Pharmacologic and Behavioral Interventions to Improve Cardiovascular Risk Factors in Adults With Serious Mental Illness: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Individuals with serious mental illness have high rates of cardiovascular disease (CVD) risk factors and mortality. This systematic review was conducted to evaluate pharmacologic and behavioral interventions to reduce CVD risk in adults with serious mental illness.

Data Sources: MEDLINE, EMBASE, PsycINFO, ClinicalTrials.gov, and Cochrane Database of Systematic Reviews were searched from January 1980 to July 2012 for English language studies. Examples of search terms used include *schizophrenia, bipolar disorder, antipsychotics, weight, glucose, lipid,* and *cardiovascular disease.*

Study Selection: Two reviewers independently screened citations and identified 33 randomized controlled trials of at least 2 months' duration that enrolled adults with serious mental illness and evaluated pharmacologic or behavioral interventions targeting weight, glucose, or lipid control.

Data Extraction: Reviewers extracted data, assessed applicability, and evaluated study quality; the team jointly graded overall strength of evidence.

Results: We included 33 studies. Most studies targeted weight control (28 studies). Compared with control groups, weight control was improved with behavioral interventions (mean difference = −3.13 kg; 95% CI, −4.21 to −2.05), metformin (mean difference = −4.13 kg; 95% CI, −6.58 to −1.68), anticonvulsive medications topiramate and zonisamide (mean difference = −5.11 kg; 95% CI, −9.48 to −0.74), and adjunctive or antipsychotic switching to aripiprazole (meta-analysis not possible). Evidence was insufficient for all other interventions and for effects on glucose and lipid control. The small number of studies precluded analyses of variability in treatment effects by patient characteristics.

Conclusions: Few studies have evaluated interventions addressing 1 or more CVD risk factors in people with serious mental illness. Glucose- and lipid-related results were mainly reported as secondary outcome assessments in studies of weight-management interventions. Comparative effectiveness studies are needed to test multimodal strategies, agents known to be effective in nonserious mental illness populations, and antipsychotic-management strategies.

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Individuals with serious mental illness have shortened life expectancies[1,2] and higher rates of morbidity from general medical conditions, including diabetes[3–5] and cardiovascular disease (CVD), relative to the general population.[6–8] Cardiovascular disease–related morbidity and mortality among people with serious mental illness (ie, schizophrenia and associated disorders, bipolar disorder, major depressive disorder) may be due to such factors as direct effects of illness, medications used to treat serious mental illness, disparities in access and quality of health care, and modifiable behavioral risk factors. Modifiable CVD risk factors, such as obesity,[9,10] physical inactivity,[11,12] and smoking,[13] are highly prevalent among adults with serious mental illness. Adverse effects of psychotropic drugs also may contribute to the development of CVD by increasing the risk of conditions such as hyperglycemia, hyperlipidemia, and obesity.[14]

Many studies have demonstrated disparities in the quality of general medical care provided to people with serious mental illness.[15–19] In contrast to individuals with less severe mental disorders, who largely receive mental health treatment in primary care settings, most patients with serious mental illness receive treatment in specialized mental health settings and have limited access to general medical care. Consequently, individuals with serious mental illness receive fewer preventive medical services[15,16] and less frequent guideline-concordant treatment to manage chronic physical illnesses.[17–19]

Given these issues, identifying intervention strategies that address CVD risk in serious mental illness populations is a pressing priority to avoid early morbidity and mortality. Our comparative effectiveness review evaluated behavioral interventions, peer or family support interventions, and pharmacologic treatments (including antipsychotic medication switching) to improve CVD risk factors in adults with serious mental illness. This article is derived from that review, which was funded by the Agency for Healthcare Research and Quality (AHRQ).[20]

DATA SOURCES AND STUDY SELECTION

We developed and followed a standard protocol for all steps of the review[21] and followed PRISMA guidelines.[22] Methods are summarized here, with details provided in the full AHRQ report[20] that presents results of the 4 key questions, 3 of which are addressed in this article.

Clinical Points

- Increasing guideline-concordant care for individuals with serious mental illness—given the current lack of evidence for serious mental illness–specific interventions—could be considered a starting point for minimizing cardiovascular disease risk in patients with serious mental illness. Guidelines for the general population should then be modified to consider the special risks for patients with serious mental illness.
- For weight control, moderate evidence supports behavioral interventions, and more limited evidence supports metformin, topiramate, or aripiprazole as an adjunctive agent or aripiprazole as an antipsychotic strategy.

In collaboration with a master librarian, we searched MEDLINE, EMBASE, PsycINFO, and Cochrane Database of Systematic Reviews for English language, peer-reviewed articles published from January 1980 to July 2012. We used medical subject headings and text words for terms relevant to populations and interventions. Examples of search terms used include *schizophrenia, bipolar disorder, antipsychotics, weight, glucose, lipid,* and *cardiovascular disease*. We supplemented electronic searches with manual searches of citations from key articles. We searched ClinicalTrials.gov to identify relevant articles from completed trials and to assess publication bias from completed but unpublished studies. Search strings are in Appendix A of the AHRQ report.[20]

Inclusion and Exclusion Criteria

Reviewer pairs used prespecified criteria to assess titles and abstracts. Eligible studies were randomized controlled trials (RCTs) of at least 2 months' duration that included adults with serious mental illness and that assessed patient-focused behavioral interventions, peer or family support interventions, or pharmacologic treatments targeting weight control, glucose levels, lipid levels, or overall CVD risk. Because there have been recent high-quality reviews of general health advice, smoking cessation interventions, and integrated mental health–general medical care,[23–27] we did not cover those interventions in our review. Full-text articles included by either reviewer underwent further evaluation. Eligibility decisions and disagreements were reconciled through discussion or by a third reviewer.

DATA EXTRACTION

For included studies, we abstracted data on study populations, interventions, outcomes, quality, and applicability. We used criteria developed by AHRQ to assess individual study quality, summarized as good, fair, or poor.[28] In brief, studies rated as good quality have the least bias and have a clear description of the population, setting, interventions, and comparison groups. A good-quality study also uses a valid approach to allocate patients to alternative treatments, has a low dropout rate, and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. A fair-quality study is susceptible to some bias but most likely not enough to invalidate results; also, it may be missing information, making it difficult to assess limitations and potential problems. A poor-quality study has substantial bias that may invalidate the results, and it may have serious errors in design, analysis, or reporting or have large amounts of missing information. We screened and abstracted data using DistillerSR software (Evidence Partners Inc; Manotick, Ontario, Canada).

Statistical Analyses

We summarized key features of included studies and performed DerSimonian and Laird random-effects meta-analyses when at least 3 studies were available with conceptually homogeneous study interventions and outcomes. Outcomes amenable to meta-analysis were continuous and were summarized as weighted difference of means, standardized such that negative values indicate greater intervention effects. When a single study reported multiple relevant outcomes, it was included in analyses for each outcome. Key outcomes were weight (kg), glycosylated hemoglobin A_{1c} (HbA_{1c}), total and low-density lipoprotein (LDL) cholesterol, and significant worsening of psychiatric status or treatment discontinuation due to adverse effects. We analyzed outcomes not amenable to meta-analysis qualitatively. We tested for heterogeneity using graphical displays and test statistics. All analyses were conducted using Comprehensive Meta-Analysis software (Version 2 [Biostat; Englewood, New Jersey]). We evaluated strength of evidence using the approach described in AHRQ's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[28,29]

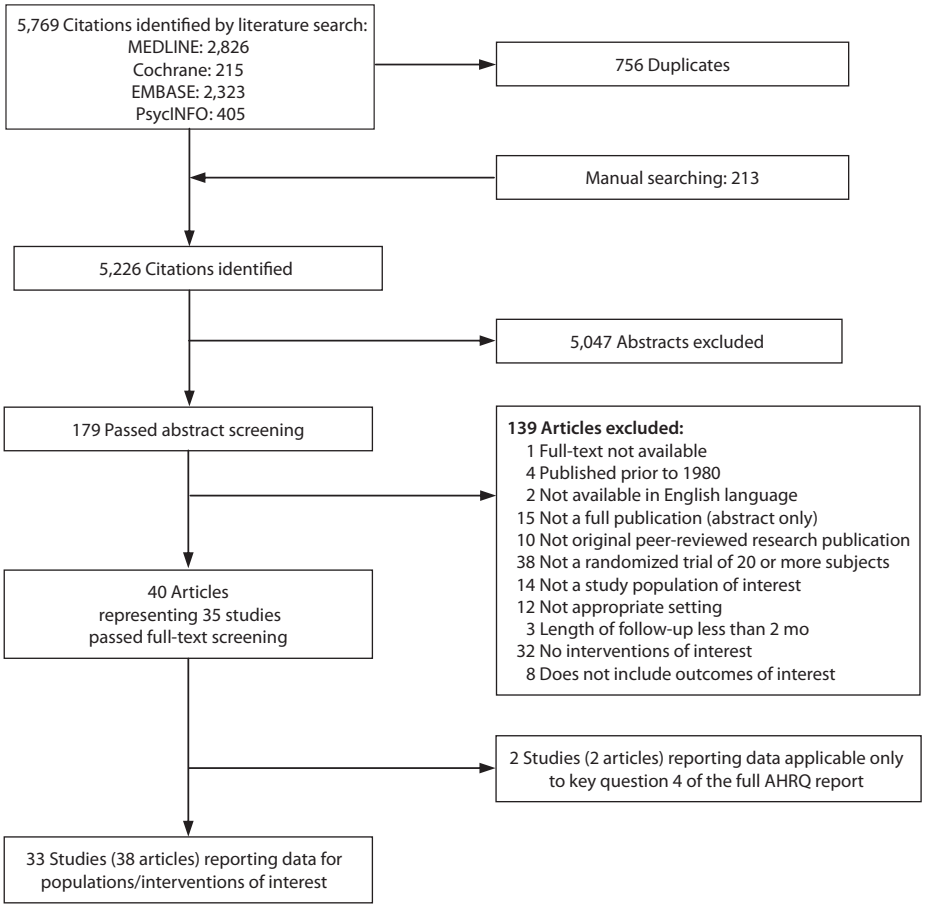
Strength of the Body of Evidence

The strength of evidence for each key question and outcome was assessed using the approach described in AHRQ's "Methods Guide."[28,29] In brief, the approach requires assessment of 4 domains: risk of bias, consistency, directness, and precision. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by 2 reviewers. In some cases, a rating of high, moderate, or low was impossible or imprudent to make: for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned.

Peer Review and Public Commentary

All AHRQ evidence reports are subject to rigorous external peer review. For this study, nominations for peer reviewers were solicited from several sources. Experts in psychiatry, mental illness, chronic medical conditions, systematic review methodology, pharmacoepidemiology of serious mental illness, public health, and integration of mental health and primary care, along with individuals representing stakeholder and user communities, were invited to provide external peer review of the draft report; AHRQ and an associate editor also provided comments.

Figure 1. Literature Flow Diagram



Abbreviations: AHRQ = Agency for Healthcare Research and Quality.

The draft report was posted on AHRQ's website for public comment for 4 weeks, from July 19, 2012, to August 17, 2012. We addressed reviewer comments, revising the evidence synthesis as appropriate, and have documented our responses in a disposition of comments report available on the AHRQ Web site (http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1618). A list of peer reviewers is given in the preface of the AHRQ report.

RESULTS

We present the flow of articles through the literature search and screening process in Figure 1. Of 5,226 unique citations, we identified 33 studies (represented by 38 articles) relevant to questions discussed in this article. We also identified 30 potentially relevant completed, but unpublished, trials in ClinicalTrials.gov, suggesting possible publication bias.

Table 1 details the characteristics of the 33 included studies. Most studies were specifically designed to control weight (28 studies); 1 was designed to target diabetes management, and no studies were designed to target dyslipidemia. Most common treatments evaluated were behavioral interventions. We found no peer or family support interventions. Most studies were rated as fair quality (21 studies).

Weight Control

We identified 33 RCTs[30,32–40,42–50,52–58,61–67] encompassing 3,722 patients that assessed effects of weight-management strategies among adults with serious mental illness. In total, 22 studies targeted weight control[32–35,37–39,43–48,50,52–55,61–63,65,66]; 6, obesity prevention[30,42,49,57,61,67]; 4, antipsychotic metabolic effects[36,40,56,64]; and 1, diabetes management.[58] Of the 33 trials that reported on weight control, 8 included HbA_{1c} and 15 included lipid outcomes; no study reported effects on mortality.

Behavioral interventions. Eleven studies[30,37,38,45,47,52–55,58,66] measured the impact of behavioral interventions versus control. Most patients were receiving antipsychotics or mood stabilizers at baseline and continued these medications throughout the interventions. Treatment ranged from 4 to 24 sessions; duration ranged from 8 weeks to 6 months. Interventions were adapted for serious mental illness populations by streamlining content, delivery by mental health personnel, and incorporating psychoeducation specific to serious mental illness.

Ten studies[30,37,38,45,47,52–55,66] involving 735 patients were amenable to meta-analysis (Figure 2). Pooled effects favored behavioral interventions (mean difference = −3.14 kg [95% CI, −4.33 to −1.96]; equivalent to −6.9 lb) but displayed

Table 1. Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a]	
								Hard Outcomes	Soft Outcomes
Alvarez-Jimenez et al, 2006[30] Alvarez-Jimenez et al, 2010[31] Europe	61	Age, mean, y: 26.8 Female, n = 15 Male, n = 46 Nonwhite, n = NR Schizophrenia, n = 61 Bipolar, n = NR Other, n = NR	Early behavioral intervention: 10–14 weekly or twice weekly individual therapy sessions following a flexible but manualized program, provided by a master's-level psychologist, focused on education, motivation, and skills training to enhance control over factors associated with antipsychotic weight gain	Enhanced usual care "designed to provide patients with the same physical care that is offered in a comprehensive early psychosis program"	BMI Weight (kg)	3 mo, 4 mo, 6 mo, 12 mo, 24 mo	Marques de Valddecilla Public Foundation (government)	Good	NA
Assuncao et al, 2006[32] South America	54	Age, mean, y: 35.2 Female, n = 22 Male, n = 32 Nonwhite, n = 18 Schizophrenia, n = 54 Bipolar, n = 0 Other, n = 0	Nizatidine 600 mg/d All participants were continued on their pretrial dose of olanzapine (5–20 mg/d)	Placebo All participants were continued on their pretrial dose of olanzapine (5–20 mg/d)	Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Discontinuation due to adverse event Treatment-emergent adverse event Psychiatric symptom severity: BPRS	4 wk, 8 wk, 12 wk	Industry	Good	Good
Atmaca et al, 2003[33] Europe	35	Age, mean, y: 27.9 Female, n = 14 Male, n = 21 Nonwhite, n = NR Schizophrenia, n = 35 Bipolar, n = NR Other, n = NR	Nizatidine 300 mg/d All participants were continued on their pretrial dose of olanzapine	Placebo All participants were continued on their pretrial dose of olanzapine	BMI Weight (kg) Psychiatric symptom severity: PANSS Any adverse event	8 wk	NR or unclear	Fair	Fair
Atmaca et al, 2004[34] Europe	28	Age, mean, y: 30.2 Female, n=12 Male, n=13 The sex of the 3 participants who did not complete the study was not reported Nonwhite, n = NR Schizophrenia, n = 28 Bipolar, n = NR Other, n = NR	Quetiapine 300–750 mg/d (mean = 479) plus nizatidine 300 mg/d	Quetiapine 300–750 mg/d (mean = 493) plus placebo	BMI Weight (kg) Psychiatric symptom severity: PANSS Leptin levels	2 mo	NR or unclear	Fair	Fair
Ball et al, 2011[35] United States	36	Age, mean, y: 47.0 Female, n = 11 Male, n = 25 Nonwhite, n = 11 Schizophrenia, n = 36 Bipolar, n = NR Other, n = NR	Atomoxetine 120 mg/d All participants attended weekly group counseling, exercise sessions 3 times per wk, and 10 wk of Weight Watchers All participants were continued on their pretrial dose of clozapine or olanzapine	Placebo All participants attended weekly group counseling, exercise sessions 3 times per wk, and 10 wk of Weight Watchers All participants were continued on their pretrial dose of clozapine or olanzapine	Weight (kg) LDL (mg/dL)	9 wk, 24 wk, 6 mo	Government, industry	Fair	Fair
Borba et al, 2011[36] United States	20	Age, mean, y: 51.1 Female, n = 7 Male, n = 13 Nonwhite, n = 2 Schizophrenia, n = 20 Bipolar, n = NR Other, n = NR	Ramelteon 8 mg/d All participants were continued on their pretrial medications	Placebo All participants were continued on their pretrial medications	BMI Weight (kg) HbA_{1c} (%) Total cholesterol (mg/dL) LDL (mg/dL)	2 mo	Government, industry	Fair	NA

(continued)

Table 1 (continued). Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a]	
								Hard Outcomes	Soft Outcomes
Brar et al, 2005[37] United States	71	Age, mean, y: 40.3 Female, n = 42 Male, n = 29 Nonwhite, n = 36 Schizophrenia, n = 71 Bipolar, n = 0 Other, n = 0	20 Manualized behavioral therapy sessions, twice weekly for 6 wk followed by weekly for 8 wk, covering diet, nutrition, exercise, and self-monitoring of behavioral changes	Usual care	BMI Weight (kg) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg)	14 wk	Industry	Fair	Fair
Brown and Goetz, 2011[38] United States	89	Age, mean, y: 44.6 Female, n = 54 Male, n = 35 Nonwhite, n = 35 Schizophrenia, n = NR Bipolar, n = NR Other, n = NR	Recovering Energy Through Nutrition and Exercise for Weight Loss (RENEW): weekly individual visits for 12 wk followed by monthly individual visits and weekly phone calls for the following 3 mo Sessions focused on weight loss strategies including social support, goal setting, skills training, and compensatory strategies for cognitive impairments	Usual care	Weight (lb)	3 mo, 6 mo	Government, industry	Fair	Fair
Bustillo et al, 2003[39] United States	30	Age, mean, y: 34.5 Female, n = 6 Male, n = 24 Nonwhite, n = 15 Schizophrenia, n = 30 Bipolar, n = NR Other, n = NR	Olanzapine 10 mg/d plus fluoxetine 20–60 mg/d (mean = 56)	Olanzapine 10 mg/d plus placebo	Weight (kg) Psychiatric symptom severity: PANSS-positive symptoms Psychiatric symptom severity: HDRS Adverse event: extrapyramidal symptoms	4 mo	Government, industry	Fair	Fair
Carrizo et al, 2009[40] Fernandez, 2010[41] South America	61	Age, mean, y: 38.9 Female, n = NR Male, n = NR Nonwhite, n = 50 Schizophrenia, n = 52 Bipolar, n = 2 The numbers for diagnoses are based on the number of individuals who completed the trial, which was 54. Sixty-one were randomized Other, n = NR	Metformin 500–1,000 mg/d All participants continued taking their pretrial clozapine, although it was unclear if dosing was changed during the trial Mean starting dose of clozapine for intervention arm was 180 mg/d	Placebo All participants continued taking their pretrial clozapine, although it was unclear if dosing was changed during the trial Mean starting dose of clozapine for placebo arm was 207 mg/d	BMI Weight (kg) HbA_{1c} (%) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Psychiatric symptom severity: BPRS	7 wk, 14 wk	Government, industry	Fair	Fair
Cavazzoni et al, 2003[42] United States	175	Age, mean, y: NR Female, n = NR Male, n = NR Nonwhite, n = NR Schizophrenia, n = 169 Bipolar, n = NR Other, n = NR 175 Randomized, 169 completed and analyzed	3-Arm trial with 2 active arms Arm 1: pretrial dose of olanzapine plus nizatidine 300 mg/d Arm 2: pretrial dose of olanzapine plus nizatidine 600 mg/d	Pretrial dose of olanzapine plus placebo	Weight (lb) Psychiatric symptom severity: BPRS	1, 2, 3, 4, 5, 6, 8, 12, and 16 wk	Industry	Fair	Poor

(continued)

Table 1 (continued). Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a]	
								Hard Outcomes	Soft Outcomes
Deberdt et al, 2008[43] United States	133	Age, mean, y: 44.0 Female, n = NR Male, n = NR Nonwhite, n = NR Schizophrenia, n = 133 Bipolar, n = 0 Other, n = 0	Antipsychotic switching: from olanzapine 10–20 mg/d to quetiapine 300–800 mg/d	Continue olanzapine 10–20 mg/d Comparators were continued on olanzapine, although the dose of olanzapine could be changed during the trial	BMI Weight (kg) HbA_{1c} (%) Total cholesterol (mmol/L) LDL (mmol/L)	1, 2, 3, 5, 7, 10, 12, 16, 18, 22, and 24 wk	Industry	Fair	Fair
Elmslie et al, 2006[44] Australia/New Zealand	60	Age, mean, y: 42.0 Female, n = 49 Male, n = 11 Nonwhite, n = NR Schizophrenia, n = NR Bipolar, n = 60 Other, n = NR	Carnitine L-tartrate 15 mg/kg/d	Placebo control	BMI Weight (kg) Waist circumference change (cm)	26 wk	Private foundation	Good	Good
Evans et al, 2005[45] Australia/New Zealand	51	Age, mean, y: 34.2 Female, n = 29 Male, n = 22 Nonwhite, n = NR Schizophrenia, n = 38 Bipolar, n = 8 Other, n = 5	Nutrition education: 6 planned, 1-h contacts including education on diet, nutrition, physical activity, and exercise and assistance in goal setting, provided every 2 wk by an accredited practicing dietitian	Usual care	BMI Weight (kg)	3 mo, 6 mo	Industry	Poor	Poor
Fleischhacker et al, 2010[46] Europe, Africa	207	Age, mean, y: 39.0 Female, n = 73 Male, n = 134 Nonwhite, n = 10 Schizophrenia, n = 207 Bipolar, n = 0 Other, n = 0	Aripiprazole 5–15 mg/d (mean = 11.1) All participants were continued on their prestudy dose of clozapine throughout the trial	Placebo All participants were continued on their prestudy dose of clozapine throughout the trial	BMI Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Discontinuation due to adverse event All-cause mortality HRQOL/physical function: Subjective Well Being Under Neuroleptics Scale score	2, 4, 6, 8, 10, 12, 14, and 16 wk	Industry	Good	Good
Gillhoff et al, 2010[47] Europe	50	Age, mean, y: 48.0 Female, n =23 Male, n=27 Nonwhite, n = NR Schizophrenia, n = NR Bipolar, n = 50 Other, n = NR	Multimodal lifestyle intervention including weekly fitness training, 7 psychotherapeutic/educational sessions, and 4 cooking and nutrition classes over the course of 5 mo	Wait list/usual care	BMI Weight (kg) HbA_{1c} (%) Total cholesterol (mmol/L) LDL (mmol/L) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg)	5 mo, 11 mo	Industry	Fair	NA
Graham et al, 2005[48] United States	21	Age, mean, y: NR Female, n = 9 Male, n = 12 Nonwhite, n = 5 Schizophrenia, n = 18 Bipolar, n = 3 Other, n = 0	Amantadine up to 300 mg/d (no further dosing details given) plus 12 weekly sessions of healthy lifestyle education program and 3-mo membership to gym or commercial weight loss program	Placebo plus 12 sessions of healthy lifestyle education program and 3-mo membership to gym or commercial weight loss program	BMI Weight (lb)	1 mo, 2 mo, 3 mo	Government, industry	Poor	NA

(continued)

Table 1 (continued). Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a]	
								Hard Outcomes	Soft Outcomes
Hoffmann et al, 2012[49] United States, Europe, Asia, Middle East, Mexico	199	Age, mean, y: 38.5 Female, n = 79 Male, n = 120 Nonwhite, n = 112 Schizophrenia, n = 199 Bipolar, n = NR Other, n = NR	3-Arm trial with 2 active arms Arm 1: pretrial dose of olanzapine plus metformin 1,000–1,500 mg/d, followed by amantadine 200 mg/d if metformin was ineffective Arm 2: pretrial dose of olanzapine plus amantadine 200 mg/d, followed by metformin 1,000–1,500 mg/d if amantadine was ineffective	Pretrial dose of olanzapine only	BMI Weight (kg) HbA_{1c} (%) Total cholesterol (mmol/L) LDL (mmol/L) Discontinuation due to adverse event Psychiatric symptom severity: BPRS Psychiatric symptom severity: CGI Psychiatric symptom severity: MADRS	22 wk	Industry	Poor	Poor
Karagianis et al, 2009[50] Karagianis et al, 2010[51] United States, Canada, Europe, Mexico	149	Age, mean, y: 39.0 Female, n = 68 Male, n = 81 Nonwhite, n = 71 Schizophrenia, n = 106 Bipolar, n = 41 Other, n = 2	Antipsychotic switching: from standard tablets of olanzapine 5–20 mg/d to orally disintegrating olanzapine 5–20 mg/d (mean = 14.3)	Continue standard tablets of olanzapine 5–20 mg/d (mean = 14.9)	BMI Weight (kg) HbA_{1c} (%) Total cholesterol (mg/dL) LDL (mg/dL) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Discontinuation due to adverse event HRQOL/Physical Function: Subjective Well Being Under Neuroleptics Scale score	2, 4, 6, 8, 10, 12, 14, and 16 wk	Industry	Good	Good
Khazaal et al, 2007[52] Europe	61	Age, mean, y: 40.7 Female, n = 33 Male, n = 28 Nonwhite, n = NR Schizophrenia, n = 49 Bipolar, n = 5 Other, n = 7	12 Weekly CBT-based manualized groups, provided by a master's-level psychologist, covering nutrition, diet, activity, exercise, and psychoeducation	One 2-h nutrition education group	BMI Weight (kg)	3 mo, 6 mo	NR or unclear	Fair	NA
Kwon et al, 2006[53] Asia	48	Age, mean, y: 31.3 Female, n = 33 Male, n = 15 Nonwhite, n = NR Schizophrenia, n = 48 Bipolar, n = 0 Other, n = 0	8-Session CBT weight management program focused on diet and exercise management, with a dietician and an exercise coordinator All participants continued their pretrial dose of olanzapine (5–20 mg/d)	Usual care All participants continued their pretrial dose of olanzapine (5–20 mg/d)	BMI Weight (kg) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) HRQOL/Physical Function: WHO-QOL-BREF, physical health subscore	4 wk, 8 wk, 12 wk	Industry	Fair	Poor
Littrell et al, 2003[54] United States	70	Age, mean, y: 34.1 Female, n = 27 Male, n = 43 Nonwhite, n = 18 Schizophrenia, n = 70 Bipolar, n = 0 Other, n = 0	Olanzapine plus 16-session manualized education intervention administered by a master's-level clinician, focused on diet, nutrition, exercise, goal and activity setting, and self-monitoring	Olanzapine only	BMI Weight (lb)	4 mo, 6 mo	Industry	Good	NA

(continued)

Table 1 (continued). Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a] Hard Outcomes	Study Quality[a] Soft Outcomes
Mauri et al, 2008[55] Europe	49	Age, mean, y: 38.9 Female, n = 28 Male, n = 21 Nonwhite, n = NR Schizophrenia, n = 5 Bipolar, n = 43 Other, n = 1	5–7 Psychoeducational groups on diet, exercise, nutrition, self-monitoring, and goal-setting All participants were continued on their pretrial dose of olanzapine	Usual care All participants were continued on their pretrial dose of olanzapine	BMI Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Psychiatric symptom severity: GAF Adverse event: drug related	3 mo	Industry	Poor	Poor
McDonnell et al, 2011[56] "26 Countries worldwide" (no further details provided)	1,065	Age, mean, y: 38.9 Female, n = 459 Male, n = 856 The sex of the participants starting the trial was reported; the total participants starting n = 1,315, but this lead-in period was not randomized. By the point of the randomized part of the trial, there were 1,065 individuals, but the breakdown for sex was not reported Nonwhite, n=299 Schizophrenia, n=921 Bipolar, n=NR Other, n=NR	Antipsychotic switching: from oral olanzapine tablets to long-acting injectable olanzapine 45 mg every 4 wk	Continue oral olanzapine tablets 10–20 mg/d (mean = 14.3)	BMI Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Discontinuation due to adverse event Adverse event: treatment-emergent adverse event	24 wk	Industry	Fair	Fair
McElroy et al, 2012[57] United States	42	Age, mean, y: 33.7 Female, n = 13 Male, n = 29 Nonwhite, n = 9 Schizophrenia, n = 1 Bipolar, n = 42 Other, n = NR	Zonisamide 100–600 mg/d (mean = 380) All participants were registered to receive personal wellness solution counseling All participants continued their pretrial dose of olanzapine	Placebo All participants were registered to receive personal wellness solution counseling All participants continued their pretrial dose of olanzapine	BMI Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Psychiatric symptom severity: CGI-S, bipolar version	1, 2, 3, 4, 6, 8, 10, 12, 14, and 16 wk	Industry	Good	Good
McKibbin et al, 2006[58] McKibbin et al, 2010[59] Leutwyler et al, 2010[60] United States	64	Age, mean, y: 54.0 Female, n = 20 Male, n = 37 Nonwhite, n = 22 Schizophrenia, n = 57 Bipolar, n = NR Other, n = NR 64 Randomized, 52 completed and analyzed	Diabetes Awareness and Rehabilitation Training: (DART) 90-min, weekly, manualized sessions (up to 24 sessions, mean number of sessions = 16.2), based on social cognitive theory, addressing diabetes, nutrition, lifestyle, exercise, self-empowerment, self-monitoring, and incentives	Usual care plus 3 brochures from the American Diabetes Association on diabetes management	BMI HbA_{1c} (%) LDL (mg/dL) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg)	6 mo, 12 mo	Government	Fair	Fair
Narula et al, 2010[61] Asia	72	Age, mean, y: 31.1 Female, n = 23 Male, n = 44 Nonwhite, n = NR Schizophrenia, n = 67 Bipolar, n = NR Other, n = NR 72 randomized, 67 completed and analyzed	Olanzapine 5–20 mg/d plus topiramate 100 mg/d	Olanzapine 5–20 mg/d plus placebo	BMI Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Psychiatric symptom severity: PANSS	3 mo	NR or unclear	Fair	Fair

(continued)

Table 1 (continued). Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a] Hard Outcomes	Study Quality[a] Soft Outcomes
Newcomer et al, 2008[62] Multinational	173	Age, mean, y: 39.2 Female, n = 62 Male, n = 111 Nonwhite, n = 55 Schizophrenia, n = 173 Bipolar, n = NR Other, n = NR	Antipsychotic switching: from olanzapine 10–20 mg/d (mean = 15.9) to aripiprazole 15 mg/d (mean = 16.0)	Continue olanzapine at 10–20 mg/d (mean = 15.9)	Weight (kg) Total cholesterol (mg/dL) LDL (mg/dL) Any adverse event Psychiatric symptom severity: CGI-I	6 wk, 8 wk, 12 wk, 14 wk	Industry	Fair	Fair
Nickel et al, 2005[63] Europe	49	Age, mean, y: 34.9 Female, n = 49 Male, n = 0 Nonwhite, n = NR Schizophrenia, n = 20 Bipolar, n = NR Other, n = NR	Topiramate 250 mg/d	Placebo	Weight (kg) HRQOL/physical function: SF-36 physical functioning HRQOL/physical function: SF-36 role	10 wk	NR or unclear	Fair	Fair
Stroup et al, 2011[64] United States	215	Age, mean, y: 41.0 Female, n = 78 Male, n = 137 Nonwhite, n = 92 Schizophrenia, n = 215 Bipolar, n = NR Other, n = NR	Antipsychotic switching: from olanzapine 5–20 mg/d (mean = 18.5) or quetiapine at 200–1,200 mg/d (mean = 502) or risperidone 1–16 mg/d (mean = 4.1) to aripiprazole 5–30 mg/d (mean = 16.9) plus a manualized behavioral intervention occurring weekly for 4 weeks and monthly thereafter, including diet, exercise, and education on reducing risk of cardiovascular disease	Continue olanzapine 5–20 mg/d (mean = 18.0) or quetiapine 200–1,200 mg/d (mean = 572) or risperidone 1–16 mg/d (mean = 4.1) Doses of medication could be adjusted during the trial, but medication could not be switched Plus a manualized behavioral intervention occurring weekly for 4 weeks and monthly thereafter, including diet, exercise, and education on reducing risk of cardiovascular disease	BMI Weight (kg) HbA_{1c} (%) Total cholesterol (mg/dL) LDL (mg/dL) Other CVD summary risk score Discontinuation due to adverse event Adverse event: death Adverse event: hospitalization Adverse event: any serious adverse event Psychiatric symptom severity: CGI	24 wk	Government, industry	Good	Good
Wang et al, 2012[65] Asia	72	Age, mean, y: NR Female, n = 32 Male, n = 34 Nonwhite, n = NR Schizophrenia, n = 66 Bipolar, n = 0 Other, n = 0	Metformin 1,000 mg/d (250 mg twice daily for first 3 days; 500 mg twice daily for remainder)	Placebo	Discontinuation due to adverse event BMI Weight (kg) Fasting glucose	4 wk, 8 wk, 12 wk	Scientific Research Fund of Liaoning Science and Technology Agency, China	Fair	Fair
Wu et al, 2008[66] Asia	128	Age, mean, y: 26.3 Female, n = 64 Male, n = 64 Nonwhite, n = NR Schizophrenia, n = 128 Bipolar, n = 0 Other, n = 0	4-Arm trial with 3 active arms Arm 1: metformin 750 mg/d Arm 2: manualized lifestyle intervention including sessions on diet, exercise, medication adherence, goal setting, and activity scheduling. Some sessions included family; some sessions were provided by an exercise physiologist or a dietician Arm 3: metformin 750 mg/d and manualized lifestyle intervention	Usual care plus placebo	BMI Weight (kg) Discontinuation due to adverse event Insulin level (μIU/mL) Psychiatric symptom severity: PANSS	4 wk, 8 wk, 12 wk	Government	Good	Good

(continued)

Table 1 (continued). Characteristics of Included Studies

Study, Country	Randomized Patients, N	Patient Characteristics	Intervention	Comparator	Outcomes	Timing	Funding	Study Quality[a] Hard Outcomes	Study Quality[a] Soft Outcomes
Wu et al, 2012[67] Asia	84	Age, mean, *y*: NR Female, n = 84 Male, n = 0 Nonwhite, n = 84 Schizophrenia, n = 84 Bipolar, n = 0 Other, n = 0	Metformin 1,000 mg/d	Placebo	BMI Weight (kg) Discontinuation due to adverse event Fasting blood glucose in mmol/L	1, 2, 3, 4, 5, and 6 mo	Government	Good	Good

[a]Good = A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. Fair = A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly not valid, while others are probably valid. Poor = A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Abbreviations: BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CBT = cognitive behavioral training, CGI = Clinical Global Impressions Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CVD = cardiovascular disease, GAF = Global Assessment of Functioning, HbA_{1c} = glycosylated hemoglobin, HDRS = Hamilton Depression Rating Scale, HRQOL = health-related quality of life, LDL = low-density lipoprotein, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, NR = not reported, PANSS = Positive and Negative Syndrome Scale, SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey, WHO-QOL-BREF = World Health Organization-Quality of Life (abbreviated).

high heterogeneity ($I^2 = 78\%$). No studies reported significant differences for serious adverse effects. Three studies[37,58,66] reported discontinuations due to adverse effects, and 1 study[53] reported effects on physical health status and found no significant differences between the behavioral weight-management group and control group. One study[58] assessed weight control only as a change in body mass index (BMI); participants in the behavioral intervention experienced greater improvements in BMI from baseline to 12-month follow-up compared with usual care (approximately −1 vs 0.05 BMI, $P < .01$).

Psychotropic agents. Single studies assessed the impact of 4 psychotropic agents, atomoxetine,[35] fluoxetine,[39] aripiprazole,[46] and ramelteon,[36] in individuals with schizophrenia treated with a second-generation antipsychotic. Because drug mechanisms of action vary importantly, we did not perform meta-analysis. Only 1 of the 4 studies demonstrated significant differences.[46] In this study, clozapine-treated outpatients with schizophrenia were randomized to adjunctive, flexible aripiprazole doses (5 to 15 mg/d) or clozapine plus placebo. At 16 weeks, adjunctive aripiprazole significantly decreased weight compared with placebo (−2.53 kg vs −0.38 kg, $P < .001$; −5.58 lb vs −0.84 lb). One participant in the placebo arm and 5 in the aripiprazole arm discontinued the trial due to adverse effects, 10 aripiprazole patients experienced serious adverse effects compared with none in the placebo group, and there was no difference in health-related quality of life between groups.

Neurologic agents. Three studies[57,61,63] assessed anticonvulsants topiramate and zonisamide, and 1 study[48] assessed amantadine. Pooled effects favored topiramate and zonisamide compared with placebo (mean difference = −5.11 kg, [95% CI, −9.48 to −0.74]; $I^2 = 0\%$; equivalent to −11.27 lb) (Figure 2). The single 12-week study of amantadine versus placebo among 21 serious mental illness patients who had gained at least 5 pounds on olanzapine also found significant but small improvements with amantadine (−0.7 kg/m^2 vs 1.24 kg/m^2).[48] Across all 4 studies, none reported significant differences in serious adverse effects, discontinuation due to adverse effects, health-related quality of life, or significant worsening of psychiatric symptoms.

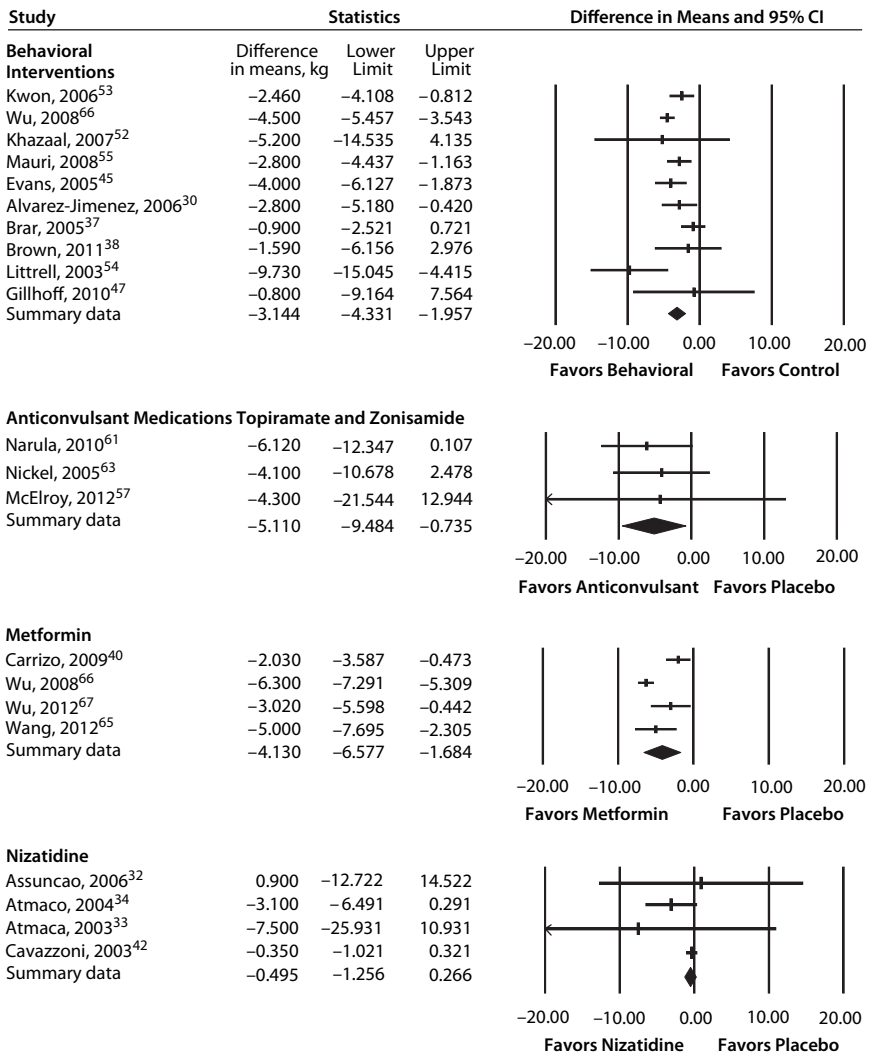
Metformin. Four studies[40,65–67] assessed effects of metformin versus placebo on weight control. Pooled effects favored metformin (mean difference = −4.13 kg [95% CI, −6.58 to −1.68]; $I^2 = 91\%$; equivalent to −9.11 lb), but results displayed high heterogeneity. No significant differences in adverse effects of interest were reported (Figure 2).

Nizatidine. Four studies[32–34,42] assessed effects of nizatidine versus placebo on antipsychotic-induced weight gain among people with schizophrenia. Pooled effects showed no significant improvement in weight control for nizatidine (mean difference = −0.49 kg [95% CI, −1.26 to 0.27]; $I^2 = 98\%$; equivalent to −1.08 lb) (Figure 2). Data on adverse effects of interest were limited, but no studies reported significant differences.

Carnitine. One study[44] assessed 15 mg/kg daily carnitine compared with placebo among 60 bipolar patients and demonstrated no significant effect on mean weight loss (−1.9 kg vs −0.9 kg, $P = .38$; −4.19 lb vs −1.98 lb). No other outcomes of interest were reported.

Antipsychotic switching. Five studies[43,50,56,62,64] assessed effects of antipsychotic-switching strategies on weight control. Two[50,56] involved switching from olanzapine to different forms of olanzapine, and others involved switching to quetiapine[43] or aripiprazole.[62,64]

Figure 2. Forest Plot of Meta-Analyses for Effects of Pharmacologic and Behavioral Interventions on Weight Control



Meta-analysis was not completed on these studies due to heterogeneity of switching strategies.

Neither study that examined switching to different forms of olanzapine[50,56] showed significant effects on weight control, nor did the study that examined switching to quetiapine from olanzapine ($P = .089$).[43] However, 2 studies that involved switching to aripiprazole demonstrated favorable results. In 1 study,[62] patients with schizophrenia who switched to aripiprazole experienced significantly more weight loss than those remaining on olanzapine (−1.84 kg vs 1.31 kg, $P = .001$; −4.06 lb vs 2.89 lb). Another study[64] evaluated switching to aripiprazole as part of a behaviorally oriented diet and exercise intervention and found that switching to a flexible dose of aripiprazole produced more weight loss than continued treatment with olanzapine, quetiapine, or risperidone (mean difference = −2.9 kg; $P < .01$; equivalent to −6.39 lb). Only 1 study[43] reported a statistically significant difference in adverse effects; discontinuation due to psychiatric adverse effects was higher in the quetiapine-treated group compared with olanzapine-maintained group ($P = .003$).

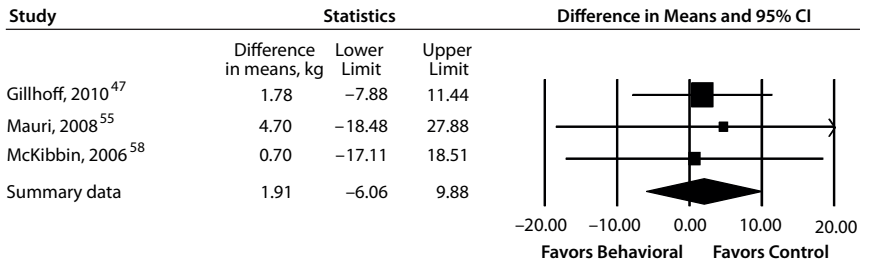
Glucose Control

We identified 8 RCTs[36,40,43,47,49,50,58,64] encompassing 896 patients that assessed glucose-control strategies among adults with serious mental illness. Only 1 study[58] tested an intervention intended specifically for individuals with diabetes mellitus; other studies reported glycemic control as a secondary outcome.

Behavioral interventions. Two studies[47,58] evaluated effects of behavioral interventions versus control on HbA_{1c}. (Table 1 summarizes intervention components.) Neither study demonstrated significant intervention effects on HbA_{1c}. Only McKibbin et al[58] reported on adverse effects and found no significant differences between treatments.

Psychotropic agents. Only 1 study[36] assessed effects of psychotropic agents on HbA_{1c} and found no significant

Figure 3. Forest Plot of Meta-Analysis for Effects of Behavioral Interventions on Lipid Control



difference in mean HbA_{1c} between psychotropic ramelteon and placebo ($P = .61$). No significant differences for adverse effects were reported between treatments.

Metformin. Two studies evaluated interventions of metformin among nondiabetics and found significant improvement in HbA_{1c}.[40,49] Carrizo et al[40] conducted a 14-week trial of extended-release metformin in individuals receiving clozapine compared with placebo. Metformin led to significantly less increase in HbA_{1c} (0.13 vs 0.23, $P = .04$). No adverse effects were reported. Hoffmann et al[49] conducted a 22-week trial of 3 treatment algorithms: olanzapine only, olanzapine plus amantadine with possible switches to metformin and then zonisamide, and olanzapine plus metformin with possible switches to amantadine and then zonisamide. The treatment algorithm beginning with metformin demonstrated statistically significant improvements in HbA_{1c} compared with olanzapine only (−0.03 vs 0.09, $P = .049$). Fourteen participants discontinued the study due to adverse effects.

Antipsychotic switching. Three studies[43,50,64] evaluated antipsychotic-switching strategies, with glycemic control measured as a secondary outcome. Patients in 2 studies began taking olanzapine and switched to quetiapine[43] or orally disintegrating olanzapine.[50] Another study[64] evaluated switching from olanzapine, quetiapine, or risperidone to aripiprazole. None reported significant changes in HbA_{1c}. One study[43] reported a statistically significant difference in discontinuation due to psychiatric adverse effects.

Lipid Control

We identified no articles reporting on trials in which the intervention was designed to target lipid levels. However, 16 studies[32,35,36,43,46–50,55–58,61,62,64] involving 2,549 patients reported on total cholesterol (13 studies) or LDL cholesterol (15 studies) as a secondary outcome.

Behavioral interventions. Three studies[47,55,58] assessed effects of behavioral interventions on LDL levels. Pooled results found no significant difference between behavioral interventions and control (mean difference = 1.91 mg/dL [95% CI, −6.06 to 9.88], $I^2 = 0\%$) (Figure 3). Only 1 study[55] reported on adverse effects and found no significant differences between groups. Only 2 studies[47,55] of behavioral interventions reported on total cholesterol. Again, no significant advantage on total cholesterol was demonstrated for behavioral interventions versus control.

Psychotropic agents. Three studies examined effects of psychotropic medications ramelteon,[36] aripiprazole,[46] and atomoxetine[35] on lipids compared with placebo. Two studies recorded data on total cholesterol, and 3 studies on LDL cholesterol.

A 24-week study[35] of patients with schizophrenia taking olanzapine or clozapine randomized to atomoxetine or placebo found no difference in LDL levels. An 8-week pilot trial[36] of ramelteon found a significant advantage for total cholesterol for ramelteon versus placebo (−9.79 mg/dL vs 3.84 mg/dL, $P = .03$). Change in LDL levels displayed a similar pattern, but group differences were not significant. In a 16-week trial[46] of aripiprazole versus placebo, patients in the aripiprazole group had greater percentage reductions in total cholesterol levels (−6.9% vs −1.2%, $P = .002$) and LDL levels (−10.3% vs 0.0%, $P = .003$). No significant differences in adverse effects were reported between groups across these studies.

Neurologic agents. Effects of neurologic agents amantadine,[48,49] topiramate,[61] and zonisamide[57] on lipids were examined in 4 trials.[48,49,57,61] Results were mixed. A 12-week study[48] of amantadine versus placebo found no differences between groups on total cholesterol or LDL levels. However, a 3-arm, 22-week study[49] examined 2 different medication treatment algorithms for prevention of weight gain compared with no medication in patients with schizophrenia or schizoaffective disorder who were taking olanzapine. The 2 algorithms using amantadine, metformin, and zonisamide were significantly more effective at preventing increases in total cholesterol than olanzapine only (0.18 mg/dL and −1.44 mg/dL vs 6.49 mg/dL). A 12-week study[61] of schizophrenia patients randomized to either olanzapine plus topiramate or olanzapine plus placebo found a significant advantage for topiramate compared with placebo (0.34 mg/dL rise vs 10.53 mg/dL rise, $P = .009$). A 16-week study[57] of zonisamide versus placebo found no significant differences between groups on total cholesterol or LDL levels. No significant differences in adverse effects were reported across these studies.

Nizatidine. A 12-week trial[32] examined nizatidine versus placebo among schizophrenia patients taking olanzapine and found no statistically significant differences between groups on lipid levels and adverse effects.

Table 2. Overview of Treatment Effects and Strength of Evidence by Intervention and Major Outcomes[a,b]

Intervention	Weight	Diabetes (HbA_{1c})	Lipids[c]
Behavioral	Small benefit (−3.1 kg) Moderate SOE	Insufficient SOE	No important effect from weight control interventions Insufficient SOE
Peer or family support	No studies Insufficient SOE	No studies Insufficient SOE	No studies Insufficient SOE
Metformin	Small benefit (−4.1 kg) Low SOE	Insufficient SOE	No studies Insufficient SOE
Topiramate, zonisamide	Small to moderate benefit (−5.1 kg) Low SOE	Insufficient SOE	Possible benefit with topiramate Insufficient SOE
Antihistamine	No benefit Low SOE	Insufficient SOE	Single study did not suggest benefit Insufficient SOE
Other medications	Insufficient SOE	Insufficient SOE	No study suggested possible benefit Insufficient SOE
Antipsychotic switching or adjunctive use	Low SOE for small benefit (−2 to −3 kg) with switching to aripiprazole or adjunctive aripiprazole	Insufficient SOE	Possible benefit with adjunctive or switching to aripiprazole Insufficient SOE
	In single studies, insufficient SOE for switching to quetiapine or parenteral olanzapine		

[a]Reprinted with permission from Gierisch et al.[20]
[b]Gray highlights strength of evidence ratings that are above insufficient.
[c]No studies of lipid-focused interventions.
Abbreviations: HbA_{1c} = glycosylated hemoglobin A_{1c}, SOE = strength of evidence.

Antipsychotic switching. Five trials[43,50,56,62,64] examined effects of antipsychotic-switching strategies on lipids. The intervention in 2 studies involved switching to different forms of olanzapine[50,56] and, in the other 3 studies, switching to quetiapine[43] or aripiprazole.[62,64]

There were mixed results in the 2 studies[50,56] that examined switching to different forms of olanzapine. In the trial[50] that involved switching from standard olanzapine tablets to orally disintegrating olanzapine tablets, no difference between groups was found. However, in another trial[56] switching from oral olanzapine to a long-acting injection of olanzapine, patients continuing oral olanzapine had significantly greater decrease in LDL levels than patients in the long-acting injection group (−6.4 mg/dL vs −1.5 mg/dL, $P = .039$). The groups did not differ on total cholesterol. These 2 studies did not report any statistically significant difference between groups for adverse effects.

Studies[43,62,64] that examined switching to a different antipsychotic medication also had mixed results. Switching to quetiapine from olanzapine did not improve lipid levels.[43] However, switching to aripiprazole demonstrated favorable results. In 1 trial,[62] patients switching from olanzapine to aripiprazole had a greater decrease in total cholesterol (−9.5% vs −3.3%, $P = .005$) and a nonsignificantly greater decrease in LDL cholesterol (−11.2% vs −4.7%, $P = .072$). Another study[64] evaluated switching from olanzapine, quetiapine, or risperidone to aripiprazole. Significant group effects were observed for total cholesterol (mean difference = −8.8 mg/dL; $P = .02$) and non-HDL cholesterol (mean difference = −9.4 mg/dL; $P = .01$). These 3 switching studies reported no significant between-group differences for adverse effects.

Strength of Evidence

Table 2 presents an overview of findings and strength of evidence by major outcomes. Evidence was insufficient for most intervention strategies, and there were too few studies to conduct a quantitative synthesis for all outcomes of interest except weight. We found moderate strength of evidence that behavioral interventions are associated with small decreases in weight (about 3 kg or 7 lb) compared with controls. We found low strength of evidence that switching to or adding adjunctive aripiprazole, adding the anticonvulsant medications topiramate and zonisamide, or adding metformin yields small to moderate weight loss. Nizatidine, an antihistamine, did not show any consistent effect on weight (low strength of evidence). The strength of evidence was insufficient for all other interventions.

DISCUSSION

We identified 33 trials that tested a wide array of pharmacologic and behavioral interventions to address 1 or more CVD risk factors in adults with serious mental illness who have elevated risk for CVD. All identified studies were published from 2003 forward, reflecting recent clinical interest in weight, lipid, and glucose control in this population. Given that CVD is the most prevalent cause of death in this population, this is a surprisingly small number of studies. Further, we identified no peer and family support interventions, nor did we find any interventions designed specifically to address lipids. Outcomes reported were primarily metabolic outcomes such as glucose control or weight; effects on physical function were reported infrequently, and overall CVD risk (eg, Framingham Risk Score) and all-cause mortality were not reported. Trials identified in the review assessed the impact of a wide variety

of pharmacologic and behavioral strategies among adults with serious mental illness. However, few of the pharmacologic strategies were medications with known efficacy to control CVD risk factors (eg, orlistat, statins).

Our results complement prior reports by examining a broad array of interventions for patients at increased risk for worsening health outcomes from CVD risk factors such as obesity, hyperlipidemia, diabetes mellitus, or chronic administration of antipsychotic medications that negatively impact metabolic parameters. Previous narrative and systematic reviews[68–74] have focused primarily on behavioral interventions for weight control in patients with schizophrenia or patients on antipsychotic medications. These reviews used differing eligibility criteria, with some including observational study designs; thus, the number of studies they included varied widely. Despite differences in methods, these review conclusions are largely consistent with our findings that behavioral interventions are associated with small improvements in weight. Further, a recent behavioral weight loss study[75] published after our search date also demonstrated consistent findings with our pooled analysis presented here (3.2 kg vs 3.13 kg). Recent qualitative syntheses[70,71] have identified that interventions adapted to individuals with serious mental illness, with durations of at least 3 months and incorporation of both education and activity-based approaches, are associated with greater effects. Such behavioral weight management approaches are endorsed by the Schizophrenia Patient Outcomes Research Team (PORT) psychosocial treatment recommendations.[76] These findings are tempered by the small number of studies and indirect comparisons. Our review builds on these findings by identifying (1) promising treatment strategies—such as aripiprazole, metformin, and topiramate—that deserve further investigation and (2) clear omissions in treatments that are known to be effective in nonserious mental illness populations (eg, orlistat). Although evidence is limited, the key finding is that, of the interventions tested in serious mental illness populations to date, effects on intermediate outcomes (eg, weight) are similar to effects found in the general population. Interventions with known efficacy in general populations may also translate to populations with serious mental illness and warrant exploration.

Physicians take an oath of *primum non nocere*: First, do no harm. The American Psychiatric Association's 2004 guidance[77] follows this principle, recommending a response to adverse medication effects by considering a change in the psychotropic medication to an alternative with less potential to induce side effects. When treating emergent metabolic abnormalities that temporally follow medication treatment, this approach is rational, but existing data show only small improvements in the cardiovascular outcomes of interest. Other high-quality systematic reviews have addressed the comparative efficacy of antipsychotics and have identified few differences in short-term efficacy between second-generation antipsychotics; clozapine reduced suicides and suicidal behavior, and clozapine and olanzapine had lower rates of discontinuation. Olanzapine resulted in greater weight gain and increased risk of new-onset diabetes.[78] In patients who have responded well to psychotropic medication, a change in treatment carries the risk of symptom worsening, an outcome not consistently reported in the studies reviewed. Further, antipsychotic-switching strategies have not been tested directly against treatments that target the metabolic abnormality directly (eg, statin for hyperlipidemia) or multimodal strategies that include medication switching and lifestyle interventions. For some medications, interactions with psychotropic medications (eg, thiazide diuretics and lithium) may limit effectiveness. Despite this caution, and in the absence of direct evidence in patients with serious mental illness, treatments established as effective in nonserious mental illness populations are a logical choice to treat risk factors for CVD in serious mental illness populations until better evidence is available.

Increasing guideline-concordant care for individuals with serious mental illness—given the lack of evidence for serious mental illness–specific interventions—could be considered a starting point for minimizing CVD risk in such patients. Integrated mental health–general medical care has shown promise as the optimal way to deliver care[79]; the current move to medical home models has the potential to make this care more readily available. Unfortunately, few medical homes have explicitly included mental health care.[80] Until integrated care is better established and more readily available, there are a number of implementation strategies to consider when changes to antipsychotics that are metabolically more neutral are not sufficient to address elevated CVD risk factors. When patients have access to both mental health specialty care and general medical care, it is important that their clinicians coordinate care across issues that may affect both physical and mental health. For example, general medical providers may be aware of adverse metabolic effects of some psychotropics but are appropriately hesitant to adjust these medications. Coordinating care with mental health professionals about roles and specific strategies for addressing CVD risk factors has the potential to improve care and clinical outcomes.

When general medical care is unavailable, 1 potential but untested strategy to consider is an expanded psychiatrist role. Weight and blood pressure screening and monitoring are low-cost measures requiring minimal time and office equipment. For patients without access to general medical care, psychiatrists could incorporate these activities into their usual clinical practice. Treating hyperlipidemia with statins is only slightly more difficult. The US Food and Drug Administration and guidelines groups have recently revised recommendations; periodic monitoring of transaminase levels is no longer recommended. In addition, some authors have made strong cases for fixed-dose statins that would further decrease the need for ongoing monitoring of lipid levels.[81] Psychiatrists would thus need only to follow National Cholesterol Education Program-Adult Treatment Panel III (NCEP-III) guidelines[82] for guidance on when to initiate treatment (and readily available Web and smartphone applications facilitate quick access to these guidelines) and consider potential but rare drug-drug interactions.

Our study and the literature have limitations: the number of studies is small, many had design limitations, the range of interventions evaluated was limited, and the number and reporting of studies precluded any analyses of variability in treatment effects by patient characteristics. Our study was limited to English language publications, but the likelihood of identifying relevant data unavailable from English language sources is low. Only 1 study was specifically designed to address diabetes, and no studies directly targeted dyslipidemia. Thus, results for those CVD risks were culled from secondary outcome assessments of, primarily, weight-management interventions. We included psychotropic studies only if the intent was to study effects on weight, glucose, or lipid control or overall CVD risk profile. Thus, we excluded studies whose primary goal was to control psychiatric symptoms and may have missed some relevant adverse event outcomes. However, a recent Drug Effectiveness Review Project (DERP) report[78] and AHRQ report[83] on the comparative effectiveness of antipsychotics provide robust reviews of these outcomes as they pertain to adverse effects.

Adults with serious mental illness are at elevated risk for CVD. In our review, surprisingly few studies addressed 1 or more CVD risk factors in patients with serious mental illness. Behavioral interventions, switching to or adding adjunctive aripiprazole, adding topiramate and zonisamide, or adding metformin yields small to moderate weight loss compared with controls; strength of evidence was insufficient for all other interventions. There are myriad challenges to sustaining weight loss; this is an important focus for continued research among populations with serious mental illness. We found no studies testing a number of important interventions (eg, orlistat, statins) known to be effective in nonserious mental illness populations. Comparative effectiveness trials are needed that test multimodal strategies, known effective agents in nonserious mental illness populations, and antipsychotic-management strategies. However, in the absence of evidence for serious mental illness–specific interventions, increasing guideline-concordant care for people with serious mental illness may help mitigate the unequal burden of CVD that serious mental illness populations sustain.

Drug names: aripiprazole (Abilify), atomoxetine (Strattera), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), lithium (Lithobid and others), metformin (Fortamet, Glucophage, and others), nizatidine (Axid and others), olanzapine (Zyprexa and others), orlistat (Xenical), quetiapine (Seroquel and others), ramelteon (Rozerem and others), risperidone (Risperdal and others), topiramate (Topamax and others), zonisamide (Zonegran and others).

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