Are Antipsychotics Effective for the Treatment of Anorexia Nervosa? Results From a Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To assess the utility of antipsychotics for weight gain and improvement of illness-related psychopathology in patients with anorexia nervosa.

Data Sources: PubMed, the Cochrane Library databases, and PsycINFO citations from the inception of the databases until March 27, 2012, were searched without language restrictions using the following keywords: *randomized, random, randomly*, and *anorexia nervosa*. In addition, we hand-searched for additional studies eligible for inclusion in this meta-analysis and contacted authors for unpublished data.

Study Selection: Included in this study were randomized placebo- or usual care–controlled trials of antipsychotics in patients with anorexia nervosa.

Data Extraction: Two independent evaluators extracted data. The primary outcome of interest was body weight, expressed as the standardized mean difference (SMD) between the 2 groups in baseline to endpoint change of body mass index (BMI), endpoint BMI, or daily weight change. SMD, risk ratio (RR), and number needed to harm (NNH) ± 95% confidence interval (CI) were calculated.

Results: Across 8 studies (mean duration = 9.6 weeks; range, 7–12 weeks), 221 patients (mean age = 22.5 years, 219 [99.1%] females) with anorexia nervosa were randomly assigned to olanzapine (n = 54), quetiapine (n = 15), risperidone (n = 18), pimozide (n = 8), sulpiride (n = 9), placebo (n = 99), or usual care (n = 18). Both individually ($P = .11$ to $P = .47$) and pooled together (SMD = 0.27, 95% CI, −0.01 to 0.56; $P = .06$, $I^2 = 0\%$; 7 studies, n = 195), weight/BMI effects were not significantly different between antipsychotics and placebo/usual care. Moreover, pooled antipsychotics and placebo/usual care did not differ regarding scores on questionnaires related to anorexia nervosa ($P = .32$, 5 studies, n = 114), body shape ($P = .91$, 4 studies, n = 100), depressive symptoms ($P = .08$, 4 studies, n = 103), and anxiety ($P = .53$, 4 studies, n = 121). Individually, quetiapine (1 study, n = 33) outperformed usual care regarding eating disorder attitudes ($P = .01$) and anxiety ($P = .02$). While rates of dropout due to any reason ($P = .83$, $I^2 = 0\%$) and due to adverse events ($P = .54$, $I^2 = 5\%$) were similar in both groups, drowsiness/sedation occurred significantly more often with antipsychotics than placebo/usual care (RR = 3.69, 95% CI, 1.37–9.95; $I^2 = 67\%$, $P = .01$; NNH = 2, $P = .001$; 5 studies, n = 129), but most other adverse effects were only sparsely reported.

Conclusions: Although limited by small samples, this meta-analysis failed to demonstrate antipsychotic efficacy for body weight and related outcomes in females with anorexia nervosa.

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Anorexia nervosa is a serious and potentially life-threatening illness that has a prevalence of approximately 0.5%.[1] The physical and psychological effects can be severe, and in approximately 15% of cases, anorexia nervosa results in death.[2] Anorexia nervosa can be comorbid with several disorders and overlaps with psychopathologies, including depression, anxiety, near-delusional thinking, and obsessions.[3] Differences in several parts of the brain and an imbalance of brain chemicals, especially serotonin and dopamine, are considered to contribute to the pathophysiology of anorexia nervosa.[4] Trait imbalances between serotonin and dopamine pathways are hypothesized to play a role in an altered interaction between ventral and dorsal neurocircuits in anorexia nervosa.[4] Since in anorexia nervosa an almost delusional body shape perception exists and since most antipsychotics have been associated with weight gain as a potential side effect,[5] antipsychotics have been used off-label for the treatment of anorexia nervosa. Second-generation antipsychotics (SGAs) have been tried the most, on the basis of the proposed neurobiology of anorexia nervosa and the effects of SGAs on both serotonin and dopamine receptors, their greater tendency to cause weight gain than most first-generation antipsychotics (FGAs),[6,7] and the beneficial effects of some SGAs on depression, dysthymia, obsessive-compulsive disorder, and anxiety.[8–11] However, although weight gain is generally quite dramatic in antipsychotic-naive subjects,[12,13] which most anorexia nervosa patients are likely to be, the exact mechanisms of antipsychotic-related weight gain are still unclear. Since one major mechanism appears to be increased appetite and related increased food intake,[14,15] the weight gain effect in anorexia nervosa patients, who are used to overcoming intense hunger signals, is not self-evident.

Several small randomized controlled trials have compared antipsychotics, especially SGAs, against placebo or usual care in patients with anorexia nervosa. However, the results have been inconsistent; some studies showed significantly greater body weight gain with antipsychotics,[16,17] while others failed to find antipsychotic superiority.[18–21] Nevertheless, one potential reason for this discrepancy is the small sample sizes of these studies that included between 18 and 57 patients in total and that had only 8 to 30 participants per treatment arm. Therefore, to overcome the limitations of the small sample sizes of individual studies,[22] inform clinical practice regarding the efficacy and tolerability of antipsychotics for

Clinical Points

- Due to their weight-inducing effects, antipsychotics, especially second-generation antipsychotics, have been used off-label for the treatment of anorexia nervosa.
- Both individually and pooled together, antipsychotics did not differ from placebo/usual care with regard to effects on weight/BMI, scores on questionnaires related to anorexia nervosa (except for quetiapine), or depressive symptoms.
- Although limited by a low number of studies including relatively small samples, this meta-analysis failed to demonstrate significant antipsychotic efficacy for body weight and related outcomes in females with anorexia nervosa.
- Larger trials are needed to extend these findings and determine if patient or treatment factors influence the success or failure of antipsychotic treatment in anorexia nervosa.

anorexia nervosa, and provide input into the future research directions in this area, we performed a meta-analysis of antipsychotic effects in patients with anorexia nervosa. Based on the weight gain–inducing effects of antipsychotics, especially in previously untreated individuals, and related benefits for psychopathology that could potentially attenuate anorexia nervosa symptoms and behaviors, we hypothesized that antipsychotics would lead to significantly more weight gain compared to the control condition in individuals with anorexia nervosa.

METHOD

Inclusion Criteria, Search Strategy, Data Extraction, and Outcomes

Included in this study were randomized placebo-controlled or usual care–controlled trials of antipsychotics in patients with anorexia nervosa. To identify relevant studies, we searched PubMed, the Cochrane Library databases, and PsycINFO citations without language restrictions from the inception of the databases until January 31, 2012, with an updated search on March 27, 2012, using the following keywords: *randomized, random, randomly,* and *anorexia nervosa.* Complementing the electronic search, pertinent review articles, prior reviews, and reference lists from identified studies were hand-searched for additional studies eligible for inclusion in this meta-analysis. Two authors (T.K. and C.U.C.) double-checked the inclusion and exclusion criteria of the identified studies. When data required for the meta-analysis were missing or available data were significantly skewed (ie, standard deviation more than double the mean, especially pertaining to change scores), first/corresponding authors were contacted for additional information (including endpoint scores). Additional, unpublished data were provided by authors of some of the studies included in the analysis (see Acknowledgments). Two authors (T.K. and C.U.C.) independently extracted data and checked and entered data into the Review Manager Version 5.1 for Windows (Review Manager version 5.0, Cochrane Collaboration, http://www.cc-ims.net/RevMan). Any discrepancies were resolved by discussion.

Data Synthesis and Statistical Analysis

To minimize the effect of chance, we meta-analyzed only outcomes for which data from at least 3 studies were available. The primary outcome was body weight, expressed as the standardized mean difference (SMD) between the 2 groups in baseline to endpoint change of body mass index (BMI) (4 studies),[17,19–21] endpoint BMI (2 studies),[16,18] or daily weight change (1 study).[23] When available and not significantly skewed, change scores were preferred over endpoint scores, as, in small samples, differences in baseline scores can already be substantial, despite randomization, which confounds the differences in endpoint scores. Secondary outcomes included dropout due to any cause, dropout due to intolerability, glucose and lipid changes (as available), eating disorder symptoms, depressive symptoms, and anxiety.

For anorexia nervosa symptoms, we pooled the total scores from the Yale-Brown-Cornell Eating Disorder Scale[24] from 3 studies,[16,18,19] Eating Disorder Inventory (EDI)[25] from 1 study,[20] and Anorectic Behavior Scale for Inpatient Observation[26] from 1 study.[23] Moreover, we also pooled attitudes toward body shape from the following questionnaires: Body Shape Questionnaire[27] total scores from 1 study,[16] EDI body dissatisfaction subscore from 1 study,[21] and Eating Disorder Examination[28] shape concerns subscore from 1 study.[19] Although Vandereycken[23] reported Body Attitudes Test total scores at study endpoint, we dropped this study from this analysis since there was a marginally significant difference in the baseline scores between both treatment groups ($P = .052$).

For depressive symptoms, we pooled total scores from the Hamilton Depression Rating Scale[29] from 1 study,[19] Beck Depression Inventory[30] from 1 study,[16] Personality Assessment Inventory depression subscore[31] from 1 study,[17] and the Center for Epidemiologic Studies Depression Scale[32] from 1 study.[20] For anxiety symptoms, we pooled data in 1 study each from the Beck Anxiety Inventory,[16,33] Personality Assessment Inventory anxiety subscore,[17,31] Mood and Anxiety Symptom Questionnaire,[20,34] and Multidimensional Anxiety Scale for Children.[21,35] In addition, we pooled data for side effects reported in at least 3 trials, applying only to drowsiness/sedation and akathisia.

We based the analyses on intention-to-treat (ITT) or modified ITT data (ie, at least 1 dose or at least 1 follow-up assessment); no observed cases data were allowed. The meta-analysis was performed using Review Manager Version 5.1 for Windows (Review Manager version 5.0, Cochrane Collaboration, http://www.cc-ims.net/RevMan). To combine studies, the random-effects model by DerSimonian and Laird[36] was used in all cases. This method is more conservative, because it statistically accounts for the possibility that the meta-analyzed studies and samples are heterogeneous.

Table 1. Study, Patient, and Treatment Characteristics of Included Randomized Controlled Trials

Study (country)	Antipsychotic	n	Study Design	Duration	Population	Age, Mean, y	% Female	Diagnostic Criteria	No. of Patients in Each Treatment Arm	Dose, Mean (range), mg/d	Psychotherapy and/or Concomitant Drugs	Body Weight–Related Outcome
Second-Generation Antipsychotics												
Attia et al,[16] 2011 (United States)	OLA	23	DBPCT	8 wk	Outpatients: 100%; AN type: NR; BMI range: ≥14 kg/m^2 to ≤19 kg/m^2, without amenorrhea; illness duration: NR; comorbidities: NR	27.7 ± 9.1	95.7	*DSM-IV* (using SCID-I)	OLA: 11 PLA: 12	7.95 ± 2.70 (2.5–10) 8.75 ± 2.50	42% ADs 36% ADs	BMI: OLA > PLA
Bissada et al,[17] 2008 (Canada)	OLA	34	DBPCT	10 wk	Outpatients: 100%; restricting type: 47.1%, binge/purge type: 52.9%; BMI ≤17.5 kg/m^2; illness duration: NR; comorbidities: no bipolar disorder, schizophrenia, other psychotic disorder, substance abuse disorder, or active suicidal intent	OLA: 23.6 ± 6.5 PLA: 29.7 ± 11.6	100	*DSM-IV*	OLA: 16 PLA: 18	6.61 ± 2.32 (2.5–10) NR	100% hospital program, including supervised meals and group therapy	BMI: OLA > PLA
Brambilla et al,[18] 2007 (Italy)	OLA	35	DBPCT	12 wk	Outpatients: 100%; binge-purge type: 40.0%, restricting type: 60.0%; BMI range: NR; illness duration: OLA = 6.3 ± 5.0 y, PLA = 4.4 ± 3.0 y; comorbidities: NR	OLA: 23.7 ± 4.8 PLA: 26.3 ± 8.5	100	*DSM-IV* (using SCID-I)	OLA: 17 PLA: 18	2.5 for first 1 mo, 5 for later 2 mo NR	100% psychotherapy and nutritional rehabilitation program	BMI: OLA = PLA
Kafantaris et al,[19] 2011 (United States)	OLA	20	DBPCT	10 wk	Inpatients: 45%, day-hospital patients: 30%, outpatients: 25%; restricting type: 100% (without past or current binge/purge type); BMI range: 13.4–18.2 kg/m^2; illness duration: NR; comorbidities: NR	17.1 (range, 12.3–21.8)	100	Eating Disorder Examination	OLA: 10 PLA: 10	8.5 (2.5–10) NR	100% individualized medical care, nutritional management, and psychological treatment consisting of individual, group, family, and multifamily group therapy	BMI: OLA = PLA
Court et al,[20] 2010 (Australia)	QUE	33	Open, TAU-controlled trial	12 wk	8 participants in QUE group and 7 in control group admitted as inpatients at some point during the trial; AN type: NR; BMI range: 12.7–19.5 kg/m^2; illness duration: NR; never previously received SGA; comorbidities: no psychotic illness	QUE: 21.0 ± 3.3 (range, 16–27) TAU: 23.8 ± 9.4 (range, 15–42)	97.0	*DSM-IV*	QUE: 15 TAU: 18	322.5 (100–400) NR	100% psychotherapy, individual, family, and supportive therapy	BMI: QUE = TAU

(continued)

Table 1 (continued). Study, Patient, and Treatment Characteristics of Included Randomized Controlled Trials

Study (country)	Antipsychotic	n	Study Design	Duration	Population	Age, Mean, y	% Female	Diagnostic Criteria	No. of Patients in Each Treatment Arm	Dose, Mean (range), mg/d	Psychotherapy and/or Concomitant Drugs	Body Weight–Related Outcome
Second-Generation Antipsychotics												
Hagman et al,[21] 2011 (United States)	RIS	40	DBPCT	11 wk	100% inpatients or day hospital patients at baseline; AN type: NR; BMI range: NR; illness duration: NR; comorbidities: depression, OCD, and anxiety disorders allowed, as long as primary diagnosis was AN	RIS: 16.2 ± 2.5 (range, 13–20) PLA: 15.8 ± 2.3 (range, 12–21)	100	*DSM-IV*	RIS: 18 PLA: 22	2.5 ± 1.2 (0.5–4) 3.0 ± 1.0 (1.5–4)	40% ADs, multivitamin, zinc, and medications for other medical conditions, such as constipation, asthma, and gastritis, during the study	Weight: RIS = PLA
First-Generation Antipsychotics												
Vandereycken and Pierloot,[40] 1982 (Belgium)	PIM	18	DBPCT (crossover)	7 wk (7- to 10-d baseline period, two 3-wk trial periods)	Inpatients: 100%; AN type: NR; BMI range: NR; illness duration: 1–14 y (median = 3 y); comorbidities: NR	21.5 (range, 15–36)	100	*DSM-III*	PIM: 8 PLA: 10	(4–6) NR	No	Mean daily weight change: PIM = PLA
Vandereycken,[23] 1984 (Belgium)	SUL	18	DBPCT (crossover)	7 wk (1-wk baseline period, two 3-wk trial periods)	Inpatients: 100%; AN type: NR; BMI range: NR; illness duration: SUL = 4.32 ± 4.1 y, PLA = 6.24 ± 8.91 y; comorbidities: NR	Group 1: 23.2 ± 6.5 Group 2: 23.7 ± 9.6	100	*DSM-III*	SUL: 9 PLA: 9	(300–400) NR	No	Daily weight gain: SUL > PLA

Abbreviations: AD = antidepressant; AN = anorexia nervosa; BMI = body mass index; DBPCT = double-blind, placebo-controlled trial; NR = not reported; OCD = obsessive-compulsive disorder; OLA = olanzapine; PIM = pimozide; PLA = placebo; QUE = quetiapine; RIS = risperidone; SCID-I = Structured Clinical Interview for *DSM-IV* Axis I Disorders; SGA = second-generation antipsychotic; SUL = sulpiride; TAU = treatment as usual.

For continuous data, standardized mean difference (SMD) was used, combining effect size (Hedges *g*) data. For dichotomous data, pooled estimates of relative risk (RR) were calculated along with 95% confidence intervals (CIs). In the case of significant group differences in categorical variables, the number of participants needed to treat (NNT) for beneficial outcomes and the number needed to harm (NNH) for adverse effects were calculated. NNT and NNH were derived from the risk difference (RD) using the following formula: NNT or NNH = 1/RD, with the 95% CIs of NNT/NNH being the inverse of the upper and lower limits of the 95% CI of the RD.

Study heterogeneity was measured using the χ^2 and I^2 statistics, with χ^2 $P < .05$ and $I^2 < 50\%$ indicating heterogeneity.[37] In cases of $I^2 \geq 50\%$, sensitivity analyses were conducted to seek reasons for the heterogeneity. Finally, funnel plots were inspected visually to explore the possibility of publication bias.

RESULTS

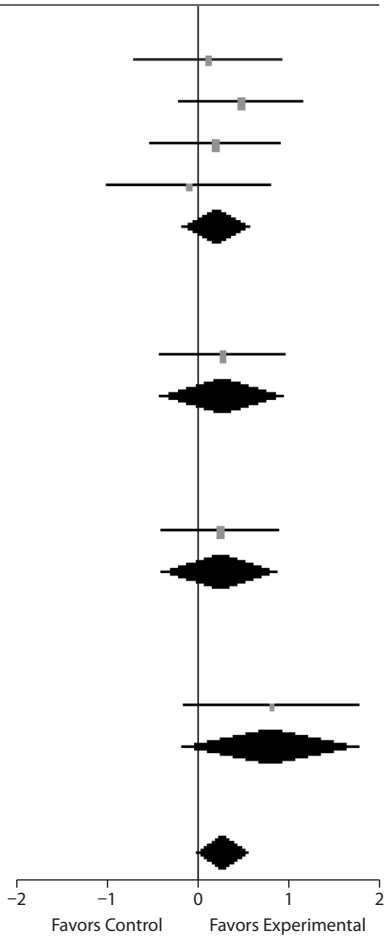
Search Results and Study, Patient, and Treatment Characteristics

The PubMed search yielded 396 references using the above-mentioned keywords *randomized, random, randomly,* and *anorexia nervosa*. We excluded 372 studies based on title and abstract review. An additional 18 full-text articles were excluded because the article was a review paper (11 studies), the study did not use an antipsychotic (4 studies), the study was not placebo- or usual care–controlled (2 studies), the study was not randomized (1 study), or the article included a report on a subsample of the larger study reported elsewhere (1 study). The online search identified 6 studies. Two additional studies were identified from review articles.[38,39] Finally, 8 randomized placebo- or usual care–controlled trials of antipsychotics for anorexia nervosa, including 221 anorexia nervosa patients, met our inclusion criteria. All studies were published in English. Seven studies used placebo[16–19,21,23,40] and 1 study used usual care as the comparison group[20] (Table 1). The mean study duration was 9.6 weeks (range, 7–12 weeks). Sample sizes ranged from 18 to 57, with 8 to 30 participants being randomly assigned to each of the groups. The mean age of the study population was 22.5 years; 2 trials focused on patients aged 12 to 21 years,[19,21] and 6 trials focused on mixed samples of adolescents and adults.[16–18,20,23,40] The overall proportion of females was 99.1%, with 6 of the 8 trials including females only[17–19,21,23,40] and 2 trials including 1 male each[16,20] (Table 1). None of the trials reported the racial/ethnic distribution.

The 221 patients were randomly assigned to olanzapine (n = 54, mean dose: 7.02 mg/d),[16–19] quetiapine (n = 15, mean dose: 322.5 mg/d),[20] risperidone (n = 18,

Figure 1. Differences in Body Weight or Body Mass Index Between Antipsychotic Treatment and Placebo or Usual Care

Study/Subgroup	Antipsychotic Mean	Antipsychotic SD	Antipsychotic n	Placebo Mean	Placebo SD	Placebo n	Weight	Standardized Mean Difference, Inverse Variance, Random-Effects [95% CI]
Olanzapine								
Attia et al,[16] 2011	17.8	2.3	11	17.6	1.3	12	12.1%	0.10 [−0.71 to 0.92]
Bissada et al,[17] 2008	3.53	1.34	16	2.96	1.08	18	17.3%	0.46 [−0.22 to 1.15]
Brambilla et al,[18] 2007	17.22	2	15	16.9	1.2	15	15.7%	0.19 [−0.53 to 0.91]
Kafantaris et al,[19] 2011	1.00	1.78	9	1.16	1.11	10	10.0%	−0.11 [−1.01 to 0.80]
Subtotal			*51*			*55*	*55.0%*	*0.20 [−0.18 to 0.59]*
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_3 = 1.06$ ($P = .79$); $I^2 = 0\%$								
Test for overall effect: $Z = 1.04$ ($P = .30$)								
Quetiapine								
Court et al,[20] 2010	1.7	1.3	15	1.3	1.6	18	17.0%	0.27 [−0.42 to 0.95]
Subtotal			*15*			*18*	*17.0%*	*0.27 [−0.42 to 0.95]*
Heterogeneity: not applicable								
Test for overall effect: $Z = 0.75$ ($P = .45$)								
Risperidone								
Hagman et al,[21] 2011	2.32	1.25	16	2.03	1.15	22	19.3%	0.24 [−0.41 to 0.88]
Subtotal			*16*			*22*	*19.3%*	*0.24 [−0.41 to 0.88]*
Heterogeneity: not applicable								
Test for overall effect: $Z = 0.72$ ($P = .47$)								
Sulpiride								
Vandereycken,[23] 1984	0.15	0.09	9	0.09	0.04	9	8.6%	0.80 [−0.17 to 1.77]
Subtotal			*9*			*9*	*8.6%*	*0.80 [−0.17 to 1.77]*
Heterogeneity: not applicable								
Test for overall effect: $Z = 1.61$ ($P = .11$)								
Total			**91**			**104**	**100.0%**	**0.27 [−0.01 to 0.56]**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_6 = 2.32$ ($P = .89$); $I^2 = 0\%$								
Test for overall effect: $Z = 1.87$ ($P = .06$)								
Test for subgroup differences: $\chi^2_3 = 1.26$ ($P = .74$), $I^2 = 0\%$								



mean dose: 2.5 mg/d),[21] pimozide (n = 8, dose range: 4–6 mg/d),[40] sulpiride (n = 9, dose range: 300–400 mg/d),[23] placebo (n = 99),[16–19,21,23,40] or usual care (n = 18).[20]

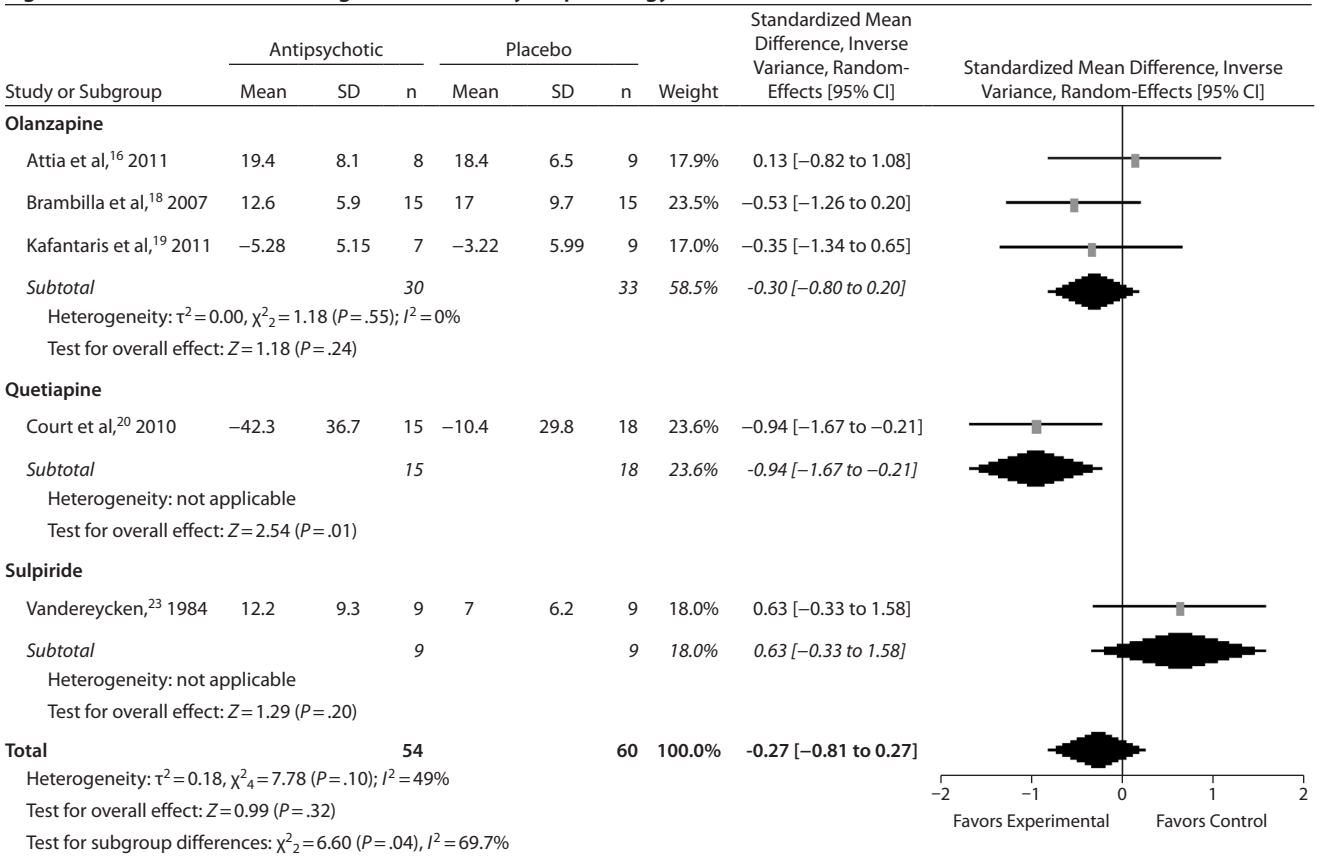
Primary Outcome: Body Mass Index/Weight

Effects on BMI/weight were not significantly different between antipsychotics and placebo/usual care for both individual antipsychotics ($P = .11$ [sulpiride] to $P = .47$ [risperidone]) and all antipsychotics pooled together (SMD = 0.27, 95% CI, −0.01 to 0.56; $P = .06$, 7 studies, n = 195) (Figure 1). These results were homogeneous ($\chi^2 = 2.32$, $P = .89$, and $I^2 = 0\%$), and the funnel plot suggested that publication bias was unlikely (data not shown). The results were not significantly different on the basis of the method of reporting of the primary outcome, ie, BMI change (4 studies)[17,19–21] or endpoint (2 studies)[16,18] or daily weight change (1 study)[23] ($P = .51$, $I^2 = 0\%$), or whether placebo (6 studies)[16–19,21,23] or usual care (1 study)[20] was used as the comparator ($P = .98$, $I^2 = 0\%$). In addition, results were similar across samples consisting of patients aged 12 to 21 years (2 studies)[19,21]or mixed adolescents and adults (5 studies)[16–18,20,23] ($P = .50$, $I^2 = 0\%$). Furthermore, results were also similar for inpatients (3 studies),[16,21,23] outpatients (2 studies),[17,18] and mixed inpatients and outpatients (2 studies)[19,20] ($P = .83$, $I^2 = 0\%$). Dividing the antipsychotics into SGAs[16–21] and FGA[23] revealed that neither of the subgroups separated from the control condition (SGAs: $P = .14$, FGA: $P = .11$). The same was true for all individual antipsychotics (olanzapine, $P = .30$; quetiapine, $P = .45$; risperidone, $P = .47$; sulpiride, $P = .11$) (Figure 1).

Metabolic Outcomes

Glucose level was the only metabolic outcome to be reported in at least 3 studies.[17,19,21] There was no difference in blood glucose levels between pooled antipsychotics and placebo/usual care (SMD = 0.29; 95% CI, −0.31 to 0.89; $P = .34$; $I^2 = 44\%$; 3 studies; n = 86). However, in one study,[19] olanzapine was associated with marginally greater glucose increase than placebo (SMD = 1.06; 95% CI, 0.01–2.11; $P = .05$; 1 study; n = 17).

Figure 2. Anorexia-Related Rating Scale–Based Psychopathology



Questionnaires Related to Anorexia Nervosa

There was no significant difference between pooled antipsychotics and placebo/usual care in the total scores of questionnaires related to anorexia nervosa symptoms (SMD = −0.27, 95% CI, −0.81 to 0.27; $P = .32$, $I^2 = 49\%$, 5 studies, n = 114) (Figure 2)[16,18–20,23] or in the attitudes toward body shape (SMD = 0.03, 95% CI, −0.52 to 0.58; $P = .91$, $I^2 = 0\%$, 4 studies, n = 100).[16,19,21] However, among individual antipsychotics, quetiapine outperformed usual care regarding the total score for eating disorder attitudes (SMD = −0.94, 95% CI, −1.67 to −0.21; $P = .01$, I^2 = not applicable, 1 study, n = 33)[20] (Figure 2).

Depressive Symptoms

There was no significant difference between individual antipsychotics (quetiapine: $P = .10$; olanzapine: $P = .37$) and pooled antipsychotics and the comparison group regarding depressive symptoms (pooled SMD = −0.39, 95% CI, −0.84 to 0.05; $P = .08$, $I^2 = 18\%$, 4 studies, n = 103).[16,17,19,20]

Anxiety Symptoms

There was no significant difference in anxiety symptoms between pooled antipsychotics and placebo/usual care (SMD = −0.17, 95% CI, −0.71 to 0.36; $P = .53$, $I^2 = 52\%$, 4 studies, n = 121).[16,17,20,21] However, among individual antipsychotics, there was a significant advantage of quetiapine over usual care[20] for reducing anxiety (SMD = −0.89, 95% CI, −1.62 to −0.17; $P = .02$, 1 study, n = 33). The same was not true for olanzapine ($P = .72$) and risperidone ($P = .92$).

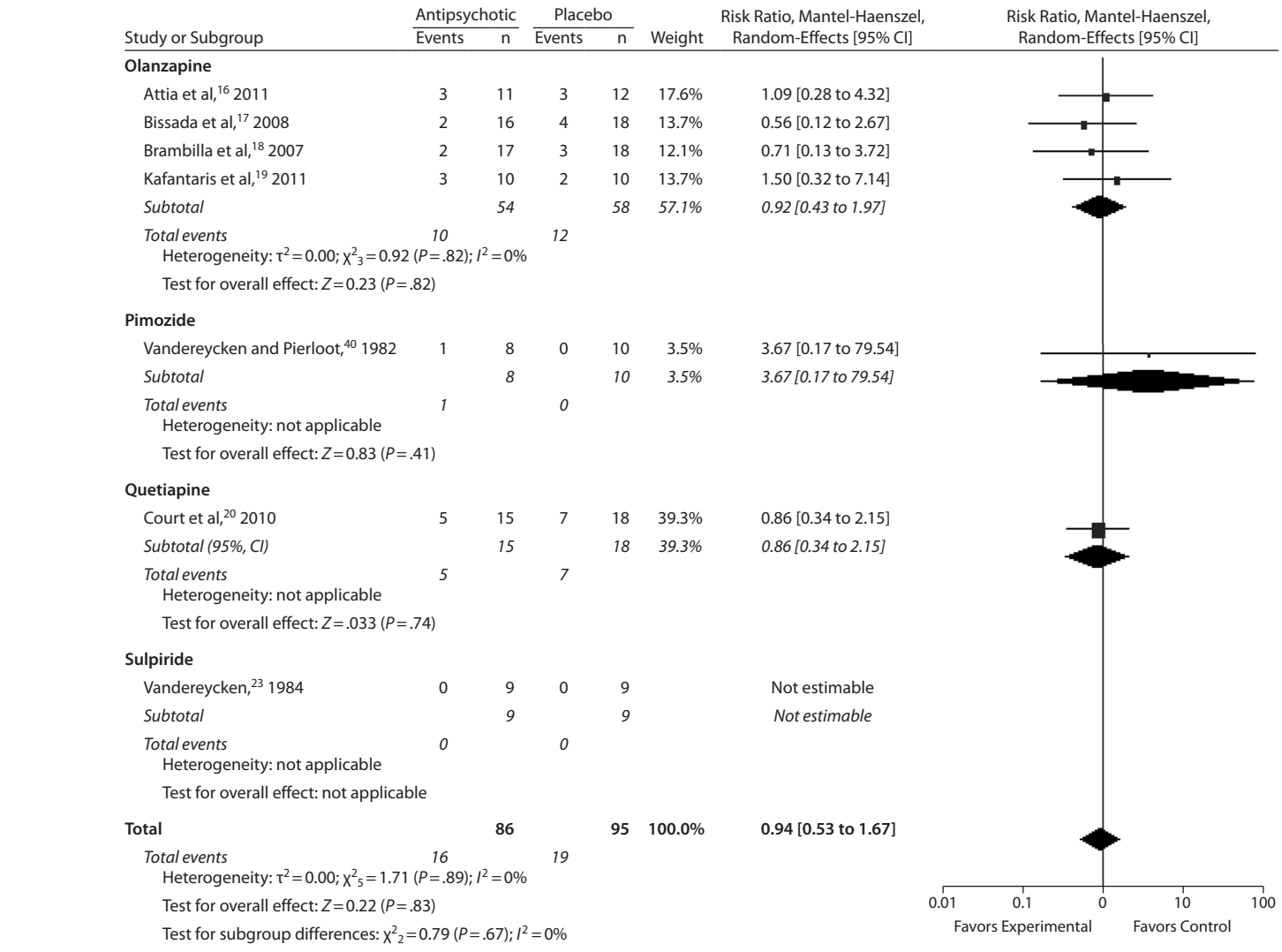
Dropout Rate

Pooled and individual antipsychotics were not different from placebo/usual care regarding either dropout due to any cause (pooled RR = 0.94, 95% CI, 0.53–1.67; $P = .83$, $I^2 = 0\%$, 7 studies, n = 181)[16–20,23,40] (Figure 3) or dropout due to adverse effects (pooled RR = 1.64, 95% CI, 0.34–8.04; $P = .54$, $I^2 = 5\%$, 4 studies, n = 106).[18–20,40]

Side Effects

Rates of akathisia and drowsiness/sedation were the only side effect rates that were reported by at least 3 studies. Akathisia was not significantly more likely with pooled antipsychotics than the control condition (pooled RR = 3.77, 95% CI, 0.70–20.3; $P = .12$, $I^2 = 0\%$, 3 studies, n = 76).[18–20] Drowsiness/sedation was significantly more likely with pooled antipsychotics (pooled RR = 3.69, 95% CI, 1.37–9.95; $P = .01$, $I^2 = 67\%$, 5 studies, n = 129; NNH = 2, 95% CI = 1–4; $P = .001$)[16,18–21] (Figure 4). Among individual antipsychotics, drowsiness/sedation was significantly more frequent in patients treated with olanzapine compared with placebo (RR = 11.45, 95% CI, 2.94–44.54; $P = .0004$, $I^2 = 0\%$; NNH = 2, 95% CI, 1–2; $P < .00001$, 3 studies, n = 68).[16,18,19] Quetiapine

Figure 3. All-Cause Discontinuation



($P = .05$, 1 study, n = 21)[20] and risperidone ($P = .06$, 1 study, n = 40)[21] led to marginally greater drowsiness/sedation (Figure 4).

DISCUSSION

To our knowledge, this is the first formal meta-analysis focusing on the efficacy and tolerability of antipsychotics in the treatment of anorexia nervosa. For this meta-analysis, 8 placebo- or usual care–controlled trials that involved 221 subjects and tested 5 different antipsychotics were examined. Although we hypothesized that antipsychotics would be beneficial in patients with anorexia nervosa, we did not find significant differences between antipsychotics and the comparison groups in analyses that included at least 3 trials regarding any efficacy outcomes, including body weight/BMI, psychopathology related to anorexia nervosa, depressive symptoms, and anxiety. Although discontinuation rates due to any cause and due to adverse effects, glucose levels, and akathisia were also not different between antipsychotics and placebo/usual care, antipsychotics were associated with a significantly greater likelihood of drowsiness/sedation. Overall, results were not significantly heterogeneous, and no obvious publication bias could be identified, although few studies were available for this meta-analysis.

Although in the pooled analyses of weight/BMI differences there was a trend favoring antipsychotics, the nonsignificant effect size was small. This means that even if the standard deviations had been smaller, potentially leading to a statistically significant result, the effects would quite likely have been of little clinical benefit. Moreover, the *P* value for olanzapine, the most weight gain–producing medication for which the most trials (4 trials)[16–19] and patients (n = 106) were available, was clearly nonsignificant ($P = .40$). Thus, these weight change results in patients with anorexia nervosa are in strong contrast to findings in patients with a variety of psychiatric disorders[5,14,15] as well as healthy controls.[41] This discordance is particularly striking, as 4 of the 8 trials involved olanzapine, which has been identified as being among the most weight gain–producing

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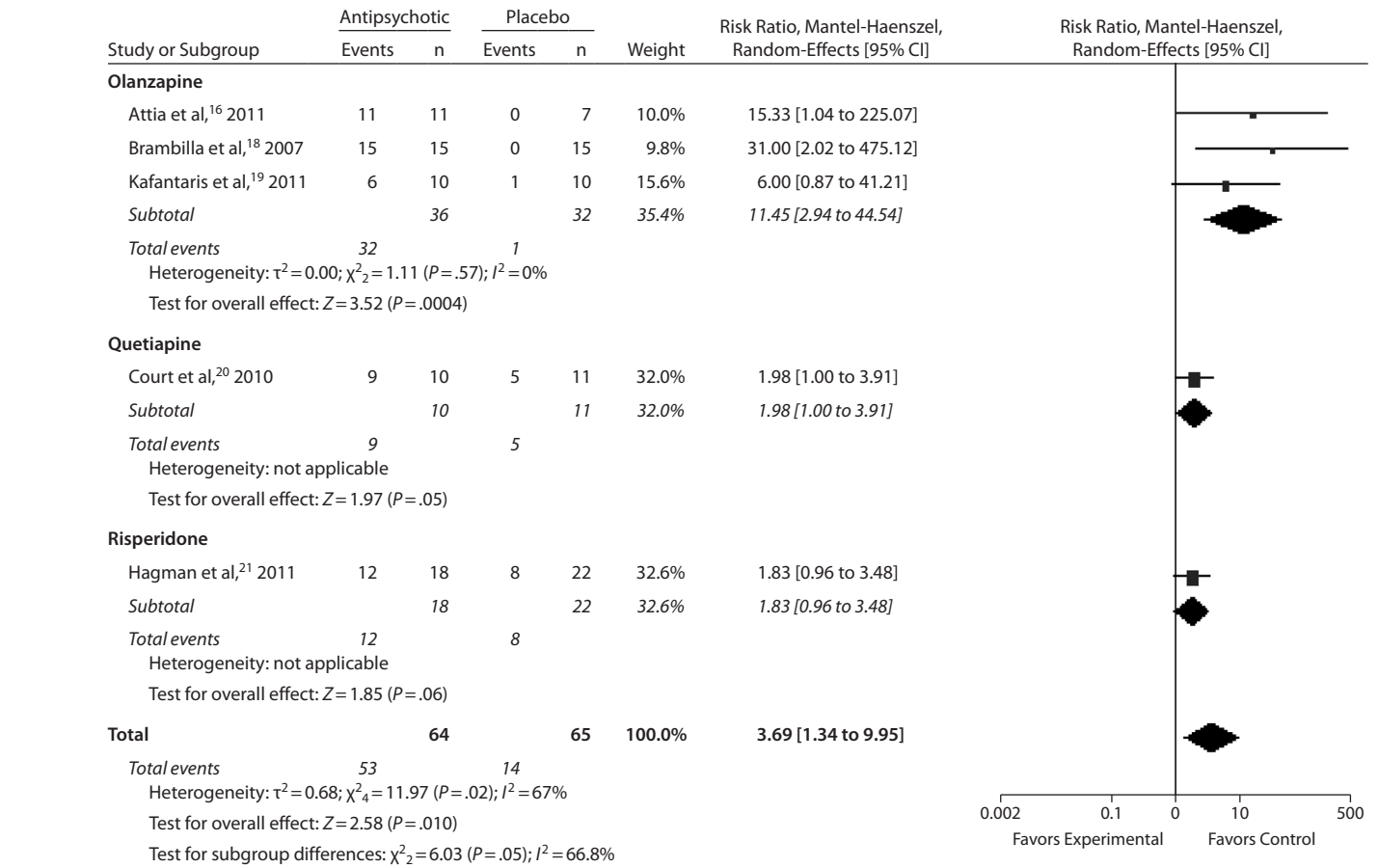
Figure 4. Drowsiness/Sedation/Somnolence



antipsychotics.[5–7,14,15,42] In addition, quetiapine and risperidone have also been associated with a moderate degree of weight gain.[5,14,15,42] Moreover, as mentioned above, most, if not all, anorexia nervosa patients can be considered to have been antipsychotic-naive, and in these individuals, weight gain is expected to be the most pronounced, occurring early in treatment.[12,13]

The reasons for the apparent discrepancy between the results in anorexia nervosa patients and those without anorexia nervosa are not entirely clear but could include the small sample size of these studies or the relatively short study durations. However, since antipsychotic-related weight gain in treatment-naive and young patients is generally substantial and begins early after treatment initiation, at least moderate and clinically relevant effects should have been identifiable with the meta-analytic technique. In fact, the mean 11-week weight gain with olanzapine in antipsychotic-naive, psychiatrically ill children and adolescents was as high as 8.4 kg in a cohort study compared to 0.2 kg in psychiatrically ill youth not receiving antipsychotic treatment.[12] On the basis of these data, it is more likely that anorexia nervosa patients can either biologically or behaviorally resist the weight gain–enhancing effects of antipsychotics. It is possible that anorexia nervosa patients are able to resist hunger signals and neuropeptide changes that gear the body toward increased energy intake. In fact, in anorexia nervosa patients, low leptin levels and high ghrelin levels have been found that would generally induce appetite and food intake.[43] However, due to their pathology and as yet unknown biological circuits, anorexia nervosa patients seem to physiologically disconnect from these orexigenic signals.[43]

In fact, the negative results found in this study might argue that antipsychotic-related weight gain may be more related to shifting the energy balance toward an orexigenic, calorie intake–geared mode, rather than to a slowing of the metabolism.[14,15] In one study,[44] patients with anorexia nervosa, restricting type, required significantly higher energy intake to gain weight than patients with anorexia nervosa, bulimic type, and both groups required greater energy intake than normal-weight bulimia patients to maintain their body weight. On the other hand, one could also argue that in anorexia nervosa patients, the metabolism is already maximally tuned down in order to conserve energy,[45] so that there would be a floor effect for any potential, additional antipsychotic-related switching to energy-conserving metabolic states. Clearly, to inform this discussion, careful studies that focus on energy metabolism and neuropeptide signaling in anorexia nervosa patients receiving antipsychotics or placebo are needed.

Whereas, overall, there was no apparent efficacy on anorexia nervosa–related psychopathology or on depression

and anxiety, patients treated with antipsychotics experienced significantly more sedation/somnolence. Although quetiapine showed a significant beneficial effect on anxiety and anorexia nervosa symptomatology, which was not the case for other antipsychotics, results were based on a single study that did not use a placebo comparator.[20] While advantages of quetiapine could possibly be explained by its different pharmacologic profile, additional, high-quality studies are needed that evaluate the effects of quetiapine in anorexia nervosa patients before any clinically relevant conclusions can be obtained. Furthermore, at least in 1 study, fasting glucose levels increased near-significantly with olanzapine,[19] and data for insulin, insulin resistance, lipid levels, and lipid abnormalities were insufficiently reported to assess potentially detrimental metabolic effects[5–7,14,15] in more detail. This is particularly relevant, as at least some antipsychotics may have additional, weight-independent, adverse metabolic effects.[12,46] Taken together, the currently available evidence seems to tilt the risk-benefit balance against antipsychotics in patients with anorexia nervosa.

However, the results of this study should be interpreted within the study's limitations. The main limitation is the paucity of studies and their small sample sizes. Specifically, there was only 1 study each with quetiapine,[20] risperidone,[21] pimozide,[40]and sulpiride.[23] Since we detected marginal differences in BMI/weight ($P = .06$) and depressive symptoms ($P = .08$) between pooled antipsychotics and placebo/usual care, the nonsignificant results could be due to a type II error. However, given the nonsignificant weight gain results in a total of 195 patients, effect sizes in larger samples are likely to be small, even in anorexia nervosa patients who are willing to sign up for a study in which they "risk" gaining weight. Furthermore, meta-analyzable data on metabolic outcomes were limited to glucose. In addition, adherence to antipsychotic treatment was not formally assessed, although it is known that anorexia nervosa patients go to great lengths to conceal attempts at countering weight gain.[47] Therefore, any future studies should perform formal adherence assessments, including random blood antipsychotic level sampling. In addition, studies rarely reported information on potentially relevant moderators of outcome that could be used to assess if certain patient subgroups may benefit more from antipsychotic treatment. Future studies should collect and report information on anorexia nervosa subtype, illness duration, number and type of prior weight gain treatment attempts, comorbid conditions, and illness insight, as well as motivation or readiness for change. In addition, more studies are needed to determine if longer treatment duration may be beneficial or if patient subgroups may derive additional benefit from antipsychotic treatment.

Another limitation is that most of the included studies did not report important tolerability outcomes, such as parkinsonian side effects, prolactin levels, electrocardiogram data (to rule out cardiac conduction prolongation/abnormalities), osteopenia, and glucose and lipid metabolism parameters with high relevance for future cardiovascular morbidity and mortality, and electrolyte disturbances (eg, refeeding syndrome, hypomagnesemia, hypokalemia, and metabolic alkalosis).[48] Finally, all 8 trials contributing data to this meta-analysis were of short duration (≤ 12 weeks). Thus, any additional studies assessing antipsychotic effects in anorexia nervosa should collect detailed, longer-term efficacy and safety data. Nevertheless, despite these shortcomings, this meta-analysis provides pooled data that help to evaluate the clinical utility of antipsychotics for anorexia nervosa, a treatment strategy often used off-label in clinical practice.

CONCLUSION

Although limited by a low number of studies including relatively small samples, this meta-analysis failed to demonstrate significant antipsychotic efficacy for body weight and related outcomes in females with anorexia nervosa. While quetiapine appeared to have at least a positive effect on anorexia nervosa symptoms and anxiety in the studied anorexia nervosa patients, results were limited to a single study in which no placebo comparator was used and weight gain was not larger than in the usual care group. Given these findings, considerable side effect concerns further mitigate the utility of antipsychotics for anorexia nervosa. Until additional data suggest otherwise, there does not appear to be an evidence-based justification for the use of antipsychotics for the enhancement of weight gain and for other core symptoms of patients with anorexia nervosa. Rather, to improve the patient's body weight and psychopathology, clinicians should focus on psychological, behavioral, and medical interventions that have at least some, albeit modest, evidence of efficacy.[49–53] Future studies are needed that investigate novel approaches to treat anorexia nervosa, which shows remarkable resistance to treatment efforts.

Drug names: olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal and others).

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Author contributions: Dr Kishi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Correll. **Acquisition of data:** Kishi and Correll. **Analysis and interpretation of data:** Kishi, Sunday, and Correll. **Drafting of the manuscript:** Kishi, Kafantaris, Sunday, Sheridan, and Correll.

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