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Pharmacological Strategies to Counteract Antipsychotic-Induced Weight Gain and Metabolic Adverse Effects in Schizophrenia: A Systematic Review and Meta-analysis

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Background: **Antipsychotic-induced metabolic adversities are often difficult to manage. Using concomitant medications to counteract these adversities may be a rational option.** ***Objective:*** **To systematically determine the effectiveness of medications to counteract antipsychotic-induced metabolic adversities in patients with schizophrenia.** ***Data Sources:*** **Published articles until November 2013 were searched using 5 electronic databases. Clinical trial registries were searched for unpublished trials.** ***Study Selection:*** **Double-blind randomized placebo-controlled trials focusing on patients with schizophrenia were included if they evaluated the effects of concomitant medications on antipsychotic-induced metabolic adversities as a primary outcome.** ***Data Extraction:*** **Variables relating to participants, interventions, comparisons, outcomes, and study design were extracted. The primary outcome was change in body weight. Secondary outcomes included clinically relevant weight change, fasting glucose, hemoglobin A1c, fasting insulin, insulin resistance, cholesterol, and triglycerides.** ***Data Synthesis:*** **Forty trials representing 19 unique interventions were included in this meta-analysis. Metformin was the most extensively studied drug in regard to body weight, the mean difference amounting to −3.17 kg (95% CI: −4.44 to −1.90 kg) compared to placebo. Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine were also different from placebo. Furthermore, metformin and rosiglitazone improved insulin resistance, while aripiprazole, metformin, and sibutramine decreased blood lipids.** ***Conclusion:*** **When nonpharmacological strategies alone are insufficient, and switching antipsychotics to relatively weight-neutral agents is not feasible, the literature supports the use of concomitant metformin as first choice among pharmacological interventions to counteract antipsychotic-induced weight gain and other metabolic adversities in schizophrenia.**

Key words: antipsychotic/meta-analysis/metabolic/concomitant/PRISMA/schizophrenia

Introduction

Antipsychotics can cause numerous side effects, including weight gain and metabolic derangements that are often difficult to manage; using concomitant medications to counteract these adversities may be a rational option. However, data are still limited regarding effective medications to counteract antipsychotic-induced metabolic adversities in schizophrenia. In an early report, Faulkner et al[1] reviewed 18 randomized trials, which assessed the effects of adjunctive medications to counter weight gain in patients with schizophrenia. Despite identifying trials showing positive results for reboxetine and topiramate, and mixed results for sibutramine, nizatidine, and amantadine, based on the paucity of data, the authors concluded that adjunctive medications should be reserved for patients in which nonpharmacological strategies alone are inadequate. In a more recent report, Maayan et al[2] performed a systematic review and meta-analysis on the effectiveness of add-on medications used to attenuate antipsychotic-induced weight gain and metabolic abnormalities. The authors concluded that metformin, D-fenfluramine, sibutramine, topiramate, and reboxetine significantly attenuated weight gain. Of note, this important work had some limitations: Study populations

were heterogeneous regarding psychiatric diagnosis, combinations of antipsychotics aiming at the reduction of metabolic adversities were excluded, and unpublished trials were not included. In the latest systematic review and meta-analysis on pharmacological interventions for antipsychotic-induced and mood stabilizer–induced weight gain, Fiedorowicz et al[3] concluded that metformin and topiramate were superior to placebo. Although this work updated the available evidence and reviewed a wider range of medications including combinations of antipsychotics, similar limitations can be pointed out: Study populations were heterogeneous regarding diagnosis, unpublished trials were not searched, and the number of trials included was limited to 32.

To our best knowledge, following the review by Fiedorowicz et al,[3] 10 double-blind randomized controlled trials (total n = 578) using concomitant drugs to counteract antipsychotic-induced metabolic adversities in patients with schizophrenia have been published, including first reports on reboxetine-betahistine combinations[4] and zonisamide.[5] To update the available evidence regarding this clinical relevant topic, we undertook a systematic review and meta-analysis regarding the effectiveness of add-on medications to counteract a wide range of antipsychotic-induced metabolic derangements, with a specific focus on patients with schizophrenia.

Methods

A study protocol was prepared before commencing data collection (supplementary appendix). The PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[6] was followed to ensure transparent and complete reporting. Two independent authors (Y.M. and H.U.) undertook the search, assessed eligibility, and extracted data. Any discrepancies during these procedures were resolved through discussion.

Search

Published articles from 1950 to November 5, 2013 were searched without language restrictions using EMBASE, MEDLINE, PsycINFO, PubMed, and the Cochrane Library. Search terms included synonyms of schizophrenia, combination treatment, metabolic derangements, and the names of medications previously reviewed by Maayan et al.[2] (supplementary appendix). Limits were set for "clinical trials" and "humans" where applicable. References of relevant articles were hand-searched for additional articles. Furthermore, unpublished studies were searched in clinical trial registries (http://clinicaltrials.gov/) using the term "schizophrenia" and synonyms of combination treatment, with a limit to "interventional studies."

Selection Criteria

Studies were included if (1) they were double-blind randomized placebo-controlled trials using concomitant medications to counteract antipsychotic-induced metabolic adversities, (2) a majority of subjects had a diagnosis of schizophrenia or related psychotic disorders according to study diagnoses, and (3) they reported on changes of metabolic adversities as a primary outcome. We included combinations of antipsychotics if a second antipsychotic was used specifically to treat a metabolic adversity of the primary antipsychotic drug. If several publications were found from the same investigators using overlapping samples, we included data with the longest duration, the most detailed information, and/or data that were most relevant to our primary outcome (ie, weight gain).

Outcome Parameters

The primary outcome was defined as changes in weight gain at endpoint. As secondary outcomes, we extracted data on the following: clinically relevant weight change as defined in individual studies (eg, 7% or more weight loss), fasting glucose, hemoglobin A1c (HbA1c), fasting insulin, the homeostasis model of assessment of insulin resistance (HOMA-IR), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Intention-to-treat (ITT) datasets were used whenever available.

Data Analysis

Prior to the meta-analysis, risk of bias of the included studies were assessed using the Cochrane Risk of Bias Tool.[7] When 2 or more studies were present per intervention, meta-analyses were performed using Review Manager, version 5.2.5 (The Cochrane Collaboration, http://ims.cochrane.org/revman). For continuous outcomes, mean differences were calculated using the inverse variance statistical method and random effects model to adjust for study heterogeneity. Unreported SD values were supplemented using procedures described in the supplementary appendix. Two-sided 95% CIs were used to assess significance, according to whether the CIs included the null value. For dichotomous outcomes, the Mantel-Haenszel statistical method and random effects model were used to calculate ORs. Furthermore, the number needed to treat (NNT) was calculated using equations described in the supplementary appendix.[8] Study heterogeneity was quantified using the I^2 statistic[9] with I^2 ≥50% indicating significant heterogeneity. The possibility of publication bias was assessed using funnel plots.[10] Finally, for the primary outcome, we conducted subgroup and sensitivity analyses according to a priori defined study characteristics: (1) prevention vs treatment, (2) inpatients vs outpatients, (3) first-episode

patients vs others, and (4) studies reporting SD values vs studies in which SD values were supplemented. Any additional, exploratory analyses that were performed were fully reported.

Results

Included Studies

Fifty double-blind randomized placebo-controlled trials (41 published,[4,5,11–49] 8 unpublished [Eli Lilly and Company; University of North Carolina, Chapel Hill; University of Maryland; Mclean Hospital; Nathan Kline Institute for Psychiatric Research; Orexigen Therapeutics, Inc.; University of Massachusetts, Worcester; GW Pharmaceuticals Ltd—unpublished data], and 1 article in press,[50] respectively) were included in the review (figure 1). The article in press was provided by one of our coauthors (W.W.F.). The total numbers of randomized subjects were $N = 2298$, 363, and 15 for published, unpublished, and in press studies, respectively.

Study characteristics are summarized in table 1, with reference to participants, interventions, comparisons, outcomes, and study design. Mean ± SD duration of randomized interventions was 12.2 ± 4.7 weeks (range: 4–24 weeks), and numbers of randomized subjects amounted to 54 ± 42 (range: 2–207). Studies were conducted in North America ($n = 19$) (Eli Lilly and Company; University of North Carolina, Chapel Hill; University of Maryland; Mclean Hospital; Nathan Kline Institute for Psychiatric Research; Orexigen Therapeutics, Inc.;

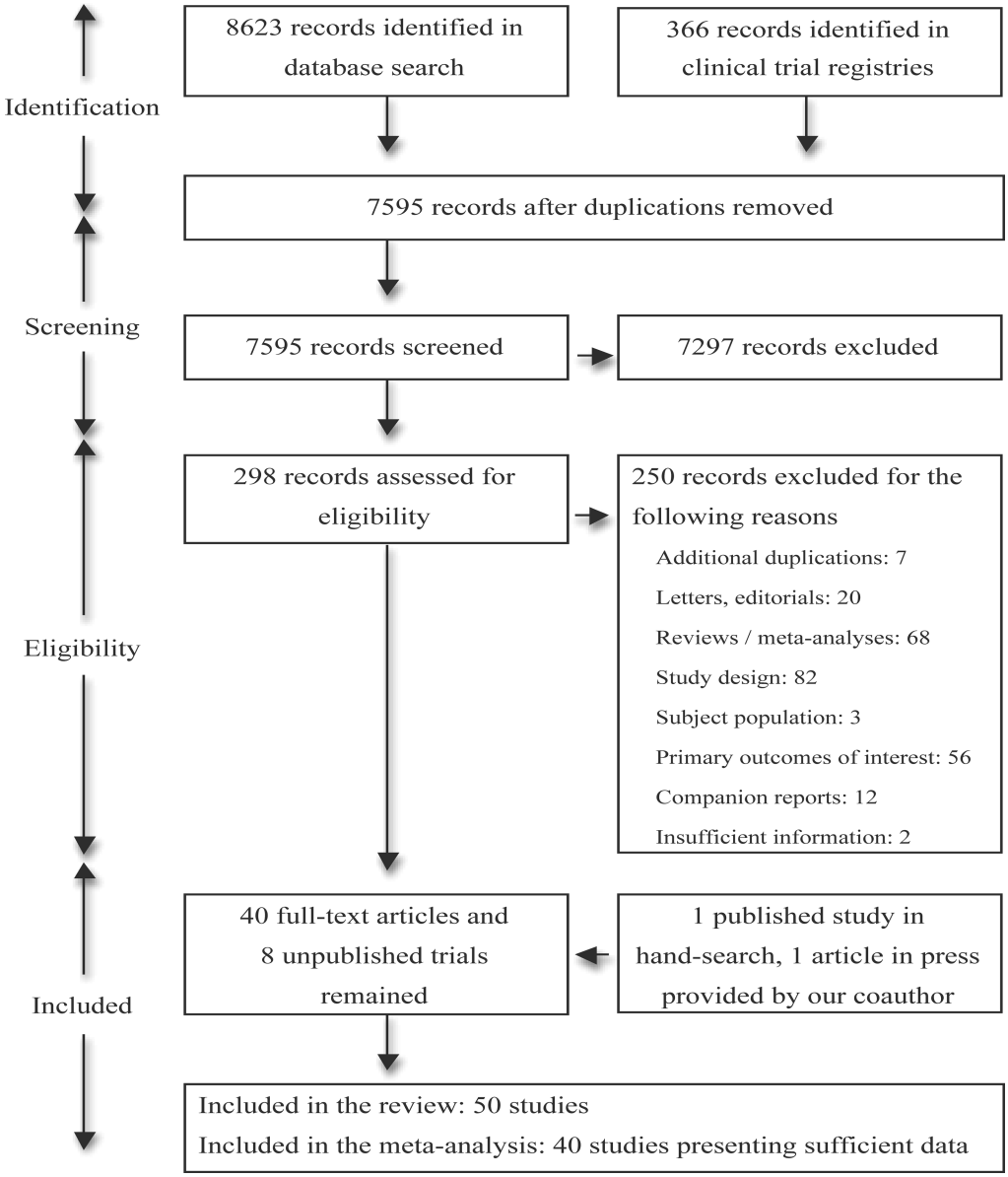


Fig. 1. Literature search results and study eligibility for meta-analysis.

Table 1. Characteristics of Included DBRCTs

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
Amantadine						
Deberdt et al (2005)[11]	8	- Inpatients and outpatients, 55% with schizophrenia and related disorders, 45% with bipolar I disorder - Previous weight gain ≥5%	OLZ	Amantadine 100–300 mg	60/52	Effects on body weight
				Placebo	65/59	
Graham et al (2005)[12]	12	- Outpatients, 86% with schizophrenia and related disorders, 14% with bipolar disorder - Previous weight gain ≥5 lb	OLZ	Amantadine up to 300 mg	12/9	Effects on BMI
				Placebo	9/9	
Aripiprazole						
Henderson et al (2009)[13]	10 (4 wk of each Tx with 2-wk interval)	- Outpatients with schizophrenia or schizoaffective disorder - Previous BMI ≥30 or BMI ≥27 with other metabolic risk factors	OLZ	Aripiprazole 15 mg	15/14 (crossover)	Effects on body weight, lipids, glucose metabolism, and psychopathology
				Placebo		
Fleischhacker et al (2010)[14]	16	- Outpatients with schizophrenia - Previous weight gain ≥2.5 kg	CLZ	Aripiprazole 5–15 mg	108/97	Effects on body weight
				Placebo	99/93	
Fan et al (2013)[15]	8	- Outpatients with schizophrenia or schizoaffective disorder	CLZ	Aripiprazole 15 mg	20/16	Effects on glucose metabolism using the frequently sampled intravenous glucose tolerance test
				Placebo	18/14	
Atomoxetine						
Ball et al (2011)[16]	24	- Outpatients with schizophrenia or schizoaffective disorder - Previous weight gain of ≥7%	OLZ, CLZ, or CLZ + RIS	Atomoxetine 40–120 mg	20/14	Effects on body weight
				Placebo	17/12	
D-Fenfluramine						
Goodall et al (1988)[17]	12	- Outpatients, 97% with schizophrenia or schizoaffective disorder (diagnostic criteria unspecified) - Receiving depot antipsychotics - Previous BMI ≥27	FPZ, FPX, or CPX	D-Fenfluramine 30 mg	17/9	Effects on body weight
				Placebo	16/7	
Dextroamphetamine						
Modell et al (1965)[18]	16 (8 wk of Tx, no Tx 4 wk before/ after)	- Male inpatients with schizophrenia (diagnostic criteria unspecified)	Thioridazine, chlorpromazine, imipramine, or chlordiazepoxide	Dextroamphetamine 5 mg	10/10	Effects on body weight and appetite

Table 1. (Continued)

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
				Placebo	10/10	
Famotidine						
Poyurovsky et al (2004)[19]	6	- Inpatients with first-episode schizophrenia or schizophreniform disorder	OLZ	Famotidine 40 mg	7/7	Effects on body weight
				Placebo	7/7	
Fluoxetine						
Poyurovsky et al (2002)[20]	8	- Inpatients with first-episode schizophrenia	OLZ	Fluoxetine 20 mg	15/11	Effects on body weight
				Placebo	15/13	
Bustillo et al (2003)[21]	16	- Outpatients with schizophrenia or schizoaffective disorder - Previous weight gain of ≥3%	OLZ	Fluoxetine 20–60 mg	15/11	Effects on body weight
				Placebo	15/9	
Intranasal insulin						
Li et al (2013)[22]	8	- Outpatients with schizophrenia or schizoaffective disorder	54% OLZ, 46% other antipsychotics	Intranasal insulin 160 IU	21/18	Effects on body composition and lipid particle sizes using whole body dual-energy X-ray absorptiometry and nuclear magnetic resonance spectroscopy
				Placebo	24/21	
Metformin						
Baptista et al (2006)[23]	14	- Inpatients with schizophrenia or schizoaffective disorder	OLZ	Metformin 850–1700 mg	20/19	Effects on body weight
				Placebo	20/18	
Baptista et al (2007)[24]	12	- Inpatients and outpatients, 95% with schizophrenia, 5% with bipolar disorder	OLZ	Metformin 850–2550 mg	40/36	Effects on body weight
				Placebo	40/36	
Arman et al (2008)[25]	12	- Inpatients with schizophrenia or schizoaffective disorder	RIS	Metformin 1000 mg	49 recruited, 16 completers in each group	Effects on body weight
		- Age <20		Placebo		
Wu et al (2008)[26]	12	- Outpatients with first-episode schizophrenia	CLZ, OLZ, RIS, or SLP	2×2 design of:	32/30	Effects on body weight, BMI, waist circumference, glucose, insulin, and HOMA-IR
		- Previous weight gain of >10%		- Lifestyle intervention [+]/[−]	32/29	
				- Metformin 750 mg/ placebo	32/30	

Table 1. (Continued)

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
					32/29	
Wu et al (2008)[27]	12	- Inpatients with first-episode schizophrenia	OLZ	Metformin 750 mg	20/18	Effects on body weight, BMI, waist circumference, waist-to-hip ratio, glucose, insulin, >7% gain in body weight, and HOMA-IR
				Placebo	20/19	
Carrizo et al (2009)[28]	14	- Outpatients, 96% with schizophrenia or schizophreniform disorder	CLZ	Metformin 500–1000 mg	31/24	Effects on body weight
				Placebo	30/30	
Wang et al (2012)[29]	12	- Outpatients with first-episode schizophrenia - Previous weight gain of >7%	CLZ, OLZ, RIS, or SLP	Metformin 1000 mg	36/32	Effects on body weight
				Placebo	36/34	
Wu et al (2012)[30]	24	- Female outpatients with first-episode schizophrenia	CLZ, OLZ, RIS, or SLP	Metformin 1000 mg	42/39	Effects on amenorrhea and body weight
		- Experiencing amenorrhea with antipsychotic Tx		Placebo	42/37	
Chen et al (2013)[31]	24	- Inpatients/outpatients with schizophrenia or schizoaffective disorder	CLZ	Metformin 1500 mg	28/28	Effects on body weight and metabolic features
		- Previous BMI ≥24 or having ≥1 defined metabolic abnormality		Placebo	27/27	
Jarskog et al (2013)[32]	16	- Outpatients with schizophrenia or schizoaffective disorder	Various antipsychotics including CLZ and OLZ	Metformin 1000–2000 mg	75/58	Effects on body weight
		- Previous BMI ≥27		Placebo	73/58	
Metformin-sibutramine combination						
Baptista et al (2008)[33]	12	- Inpatients with schizophrenia	OLZ	Metformin 850–1700mg and sibutramine 10–20 mg	15/13	Effects on body weight, BMI, and waist circumference
				Placebo	15/15	
Modafinil						
Sudhakar et al (2008)[34]	12	- Inpatient/outpatient status undescribed, 57% with schizophrenia	CLZ, OLZ, or RIS	Modafinil 200 mg	36/32	Effects on body weight and daytime drowsiness
		- On atypical antipsychotics for <2 wk		Placebo	36/31	
Nizatidine						
Atmaca et al (2003)[35]	8	- Inpatients and outpatients with schizophrenia	OLZ	Nizatidine 300 mg	18/17	Effects on body weight and leptin

Table 1. (Continued)

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
		- Previous weight gain of >2.5 kg		Placebo	17/17	
Cavazzoni et al (2003)[36]	16	- Inpatients/outpatients with schizophrenia, schizoaffective disorder or schizophreniform disorder	OLZ	Nizatidine 300 mg/600 mg	57/35	Effects on body weight
				Placebo	58/33 60/37	
Atmaca et al (2004)[37]	8	- Inpatient/outpatient status undescribed	QTP	Nizatidine 300 mg	14/13	Effects on body weight and leptin
		- Schizophrenia patients with "considerable weight gain"		Placebo	14/12	
Assunção et al (2006)[38]	12	- Outpatients with schizophrenia, schizoaffective disorder, or schizophreniform disorder	OLZ	Nizatidine 600 mg	27 randomized to each group, 45 subjects completed	Effects on body weight
		- Previous weight gain of ≥5%		Placebo		
Orlistat						
Joffe et al (2008)[39]	16	- Inpatients/outpatients with "serious mental conditions" (diagnostic criteria unspecified)	CLZ or OLZ	Orlistat 360 mg	35/28	Effects on body weight
				Placebo	36/29	
Phenylpropanolamine						
Borovicka et al (2002)[40]	12	- Outpatients with treatment intolerant or resistant schizophrenia	CLZ	Phenylpropanolamine 75 mg	8/6	Effects on body weight
		- Previous weight gain of >10%		Placebo	8/6	
Reboxetine						
Poyurovsky et al (2003)[41]	6	- Inpatients with first-episode schizophrenia	OLZ	Reboxetine 4 mg	13/10	Effects on body weight
				Placebo	13/10	
Poyurovsky et al (2007)[42]	6	- Inpatients with first-episode schizophrenia	OLZ	Reboxetine 4 mg	31/22	Effects on body weight
				Placebo	28/19	
Reboxetine-betahistine combination						
Poyurovsky et al (2013)[4]	6	- Inpatients with schizophrenia or schizophreniform disorder	OLZ	Reboxetine 4 mg and Betahistine 48 mg	29/22	Effects on body weight
		- Predominantly first-episode patients		Placebo	14/10	
Rosiglitazone						
Baptista et al (2009)[43]	12	- Inpatients with schizophrenia	OLZ	Rosiglitazone 4–8 mg	15/14	Effects on body weight, waist circumference, HOMA-IR, HbA1c, and serum lipid levels
				Placebo	15/15	
Henderson et al (2009)[44]	8	- Outpatients with schizophrenia or schizoaffective disorder	CLZ	Rosiglitazone 4 mg	8/8	Effects on HOMA-IR

Table 1. (Continued)

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
		- Previously showing insulin resistance or impaired glucose metabolism		Placebo	10/10	
Sibutramine						
Henderson et al (2005)[45]	12	- Outpatients with schizophrenia or schizoaffective disorder - Previous BMI ≥30 or BMI ≥27 with other defined risk factors	OLZ	Sibutramine 5–15 mg Placebo	19/16 18/15	Effects on body weight
Henderson et al (2007)[46]	12	- Outpatients with schizophrenia or schizoaffective disorder - Previous BMI ≥30 or BMI ≥27 with other defined risk factors	CLZ	Sibutramine 5–15 mg Placebo	11/10 10/8	Effects on body weight
Biedermann (in press)[50]	24	- Outpatients with schizophrenia - Previous weight gain of >7% or BMI >27	Various antipsychotics including CLZ	Sibutramine 10 mg Placebo	7/5 8/5	Effects on body weight
Topiramate						
Ko et al (2005)[47]	12	- Inpatients with schizophrenia - Previous BMI ≥25	RIS, OLZ, QTP, or CLZ	Topiramate 200 mg/100 mg Placebo	66 recruited, 17, 16, and 20 completers in each group	Efficacy and tolerability as a weight-controlling agent
Afshar et al (2009)[48]	8	- Outpatients with schizophrenia - Poor clinical outcome despite Tx with several antipsychotics	CLZ	Topiramate 50–300 mg Placebo	16 randomized to each group, numbers of dropouts are unclear	Efficacy and tolerability as an adjuvant to CLZ
Narula et al (2010)[49]	12	- Inpatients and outpatients with first-episode schizophrenia	OLZ	Topiramate 50–100 mg Placebo	36/34 36/33	Effects on body weight and biochemical/ metabolic abnormalities
Zonisamide						
Ghanizadeh et al (2013)[5]	10	- Outpatients, and inpatients close to discharge - Schizophrenia	Various antipsychotics including CLZ and OLZ	Zonisamide 50–100 mg Placebo	21/19 20/20	Effects on BMI and body weight
Sibutramine						
NCT00044187 (Eli Lilly and Company, unpublished data)	Unspecified	- Schizophrenia, schizophreniform disorder, schizoaffective disorder, and bipolar I disorder	OLZ	Sibutramine (dose unreported)	Estimated enrollment: 130	Effects on body weight (no data)

Table 1. (Continued)

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
				Placebo	Study completed	
Amantadine						
NCT00287352 (University of North Carolina, Chapel Hill, unpublished data)	16	- First-episode psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, and mood disorders with psychotic features	OLZ	Amantadine 300 mg	Enrollment: 40	Effects on percentages of body fat, fat utilization, and other metabolic profiles (no data)
				Placebo	Study completed	
Rimonabant						
NCT00547118 (University of Maryland, unpublished data)	16	- Clinically stable inpatients and outpatients with schizophrenia or schizoaffective disorder	Second-generation antipsychotics (details undescribed)	Rimonabant 20 mg	16 in total	Effects on body weight, metabolic parameters, cardiovascular disease risk, and food satiety (no data)
		- Previous BMI ≥30 or BMI ≥27 with hyperlipidemia/hypertriglyceridemia		Placebo	Study terminated	
Naltrexone						
NCT00567034 (Mclean Hospital, unpublished data)	12	- Schizophrenia or schizoaffective disorder	OLZ	Naltrexone 50 mg	Estimated enrollment: 52	Effects on body weight and BMI (no data)
		- Previous BMI ≥30 or BMI ≥27 with symptoms of the metabolic syndrome		Placebo	Recruitment status unknown	
Betahistine						
NCT00709202 (Nathan Kline Institute for Psychiatric Research, unpublished data)	12	- Adolescents/young adults with schizophrenia and related psychotic disorders, bipolar disorder, autism	CLZ, OLZ, RIS or QTP	Betahistine 8–24 mg	Estimated enrollment: 40	Effects on body weight and BMI (no data)
		- Previous weight gain of >2%		Placebo	Recruitment status unknown	
Zonisamide SR						
NCT00734435 (Orexigen Therapeutics, Inc., unpublished data)	16	- Outpatients with schizophrenia, schizoaffective disorder, or schizophreniform disorder	OLZ	Zonisamide SR 360 mg	Enrollment: 26	Effects on body weight (no data)
				Placebo	Study terminated	

Table 1. (Continued)

Concomitant Drug/ Study (Year)	Duration (wk)	Study Population	Primary Antipsychotic	Intervention Groups (Daily Dose)	*n*, Randomized/ Completed[a]	Defined Primary Outcome
Telmisartan						
NCT00981526 (University of Massachusetts, Worcester, unpublished data)	12	- Outpatients with schizophrenia or schizoaffective disorder	CLZ or OLZ	Telmisartan 40–80 mg	Enrollment: 57	Effects on insulin resistance and fasting triglycerides (no data)
				Placebo	Study completed	
GWP42003:GWP42004 (40:1)						
NCT01491490 (GW Pharmaceuticals Ltd., unpublished data)	6	- Schizophrenia, schizophreniform disorder, or acute psychosis with schizophrenia symptoms	OLZ	GWP42003:GWP42004 (40:1)	Enrollment: 2	Effects on body weight
				Placebo	Study terminated	

Notes: BMI, body mass index (kg/m^2); CLZ, clozapine; CPX, clopenthixol decanoate; DBRCT, double-blind randomized controlled trial; HOMA-IR, homeostasis assessment for insulin resistance model (fasting insulin [10^3 μIU/l] × fasting glucose [mmol/l]/22.5); FPX, flupenthixol decanoate; FPZ, fluphenazine decanoate; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SLP, sulpiride; SR, sustained release; Tx, treatment.
[a]Numbers of randomized/completed subjects do not always match the numbers of subjects included in the analysis.

University of Massachusetts, Worcester—unpublished data),[12,13,15,16,18,21,22,32,40,44–46] Middle-East Asia (n = 10),[4,5,19,20,25,35,37,41,42,48] East Asia (n = 6),[26,27,29–31,47] South America (n = 6),[23,24,28,33,38,43] Europe (n = 4) (GW Pharmaceuticals Ltd, unpublished data),[17,39,50] and South Asia (n = 2),[34,49] while one study was a multicontinental investigation.[14] Recruitment locations were unreported in 2 studies.[11,36] Regarding sources of funding, 18 studies (36%) received direct financial or material support from pharmaceutical companies (Eli Lilly and Company; University of North Carolina, Chapel Hill; Orexigen Therapeutics, Inc.; GW Pharmaceuticals Ltd—unpublished data),[11,14,16,18,24,28,33,34,36,38,39,41,46,50] 8 studies (16%) had unclear roles of funding,[17,19,25,35,37,47–49] and 5 studies (10%) received investigator-initiated grants from pharmaceutical companies.[12,13,21,22,45] The remaining studies did not have direct support from industry (University of Maryland; Mclean Hospital; Nathan Kline Institute for Psychiatric Research; University of Massachusetts, Worcester—unpublished data).[4,5,15,20,23,26,27,29–32,40,42–44,46]

The effects of 20 and 8 unique interventions were investigated in published and unpublished trials, respectively. Medications used were the following: amantadine (total number of studies n = 2, total number of randomized subjects n = 146),[11,12] aripiprazole (n = 3, n = 260),[13–15] atomoxetine (n = 1, n = 37),[16] D-fenfluramine (n = 1, n = 33),[17] dextroamphetamine (n = 1, n = 20),[18] famotidine (n = 1, n = 14),[19] fluoxetine (n = 2, n = 60),[20,21] intranasal insulin (n = 1, n = 45),[22] metformin (n = 10, n = 757),[23–32] metformin-sibutramine combination (n = 1, n = 30),[33] modafinil (n = 1, n = 72),[34] nizatidine (n = 4, n = 292),[35–38] orlistat (n = 1, n = 71),[39] phenylpropanolamine (n = 1, n = 16),[40] reboxetine (n = 2, n = 85),[41,42] reboxetine-betahistine combination (n = 1, n = 43),[4] rosiglitazone (n = 2, n = 48),[43,44] sibutramine (n = 3, n = 73),[45,46,50] topiramate (n = 3, n = 170),[47–49] and zonisamide (n = 1, n = 41).[5] Unpublished studies used sibutramine (Eli Lilly and Company, unpublished data), amantadine (University of North Carolina, Chapel Hill, unpublished data), rimonabant (University of Maryland, unpublished data), naltrexone (Mclean Hospital, unpublished data), betahistine (Nathan Kline Institute for Psychiatric Research, unpublished data), zonisamide (Orexigen Therapeutics, Inc., unpublished data), telmisartan (University of Massachusetts, Worcester, unpublished data), and GWP42003:GWP42004 (40:1; GW Pharmaceuticals Ltd, unpublished data).

Thirty-seven studies (74%) used concomitant drugs as a treatment for preexisting metabolic adversities, while 13 studies (26%) initiated adjunctive medications simultaneously with antipsychotics in an effort to prevent such derangements. Forty-nine studies described the primary antipsychotic used; most studies included subjects using either clozapine or olanzapine (n = 45, 91.8%), while 4 studies (8.2%) investigated subjects who used neither of these drugs. Forty studies reported data on changes in body weight, while 21 and 16 studies reported

additional outcomes related to glucose metabolism and lipids, respectively. Two published studies[34,48] did not report sufficient data and thus were excluded from the meta-analysis. Moreover, none of the unpublished trials reported sufficient data to include in the meta-analysis: 7 studies (Eli Lilly and Company; University of North Carolina, Chapel Hill; University of Maryland; Mclean Hospital; Nathan Kline Institute for Psychiatric Research; Orexigen Therapeutics, Inc.; University of Massachusetts, Worcester—unpublished data) reported no data, and 1 study (GW Pharmaceuticals Ltd, unpublished data) reported data from only 2 subjects.

Risk of Bias

Risks of bias of the included studies are summarized in supplementary table 1. Although all studies were randomized trials, the methodology of random sequence generation and allocation concealment were often unreported, leading to "unclear risk" for selection bias in 40 studies (80%). Similarly, blinding of outcome assessors was often unspecified, resulting in "unclear risk" for detection bias in 34 studies (68%). In general, dropout cases were adequately explained, and data from ITT analyses were reported; only 7 studies (14%) had "high risk" for attrition bias for reasons including unbalanced dropouts between groups and reporting of completers analysis only. Six studies (12%) did not report full data on secondary outcomes and were judged to have "high risk" of selective reporting. For other bias, 3 reports (6%) did not specify the diagnostic criteria used and were judged to have "high risk" regarding study diagnoses. Taken together, only 6 studies (12%) showed a "low risk" for bias in all assessment criteria.

Meta-analyses

Effects on Body Weight. Forty published studies representing 19 unique interventions reported data on changes in body weight (table 2). One study each, investigating nizatidine[36] and topiramate,[47] compared 2 different doses of active drugs with placebo; thus, placebo groups were included twice for these studies, in order to investigate a potential dose-effect relationship. Furthermore, Wu et al[26] compared the effects of concomitant metformin to placebo in combination with or without lifestyle interventions, resulting in analyses of 2 sets of groups. Hence, the meta-analysis for effects on body weight consisted of 43 (ie, 40 + 3) comparisons between active drugs and placebo, and 76 (ie, 56 + 20)[36,47] more subjects in the placebo groups than actually recruited.

The results of the meta-analyses are displayed in table 2. Eight interventions (ie, aripiprazole, D-fenfluramine, metformin, reboxetine, reboxetine-betahistine combination, sibutramine, topiramate, and zonisamide) showed significant effects compared to placebo; of note, there was only one study each for D-fenfluramine,[17] the reboxetine-betahistine combination,[4] and zonisamide.[5] Metformin was the most extensively studied drug, both regarding the number of studies and randomized subjects (n = 10, n = 757). This was followed by nizatidine (n = 4, n = 292) and aripiprazole (n = 3, n = 260).

Meta-analysis of 10 studies investigating the effects of metformin yielded a significant mean difference of −3.17 kg (95% CI: −4.44 to −1.90 kg) compared to placebo (figure 2a). However, the results were heterogeneous (I^2 = 88%), with a mixture of 3 negative[23–25] and 7 positive studies.[26–32] Most studies focused on adult patients who were, at least in part, treated with either clozapine or olanzapine; the exception was a negative trial in which the participants were adolescents receiving risperidone.[25]

Four trials investigating the effects of nizatidine on body weight showed mixed results;[35–38] the mean difference was not different from placebo (figure 2b). Again, the results were shown to be highly heterogeneous (I^2 = 97%).

Three studies reported on effects of add-on aripiprazole as a weight-controlling agent; the mean difference amounted to −2.13 kg (95% CI: −2.87 to −1.39 kg) compared to placebo (figure 2c). In a multicontinental investigation of 207 patients with schizophrenia who were receiving stable doses of clozapine, a significant weight loss was observed in those randomized to adjunctive aripiprazole.[14] The remaining 2 studies were relatively small ($n \leq 30$), with one study each showing positive[13] and negative results.[15]

Among the remaining 16 interventions, sibutramine (n = 73) had 3 publications, while the following had 2 publications each: topiramate (n = 170), amantadine (n = 146), reboxetine (n = 85), fluoxetine (n = 60), and rosiglitazone (n = 48). Of these, pooled effects of topiramate, reboxetine, and sibutramine were superior to placebo.

Trials using the following medications were reported in one publication each: orlistat (n = 63), zonisamide (n = 41), intranasal insulin (n = 39), atomoxetine (n = 37), dextroamphetamine (n = 20), D-fenfluramine (n = 16), phenylpropanolamine (n = 16), and famotidine (n = 14). Of these, studies using zonisamide and D-fenfluramine showed positive results. Ghanizadeh et al[5] reported modest but significant effects of zonisamide to decrease body weight in patients treated with various antipsychotics. Another trial performed by Li et al[22] was the only study employing a nonoral form (intranasal insulin) of medication; however, no benefits were observed regarding body weight. Goodall et al[17] were the only group to examine the effects of weight-modifying agents in subjects receiving depot antipsychotics; D-fenfluramine showed significant weight reduction compared to placebo.

Two studies investigated the synergetic effects of "polypill" to counteract weight gain. Baptista et al[33] investigated the efficacy of a metformin-sibutramine combination on weight gain; weight reduction in the combination group was numerically higher but nonsignificant. Poyurovsky

Table 2. Effects of Concomitant Drugs on Body Weight (kg), Results of 40 Studies, and Meta-analyses of 19 Interventions

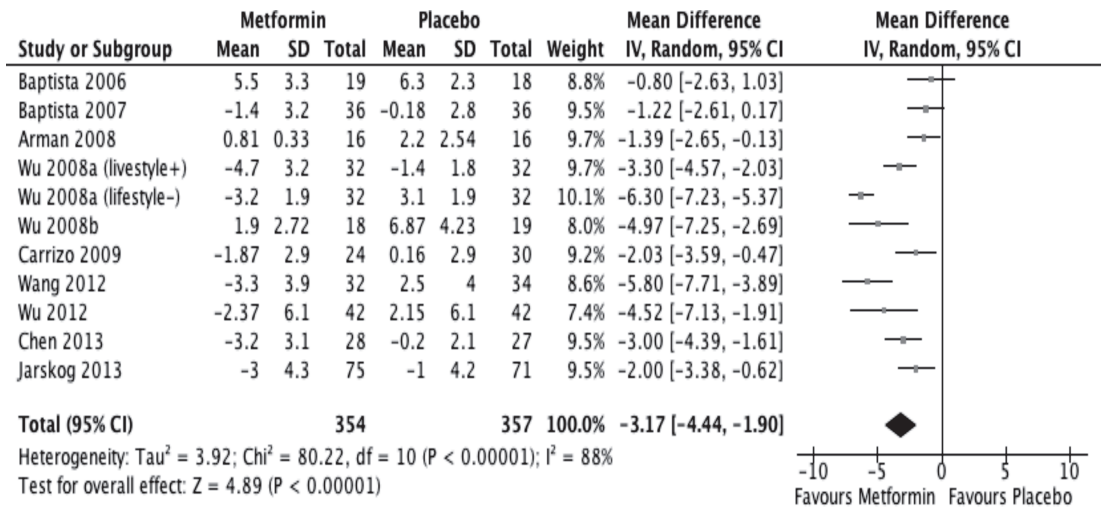
Concomitant Drug/Study	*n*, Analyzed		Mean ± SD Change at Endpoint (kg)		Mean Difference (95% CI) (kg)	I^2 (%)
Author (Year)	Active Drug	Placebo	Active Drug	Placebo		
Amantadine (*N* = 2)						
Deberdt et al (2005)[11]	59	64	**−0.19 ± 4.58**	**1.28 ± 4.26**	−2.27 (−4.76, 0.23)	40
Graham et al (2005)[12]	12	9	**−0.4 ± 3.5**	**3.9 ± 5.3**		
Aripiprazole (*N* = 3)						
Henderson et al (2009)[13]	15	15	**−1.3 ± 2.1**	**1.0 ± 1.5**	**−2.13 (−2.87, −1.39)**	0
Fleischhacker et al (2010)[14]	107	99	**−2.53 ± 3.9**[a]	**−0.38 ± 3.9**[a]		
Fan et al (2013)[15]	16	14	−1.5 ± 2.3	0.3 ± 2.3		
Atomoxetine (*N* = 1)						
Ball et al (2011)[16]	19	17	−1.7 ± 6.1[b]	−2.1 ± 5.8[b]	—	—
D-Fenfluramine (*N* = 1)						
Goodall et al (1988)[17]	9	7	**−5.4 ± 3.4**	**−2.8 ± 1.65**	—	—
Dextroamphetamine (*N* = 1)						
Modell et al (1965)[18]	10	10	0.9 ± 4.3	0.1 ± 2.3	—	—
Famotidine (*N* = 1)						
Poyurovsky et al (2004)[19]	7	7	4.8 ± 3.2	4.9 ± 1.6	—	—
Fluoxetine (*N* = 2)						
Poyurovsky et al (2002)[20]	15	15	6.1 ± 5.3	5.9 ± 4.6	0.75 (−1.76, 3.26)	0
Bustillo et al (2003)[21]	15	15	3.0 ± 5.3[c]	1.7 ± 4.6[c]		
Intranasal Insulin (*N* = 1)						
Li et al (2013)[22]	18	21	0.8 ± 1.9	−2.8 ± 9.6	—	—
Metformin (*N* = 10)						
Baptista et al (2006)[23]	19	18	5.5 ± 3.3[d]	6.3 ± 2.3[d]	**−3.17 (−4.44, −1.90)**	88
Baptista et al (2007)[24]	36	36	−1.40 ± 3.2	−0.18 ± 2.8		
Arman et al (2008)[25]	16	16	0.81 ± 0.33	2.2 ± 2.54		
Wu et al (2008) lifestyle [+][26]	32	32	**−4.7 ± 3.2**[e]	**−1.4 ± 1.8**[e]		
Wu et al (2008) lifestyle [−][26]	32	32	**−3.2 ± 1.9**[e]	**3.1 ± 1.9**[e]		
Wu et al (2008)[27]	18	19	**1.9 ± 2.72**	**6.87 ± 4.23**		
Carrizo et al (2009)[28]	24	30	**−1.87 ± 2.9**	**0.16 ± 2.9**		
Wang et al (2012)[29]	32	34	**−3.3 ± 3.9**[e]	**2.5 ± 4.0**[e]		
Wu et al (2012)[30]	42	42	**−2.37 ± 6.1**[f]	**2.15 ± 6.1**[f]		
Chen et al (2013)[31]	28	27	**−3.2 ± 3.1**	**−0.2 ± 2.1**		
Jarskog et al (2013)[32]	75	71	**−3.0 ± 4.3**[e]	**−1.0 ± 4.2**[e]		
Metformin-sibutramine combination (*N* = 1)						
Baptista et al (2008)[33]	13	15	−2.8 ± 3.2	−1.4 ± 2.6	—	—
Nizatidine (*N* = 4)						
Atmaca et al (2003)[35]	17	17	**−4.5 ± 2.2**	**2.3 ± 0.9**	−2.03 (−4.53, 0.47)	97
Cavazzoni et al (2003)[36]; 600 mg	57	56	3.29 ± 5.33	4.18 ± 4.33		
Cavazzoni et al (2003)[36]; 300 mg	56	56	3.56 ± 4.95	4.18 ± 4.33		
Atmaca et al (2004)[37]	14	14	−1.0 ± 0.6	1.2 ± 1.2		
Assunção et al (2006)[38]	27	27	1.1 ± 0.6[g]	0.7 ± 1.2[g]		
Orlistat (*N* = 1)						
Joffe et al (2008)[39]	31	32	−1.25 ± 4.33	0.44 ± 3.73	—	—

Table 2. (Continued)

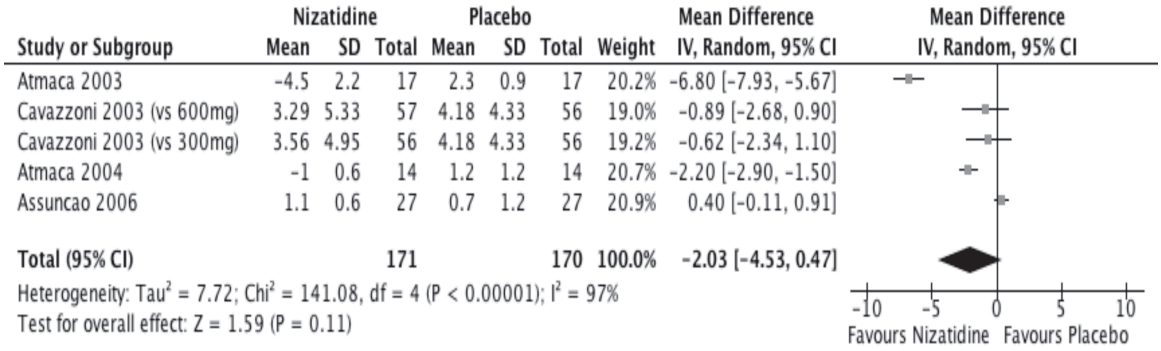
Concomitant Drug/Study	*n*, Analyzed		Mean ± SD Change at Endpoint (kg)		Mean Difference (95% CI) (kg)	I^2 (%)
Author (Year)	Active Drug	Placebo	Active Drug	Placebo		
Phenylpropanolamine (*N* = 1)						
Borovicka et al (2002)[40]	8	8	1.36 ± 21.8[h]	1.36 ± 16.6[h]	—	—
Reboxetine (*N* = 2)						
Poyurovsky et al (2003)[41]	10	10	**2.45 ± 2.72**	**5.45 ± 3.09**	**−1.90 (−3.07, −0.72)**	0
Poyurovsky et al (2007)[42]	31	28	**3.31 ± 2.73**	**4.91 ± 2.45**		
Reboxetine-betahistine combination (*N* = 1)						
Poyurovsky et al (2013)[4]	29	14	**2.02 ± 2.37**	**4.77 ± 3.16**	—	—
Rosiglitazone (*N* = 2)						
Baptista et al (2009)[43]	14	15	3.2 ± 4.5	2.2 ± 2.3	0.26 (−1.83, 2.35)	0
Henderson et al (2009)[44]	8	10	−0.5 ± 4.5[i]	0.5 ± 2.3[i]		
Sibutramine (*N* = 3)						
Henderson et al (2005)[45]	19	18	**−3.8 ± 1.1**	**−0.8 ± 0.7**	**−2.86 (−4.72, −1.01)**	49
Henderson et al (2007)[46]	10	8	−1.9 ± 3.0[b]	−0.5 ± 2.2[b]		
Biedermann (in press)[50]	5	6	**−6.1 ± 6.7**	**1.9 ± 3.5**		
Topiramate (*N* = 2)						
Ko et al (2005)[47]; 200 mg	17	20	**−5.45 ± 13.1**[j]	**−0.3 ± 13.1**[j]	**−5.20 (−9.55, −0.84)**	0
Ko et al (2005)[47]; 100 mg	16	20	−1.68 ± 13.1[j]	−0.3 ± 13.1[j]		
Narula et al (2010)[49]	33	34	**−1.27 ± 13.1**[f]	**6.03 ± 13.1**[f]		
Zonisamide (*N* = 1)						
Ghanizadeh et al (2013)[5]	21	20	**−1.1 ± 1.4**	**1.9 ± 2.2**	—	—

Notes: Statistically significant effects compared to placebo are shown in bold.
SD values were supplemented using the following methods:
[a]Calculated from 95% CIs of mean group difference.
[b]Calculated from SEs of within group difference.
[c]Imputed from Poyurovsky et al (2002)[20].
[d]Additional data were provided by the authors.
[e]Calculated from 95% CIs of within group difference.
[f]Calculated from *t* values of between group difference.
[g]Imputed from Atmaca et al (2004)[37].
[h]Calculated from SEs measured in figures.
[i]Imputed from Baptista et al (2009)[43].
[j]Imputed from Narula et al (2010)[49].

a



b



c

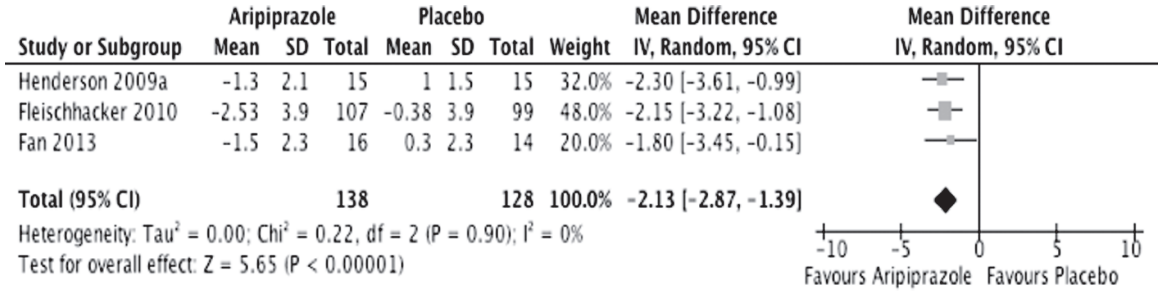


Fig. 2. Effects of metformin, nizatidine, and aripiprazole on body weight, mean difference (kg). (**a**) Metformin vs placebo. (**b**) Nizatidine vs placebo. (**c**) Aripiprazole vs placebo. IV, inverse variance. For each comparison, the small square represents the mean difference, and the horizontal line is the 95% CI. The diamonds represent the overall weighted mean differences. The width of the diamonds represents their 95% CI.

et al[4] reported significant preventive effects of a reboxetine-betahistine combination on olanzapine-induced weight gain in comparison to placebo.

Subgroup and Sensitivity Analysis

In regard to body weight, the mean differences of trials performed in all a priori defined subgroups were different from placebo (supplementary figures 1–3). The mean difference of studies recruiting first-episode patients was especially large, amounting to −3.52 kg (95% CI: −4.93 to −2.11 kg) compared to placebo. To address whether first-episode patients would derive larger benefits in prevention trials, an exploratory subgroup analysis separating prevention studies into those recruiting first-episode patients vs others was performed; studies recruiting

first-episode patients yielded a numerically larger mean difference of −2.41 kg (95% CI: −3.82 to −1.01 kg) (supplementary figure 4).

Subgroup analyses were also performed on the 10 metformin trials and 4 nizatidine trials to investigate reasons for heterogeneity (supplementary figures 5–6). An a priori defined subgroup analysis dividing metformin trials into those recruiting first-episode patients vs others decreased the heterogeneity in both subgroups to I^2 = 73% and 5%, respectively. In an additional, exploratory sensitivity analysis, a single comparison combining comprehensive lifestyle interventions with metformin[26] was removed from the subgroup of first-episode trials; this decreased the heterogeneity to I^2 = 0%. Similarly, reasons for heterogeneity in the nizatidine trials were investigated; however, a priori defined subgroup analyses did not decrease the degree of heterogeneity. In an exploratory sensitivity analysis, the first published study[35] which had an outlier effect size was excluded; however, heterogeneity still remained high at I^2 = 91%.

Finally, in an a priori defined sensitivity analysis, trials reporting SD values were analyzed separately from those in which unreported SD values were supplemented; mean differences remained significant in both groups (supplementary figure 7). Likewise, we examined the mean differences of metformin, nizatidine, aripiprazole, and sibutramine trials that reported SD values; the conclusions regarding their pooled effects remained largely the same, with exception to sibutramine which became nonsignificant (supplementary figure 8).

Publication Bias

Funnel plots of studies investigating the effects of concomitant metformin, nizatidine, and aripiprazole with respect to body weight are shown in supplementary figure 9. Asymmetry was observed among the metformin studies with smaller sample sizes, indicating a possibility of publication bias. Furthermore, all 8 unpublished trials reported insufficient data, suggesting a possibility of publication bias.

Clinically Relevant Weight Change

A limited number of studies presented data on percentages of clinically relevant weight change; 8 and 9 studies reported on weight loss and weight gain, respectively (supplementary tables 2–3). Cutoff points were defined as ≥7% change in body weight in most studies. All studies reporting on clinically relevant weight loss were treatment studies; aripiprazole (n = 1) and metformin (n = 4) showed significant effects compared to placebo, with a NNT of 9 and 3, respectively. In contrast, 7 of 9 studies reporting on clinically relevant weight gain were prevention studies. Metformin (n = 2), reboxetine (n = 2), and the reboxetine-betahistine combination (n = 1) were effective in preventing 7% or more weight gain, with a NNT of 10, 7, and 4, respectively.

Effects on Glucose Metabolism

Effects of concomitant medications on fasting glucose, HbA1c, fasting insulin, and HOMA-IR are displayed in supplementary tables 4–7. Metformin and topiramate significantly decreased fasting glucose levels, but the latter finding was supported by a single study.[49] Pooling of a limited number of studies for aripiprazole[13,15] and metformin[24,28,32] resulted in a significant mean difference in HbA1c levels. In contrast, 9 and 8 metformin trials reported data on changes in fasting insulin and HOMA-IR, respectively; relatively consistent and robust effects were observed compared to placebo.

Effects on Blood Lipids

Changes in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are shown in supplementary tables 8–11. Pooling of 5 trials[23,24,28,31,32] showed significant effects of metformin to improve triglycerides, while 3 aripiprazole trials[13–15] resulted in significant mean differences for total cholesterol and LDL cholesterol. Two sibutramine studies[45,46] also yielded a significant mean difference in total cholesterol. Only one study presented data in the context of clinical significance[31]: When applying the diagnostic criteria for metabolic syndrome, metformin was effective in reversing hypertriglyceridemia, but ineffective in enhancing HDL cholesterol.

Discussion

By pooling the effects of 40 studies representing 19 unique interventions with regard to body weight, we found concomitant metformin to be supported by the evidence, with a mean difference of −3.17 kg (95% CI: −4.44 to −1.90 kg) compared to placebo. Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine were also significant. Interventions were effective in all a priori defined subgroups, while first-episode patients may derive the most benefit. Patients receiving metformin were more likely to achieve clinically relevant weight loss in treatment trials, and less likely to experience clinically relevant weight gain in prevention trails, although the limited number of reports should be noted. The limited data with respect to glucose metabolism and lipids suggest that metformin and rosiglitazone improve insulin resistance, while aripiprazole, metformin, and sibutramine decrease cholesterol and triglyceride levels.

Obesity is prevalent among patients with schizophrenia,[51–53] which can lead to various medical complications.[54–57] Moreover, many antipsychotics precipitate

weight gain,[58–60] thereby increasing risks for metabolic complications. In this context, when the use of nonpharmacological interventions alone are insufficient, and switching antipsychotics to relatively weight-neutral agents is not feasible (eg, treatment-resistant patients receiving clozapine), pharmacological strategies to counteract these metabolic adversities need to be considered. In such instances, the use of adjunctive metformin appears to be the first choice, as positive effects on body weight, insulin resistance, and lipids have been consistently reported. A weight loss of −3.17 kg, albeit modest, may have clinically meaningful long-term benefits such as reduced risk of hypertension[61] and diabetes[62]; however, such consequences will need replication in patients with schizophrenia.

The paucity of data regarding the genetic background, which affect response to medications that alleviate metabolic adversities, leaves an important question. For example, Fernández et al[63] reported that specific genetic polymorphisms in the leptin promoter and leptin receptor genes were related to a blunted response to metformin in clozapine-treated patients. In a secondary analysis of the same patient group, they failed to find associations between peroxisome proliferator-activated receptor gamma 2 (PPAR-γ2) genotypes and the response to metformin.[64] Future pharmacogenetic studies that control for sex and ethnicity in larger patient populations may identify subsets of patients who will benefit more from such pharmacological interventions.

Our findings align with the meta-analysis by Maayan et al[2]; we also found metformin, topiramate, reboxetine, and sibutramine to be effective in countering weight gain. Pooled effects on glucose metabolism and lipids were also similar with their report. In this updated report, we found effects of metformin to be supported by 4 additional studies (n = 359),[29–32] thereby strengthening confidence regarding its efficacy. Differing from their report, we identified 3 studies[13–15] investigating the effects of add-on aripiprazole, which resulted in modest but significant effects on weight gain, although such results should be interpreted in the context of risks and benefits of antipsychotic polypharmacy.[65] Furthermore, our results align with the meta-analysis by Fiedorowicz et al.[3] Similar to their conclusions, we found metformin and topiramate to be effective in countering weight gain, despite our meta-analysis having different numbers of studies included due to an updated search and different inclusion criteria. Moreover, while their report included a single study that examined the effectiveness of add-on aripiprazole to counter antipsychotic-induced weight gain,[14] the present report identified 2 additional studies (n = 53),[13,15] thereby enabling a meta-analysis. Differing from our report, Fiedorowicz et al meta-analyzed the effects of reboxetine[41,42] with atomoxetine[16] under the category of "norepinephrine reuptake inhibitors," in which mean differences were not different from placebo. Finally, their review concluded that the use of sibutramine could not be recommended, taken that the drug has been withdrawn from markets worldwide[66] due to evidence of increased risk of cardiovascular outcomes.[67] Although our meta-analysis of 3 studies[45,46,50] found sibutramine to be effective in regard to weight gain, and no serious adverse events were observed, we too caution its use in light of their potentially serious side effects.

Our results must be interpreted in light of various strengths and limitations. Although similar main conclusions were reached in previous reports,[2,3] our main strength was that we followed the PRISMA statement to ensure transparent and complete reporting. Also, our search covered a wide range of metabolic adversities in published and unpublished studies. Addition, our focus on patients with schizophrenia will better guide evidence-based clinical decision making in this population. The present report also has some limitations. Firstly, the sample sizes and numbers of studies for most types of interventions were limited, and long-term effects beyond 24 weeks have not been investigated. Secondly, our report focused on the effects of concomitant drugs, and although interventions were generally well tolerated, a possibility of rare or long-term adverse effects of concomitant medications should be considered. Thirdly, a possibility of pharmacokinetic interactions remains and we did not review the specific mechanisms by which concomitant drugs counteract antipsychotic-induced metabolic adversities. Fourth, although blinding of outcome assessors may not be essential for trials investigating hard outcomes, only 10% of the studies reviewed had a "low risk" of bias in all assessment criteria, and sources of bias should be taken into account. Fifth, although funnel plots were used and unpublished trials were searched, a possibility of publication bias cannot be ruled out. Sixth, our search was designed to identify an extensive list of relevant studies; nevertheless, a possibility remains that we were not able to identify all relevant studies. Seventh, more than 90% of the included studies described either clozapine or olanzapine as primary antipsychotics; thus, it is unclear if our results are generalizable to patients receiving other types of antipsychotics. Eighth, our focus on pharmacological interventions to counter metabolic adversities is not intended to undermine the importance of nonpharmacological interventions; indeed, combining both may have synergetic and greater effects.[26] Ninth, the application of our results to patients with other psychiatric disorders is cautioned. Finally, cost-effectiveness of concomitant drugs should also be taken into account. Moreover, the use of many agents included in this review entails off-label use.

We suggest that future studies should focus on long-term outcomes including potential consequences of metabolic adversities. Pharmacogenetic studies aiming to elucidate the individual responses to add-on medications are warranted. Finally, safety and tolerability of combination treatments should be given more attention. Notwithstanding these future tasks, the current literature suggests the use

of metformin to counteract antipsychotic-induced weight gain and metabolic derangements in schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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