0 (16.8)	74.6 (17.6)	75.4 (17.4)	78.3 (17.1)	76.8 (17.9)	<0.001
Total PANSS positive, mean (sd)	17.4 (5.4)	18.0 (5.5)	17.9 (5.6)	19.2 (5.3)	19.1 (5.8)	<0.001
Total PANSS negative, mean (sd)	19.7 (6.5)	20.1 (6.5)	20.4 (6.6)	20.8 (6.3)	20.1 (6.3)	<0.001
Baseline weight, lb. (sd)	198.3 (51.7)	201.1 (46.5)	198.4 (48.8)	186.7 (45.1)	194.8 (44.8)	0.004

[a] Missing values on weight gain at 6 months imply that participants have dropped out the study within the first 6 months.
[b] Calculated with Pearson chi-squared test, for binary/categorical covariates, and as *p* for trend for continuous covariates.

We did not find any evidence of an association between weight gain and PANSS score (mediator-outcome associations), thus suggesting limited evidence of an indirect effect of antipsychotic drugs on PANSS score acting through changes in weight gain. Nevertheless, our regression analysis indicates a marginally significant weight gain-treatment interactions (Table S2) and results from the mediation model provided evidence of a CDE of the treatments, dependent on the value of weight gain (Table 4) due to a treatment-weight gain interaction. Coefficients reported in Table 4 can be interpreted as the effects of each second-generation antipsychotic relative to perphenazine on the outcome had the mediator been set to a specific value, and reflect the treatment effects, conditional on covariates. The relative improvement in PANSS scores among participants assigned to second-generation drugs would be considerably higher in the hypothetical scenario of all patients gaining <1% of weight. In this scenario, patients assigned to olanzapine would experience improvement in both PANSS+ (CDE = −2.66; 95% CI: −4.98, −0.35), PANSS- (CDE = −1.59; 95% CI: −4.31, 1.14), and total PANSS (CDE = −6.11; 95% CI: −13.13, 0.92). The relative improvement in PANSS scores among participants assigned to second-generation drugs would be antagonized by weight gain in the hypothetical scenario of all patients gaining >1% of weight. As we observe in Table 4 in the hypothetical scenario of all participants experiencing weight gain (1 to 4%), all second-generation drugs would show negative performances, with higher PANSS+ scores up to 4 points for patients assigned to quetiapine (CDE = 3.85; 95% CI: 1.09, 6.60). Results in the >4% categories are in the same direction but have very broad confidence intervals. We therefore can conclude based on the stratified analyses (Table 4) along with the interaction analyses (Table 2) that there is suggestive evidence that increase in weight in the long term can reduce the beneficial effect of the antipsychotics, however additional studies powered to test this antagonistic effect should be pursued.

Table 2
Differences in PANSS+ score, PANSS- negative score, and PANSS total score after 9 months, between perphenazine and new-generation treatments, with 95% Confidence Interva.

	PANSS positive score	PANSS negative score	PANSS total score
Olanzapine	−0.85 (−1.83, 0.12)	−0.67 (−1.78, 0.45)	−2.81 (−5.70, 0.09)
Quetiapine	0.58 (0.02, 1.15)	−0.22 (−0.84, 0.39)	0.93 (−0.70, 2.56)
Risperidone	0.30 (−0.09, 0.69)	0.10 (−0.29, 0.50)	1.17 (0.07, 2.26)
Ziprasidone	−0.04 (−0.43, 0.35)	0.05 (−0.36, 0.46)	0.54 (−0.59, 1.67)
Perphenazine	Ref	Ref	Ref

All models adjusted for age, gender, race, education years, number of previous hospitalizations, systolic BP, diastolic BP, waist-hip ratio, employment status, marital status, PANSS total at baseline, use of previous medication, baseline weight.

4. Discussion

In this paper we found that the effects of second-generation antipsychotics in terms of improved positive and negative symptoms are potentially dependent on the eventual occurrence of excessive weight gain during the course of treatment. By using recent developments in the field of causal interaction and mediation, we could quantify the extent of such interplay between treatment and side effects. In the hypothetical scenario where interventions aimed at controlling weight gain within a normal range (−2 to 1%) were implemented, olanzapine would provide the highest benefits, with improvements of ~3 points in the positive symptoms scale, ~2 points in the negative, and ~6 points in the total symptoms scale.

Since the introduction of second-generation antipsychotics in the '90s, several observational and clinical studies have attempted to elucidate their efficacy and effectiveness in comparison both to placebo and to first-generation drugs (Leucht et al., 2013). The CATIE Project Schizophrenia Trial has played a critical role in evaluating and understanding the performances of these second-generation drugs (Stroup and Lieberman, 2010). Results from the first phase of CATIE showed that perphenazine, a common first-generation drug chosen as referent group, was similar in effectiveness to most of the new treatments (Lieberman et al., 2005). These findings were in contrast with the original belief that second-generation drugs were superior in terms of both performances and safety (Heres et al., 2006; Lewis and Lieberman,

Table 3
Multivariable adjusted differences in percent weight gain after 6 months, between perphenazine and new-generation treatments, with 95% Confidence Intervals.

Olanzapine	3.65 (2.42, 4.87)
Quetiapine	1.03 (0.44, 1.62)
Risperidone	0.58 (0.22, 0.94)
Ziprasidone	0.00 (−0.44, 0.43)
Perphenazine	Ref

All models adjusted for age, gender, race, education years, n of previous hospitalizations, systolic BP, diastolic BP, waist-hip ratio, employment status, marital status, PANSS total at baseline, use of previous medication, baseline weight.

Table 4
Differences in PANSS+, PANSS−, and total PANSS score at 9 months over treatment groups (perphenazine vs new-generation treatments, in four scenarios defined by hypothetical interventions to fix weight gain at 6 months at different predefined levels, with 95% Confidence Intervals.

Outcome	Level of weight gain	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Perphenazine
PANSS+	less than −2%	−0.55 (−2.59, 1.50)	0.80 (−1.57, 3.16)	−0.11 (−2.71, 2.48)	−0.87 (−3.99, 2.26)	Ref
	−2% to 1%	−2.66 (−4.98, −0.35)*	−0.82 (−3.36, 1.72)	0.69 (−1.91, 3.29)	−2.49 (−5.97, 1.00)	Ref
	1% to 4%	0.69 (−1.60, 2.98)	3.83 (1.13, 6.54)*	2.00 (−0.67, 4.66)	2.35 (−1.48, 6.19)	Ref
	>4%	0.22 (−1.94, 2.37)	2.24 (−0.51, 4.98)	1.86 (−0.99, 4.72)	1.63 (−2.64, 5.90)	Ref
PANSS−	less than −2%	−0.50 (−2.91, 1.91)	−0.85 (−3.42, 1.72)	−0.15 (−2.82, 2.53)	1.18 (−2.17, 4.53)	Ref
	−2% to 1%	−1.59 (−4.31, 1.14)	−1.02 (−3.79, 1.74)	0.75 (−1.93, 3.43)	−1.02 (−4.75, 2.72)	Ref
	1% to 4%	−0.77 (−3.47, 1.93)	−0.27 (−3.21, 2.68)	−0.81 (−3.57, 1.94)	0.37 (−3.74, 4.48)	Ref
	>4%	−0.35 (−2.88, 2.19)	−0.51 (−3.49, 2.48)	1.59 (−1.36, 4.53)	−0.17 (−4.74, 4.41)	Ref
PANSS total	less than −2%	−2.39 (−8.58, 3.81)	−0.03 (−7.02, 6.94)	2.41 (−5.01, 9.82)	2.40 (−6.67, 11.46)	Ref
	−2% to 1%	−6.11 (−13.13, 0.92)	−2.73 (−10.23, 4.77)	4.76 (−2.67, 12.19)	−4.26 (−14.38, 5.85)	Ref
	1% to 4%	−1.28 (−8.23, 5.68)	6.06 (−1.93, 14.06)	2.54 (−5.08, 10.16)	7.98 (−3.15, 19.11)	Ref
	>4%	−0.36 (−6.89, 6.17)	4.14 (−3.96, 12.24)	5.30 (−2.85, 13.46)	1.44 (−10.95, 13.84)	Ref

All models adjusted for age, gender, race, education years, n of previous hospitalizations, systolic BP, diastolic BP, waist-hip ratio, employment status, marital status, PANSS total at baseline, use of previous medication, baseline weight.
*Indicate statistically significant results (p value < 0.05).

2008), and elucidated a somewhat complex mechanism of action (Lieberman and Stroup, 2011). For example, with regards to positive and negative symptoms, the standard measure of schizophrenia severity (Kay et al., 1987), results from the first phase of CATIE only suggested a beneficial effect of second-generation drugs, which later diminished over time (Lieberman et al., 2005). Among the drugs that were evaluated, olanzapine has been claimed to be the most effective antipsychotic medication, despite lacking any statistically significant advantage over perphenazine (Davis et al., 2009). A major concern with second-generation antipsychotics is the high rate of metabolic side-effects (Allison et al., 1999; Daumit et al., 2008; Leucht et al., 2013; Wetterling, 2001), which increase the risk of treatment discontinuation thus limiting the potential efficacy and effectiveness of the drugs (Kilzieh et al., 2008). Olanzapine, in particular, has been associated with the most adverse metabolic effects, especially in terms of weight gain, and highest discontinuation rate as a result of intolerability (Allison et al., 1999; Lieberman et al., 2005). Different studies have suggested that the effectiveness of second-generation antipsychotic may be hampered by the high rates of medication self-discontinuation in outpatient practice settings (Centorrino et al., 2012; Hermes et al., 2011; Kilzieh et al., 2008), advocating the need of individualized treatments (Centorrino et al., 2004; Lieberman and Stroup, 2011). On the other hand, other studies have not supported the finding that reduced weight gain is associated with clinical improvements (Raben et al., 2018). Notably, most of the studies reported in a recent review (Raben et al., 2018) conduct simple correlation analyses, which could lead to unmeasured confounding bias, and only 6 out of the 37 studies adjusted for confounders of the weight-gain – symptoms relationships, such as treatment dose. Furthermore, treatment-weight gain interaction is rarely investigated, which could lead to model misspecification bias.

To take into account the complex effects of antipsychotic and clarify the relative efficacy and effectiveness of second-generation drugs, it is critical to investigate the interplay of treatment and side effects over the course of treatment. To the best of our knowledge, no study has attempted to investigate the effects of second-generation antipsychotic on schizophrenia outcomes within a methodological framework that simultaneously accounts for the side-effects.

By taking into account the development of excessive weight gain over the course of treatment, we documented clinically relevant differences in the performances of all second-generation drugs evaluated in the CATIE study on reducing positive and negative symptoms. Results from our mediation and interaction analysis show that the moderate non-significant benefits observed in the overall sample would be strongly improved in the hypothetical scenario of all participants avoiding excessive weight gain or loss, especially among patients treated with olanzapine. The only exception was observed in the comparison between perphenazine and risperidone, where the second-generation drug had worse performances independently on weight gain. These results indicate that a continuous weight gain monitoring on schizophrenia patients undergoing any antipsychotic treatment is critical to identify optimal individual regimes. By controlling excessive weight gain, olanzapine, and to a certain extent quetiapine and ziprasidone, are superior in terms of improved positive and negative symptoms, with potential beneficial effects for the future health and quality of life of the patients. These improvements would meet the clinical relevance criteria as defined by Hermes et al. with regards to positive and negative symptoms improvements (Hermes et al., 2012). We observed the highest improvement in positive symptoms, as compared to negative and total symptoms. This is not surprising as second-generation drugs are designed to target positive symptoms and are hypothesized to affect negative symptoms only through indirect pathways (Glick et al., 2015; Lieberman et al., 2005). The potential biological mechanisms connecting weight gain and PANSS scores, and how these can influence antipsychotics effects are not clear and debatable. A recent review (Raben et al., 2018) discussed several studies and identified potential metabolic parameters that may play an important role such as insulin, leptin, and serum lipids. Nevertheless, they largely concluded that the link between therapeutic benefits and metabolic health remains unclear, underlying the need of additional studies.

Our analysis represents a novel approach for jointly evaluating the interplay of antipsychotic treatments and side-effects in explaining efficacy outcomes. By using recently developed methods for causal mediation and interaction analysis we could investigate and formally test the contribution of weight gain in explaining treatment effects on positive and negative symptoms. Techniques involving mediation approaches have been originally proposed in the '80s and used in different settings including clinical trials (Baron and Kenny, 1986; Kraemer et al., 2002). However, the classical approach to mediation analysis is subjects to important limitations such as the inability of allowing for potential interactions between the mediator and the treatment (Valeri and VanderWeele, 2013). In the context of antipsychotic drugs, the reportedly complex operating mechanisms may likely be due to the presence of both interactive and mediating mechanisms. Treatment-mediator interactions can be accommodated by conducting mediation and interaction analysis within a counterfactual approach (VanderWeele, 2015). For example, in our study we could simultaneously investigate weight gain as an effect modifier and mediator of the treatment effects.

Effects estimated within the counterfactual approach to mediation analysis can be interpreted in causal terms. For example, the CDEs reported in this paper illustrate what the effect of the drug would be had a hypothetical intervention fixed the mediator (i.e. weight gain) to a specific value (Pearl, 2001; Robins and Greenland, 1992; VanderWeele, 2013). In our example, we observed that, conditional on the covariates, treatment effects are only detected among those

whose weight only changed within a limited range (around −2% and 1%). This finding has relevant clinical implications as it suggests that in case of developing excess weight gain or loss the superiority of new-generation antipsychotic is not anymore evident, and might support the clinician in identifying targeted individual treatments. Two assumptions are required for this interpretation of CDEs to hold: i) no unmeasured confounding of the treatment-outcome association and ii) no unmeasured confounding of the mediator-outcome association (Vanderweele, 2011). While treatment randomization will likely assure that assumption i) is met, the same does not apply for assumption ii). To limit the possibility of residual confounding we included in our statistical models several potential confounders of the mediator-outcome association. In addition, the temporal ordering of treatment (baseline), mediator (weight gain at 6 months), and outcome assessment (PANSS score at 9 months), are a crucial feature to strengthen the causal interpretation of our results (VanderWeele and Vansteelandt, 2009). Additional strengths of the study are large size of the CATIE trial and its broad inclusion criteria that increase the generalizability of the results.

The main limitation of this study is that an intent-to-treat analysis was assumed. Future studies should assess the impact of treatment discontinuation and adherence on our results and how these are related to weight gain, as switching antipsychotic is a common practice with relevant effects on efficacy and effectiveness (Essock et al., 2006; Stroup et al., 2007). This could lead to a certain degree of confounding-by-indication, as patients with more weight gain may be more likely to switch treatment. The rate of treatment switching can be influenced by baseline covariates such as medication and time under medication at baseline (Essock et al., 2006), and patients in different antipsychotic groups might have been on the same antipsychotic to which they were randomized for. Such factors should be thoroughly investigated by future studies. Another potential limitation is due to the fact that responders who were more likely to stay on the assigned treatment for a longer period of time also had longer time to gain weight, thus potentially weakening the causal interpretation of our findings. Our estimates often presented a large variability, which prevented several effects to reach statistical significance. However, this is most likely due to the fact that mediation and interaction analysis require greater power than conventional statistical models for detecting significant treatment effects (Greenland, 1983; Vittinghoff et al., 2009). It is important for future studies to incorporate questions on mediation and interaction from the phase of study design, identifying the required sample size to detect significant interactions or indirect effects. Finally, further developments in mediation analysis have provided the framework to evaluate multiple mediators and interactions (VanderWeele and Vansteelandt, 2014). These approaches could be used to further include and investigate the contribution of other metabolic or neurological side-effects in the evaluated scenario, and to investigate and incorporate the biological and social mechanisms through which antipsychotic drugs affect weight gain, and weight gain affects PANSS score in turns.

In conclusion, we found that the effects of second-generation drugs for the treatments of schizophrenia in terms of improved positive and negative symptoms are potentially influenced by the eventual occurrence of excessive weight gain over the course of treatment, which significantly differs among drugs. The benefits of these drugs, and in particular of olanzapine, would be largely improved and be clinically relevant if interventions and recommendations aimed at controlling weight gain were implemented. This study has the potential to improve the identification of optimal individualized antipsychotic regimes, with future benefits on the well-being of the patient.

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Conflict of interest

Nothing to declare.

CRediT authorship contribution statement

Andrea Bellavia: Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Franca Centorrino:** Conceptualization, Investigation, Writing - review & editing. **John W. Jackson:** Writing - review & editing. **Garrett Fitzmaurice:** Writing - review & editing. **Linda Valeri:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing - review & editing.

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