Antipsychotics in Adults With Schizophrenia: Comparative Effectiveness of First-Generation Versus Second-Generation Medications

A Systematic Review and Meta-analysis

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Background: Debate continues about the comparative benefits and harms of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in treating schizophrenia.

Purpose: To compare the effects of FGAs with those of SGAs in the treatment of adults aged 18 to 64 years with schizophrenia and related psychosis on illness symptoms, diabetes mellitus, mortality, tardive dyskinesia, and a major metabolic syndrome.

Data Sources: English-language studies from 10 electronic databases to March 2012, reference lists of relevant articles, and gray literature.

Study Selection: Randomized trials for efficacy and cohort studies at least 2 years in duration for adverse events.

Data Extraction: Two independent reviewers extracted data from 114 studies involving 22 comparisons and graded the strength of evidence for primary outcomes as insufficient, low, moderate, or high using the Grading of Recommendations Assessment, Development and Evaluation approach.

Data Synthesis: Few differences of clinical importance were found for core illness symptoms; lack of precision in effect estimates precluded firm conclusions for many comparisons. Moderate-strength evidence showed a clinically important benefit of haloperidol over olanzapine for improving positive symptoms, but the benefit was scale-dependent: It was seen when the Scale for the Assessment of Positive Symptoms was used but not when the Positive and Negative Syndrome Scale (PANSS) was used. Moderate-strength evidence showed a clinically important benefit of olanzapine over haloperidol in improving negative symptoms when the PANSS and the Scale for the Assessment of Negative Symptoms were used. Low-strength evidence showed no difference in mortality for chlorpromazine verus clozapine or haloperidol versus aripiprazole, increased incidence of the metabolic syndrome for olanzapine versus haloperidol (risk differences, 2% and 22%), and higher incidence of tardive dyskinesia for chlorpromazine versus clozapine (risk differences, 5% and 9%). Evidence was insufficient to draw conclusions for diabetes mellitus.

Limitations: All studies had high or unclear risk of bias. Length of study follow-up was often too brief to adequately measure adverse events. Medication comparisons, dosage, and outcome measurement were heterogenous for head-to-head comparisons. Selective patient populations limit generalizability.

Conclusion: Clear benefits of FGAs versus SGAs for treating schizophrenia remain inconclusive because of variation in assessing outcomes and lack of clinically important differences for most comparisons. The strength of evidence on safety for major medical events is low or insufficient.

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The introduction of second-generation antipsychotics (SGAs) for treatment of schizophrenia was an important effort to improve symptom management, reduce extrapyramidal symptoms caused by first-generation antipsychotics (FGAs), and offer patients improved quality of life and functioning. Today, 20 commercial FGAs and SGAs that have been approved by the U.S. Food and Drug Administration (FDA) are available in the United States (**Appendix Table 1**, available at www.annals.org). Of these, SGAs are more frequently prescribed by physicians. In 2003, three quarters of the 2 million adult patients in the United States who were prescribed an antipsychotic medication were prescribed an SGA, which accounted for 93% of the estimated $2.82 billion spent on these medications in the United States (1).

Recent large-scale trials and meta-analyses have called into question whether SGAs and FGAs provide clinically important differences for patient outcomes (1–3), and the question of which medication is more efficacious has yet to be definitively answered. Part of the uncertainty about medication efficacy relates to the lack of studies focused on long-term management. Such issues as how patient management should be influenced by medication heterogeneity within the 2 classes also add ambiguity for physician decision making (1, 4–6), as do differences between recently published reviews in defining eligible medication comparisons, patients, and clinically important outcomes and evaluating the strength of evidence (1, 7–19).

This comparative effectiveness review summarizes the benefits and harms associated with commercially available, FDA-approved FGAs and SGAs. Broad inclusion criteria were used for comparisons among FGAs and SGAs, patients, and study outcomes to address the diversity of previously published reviews.

Methods

We followed an open process for this review with input from various stakeholders, including the public (20),

and a protocol that followed standards for systematic reviews (21–23). A full technical report with detailed search strategies, methods, and evidence tables is available from the Agency for Healthcare Research and Quality (21).

Literature Search

We conducted comprehensive searches in MEDLINE (**Appendix Table 2**, available at www.annals.org), EMBASE, PsycINFO, International Pharmaceutical Abstracts, CINAHL, ProQuest Dissertations and Theses—Full Text, the Cochrane Central Register of Controlled Trials, and Scopus for studies published from 1950 to March 2012. For adverse events, we also searched the U.S. National Library of Medicine's TOXLINE and the MedEffect Canada Adverse Reaction Database.

We hand-searched proceedings from the annual meetings of the American Psychiatric Association (2008–2010) and the International College of Neuropsychopharmacology (2008–2010). We searched clinical trial registries and contacted experts in the field and authors of relevant studies. We retrieved new drug applications for each of the included interventions from the FDA Web site. We reviewed the reference lists of reviews, guidelines, and new drug applications and searched for articles citing relevant studies using Scopus Citation Tracker.

Study Selection

Two reviewers independently screened titles and abstracts. We retrieved the full text of potentially relevant studies. Two reviewers independently reviewed each article using a standardized form with a priori eligibility criteria (**Appendix Table 3**, available at www.annals.org). We resolved discrepancies through discussion or third-party adjudication. We included studies if they were randomized, controlled trials (RCTs); were nonrandomized, controlled trials (non-RCTs); were cohort studies with a minimum follow-up of 2 years; included adults aged 18 to 64 years with schizophrenia or related psychoses; compared a commercially available FDA-approved FGA with an FDA-approved SGA; and provided data on illness symptoms (**Appendix Table 4**, available at www.annals.org) or the following adverse events: diabetes mellitus, death, tardive dyskinesia, or a major metabolic syndrome.

Quality Assessment and Rating the Body of Evidence

Two reviewers independently assessed the methodological quality of included studies and resolved disagreements through discussion. We assessed RCTs and non-RCTs using the Cochrane Risk of Bias Tool (22) and cohort studies using the Newcastle–Ottawa Scale (24).

Two reviewers independently evaluated strength of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach of the Evidence-based Practice Center Program and resolved discrepancies through discussion (25). We examined 4 domains: risk of bias, consistency, directness, and precision. Within the grading system, randomized trials always begin with a "high" strength of evidence that can be downgraded on the basis of shortcomings in the body of evidence (for example, overall risk of bias, inconsistency between study results, indirectness of the measured outcomes, and imprecision of the pooled estimate). In contrast, observational studies (for example, cohort studies) begin with a "low" strength of evidence that can be further downgraded (similar to randomized trials) but can also, in rare cases, be upgraded. We assigned an overall grade of "high," "moderate," "low," or "insufficient" strength of evidence. We graded core illness symptoms in the categories of positive symptoms, negative symptoms, general psychopathology, and global ratings or total scores (typically a compilation of positive and negative symptoms or general psychopathology, which included these symptoms plus mood states). We provided a grade for each scale that was reported in the relevant studies. We also graded the adverse events listed in the previous section.

Data Extraction

Two reviewers independently extracted data using standardized forms and resolved discrepancies by referring to the original report. We extracted information on study characteristics, populations, interventions, outcomes, and results. Primary outcomes were improved core symptoms

Figure. **Summary of evidence search and selection.**

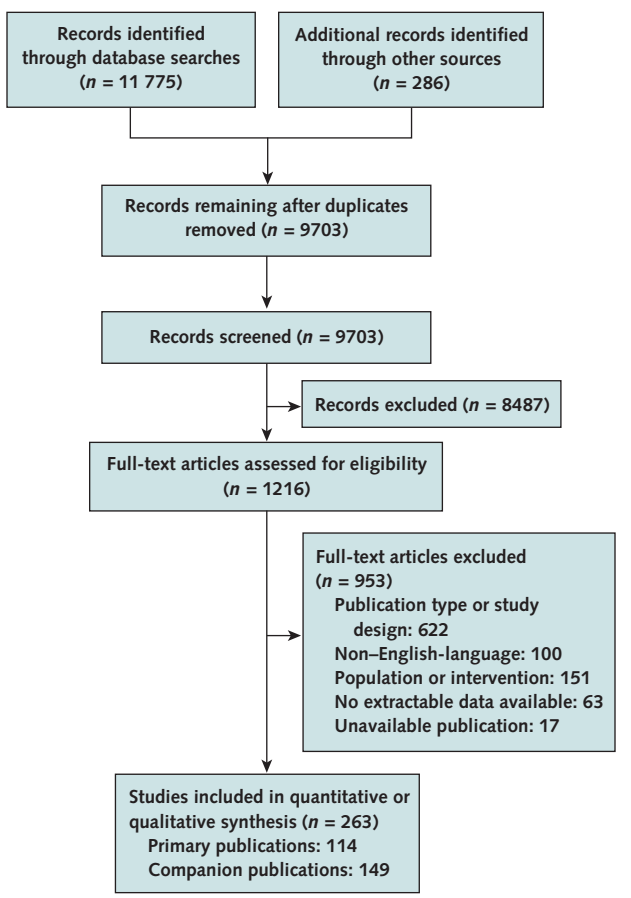

Table 1. **Summary of Results and Strength of Evidence for Core Illness Symptoms***

Variable, Scale, and Comparison	Studies (Participants), *n (n)*	Risk of Bias	Consistency	Precision	Mean Difference (95% CI)	Favored Drug	Strength of Evidence
Positive symptoms							
PANSS							
Haloperidol vs. risperidone	22 (4142)	Medium	Consistent	Precise	0.77 (0.09 to 1.45)†	Risperidone‡	Low§
Haloperidol vs. clozapine	3 (184)	Medium	Consistent	Imprecise	−0.82 (−2.21 to 0.57)	–	Low
Haloperidol vs. olanzapine	14 (3742)	Medium	Consistent	Imprecise	0.43 (−0.22 to 1.08)	–	Low
Haloperidol vs. quetiapine	3 (358)	Medium	Consistent	Imprecise	0.83 (−0.29 to 1.95)	–	Low
Haloperidol vs. aripiprazole	2 (407)	Medium	Consistent	Imprecise	−0.99 (−2.64 to 0.67)	–	Low
SAPS							
Haloperidol vs. olanzapine	2 (178)	Medium	Consistent	Precise	−3.14 (−4.90 to −1.37)†	Haloperidol	Moderate
Haloperidol vs. risperidone	2 (195)	Medium	Consistent	Imprecise	−0.26 (−1.90 to 1.38)	–	Low
Negative symptoms							
PANSS							
Haloperidol vs. olanzapine	14 (3742)	Medium	Consistent	Precise	1.06 (0.46 to 1.67)†	Olanzapine	Moderate
Haloperidol vs. aripiprazole	3 (1701)	Medium	Consistent	Precise	0.80 (0.14 to 1.46)†	Aripiprazole‡	Moderate
Haloperidol vs. risperidone	22 (4142)	Medium	Consistent	Precise	0.61 (0.07 to 1.16)†	Risperidone‡	Moderate
Haloperidol vs. clozapine	3 (184)	Medium	Consistent	Imprecise	0.28 (−0.96 to 1.51)	–	Low
Haloperidol vs. quetiapine	3 (358)	Medium	Consistent	Imprecise	0.53 (−0.81 to 1.87)	–	Low
Haloperidol vs. ziprasidone	2 (900)	Medium	Consistent	Imprecise	0.56 (−0.30 to 1.42)	–	Low
SANS							
Haloperidol vs. olanzapine	5 (535)	Medium	Consistent	Precise	2.56 (0.94 to 4.18)†	Olanzapine	Moderate
Haloperidol vs. risperidone	4 (508)	Medium	Consistent	Imprecise	0.30 (−2.79 to 3.38)	–	Low
Haloperidol vs. clozapine	2 (157)	Medium	Consistent	Imprecise	0.94 (−2.60 to 4.48)	–	Low
Global ratings and total scores							
PANSS							
Haloperidol vs. risperidone	21 (4020)	Medium	Consistent	Precise	3.24 (1.62 to 4.86)‖	Risperidone	Moderate
Haloperidol vs. olanzapine	15 (4209)	Medium	Consistent	Precise	2.31 (0.44 to 4.18)†	Olanzapine	Moderate
Haloperidol vs. clozapine	4 (607)	Medium	Consistent	Imprecise	2.69 (−1.28 to 6.65)	–	Low
Haloperidol vs. quetiapine	5 (1013)	Medium	Consistent	Imprecise	0.31 (−2.34 to 2.96)	–	Low
Haloperidol vs. ziprasidone	4 (1105)	Medium	Consistent	Imprecise	1.22 (−0.62 to 3.07)	–	Low
BPRS							
Chlorpromazine vs. clozapine	6 (535)	Medium	Consistent	Precise	8.40 (5.92 to 10.88)†	Clozapine	Moderate
Haloperidol vs. aripiprazole	3 (779)	Medium	Consistent	Imprecise	−0.01 (−2.82 to 2.81)	–	Low
Haloperidol vs. risperidone	14 (2659)	Medium	Consistent	Imprecise	0.67 (−0.53 to 1.88)	–	Low
Haloperidol vs. quetiapine	4 (756)	Medium	Consistent	Imprecise	1.23 (−0.50 to 2.96)	–	Low
Haloperidol vs. clozapine	4 (268)	Medium	Consistent	Imprecise	2.16 (−0.56 to 4.87)	–	Low
Haloperidol vs. olanzapine	13 (4014)	Medium	Consistent	Imprecise	0.19 (−2.09 to 2.47)	–	Low
Haloperidol vs. ziprasidone	4 (1078)	Medium	Consistent	Imprecise	0.24 (−0.57 to 1.06)	–	Low
CGI-S							
Haloperidol vs. olanzapine	8 (3564)	Medium	Consistent	Precise	0.16 (0.01 to 0.31)†	Olanzapine‡	Moderate
Haloperidol vs. quetiapine	4 (1253)	Medium	Consistent	Precise	−0.23 (−0.42 to −0.04)†	Haloperidol‡	Moderate
Haloperidol vs. aripiprazole	5 (1366)	Medium	Consistent	Imprecise	−0.03 (−0.20 to 0.14)	–	Low
Haloperidol vs. risperidone	8 (2348)	Medium	Consistent	Imprecise	0.07 (−0.11 to 0.25)	–	Low
Haloperidol vs. ziprasidone	4 (1143)	Medium	Consistent	Imprecise	−0.00 (−0.26 to 0.26)	–	Low
CGI-I							
Haloperidol vs. olanzapine	2 (281)	Medium	Consistent	Imprecise	0.11 (−0.30 to 0.51)	–	Low
Haloperidol vs. quetiapine	3 (623)	Medium	Consistent	Imprecise	0.02 (−0.24 to 0.27)	–	Low
Haloperidol vs. risperidone	3 (657)	Medium	Consistent	Imprecise	−0.02 (−0.39 to 0.36)	–	Low
GAF							
Haloperidol vs. ziprasidone	3 (1085)	Medium	Consistent	Imprecise	0.30 (−1.58 to 2.19)	–	Low
General psychopathology							
PANSS							
Haloperidol vs. clozapine	3 (184)	Medium	Consistent	Imprecise	1.77 (−2.99 to 6.53)	–	Low
Haloperidol vs. olanzapine	10 (1187)	Medium	Consistent	Imprecise	0.53 (−1.20 to 2.25)	–	Low
Haloperidol vs. quetiapine	3 (358)	Medium	Consistent	Imprecise	1.55 (−0.29 to 3.38)	–	Low
Haloperidol vs. risperidone	16 (3036)	Medium	Consistent	Imprecise	0.87 (−0.48 to 2.21)	–	Low
HAM-D							
Haloperidol vs. olanzapine	3 (209)	Medium	Consistent	Imprecise	1.14 (−0.60 to 2.89)	–	Low
Haloperidol vs. risperidone	2 (408)	Medium	Consistent	Imprecise	−0.64 (−1.97 to 0.69)	–	Low
HAM-A							
Haloperidol vs. olanzapine	2 (283)	Medium	Consistent	Imprecise	0.90 (−0.43 to 2.23)	–	Low
MADRS							
Haloperidol vs. olanzapine	6 (2639)	Medium	Consistent	Precise	2.46 (1.78 to 3.14)†	Olanzapine	Moderate

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Table 1—**Continued**

Variable, Scale, and Comparison	Studies (Participants), *n (n)*	Risk of Bias	Consistency	Precision	Mean Difference (95% CI)	Favored Drug	Strength of Evidence
CDSS							
Haloperidol vs. olanzapine	3 (344)	Medium	Consistent	Imprecise	0.61 (−0.47 to 1.68)	–	Low
Haloperidol vs. quetiapine	2 (232)	Medium	Consistent	Imprecise	0.03 (−0.52 to 0.58)	–	Low
Haloperidol vs. risperidone	3 (485)	Medium	Consistent	Imprecise	−0.24 (−0.94 to 0.46)	–	Low
ABS							
Haloperidol vs. olanzapine	2 (482)	Medium	Consistent	Imprecise	0.80 (−1.22 to 2.83)	–	Low
ACES							
Haloperidol vs. olanzapine	2 (482)	Medium	Consistent	Imprecise	0.06 (−0.40 to 0.53)	–	Low
YMRS							
Haloperidol vs. risperidone	2 (408)	Medium	Consistent	Imprecise	0.02 (−0.67 to 0.71)	–	Low

ABS = Agitated Behavior Scale; ACES = Agitation–Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impression—Improvement; CGI-S = Clinical Global Impression—Severity; GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery–Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; YMRS = Young Mania Rating Scale.
* All trials provided results from direct comparisons.
† Statistically significant result.
‡ Result was not clinically important (difference <20%).
§ Downgraded from moderate to low for publication bias.
‖ Statistically significant result with outlier removed.

of illness (positive and negative symptoms and general psychopathology) and 4 adverse events specified a priori. Secondary outcomes included functional outcomes; health care system use; response, remission, and relapse rates and medication adherence; health-related quality of life; other patient-oriented outcomes (for example, patient satisfaction); and general and specific measures of other adverse events (for example, extrapyramidal symptoms and weight gain).

When studies incorporated multiple relevant treatment groups or multiple follow-up periods, we extracted data from all groups for the longest follow-up period. In cases of multiple reports of the same study, we referenced the primary, or most relevant, study and extracted additional data from companion reports.

Data Analysis

We conducted meta-analyses in RevMan, version 5.01 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark), using a random-effects model (26) when studies were sufficiently similar in terms of design, population, interventions, and outcomes. We combined risk ratios for dichotomous outcomes using the DerSimonian and Laird random-effects model and combined continuous outcomes using mean differences with 95% CIs. We quantified statistical heterogeneity using the I^2 statistic. For trials with multiple study groups, we pooled the data for all relevant groups in the same trial before including the study in any meta-analysis so that the same groups were never represented more than once in any given meta-analysis. Where measures of variance were not reported in the studies, we imputed the variance from the largest reported SD in the given meta-analysis.

We conducted subgroup and sensitivity analyses for illness or disorder subtypes, sex, age group (18 to 35 years, 36 to 54 years, and 55 to 64 years), race, comorbid conditions, drug dosage, follow-up period, previous exposure to antipsychotics, treatment of a first episode versus prior episodes, and treatment resistance. Details of these analyses are presented in the appendices to the full technical report. We report subgroup and sensitivity analyses if there was substantial heterogeneity ($I^2 \geq 50\%$). For comparisons with at least 10 studies, we assessed publication bias using funnel plots and statistical tests (27–29). For our primary outcome of core symptoms, we considered a difference of 20% to be clinically important (7, 30). We calculated absolute differences (that is, risk differences) for adverse events to enhance interpretation of results.

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the initial questions and approved copyright assertion for the manuscript but did not participate in the literature search, data analysis, or interpretation of the results.

RESULTS

A total of 9703 unique study reports were identified; we included 114 primary publications (2, 31–143) (110 RCTs, 2 non-RCTs, and 2 retrospective cohort studies) and 149 companion publications (**Figure**). The studies were published between 1974 and 2012 and involved 22 drug comparisons. Most studies were multicenter (54%), involved inpatients (48%), and were conducted in North America (42%). The number of participants ranged from 10 to 118 522 (median, 78; interquartile range, 38 to 296). The average participant age ranged from 21 to 50 years (median, 37 years; interquartile range, 32 to 40 years). The length of follow-up (that is, study duration) ranged from less than 1 day to 4 years (median, 8 weeks;

Table 2. **Summary of Results for Other Outcomes**

Variable and Comparison	Events/Participants, *n/N**		Effect Estimate (95% CI)
	FGAs	SGAs	
Medication adherence			
Chlorpromazine vs. clozapine	8/83	21/81	RR, 0.37 (0.17 to 0.79)†
Haloperidol vs. aripiprazole‡	0/33	1/66	RR, 0.66 (0.03 to 15.70)
Haloperidol vs. olanzapine	99/153	127/214	RR, 1.12 (0.86 to 1.46)
Haloperidol vs. risperidone	283/361	307/419	RR, 1.04 (0.89 to 1.21)
Time to all-cause medication discontinuation			
Perphenazine vs. olanzapine	48	229	MD, −78.70 (−119.34 to −38.06)†
Perphenazine vs. risperidone	48	221	MD, −33.40 (−75.18 to 8.38)
Response rates§			
Chlorpromazine vs. clozapine	6/169	48/154	RR, 0.13 (0.06 to 0.28)†
Chlorpromazine vs. olanzapine	0/42	3/42	RR, 0.14 (0.01 to 2.68)
Chlorpromazine vs. quetiapine	52/100	65/101	RR, 0.81 (0.64 to 1.02)
Chlorpromazine vs. ziprasidone	85/154	88/152	RR, 0.95 (0.78 to 1.16)
Haloperidol vs. olanzapine	747/1606	1312/2493	RR, 0.86 (0.78 to 0.96)†
Haloperidol vs. clozapine	23/87	43/91	RR, 0.52 (0.22 to 1.23)
Haloperidol vs. quetiapine	275/611	370/810	RR, 0.99 (0.76 to 1.30)
Haloperidol vs. risperidone	641/1113	1404/2374	RR, 0.94 (0.86 to 1.02)
Haloperidol vs. aripiprazole	374/816	652/1369	RR, 1.01 (0.76 to 1.34)
Haloperidol vs. asenapine	49/115	115/220	RR, 0.82 (0.64 to 1.04)
Haloperidol vs. ziprasidone	250/482	489/801	RR, 0.98 (0.74 to 1.30)
Fluphenazine vs. olanzapine	17/30	23/30	RR, 0.74 (0.51 to 1.07)
Fluphenazine vs. quetiapine	2/13	3/12	RR, 0.62 (0.12 to 3.07)
Fluphenazine vs. risperidone	2/13	3/13	RR, 0.67 (0.13 to 3.35)
Perphenazine vs. aripiprazole	36/146	40/154	RR, 0.95 (0.64 to 1.40)
Remission rates			
Chlorpromazine vs. clozapine	69/95	70/94	RR, 0.69 (0.23 to 2.06)
Haloperidol vs. olanzapine	89/291	133/291	RR, 0.65 (0.45 to 0.94)†
Haloperidol vs. clozapine	1/34	7/37	RR, 0.16 (0.02 to 1.20)
Haloperidol vs. quetiapine	17/103	24/104	RR, 0.72 (0.41 to 1.25)
Haloperidol vs. risperidone	28/87	36/92	RR, 0.84 (0.56 to 1.24)
Haloperidol vs. ziprasidone	99/407	199/678	RR, 0.89 (0.71 to 1.12)
Relapse rates			
Chlorpromazine vs. clozapine	11/83	13/81	RR, 0.83 (0.39 to 1.73)
Haloperidol vs. risperidone	244/704	179/701	RR, 1.35 (1.17 to 1.57)†
Haloperidol vs. clozapine	2/37	3/38	RR, 0.68 (0.12 to 3.87)
Rates of hospitalization or rehospitalization			
Chlorpromazine vs. clozapine	5/83	7/81	RR, 0.70 (0.23 to 2.11)
Haloperidol vs. olanzapine	14/103	18/105	RR, 0.79 (0.42 to 1.51)
Haloperidol vs. quetiapine	14/103	14/104	RR, 1.01 (0.51 to 2.01)
Haloperidol vs. risperidone	28/209	16/213	RR, 1.94 (0.99 to 3.79)
Haloperidol vs. ziprasidone	16/256	5/230	RR, 2.62 (0.99 to 6.97)
Perphenazine vs. olanzapine	41/261	38/336	RR, 1.39 (0.92 to 2.09)
Perphenazine vs. quetiapine	41/261	68/337	RR, 0.78 (0.55 to 1.11)
Perphenazine vs. risperidone	41/261	51/341	RR, 1.05 (0.72 to 1.53)
Perphenazine vs. ziprasidone	41/261	33/185	RR, 0.88 (0.58 to 1.34)
Mean hospital bed days			
Haloperidol vs. clozapine	218	205	MD, −7.10 (−19.02 to 4.82)
Haloperidol vs. olanzapine	150	159	MD, −7.10 (−20.95 to 6.75)
Health-related quality of life			
20% improvement			
Perphenazine vs. aripiprazole	31/146	55/154	RR, 0.59 (0.41 to 0.87)†
QLS			
Haloperidol vs. ziprasidone	151	448	MD, −12.12 (−22.06 to −2.17)†
Haloperidol vs. olanzapine	103	227	MD, −2.62 (−6.39 to 1.15)
Haloperidol vs. risperidone	30	33	MD, 0.10 (−0.17 to 0.37)
Perphenazine vs. olanzapine	261	336	MD, 0.00 (−0.16 to 0.16)
Perphenazine vs. quetiapine	261	337	MD, 0.10 (−0.07 to 0.27)
Perphenazine vs. risperidone	261	341	MD, −0.07 (−0.24 to 0.10)
Perphenazine vs. ziprasidone	261	185	MD, −0.07 (−0.27 to 0.13)

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Table 2—**Continued**

Variable and Comparison	Events/Participants, *n/N**		Effect Estimate (95% CI)
	FGAs	SGAs	
MANSA			
Haloperidol vs. olanzapine	103	105	MD, 0.00 (−1.38 to 1.38)
Haloperidol vs. quetiapine	103	104	MD, 0.00 (−1.38 to 1.38)
Haloperidol vs. ziprasidone	103	82	MD, −0.10 (−1.48 to 1.28)
LQLP			
Haloperidol vs. risperidone	146	143	MD, 0.10 (−0.20 to 0.40)
Schizophrenia-specific QLS			
Haloperidol vs. olanzapine	132	144	MD, −3.62 (−8.94 to 1.70)
Other			
Haloperidol vs. olanzapine	10	17	MD, −2.05 (−25.81 to 21.71)
Patient satisfaction			
Haloperidol vs. aripiprazole	7/33	42/66	RR, 0.33 (0.17 to 0.66)†
Haloperidol vs. clozapine	9/17	11/17	RR, 0.82 (0.46 to 1.45)
Haloperidol vs. risperidone	11/33	17/34	RR, 0.67 (0.37 to 1.20)
Caregiver satisfaction: haloperidol vs. aripiprazole	6/33	38/66	RR, 0.32 (0.15 to 0.67)†
Patients with paid employment in past month			
Perphenazine vs. olanzapine	19/261	19/336	RR, 1.29 (0.70 to 2.38)
Perphenazine vs. quetiapine	19/261	14/337	RR, 1.75 (0.90 to 3.43)
Perphenazine vs. risperidone	19/261	18/341	RR, 1.38 (0.74 to 2.57)
Perphenazine vs. ziprasidone	19/261	11/185	RR, 1.22 (0.60 to 2.51)
Sexual dysfunction			
Fluphenazine vs. quetiapine	7/13	3/12	RR, 2.15 (0.72 to 6.48)
Fluphenazine vs. risperidone	7/13	5/13	RR, 1.40 (0.60 to 3.28)
Haloperidol vs. quetiapine	26/103	26/104	RR, 1.01 (0.63 to 1.62)
Haloperidol vs. olanzapine	27/159	34/160	RR, 0.81 (0.52 to 1.24)
Haloperidol vs. ziprasidone	26/103	30/82	RR, 0.69 (0.45 to 1.07)
Haloperidol vs. risperidone	1/76	5/84	RR, 0.30 (0.05 to 1.78)
Alleviation of sexual dysfunction after treatment			
Fluphenazine vs. quetiapine	1/13	2/12	RR, 0.46 (0.05 to 4.46)
Fluphenazine vs. risperidone	1/13	6/13	RR, 0.17 (0.02 to 1.20)
Patient insight into illness: haloperidol vs. olanzapine	132	131	MD, −1.10 (−3.95 to 1.75)
Attitude about drugs: haloperidol vs. risperidone	146	143	MD, −0.80 (−2.12 to 0.52)
Economic independence: haloperidol vs. risperidone	29/50	31/50	RR, 0.94 (0.68 to 1.29)
Positive urine toxicology test result: haloperidol vs. olanzapine	6/15	2/16	RR, 3.20 (0.76 to 13.46)

FGA = first-generation antipsychotic; LQLP = Lancashire Quality of Life Profile; MANSA = Manchester Short Assessment of Quality of Life; MD = mean difference; QLS = Quality-of-Life Scale; RR = risk ratio; SGA = second-generation antipsychotic.
* For continuous outcomes, only the number of participants is presented.
† Statistically significant result that favored the SGA.
‡ The outcome in this comparison was low adherence.
§ The definition of "response rate" varied across studies (for example, a 50% reduction on the Positive and Negative Syndrome Scale and a 40% improvement on the Brief Psychiatric Rating Scale).

interquartile range, 6 to 26 weeks) for RCTs and non-RCTs; the cohort studies were 3 and 22 years in duration. The route of medication administration was primarily oral; intramuscular administration occurred in 10 studies (9%). Sixty-eight percent of studies were supported by the pharmaceutical industry.

None of the RCTs and non-RCTs had low risk of bias, 67% had unclear risk of bias, and 33% had high risk of bias. Trials were commonly assessed as having unclear risk of bias because of incomplete reporting of sequence generation, allocation concealment, and blinding methods. The most common reasons for trials to be assessed as having high risk of bias were lack of blinding and inadequate handling or reporting of outcome data. Methodological quality of the cohort studies was good; both collected data retrospectively.

Core Illness Symptoms

The findings for core illness symptoms are presented in **Table 1**. Comparisons and outcomes for which strength of evidence was insufficient (for example, evidence from single trials) to draw a conclusion are not displayed; these

Table 3. **Summary of Results and Strength of Evidence for Key Adverse Events**

Adverse Event and Comparison	Study Design	Study Duration	Studies (Participants), *n (n)*	Events/ Participants, *n/N*	Events/ Participants, *n/N*	Risk Difference (95% CI)	Risk Ratio (95% CI)
Death							
Chlorpromazine vs. clozapine	Overall	–	2 (214)	–	–	–	–
	RCT	208 wk	1 (50)	0/25	1/25	−0.04 (−0.14 to 0.06)	0.33 (0.01 to 7.81)
	RCT	12 mo	1 (164)	1/83	0/81	0.01 (−0.02 to 0.05)	2.93 (0.12 to 70.85)
Haloperidol vs. aripiprazole	Overall	–	2 (655)	–	–	–	–
	RCT	24 h	1 (360)	0/185	0/175	0.00 (−0.01 to 0.01)	NE
	RCT	24 h	1 (295)	0/60	2/235	−0.01 (−0.03 to 0.02)	0.77 (0.04 to 15.91)
The metabolic syndrome							
Haloperidol vs. olanzapine	Overall	–	2 (139)	–	–	–	–
	RCT	12 wk	1 (72)	4/36	5/37	−0.02 (−0.17 to 0.13)	0.82 (0.24 to 2.82)
	RCT	6 wk	1 (66)	1/31	9/35	−0.22 (−0.38 to −0.07)	0.13 (0.02 to 0.93)
Tardive dyskinesia							
Chlorpromazine vs. clozapine	Overall	–	2 (204)	–	–	–	–
	RCT	9 y	1 (164)	17/83	9/81	0.09 (−0.02 to 0.20)	1.84 (0.87 to 3.89)
	RCT	12 wk	1 (40)	1/19	0/21	0.05 (−0.08 to 0.18)	3.30 (0.14 to 76.46)

NE = not estimable; RCT = randomized, controlled trial.

results for the Positive and Negative Syndrome Scale (PANSS) are displayed in **Appendix Table 5** (available at www.annals.org). The following sections describe the results for which there was at least low strength of evidence.

Two differences were found in positive symptom alleviation in comparisons of haloperidol with 5 SGAs, as measured by the PANSS and the Scale for the Assessment of Positive Symptoms. Low-strength evidence showed a benefit for risperidone compared with haloperidol on the PANSS; the difference was not considered clinically important, and there was indication of publication bias. Moderate-strength evidence showed a clinically important benefit of haloperidol over olanzapine on the Scale for the Assessment of Positive Symptoms (**Appendix Figure 1**, available at www.annals.org). The low strength of evidence for all remaining comparisons was driven by lack of precision in effect estimates.

Evidence of benefit for treating negative symptoms with SGAs was stronger. Haloperidol was compared with 6 SGAs by using the PANSS and the Scale for the Assessment of Negative Symptoms. Moderate-strength evidence showed that olanzapine had a clinically important benefit compared with haloperidol for both scales (**Appendix Figure 2**, available at www.annals.org), with no indication of publication bias. Risperidone also showed moderate-strength evidence of benefit compared with haloperidol on the PANSS, although results were not considered clinically important. There was also no indication of publication bias. Aripiprazole showed moderate-strength evidence of benefit compared with haloperidol, although the difference was not considered clinically important. Strength of evidence for haloperidol versus clozapine, quetiapine, and ziprasidone was low due to lack of precision in effect estimates.

There were few differences between FGAs and SGAs in global rating and total symptom score improvement. Moderate-strength evidence showed that olanzapine had a clinically important benefit compared with haloperidol on the PANSS (**Appendix Figure 3**, available at www.annals.org), with no indication of publication bias. Olanzapine also showed a difference compared with haloperidol on the Clinical Global Impression—Severity scale, but it was not considered clinically important. Moderate-strength evidence showed a clinically important benefit of risperidone compared with haloperidol on the PANSS (**Appendix Figure 4**, available at www.annals.org), although there was substantial heterogeneity ($I^2 = 76\%$). When 1 outlier (significantly favoring haloperidol) was removed, heterogeneity decreased and results remained in favor of risperidone (**Appendix Figure 5**, available at www.annals.org); there was no indication of publication bias. The outlying study ($n = 100$) used a relatively small fixed dose of risperidone (2 mg/d), whereas most of the other studies used a range from 1 mg/d to 5 to 20 mg/d. Subgroup analyses by dosage showed less heterogeneity and more benefits for higher doses of risperidone (data in technical report). Moderate-strength evidence showed a benefit for haloperidol compared with quetiapine on the Clinical Global Impression—Severity scale, but the difference was not clinically important. Moderate-strength evidence showed a clinically important benefit for clozapine compared with chlorpromazine based on the total score from the Brief Psychiatric Rating Scale (**Appendix Figure 6**, available at www.annals.org).

Haloperidol was compared with 4 SGAs, most commonly olanzapine, and results were reported for 8 scales assessing an overall change in general psychopathology. Moderate-strength evidence showed a difference for 1 of

Table 3—Continued

Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Medium	Consistent	Direct	Imprecise	Low
–	–	–	–	–
–	–	–	–	–
Medium	Consistent	Direct	Imprecise	Low
–	–	–	–	–
–	–	–	–	–
Medium	Consistent	Direct	Imprecise	Low
–	–	–	–	–
–	–	–	–	–
Medium	Consistent	Direct	Imprecise	Low
–	–	–	–	–
–	–	–	–	–

14 comparisons: Olanzapine showed a clinically important benefit on the Montgomery–Asberg Depression Rating Scale (**Appendix Figure 7**, available at www.annals.org).

Response, Remission, and Relapse Rates and Medication Adherence

Findings for these outcomes are presented in **Table 2** and were available for 17 head-to-head comparisons. A statistically significant difference in response rates was found favoring clozapine over chlorpromazine (3 studies) (75, 84, 91). Olanzapine was favored over haloperidol for remission (3 trials) (88, 144, 145) and response rates (14 trials) (40, 85, 88, 98, 101–103, 107, 112, 126, 135, 140, 144, 145). Risperidone was favored over haloperidol for relapse rates (6 trials) (63, 67, 110, 115, 127, 130). Olanzapine was favored over perphenazine for time to all-cause medication discontinuation (37). Clozapine was favored over chlorpromazine for medication adherence (77). These last 2 findings are based on single studies and should be interpreted with caution.

Patient-Oriented Outcomes and Health Care System Use

Patient-oriented outcomes broadly refer to functional outcomes (for example, sexual dysfunction, employment, and economic independence) and outcomes that are important to patients (for example, health-related quality of life). Results for functional outcomes were available for 9 head-to-head comparisons (**Table 2**), with no statistically significant differences in any comparisons. In terms of health-related quality of life, aripiprazole compared with perphenazine showed 20% improvement (1 trial) (90), and ziprasidone compared with haloperidol showed benefits on the Quality-of-Life Scale (1 trial) (118). Statistically significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (1 trial) (66) and patient satisfaction (1 trial) (66). Results for health care system use were available for 10 head-to-head comparisons, with no statistically significant differences for any comparison (**Table 2**). Some of the results described in this section and **Table 2** are based on single trials and should be interpreted with caution.

Medication-Associated Adverse Events and Safety

For the 4 key adverse events, the strength of evidence was insufficient to draw conclusions for most comparisons (**Appendix Table 6**, available at www.annals.org). Two trials each provided data on mortality for chlorpromazine versus clozapine (105, 106) and haloperidol versus aripiprazole (**Table 3**) (34, 136). Absolute differences were small, ranging from 1% to 4% and 0% to 1%, respectively. The length of follow-up (that is, duration) of the trials for the latter comparison was only 24 hours, and the drug was administered via intramuscular injection in both studies. Low-strength evidence showed a higher incidence of the metabolic syndrome for olanzapine than for haloperidol; risk differences were 2% and 22%, respectively, in the 2 relevant studies (88, 102). Low-strength evidence showed a higher incidence of tardive dyskinesia for chlorpromazine than for clozapine; risk differences were 5% and 9% at 12 weeks and 9 years, respectively (77, 84). Across all studies involving adverse events, the strength of evidence was driven by lack of precision in the estimates of effect because of the small numbers of participants studied and events observed.

Data were also recorded for general measures of adverse events and specific adverse events by physiologic system; extrapyramidal symptoms were the most frequently reported event (detailed data and analyses available in technical report). For general measures of adverse events, statistically significant differences were found in the incidence of adverse events and withdrawals due to adverse events for several comparisons. The comparison usually included haloperidol, and the risk was consistently higher with the FGA.

Discussion

Despite FGAs and SGAs being a mainstay in the treatment of schizophrenia in adults, questions remain about whether and how the various commercially available medications differ in efficacy and safety profiles (1–6). This review provides a comprehensive synthesis of the evidence on the comparative benefits and harms of FDA-approved FGAs and SGAs. We used a broad approach to inclusion criteria for comparisons, patients, and study outcomes to bring together the diversity of previously published reviews and provide a broader perspective on evidence in the field (1, 7–19).

We identified a large number of relevant studies (114 studies and 22 different comparisons), the majority of which were efficacy trials (146). The most frequent comparisons involved haloperidol and risperidone (40 studies) or olanzapine (35 studies); however, the number of studies

available for each comparison and outcome was often limited.

Overall, we found few differences of clinical importance between the active drugs; however, this does not imply that they are equivalent. The strength of evidence from these studies was generally low or insufficient, with considerable variation in scales and subscales used to measure symptoms. This heterogeneity, coupled with the small number of studies within specific comparisons, suggests that there is insufficient power to explain some of the negative findings and precludes firm conclusions that are needed for front-line clinical decision making.

At this time, evidence supporting the use of SGAs for negative symptoms is stronger than that supporting their use for positive symptoms; olanzapine and risperidone were found to be more efficacious than haloperidol in reducing such symptoms as blunted affect and withdrawal. This effect, however, was not observed for improving overall (global) functioning and general psychopathology. Contrary to recent reviews (7, 8), we found no evidence of benefit in improving symptoms with clozapine compared with haloperidol, although moderate-strength evidence showed benefits for clozapine compared with chlorpromazine. Differences in study inclusion criteria between our review and previously published reviews probably account for the different outcomes, with our review including more studies from which to base conclusions. In light of the totality of evidence in this review, the ample low-quality evidence showing no difference between haloperidol and various SGAs in improving symptoms provides an inadequate evidence base to advocate for one medication over another.

The data for adverse events were of low to insufficient strength, suggesting the need for a more focused evaluation of drug safety. Despite our efforts to identify long-term safety data from observational studies, only 2 retrospective cohort studies provided follow-up data at least 2 years in duration. Short-term efficacy trials, which are accepted by the regulatory authorities, may not identify time-dependent adverse events, such as tardive dyskinesia, diabetes mellitus, the metabolic syndrome, or death. Although few studies measured mortality, some evidence suggests that treatment with FGAs or SGAs is no different after immediate use (within 24 hours) or long-term use (>12 months). The strength of evidence for other mortality-related outcomes (such as suicide-related behaviors, which is a risk in this clinical population) (147–149) was insufficient to draw conclusions.

We found low-strength evidence for an increased incidence of the metabolic syndrome with use of olanzapine. In general, most studies showed no difference between FGAs and SGAs in terms of increased risk for the metabolic syndrome or diabetes mellitus; however, the strength of evidence was usually insufficient. Although the methodological and reporting limitations of these studies make conclusions about these outcomes premature (150), several reviews have identified clozapine and olanzapine as contributing to greater weight gain (7, 151–153), but this may not necessarily translate into increased risk for more severe outcomes. Further study of this trajectory is warranted with higher-quality longitudinal studies.

Our results are consistent with those of CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) (2), a widely cited trial in this field. CATIE was designed to evaluate whether FGAs were inferior to SGAs in efficacy and safety. Findings from CATIE suggested that the FGA perphenazine and various SGAs (olanzapine, quetiapine, risperidone, and ziprasidone) differed more in their adverse effect profiles than in their therapeutic effect profiles. The study, like this review, also showed that effectiveness across medications varied and that the difference was clinically important in some cases.

Our results are also similar to those of a recent systematic review of SGAs versus FGAs, although our review is broader in scope in terms of medications included, patient populations, and outcomes (1). There were several methodological differences between the previous review and this one: The previous review included non–FDA-approved antipsychotics, restricted the analysis to only double-blind trials, included only studies examining optimum SGA dosage and oral route of administration, pooled data across efficacy outcome measures, and pooled different FGAs. The different methodologies may have led to slightly different conclusions about individual SGAs.

One of the unique features of our review is the strength-of-evidence assessments, which provide information on the level of confidence one can place on the results of existing studies. In most cases, the strength of evidence was insufficient or low, highlighting the likelihood that future research may change the estimates of effect and the need for a stronger evidence base to inform clinical practice. Current treatment guidelines from the American Psychiatric Association for patients with schizophrenia provide specific recommendations on medication timing (for example, acute phase or first episode) but broad variables for medication options (154). This approach may reflect the current state of evidence for FGAs and SGAs, and as stronger evidence emerges, it may come to reflect more specific recommendations for prescribing physicians.

There were limitations in the design and quality of the primary studies. Most studies were short-term RCTs, often with an a priori hypothesis that the SGA would be more efficacious (155). Most trials did not sufficiently report methods to prevent selection and performance bias. Few trials reported blinding study investigators and participants; single-blinded and open-label trials in this field have been found to favor SGAs over FGAs (1). Furthermore, the individual studies and, in many cases, the pooled results may not have sufficient power to detect equivalence or noninferiority between drugs.

Most studies in this review were industry-funded (69%), which can increase the chance of proindustry findings (156). Funding was not disclosed for 19% of studies, highlighting the need for transparency in reporting the nature and extent of financial support. The choice of medication comparisons, dosages, and outcomes in the studies included in this review may have been driven by the funder's interests and priorities. Publication and reporting of select comparisons and outcomes are other potential limitations of this body of evidence.

Few studies provided evidence for comparable patient populations. We found notable heterogeneity across studies for disorder subtypes, comorbid drug or alcohol use, treatment resistance, and number of previous episodes, which result in differential response to treatment. Furthermore, many studies were highly selective in patient enrollment, which may increase the likelihood of drug benefit and decrease the likelihood of adverse events. Detailed subgroup analyses are reported elsewhere (21). Characteristics of the research, including drug dosages (for example, lower doses of FGAs in more recent studies) and patient populations (for example, fewer patients already exposed to FGAs or proven treatment resistance to FGAs in recent studies), also changed over time. Finally, differences in medication comparisons and dosage and outcome measurement limited our synthesis, and outcomes that are important for understanding medication adherence and persistence (a common clinical encounter in this patient population), such as sedation and restlessness, were rarely reported.

More longitudinal research is needed on the long-term safety of FGAs versus SGAs. Despite our efforts to identify long-term safety data from observational studies, only 2 retrospective cohort studies were identified. Consensus is needed on the most important comparisons between FGAs and SGAs for future studies. Short- and long-term evaluations with patient subpopulations, including those with medical and neurologic comorbid conditions, are needed. There is a need for studies investigating the influence of dose, age, and other factors, such as comorbid conditions, on serious adverse events, which would help estimate possible risks in specific patient populations. Future studies should also examine functional outcomes that are important to patients, including health-related quality of life, relationships, academic and occupational performance, and legal interactions.

Existing studies on the comparative effectiveness of individual FGAs and SGAs preclude drawing firm conclusions because of sparse data and imprecise effect estimates. There were relatively few differences of clinical importance among 114 studies. The current evidence base is inadequate for clinicians and patients to make informed decisions about treatment. Outcomes potentially important to patients were rarely assessed. Data on long-term safety are lacking and urgently needed.

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References

1. **Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM.** Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31-41. [PMID: 19058842]

2. **Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators.** Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-23. [PMID: 16172203]

3. **Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al.** Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63:1079-87. [PMID: 17015810]

4. **McDonagh M, Peterson K, Carson S, Fu R, Thakurta S.** Drug Class Review: Atypical Antipsychotic Drugs: Final Update 3 Report. Portland, OR: Oregon Health & Science Univ; 2010. Accessed at www.ncbi.nlm.nih.gov/books/NBK50583 on 30 July 2012.

5. **Barnes TR; Schizophrenia Consensus Group of British Association for Psychopharmacology.** Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2011;25:567-620. [PMID: 21292923]

6. **Kane JM, Correll CU.** Past and present progress in the pharmacologic treatment of schizophrenia. J Clin Psychiatry. 2010;71:1115-24. [PMID: 20923620]

7. **Klemp M, Tvete IF, Skomedal T, Gaasemyr J, Natvig B, Aursnes I.** A review and Bayesian meta-analysis of clinical efficacy and adverse effects of 4 atypical neuroleptic drugs compared with haloperidol and placebo. J Clin Psychopharmacol. 2011;31:698-704. [PMID: 22020356]

8. **Glick ID, Correll CU, Altamura AC, Marder SR, Csernansky JG, Weiden PJ, et al.** Mid-term and long-term efficacy and effectiveness of antipsychotic medications for schizophrenia: a data-driven, personalized clinical approach. J Clin Psychiatry. 2011;72:1616-27. [PMID: 22244023]
9. **Bhattacharjee J, El-Sayeh HG.** Aripiprazole versus typical antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev. 2008:CD006617. [PMID: 18646161]
10. **Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Bhoopathi PS, Kissling W, et al.** Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2009:CD006627. [PMID: 19821380]
11. **Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, et al.** Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010:CD006624. [PMID: 20091599]
12. **Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, et al.** Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010:CD006625. [PMID: 20091600]
13. **Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, et al.** Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010:CD006654. [PMID: 20238348]
14. **Gilbody SM, Bagnall AM, Duggan L, Tuunainen A.** Risperidone versus other atypical antipsychotic medication for schizophrenia. Cochrane Database Syst Rev. 2000:CD002306. [PMID: 10908551]
15. **Essali A, Al-Haj Haasan N, Li C, Rathbone J.** Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev. 2009: CD000059. [PMID: 19160174]
16. **Cipriani A, Boso M, Barbui C.** Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. Cochrane Database Syst Rev. 2009:CD006324. [PMID: 19588385]
17. **Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ Jr, Okasha A, Singh B, et al; Section of Pharmacopsychiatry, World Psychiatric Association.** World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res. 2008;100:20-38. [PMID: 18243663]
18. **Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al.** A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry. 2009;166:152-63. [PMID: 19015230]
19. **Leucht S, Arbter D, Engel RR, Kissling W, Davis JM.** How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol Psychiatry. 2009;14:429-47. [PMID: 18180760]
20. **Agency for Healthcare Research and Quality.** What Is The Research Process? Rockville, MD: Agency for Healthcare Research and Quality; 2012. Accessed at www.effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/what-is-the-research-process on 30 July 2012.
21. **Agency for Healthcare Research and Quality.** Comparative Effectiveness of First and Second Generation Antipsychotics in the Adult Population. Rockville, MD: Agency for Healthcare Research and Quality; 2010. Accessed at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=583 on 30 July 2012.
22. **Higgins JPT, Green S, eds.** Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. The Cochrane Collaboration; 2008.
23. **Institute of Medicine.** Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: National Academies Pr; 2011.
24. **Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Univ of Ottawa; 2009. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 30 July 2012.
25. **Owens DK, Lohr KN, Atkins D, Treadwell JR, Reston JT, Bass EB, et al.** AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010;63:513-23. [PMID: 19595577]
26. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88. [PMID: 3802833]
27. **Hayashino Y, Noguchi Y, Fukui T.** Systematic evaluation and comparison of statistical tests for publication bias. J Epidemiol. 2005;15:235-43. [PMID: 16276033]
28. **Begg CB, Mazumdar M.** Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-101. [PMID: 7786990]
29. **Egger M, Davey Smith G, Schneider M, Minder C.** Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34. [PMID: 9310563]
30. **Mortimer AM.** Symptom rating scales and outcome in schizophrenia. Br J Psychiatry Suppl. 2007;50:s7-14. [PMID: 18019038]
31. **Abdollahian EM.** Comparing the Effects of Risperidone and Haloperidol in Chronic Schizophrenic Patients. Presented at the World Psychiatric Association International Congress "Treatments in Psychiatry: An Update," Florence, Italy, 10–13 November 2004.
32. **Altamura AC, Velonà I, Curreli R, Mundo E, Bravi D.** Is olanzapine better than haloperidol in resistant schizophrenia? A double-blind study in partial responders. International Journal of Psychiatry in Clinical Practice. 2002;6:107-11.
33. **Alvarez-Jiménez M, González-Blanch C, Vázquez-Barquero JL, Pérez-Iglesias R, Martínez-García O, Pérez-Pardal T, et al.** Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: a randomized controlled trial. J Clin Psychiatry. 2006;67:1253-60. [PMID: 16965204]
34. **Andrezina R, Josiassen RC, Marcus RN, Oren DA, Manos G, Stock E, et al.** Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. Psychopharmacology (Berl). 2006; 188:281-92. [PMID: 16953381]
35. **Apiquian R, Fresán A, Muñoz-Delgado J, Kiang M, Ulloa RE, Kapur S.** Variations of rest–activity rhythm and sleep–wake in schizophrenic patients versus healthy subjects: an actigraphic comparative study. Biol Rhythm Res. 2008; 39:69-78.
36. **Arvanitis LA, Miller BG.** Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol Psychiatry. 1997;42:233-46. [PMID: 9270900]
37. **Ascher-Svanum H, Nyhuis AW, Faries DE, Heiler L, Kinon BJ.** Treatment discontinuation following randomization to open-label olanzapine, risperidone or typical antipsychotics during a one-year treatment for schizophrenia. Clin Schizophr Relat Psychoses. 2008;2:226-34.
38. **Atmaca M, Kuloglu M, Tezcan E, Canatan H, Gecici O.** Quetiapine is not associated with increase in prolactin secretion in contrast to haloperidol. Arch Med Res. 2002;33:562-5. [PMID: 12505103]
39. **Avasthi A, Kulhara P, Kakkar N.** Olanzapine in the treatment of schizophrenia : an open label comparative clinical trial from north India. Indian J Psychiatry. 2001;43:257-63. [PMID: 21407865]
40. **Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S.** Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology. 1996;14: 111-23. [PMID: 8822534]
41. **Beasley CM Jr, Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, et al.** Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol. 1997;7:125-37. [PMID: 9169300]
42. **Bernardo M, Parellada E, Lomeña F, Catafau AM, Font M, Gómez JC, et al.** Double-blind olanzapine vs. haloperidol D2 dopamine receptor blockade in schizophrenic patients: a baseline-endpoint. Psychiatry Res. 2001;107:87-97. [PMID: 11530275]
43. **Blin O, Azorin JM, Bouhours P.** Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. J Clin Psychopharmacol. 1996;16:38-44. [PMID: 8834417]
44. **Borison RL, Pathiraja AP, Diamond BI, Meibach RC.** Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacol Bull. 1992;28:213-8. [PMID: 1381102]
45. **Boulay LJ, Labelle A, Bourget D, Robertson S, Habib R, Tessier P, et al.** Dissociating medication effects from learning and practice effects in a neurocognitive study of schizophrenia: olanzapine versus haloperidol. Cogn Neuropsychiatry. 2007;12:322-38. [PMID: 17558641]
46. **Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, et al.** Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry. 1994;151:20-6. [PMID: 8267129]
47. **Breier A, Meehan K, Birkett M, David S, Ferchland I, Sutton V, et al.** A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Arch Gen Psychiatry. 2002;59:441-8. [PMID: 11982448]
48. **Brook S, Walden J, Benattia I, Siu CO, Romano SJ.** Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaf-

fective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology (Berl). 2005;178: 514-23. [PMID: 15650846]

49. **Buchanan RW, Ball MP, Weiner E, Kirkpatrick B, Gold JM, McMahon RP, et al.** Olanzapine treatment of residual positive and negative symptoms. Am J Psychiatry. 2005;162:124-9. [PMID: 15625210]

50. **Cavallaro R, Mistretta P, Cocchi F, Manzato M, Smeraldi E.** Differential efficacy of risperidone versus haloperidol in psychopathological subtypes of subchronic schizophrenia. Hum Psychopharmacol. 2001;16:439-48. [PMID: 12404552]

51. **Cesková E, Svestka J.** Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. Pharmacopsychiatry. 1993; 26:121-4. [PMID: 7694306]

52. **Chiu E, Burrows G, Stevenson J.** Double-blind comparison of clozapine with chlorpromazine in acute schizophrenic illness. Aust N Z J Psychiatry. 1976; 10:343-7. [PMID: 798582]

53. **Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, et al.** A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol. 1993;13:25-40. [PMID: 7683702]

54. **Citrome L, Volavka J, Czobor P, Sheitman B, Lindenmayer JP, McEvoy J, et al.** Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psychiatr Serv. 2001;52:1510-4. [PMID: 11684748]

55. **Claghorn J, Honigfeld G, Abuzzahab FS Sr, Wang R, Steinbook R, Tuason V, et al.** The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol. 1987;7:377-84. [PMID: 3323261]

56. **Claus A, Bollen J, De Cuyper H, Eneman M, Malfroid M, Peuskens J, et al.** Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand. 1992;85:295-305. [PMID: 1375801]

57. **Conley RR, Tamminga CA, Bartko JJ, Richardson C, Peszke M, Lingle J, et al.** Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry. 1998;155:914-20. [PMID: 9659857]

58. **Conley RR, Kelly DL, Nelson MW, Richardson CM, Feldman S, Benham R, et al.** Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia. Clin Neuropharmacol. 2005;28:163-8. [PMID: 16062094]

59. **Copolov DL, Link CG, Kowalcyk B.** A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia. Psychol Med. 2000;30:95-105. [PMID: 10722180]

60. **Corripio I, Catafau AM, Perez V, Puigdemont D, Mena E, Aguilar Y, et al.** Striatal dopaminergic D2 receptor occupancy and clinical efficacy in psychosis exacerbation: a 123I-IBZM study with ziprasidone and haloperidol. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29:91-6. [PMID: 15610950]

61. **Covington L, Cola PA.** Clozapine vs. haloperidol: antipsychotic effects on sexual function in schizophrenia. Sex Disabil. 2000;18:41-8.

62. **Crespo-Facorro B, Pérez-Iglesias R, Mata I, Martínez-Garcia O, Ortiz V, Pelayo-Terán JM, et al.** Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis. Psychopharmacology (Berl). 2012; 219:225-33. [PMID: 21735072]

63. **Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group.** A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med. 2002;346:16-22. [PMID: 11777998]

64. **Daniel DG, Currier GW, Zimbroff DL, Allen MH, Oren D, Manos G, et al.** Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. J Psychiatr Pract. 2007;13:170-7. [PMID: 17522560]

65. **Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS, et al.** Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am J Psychiatry. 2009;166:675-82. [PMID: 19369319]

66. **de Oliveira IR, Elkis H, Gattaz WF, Chaves AC, de Sena EP, de Matos E Souza FG, et al.** Aripiprazole for patients with schizophrenia and schizoaffective disorder: an open-label, randomized, study versus haloperidol. CNS Spectr. 2009; 14:93-102. [PMID: 19238124]

67. **de Sena EP, Santos-Jesus R, Miranda-Scippa A, Quarantini Lde C, Oliveira IR.** Relapse in patients with schizophrenia: a comparison between risperidone and haloperidol. Rev Bras Psiquiatr. 2003;25:220-3. [PMID: 15328547]

68. **de Haan L, van Bruggen M, Lavalaye J, Booij J, Dingemans PM, Linszen D.** Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am J Psychiatry. 2003;160:303-9. [PMID: 12562577]

69. **Ekblom B, Haggstrom JE.** Clozapine (Leponex) compared with chlorpromazine: a double-blind evaluation of pharmacological and clinical properties. Curr Ther Res Clin Exp. 1974;16:945-57. [PMID: 4154183]

70. **Emsley RA, Raniwalla J, Bailey PJ, Jones AM.** A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol. 2000;15:121-31. [PMID: 10870870]

71. **Emsley RA.** Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. Schizophr Bull. 1999;25:721-9. [PMID: 10667742]

72. **Emsley R, Turner HJ, Schronen J, Botha K, Smit R, Oosthuizen PP.** Effects of quetiapine and haloperidol on body mass index and glycaemic control: a long-term, randomized, controlled trial. Int J Neuropsychopharmacol. 2005;8: 175-82. [PMID: 15737251]

73. **Fakra E, Khalfa S, Da Fonseca D, Besnier N, Delaveau P, Azorin JM, et al.** Effect of risperidone versus haloperidol on emotional responding in schizophrenic patients. Psychopharmacology (Berl). 2008;200:261-72. [PMID: 18575849]

74. **Gaszner P, Makkos Z.** Clozapine maintenance therapy in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28:465-9. [PMID: 15093952]

75. **Gelenberg AJ, Doller JC.** Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double-blind study. J Clin Psychiatry. 1979;40:238-40. [PMID: 374401]

76. **Ghaleiha A, Honarbakhsh N, Boroumand MA, Jafarinia M, Tabrizi M, Rezaei F, et al.** Correlation of adenosinergic activity with superior efficacy of clozapine for treatment of chronic schizophrenia: a double blind randomised trial. Hum Psychopharmacol. 2011;26:120-4. [PMID: 21412846]

77. **Girgis RR, Phillips MR, Li X, Li K, Jiang H, Wu C, et al.** Clozapine v. chlorpromazine in treatment-naive, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial. Br J Psychiatry. 2011;199:281-8. [PMID: 21292928]

78. **Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, et al.** An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol. 1998;18:296-304. [PMID: 9690695]

79. **Goldman MB, Hussain N.** Absence of effect of olanzapine on primary polydipsia: results of a double-blind, randomized study. J Clin Psychopharmacol. 2004;24:678-80. [PMID: 15538138]

80. **Guirguis E, Voineskos G, Gray J, Schlieman E.** Clozapine (Leponex) vs chlorpromazine (Largactil) in acute schizophrenia: a double-blind controlled study. Curr Ther Res Clin Exp. 1977;21:707-19.

81. **Heck AH, Haffmans PM, de Groot IW, Hoencamp E.** Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: a double-blind, multi-center trial. Schizophr Res. 2000;46:97-105. [PMID: 11120421]

82. **Hennessy S, Bilker WB, Knauss JS, Margolis DJ, Kimmel SE, Reynolds RF, et al.** Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ. 2002;325:1070. [PMID: 12424166]

83. **Hirsch SR, Kissling W, Bäuml J, Power A, O'Connor R.** A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry. 2002;63:516-23. [PMID: 12088164]

84. **Hong CJ, Chen JY, Chiu HJ, Sim CB.** A double-blind comparative study of clozapine versus chlorpromazine on Chinese patients with treatment-refractory schizophrenia. Int Clin Psychopharmacol. 1997;12:123-30. [PMID: 9248867]

85. **Ishigooka J, Inada T, Miura S.** Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: results of the Japan multicenter, double-blind olanzapine trial. Psychiatry Clin Neurosci. 2001;55:403-14. [PMID: 11442893]

86. **Itoh H, Miura S, Yagi G, Sakurai S, Ohtsuka N.** Some methodological considerations for the clinical evaluation of neuroleptics—comparative effects of clozapine and haloperidol on schizophrenics. Folia Psychiatr Neurol Jpn. 1977; 31:17-24. [PMID: 863344]

87. **Jakovljevic M, Dossenbach MKR, Friedel P, Schausberger B, Grundy SL, Hotujac L, et al; Olanzapine HGCH Study Group.** Olanzapine versus fluphenazine in the acute (6-week) treatment of schizophrenia. Psychiatr Danub. 1999;11:3-11.

88. **Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al; EUFEST study group.** Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371:1085-97. [PMID: 18374841]

89. **Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al.** Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2002; 63:763-71. [PMID: 12363115]

90. **Kane JM, Meltzer HY, Carson WH Jr, McQuade RD, Marcus RN, Sanchez R; Aripiprazole Study Group.** Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. J Clin Psychiatry. 2007;68:213-23. [PMID: 17335319]

91. **Kane J, Honigfeld G, Singer J, Meltzer H.** Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45:789-96. [PMID: 3046553]

92. **Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht D, Baker RW, et al.** Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. Arch Gen Psychiatry. 2001; 58:965-72. [PMID: 11576036]

93. **Kane JM, Khanna S, Rajadhyaksha S, Giller E.** Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2006;21:21-8. [PMID: 16317313]

94. **Kane JM, Cohen M, Zhao J, Alphs L, Panagides J.** Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol. 2010;30:106-15. [PMID: 20520283]

95. **Kasper S, Lerman MN, McQuade RD, Saha A, Carson WH, Ali M, et al.** Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol. 2003;6:325-37. [PMID: 14609439]

96. **Kee KS, Kern RS, Marshall BD Jr, Green MF.** Risperidone versus haloperidol for perception of emotion in treatment-resistant schizophrenia: preliminary findings. Schizophr Res. 1998;31:159-65. [PMID: 9689720]

97. **Keefe RS, Poe MP, McEvoy JP, Vaughan A.** Source monitoring improvement in patients with schizophrenia receiving antipsychotic medications. Psychopharmacology (Berl). 2003;169:383-9. [PMID: 12759802]

98. **Keefe RS, Young CA, Rock SL, Purdon SE, Gold JM, Breier A; HGGN Study Group.** One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res. 2006; 81:1-15. [PMID: 16202565]

99. **Kim SH, Han DH, Joo SY, Min KJ.** The effect of dopamine partial agonists on the nicotine dependency in patients with schizophrenia. Hum Psychopharmacol. 2010;25:187-90. [PMID: 20033907]

100. **Klieser E, Strauss WH, Lemmer W.** The tolerability and efficacy of the atypical neuroleptic remoxipride compared with clozapine and haloperidol in acute schizophrenia. Acta Psychiatr Scand Suppl. 1994;380:68-73. [PMID: 8048341]

101. **Kongsakon R, Trinidad-Oñate P, Chaudhry HR, Raza SB, Leynes CR, Khan IU, et al.** Asian outpatients with schizophrenia: a double-blind randomized comparison of quality of life and clinical outcomes for patients treated with olanzapine or haloperidol. J Med Assoc Thai. 2006;89:1157-70. [PMID: 17048425]

102. **Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB.** Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry. 2006;63:622-9. [PMID: 16754835]

103. **Lahti AC, Weiler MA, Holcomb HH, Tamminga CA, Cropsey KL.** Modulation of limbic circuitry predicts treatment response to antipsychotic medication: a functional imaging study in schizophrenia. Neuropsychopharmacology. 2009;34:2675-90. [PMID: 19675535]

104. **Lee SM, Chou YH, Li MH, Wan FJ, Yen MH.** Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1101-7. [PMID: 17475386]

105. **León CA.** Therapeutic effects of clozapine. A 4-year follow-up of a controlled clinical trial. Acta Psychiatr Scand. 1979;59:471-80. [PMID: 380268]

106. **Lieberman JA, Phillips M, Gu H, Stroup S, Zhang P, Kong L, et al.** Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology. 2003;28:995-1003. [PMID: 12700715]

107. **Lindenmayer JP, Khan A, Iskander A, Abad MT, Parker B.** A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. J Clin Psychiatry. 2007;68:368-79. [PMID: 17388705]

108. **Liu SK, Chen WJ, Chang CJ, Lin HN.** Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: a trial of risperidone versus haloperidol. Neuropsychopharmacology. 2000;22:311-9. [PMID: 10693159]

109. **Ljubin T, Zakić Milas D, Mimica N, Folnegović-Smalc V, Makarić G.** A preliminary study of the comparative effects of olanzapine and fluphenazine on cognition in schizophrenic patients. Hum Psychopharmacol. 2000;15:513-519. [PMID: 12404620]

110. **Marder SR, Glynn SM, Wirshing WC, Wirshing DA, Ross D, Widmark C, et al.** Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. Am J Psychiatry. 2003;160:1405-12. [PMID: 12900301]

111. **Marder SR, Meibach RC.** Risperidone in the treatment of schizophrenia. Am J Psychiatry. 1994;151:825-35. [PMID: 7514366]

112. **McCue RE, Waheed R, Urcuyo L, Orendain G, Joseph MD, Charles R, et al.** Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. Br J Psychiatry. 2006;189:433-40.

113. **Miceli JJ, Tensfeldt TG, Shiovitz T, Anziano RJ, O'Gorman C, Harrigan RH.** Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder. Clin Ther. 2010;32:472-91. [PMID: 20399985]

114. **Min SK, Rhee CS, Kim CE, Kang DY.** Risperidone versus haloperidol in the treatment of chronic schizophrenic patients: a parallel group double-blind comparative trial. Yonsei Med J. 1993;34:179-90. [PMID: 7691017]

115. **Möller HJ, Riedel M, Jäger M, Wickelmaier F, Maier W, Kühn KU, et al.** Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on Schizophrenia. Int J Neuropsychopharmacol. 2008;11:985-97. [PMID: 18466670]

116. **Peuskens J.** Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. Br J Psychiatry. 1995;166:712-26; discussion 727-33. [PMID: 7545060]

117. **Peuskens J, Link CG.** A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand. 1997;96:265-73. [PMID: 9350955]

118. **Potkin SG, Weiden PJ, Loebel AD, Warrington LE, Watsky EJ, Siu CO.** Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone vs. haloperidol. Int J Neuropsychopharmacol. 2009;12:1233-48. [PMID: 19419595]

119. **Purdon SE, Malla A, Labelle A, Lit W.** Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci. 2001;26:137-49. [PMID: 11291531]

120. **Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, et al.** Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch Gen Psychiatry. 2000;57:249-58. [PMID: 10711911]

121. **Rémillard S, Pourcher E, Cohen H.** Long-term effects of risperidone versus haloperidol on verbal memory, attention, and symptomatology in schizophrenia. J Int Neuropsychol Soc. 2008;14:110-8. [PMID: 18078537]

122. **Rinieris P, Christodoulou GN, Souvatzoglou A, Koutras DA, Stefanis C.** Free-thyroxine index in schizophrenic patients before and after neuroleptic treatment. Neuropsychobiology. 1980;6:29-33. [PMID: 6102744]

123. **Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, et al.** A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med. 1997;337:809-15. [PMID: 9295240]

124. **Rosenheck R, Perlick D, Bingham S, Liu-Mares W, Collins J, Warren S, et al; Department of Veterans Affairs Cooperative Study Group on the Cost-Effectiveness of Olanzapine.** Effectiveness and cost of olanzapine and haloperidol

in the treatment of schizophrenia: a randomized controlled trial. JAMA. 2003; 290:2693-702. [PMID: 14645311]

125. **Saddichha S, Ameen S, Akhtar S.** Predictors of antipsychotic-induced weight gain in first-episode psychosis: conclusions from a randomized, double-blind, controlled prospective study of olanzapine, risperidone, and haloperidol. J Clin Psychopharmacol. 2008;28:27-31. [PMID: 18204337]

126. **Sayers SL, Campbell EC, Kondrich J, Mann SC, Cornish J, O'Brien C, et al.** Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. J Nerv Ment Dis. 2005;193:379-86. [PMID: 15920378]

127. **Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, et al; Early Psychosis Global Working Group.** Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry. 2005;162: 947-53. [PMID: 15863797]

128. **Sergi MJ, Green MF, Widmark C, Reist C, Erhart S, Braff DL, et al.** Social cognition [corrected] and neurocognition: effects of risperidone, olanzapine, and haloperidol. Am J Psychiatry. 2007;164:1585-92. [PMID: 17898351]

129. **Shopsin B, Klein H, Aaronsom M, Collora M.** Clozapine, chlorpromazine, and placebo in newly hospitalized, acutely schizophrenic patients: a controlled, double-blind comparison. Arch Gen Psychiatry. 1979;36:657-64. [PMID: 375865]

130. **Shrivastava A, Gopa S.** Comparative study of risperidone and haloperidol on clinical and psychosocial parameters in treatment of schizophrenia: a randomised open trial. Indian J Psychiatry. 2000;42:52-6. [PMID: 21407908]

131. **Singer L, Law SK.** A double-blind comparison of clozapine (Leponex) and chlorpromazine in schizophrenia of acute symptomatology. J Int Med Res. 1974; 2:433-5.

132. **Smelson DA, Ziedonis D, Williams J, Losonczy MF, Williams J, Steinberg ML, et al.** The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. J Clin Psychopharmacol. 2006;26:9-12. [PMID: 16415698]

133. **Smith RC, Infante M, Singh A, Khandat A.** The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. Int J Neuropsychopharmacol. 2001;4:239-50. [PMID: 11669086]

134. **Tamrakar SM, Nepal MK, Koirala NR, Sharma VD, Gurung CK, Adhikari SR.** An open, randomized, comparative study of efficacy and safety of risperidone and haloperidol in schizophrenia. Kathmandu Univ Med J (KUMJ). 2006;4:152-60. [PMID: 18603890]

135. **Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al.** Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry. 1997;154:457-65. [PMID: 9090331]

136. **Tran-Johnson TK, Sack DA, Marcus RN, Auby P, McQuade RD, Oren DA.** Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2007;68:111-9. [PMID: 17284138]

137. **Velligan DI, Newcomer J, Pultz J, Csernansky J, Hoff AL, Mahurin R, et al.** Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res. 2002;53:239-48. [PMID: 11738537]

138. **Volavka J, Czobor P, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, et al.** Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry. 2002;159:255-62. [PMID: 11823268]

139. **Wirshing DA, Marshall BD Jr, Green MF, Mintz J, Marder SR, Wirshing WC.** Risperidone in treatment-refractory schizophrenia. Am J Psychiatry. 1999; 156:1374-9. [PMID: 10484947]

140. **Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, et al.** Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry. 2001;158:1149-51. [PMID: 11431240]

141. **Wynn JK, Green MF, Sprock J, Light GA, Widmark C, Reist C, et al.** Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. Schizophr Res. 2007;95:134-42. [PMID: 17662577]

142. **Yen YC, Lung FW, Chong MY.** Adverse effects of risperidone and haloperidol treatment in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28:285-90. [PMID: 14751424]

143. **Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY, Shen YC.** Risperidone versus haloperidol in the treatment of acute exacerbations of chronic inpatients with schizophrenia: a randomized double-blind study. Int Clin Psychopharmacol. 2001;16:325-30. [PMID: 11712620]

144. **Crespo-Facorro B, Pérez-Iglesias R, Ramirez-Bonilla M, Martínez-García O, Llorca J, Luis Vázquez-Barquero J.** A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. J Clin Psychiatry. 2006;67:1511-21. [PMID: 17107241]

145. **Lieberman JA, Tollefson G, Tohen M, Green AI, Gur RE, Kahn R, et al; HGDH Study Group.** Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry. 2003;160:1396-404. [PMID: 12900300]

146. **Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS.** Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews. Technical Review no. 12. AHRQ Publication no. 06-0046. Rockville, MD: Agency for Healthcare Research and Quality; 2006.

147. **Heilä H, Isometsä ET, Henriksson MM, Heikkinen ME, Marttunen MJ, Lönnqvist JK.** Suicide and schizophrenia: a nationwide psychological autopsy study on age- and sex-specific clinical characteristics of 92 suicide victims with schizophrenia. Am J Psychiatry. 1997;154:1235-42. [PMID: 9286182]

148. **Meltzer HY.** Suicidality in schizophrenia: a review of the evidence for risk factors and treatment options. Curr Psychiatry Rep. 2002;4:279-83. [PMID: 12126596]

149. **Pompili M, Amador XF, Girardi P, Harkavy-Friedman J, Harrow M, Kaplan K, et al.** Suicide risk in schizophrenia: learning from the past to change the future. Ann Gen Psychiatry. 2007;6:10. [PMID: 17367524]

150. **Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K.** First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2008;192:406-11. [PMID: 18515889]

151. **Gentile S.** Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. Drug Saf. 2006;29:303-19. [PMID: 16569080]

152. **Taylor DM, McAskill R.** Atypical antipsychotics and weight gain—a systematic review. Acta Psychiatr Scand. 2000;101:416-32. [PMID: 10868465]

153. **Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al.** Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry. 1999;156:1686-96. [PMID: 10553730]

154. **American Psychiatric Association.** Practice Guideline for the Treatment of Patients With Schizophrenia. 2nd ed. Arlington, VA: American Psychiatric Assoc; 2004.

155. **Lieberman JA, Stroup TS.** The NIMH-CATIE Schizophrenia Study: what did we learn? Am J Psychiatry. 2011;168:770-5. [PMID: 21813492]

156. **Sismondo S.** Pharmaceutical company funding and its consequences: a qualitative systematic review. Contemp Clin Trials. 2008;29:109-13. [PMID: 17919992]

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157. Drugstore.com Web site. Accessed at www.drugstore.com on 30 March 2012.
158. Universal Drugstore Web site. Accessed at www.universaldrugstore.com on 30 March 2012.
159. **Kay SR, Fiszbein A, Opler LA.** The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261-76. [PMID: 3616518]

Appendix Table 1. **Antipsychotics Included in the Systematic Review**

Generic Name	Trade Name	Mode of Administration	Recommended Dose	FDA Status	Indications	Drug Cost per Minimum Dose, *U.S. $**
First-generation antipsychotics						
Chlorpromazine	Chlorpromazine hydrochloride	Oral; intramuscular/ intravenous	200 to 600 mg/d	Approved in 1974	Schizophrenia and BD	1.90/200 mg
Droperidol	Inapsine	Intramuscular/intravenous	Initial 2.5 mg/dose	Approved in 1988	Antiemetic and acute psychosis	1.84/1 mg
Fluphenazine	Fluphenazine decanoate Fluphenazine hydrochloride	Oral Intramuscular	2.5 to 10 mg/d 2.5 to 10 mg/dose	Approved in 1960	Schizophrenia and BD	0.26/2.5 mg
Haloperidol	Haldol Haloperidol decanoate	Oral Intramuscular	4 to 12 mg/d	Approved in 1986	Schizophrenia	0.44/4 mg
Loxapine	Loxapine	Oral	60 to 100 mg/d	Approved in 1975	Schizophrenia	1.55/60 mg
Perphenazine	Perphenazine	Oral (nonhospitalized) Oral (hospitalized)	12 to 18 mg/d 16 to 64 mg/d	Approved in 1965	Schizophrenia	1.80/16 mg
Pimozide	Orap	Oral	7 to 10 mg/d	Approved in 1984	Schizophrenia	6.40/7 mg
Prochlorperazine	Compro Prochlorperazine edisylate Prochlorperazine maleate	Oral Intramuscular Intravenous	15 to 40 mg/d 15 to 40 mg/d 7.5 to 40 mg/d	Approved in 1956	Schizophrenia	1.40/15 mg
Thioridazine	Mellaril	Oral	150 to 300 mg/d	Approved in 1962	Schizophrenia	1.20/150 mg
Thiothixene	Navane	Oral	6 to 30 mg/d	Approved in 1967	Schizophrenia	1.00/6 mg
Trifluoperazine	Trifluoperazine hydrochloride	Oral (nonhospitalized)	1 to 2 mg	Approved in 1959	Schizophrenia	0.31/1 mg
Second-generation antipsychotics						
Aripiprazole	Abilify	Oral Injection	10 to 15 mg/d Maximum of 30 mg/d	Approved in 2002 Approved in 2004	Schizophrenia BD	6.56/10 mg
Asenapine	Saphouris	Oral	Schizophrenia, 5 mg BD, 10 mg	Approved in 2009	Acute schizophrenia and BD	10.80/10 mg
Clozapine	Clozaril	Oral	300 to 450 mg/d	Approved in 1989	Treatment-resistant schizophrenia	2.23/300 mg
Iloperidone	Fanapt	Oral	12 to 24 mg/d	Approved in 2009	Acute schizophrenia	4.50/12 mg
Olanzapine	Zyprexa	Oral; intramuscular injection	Schizophrenia, 10 mg/d BD I, 10 to 15 mg/d	Approved in 1996	Schizophrenia and BD	9.00/10 mg
Lurasidone	Latuda	Oral	40 to 80 mg/d	Approved in 2010	Schizophrenia	17.8/40 mg
Paliperidone	Invega	Oral	6 mg/d	Approved in 2006	Schizophrenia and schizoaffective disorder	9.78/6 mg
Quetiapine	Seroquel	Oral	Schizophrenia, 150 to 750 mg/d BD, 400 to 800 mg/d	Approved in 1997 Approved in 2004	Schizophrenia BD	2.78/150 mg
Risperidone	Risperdal	Oral; intramuscular injection	Schizophrenia, 4 to 8 mg/d BD (mania), 1 to 6 mg/d	Approved in 1993 Approved in 2007	Schizophrenia BD	7.30/4 mg
Ziprasidone	Geodon	Oral; intramuscular injection	Schizophrenia, maximum of 80 mg BD (manic/mixed, maintenance), 40 to 80 mg	Approved in 2001	Schizophrenia and BD	4.75/40 mg

BD = bipolar disorder; FDA = U.S. Food and Drug Administration.
* Data obtained from references 157 and 158.

Appendix Table 2. Ovid MEDLINE Search Strategy

1	exp Schizophrenia/
2	Schizophrenia, Catatonic/
3	Schizophrenia, Disorganized/
4	Schizophrenia, Paranoid/
5	Psychotic Disorders/
6	Schizotypal Personality Disorder/
7	schizophreniform.tw.
8	(schizoaffective or schizo-affective).tw.
9	schizophren$.mp.
10	(dementia adj (praecox or precox)).tw.
11	(delusional adj2 disorder*).tw.
12	((negative or positive) adj syndrome*).tw.
13	hebephrenia.tw.
14	exp Bipolar Disorder/
15	(((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress$)) or mania*).tw.
16	(BPD or hypoman$ or manic-depressive).tw.
17	(BP 1 or BP 2 or BP I or BP II).tw.
18	(cyclothym$ or euthymic).tw.
19	(acute adj2 mania).tw.
20	(acute adj2 mixed adj episode*).tw.
21	(rapid-cycling adj5 bipolar).tw.
22	(rapid adj2 cycling adj5 bipolar).tw.
23	(mixed adj2 state* adj3 bipolar).tw.
24	or/1-23
25	exp Antipsychotic Agents/
26	exp Tranquilizing Agents/
27	(neuroleptic adj2 (agent* or drug*)).tw.
28	or/25-27
29	((first or 1st) adj generation adj antipsychotic*).tw.
30	chlorpromazine/
31	50-53-3.rn.
32	(Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
33	Droperidol/
34	548-73-2.rn.
35	(Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
36	fluphenazine/
37	69-23-8.rn.
38	(Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
39	haloperidol/
40	52-86-8.rn.
41	(Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
42	loxapine/
43	1977-10-2.rn.
44	(Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
45	perphenazine/
46	58-39-9.rn.
47	(Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
48	Pimozide/
49	2062-78-4.rn.
50	(Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
51	Prochlorperazine/
52	58-38-8.rn.
53	(Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
54	thiothixene/
55	5591-45-7.rn.
56	(Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.

Continued on following page

Appendix Table 2—**Continued**

57	trifluoperazine/
58	117-89-5.rn.
59	(Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
60	thioridazine/
61	50-52-2.rn.
62	(Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
63	methotrimeprazine/
64	60-99-1.rn.
65	(Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
66	Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects]
67	Butyrophenones/ad, to, tu, ct, po, ae
68	Thioxanthenes/ad, to, tu, ct, po, ae
69	Dibenzoxazepines/ad, to, tu, ct, po, ae
70	Indoles/ad, to, tu, ct, po, ae
71	or/29-70
72	atypical antipsychotic$.tw.
73	((second or 2nd) adj generation adj antipsychotic*).tw.
74	((third or 3rd) adj generation adj antipsychotic*).tw.
75	Asenapine/
76	65576-45-6.rn.
77	(Asenapine or EINECS 265-829-4).mp.
78	clozapine/
79	5786-21-0.rn.
80	(Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
81	risperidone/
82	106266-06-2.rn.
83	(Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
84	olanzapine.mp.
85	132539-06-1.rn.
86	(Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera or Symbyax).mp.
87	quetiapine.mp.
88	(111974-69-7 or 111974-72-2).rn.
89	(Co-Quetiapine or HSDB 7557 or Seroquel).mp.
90	ziprasidone.mp.
91	146939-27-7.rn.
92	(Zeldox or zeldrox or geodon).mp.
93	aripiprazole.mp.
94	129722-12-9.rn.
95	(Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
96	paliperidone.mp.
97	144598-75-4.rn.
98	(9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
99	Iloperidone/
100	133454-47-4.rn.
101	(Fanapt or Iloperidone or HP 873 or Zomaril).mp.
102	Isoxazoles/ad, to, tu, ct, po, ae
103	Dibenzazepines/ad, to, tu, ct, po, ae
104	Pyrimidinones/ad, to, tu, ct, po, ae
105	Piperidines/ad, to, tu, ct, po, ae
106	Dibenzothiazepines/ct, ad, to, tu, ae, po
107	Piperazines/ad, tu, to, ct, po, ae
108	Pirenzepine/tu, ad, to, ct, po, ae
109	Thiazoles/ad, th, ct, po, to, ae
110	Quinolones/to, po, ct, ad, tu, ae
111	or/72-110
112	and/71,111
113	and/28,71,111
114	or/112-113
115	randomized controlled trial.pt.
116	controlled clinical trial.pt.
117	randomi?ed.ab.
118	placebo*.ab.
119	drug therapy.fs.
120	randomly.ab.

Continued on following page

Appendix Table 2—Continued

121	trial.ab.
122	groups.ab.
123	or/115-122
124	humans/ not (animals and humans).hw,sh.
125	123 and 124
126	and/24,114,125
127	limit 126 to yr="1987–2010"
128	limit 127 to english language
129	limit 126 to yr="1950–1986"
130	limit 129 to english language
131	cohort studies/
132	followup studies/
133	longitudinal studies/
134	prospective studies/
135	Retrospective Studies/
136	(observation$ or prospectiv$ or retrospectiv$ or cohort$ or control$ or volunteer$ or evaluat$ or compar$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial$).ti,ab,sh.
137	or/131-136
138	humans.hw,sh.
139	and/137-138
140	meta-analysis.mp,pt.
141	review.pt.
142	search:.tw.
143	or/140-142
144	and/24,114,139
145	and/24,114,143
146	limit 145 to yr="1987–2010"
147	limit 146 to english language
148	limit 145 to yr="1950–1986"
149	limit 148 to english language
150	limit 144 to yr="1987–2010"
151	limit 150 to english language
152	limit 144 to yr="1950–1986"
153	limit 152 to english language

Appendix Table 3. Inclusion and Exclusion Criteria

Characteristic	Inclusion Criteria	Exclusion Criteria
Publication type	English language, full-text publications from 1950 to present	Non–English-language publications; conference abstracts
Study design	RCTs, non-RCTs, and prospective and retrospective cohort studies	Observational design with no comparison group (e.g., case reports, case series, and cross-sectional studies); case–control studies
Participants	Adults (aged 18 to 64 y) with schizophrenia or related psychoses	Pediatric population (aged <18 y); geriatric population (aged >64 y)
Interventions	Any available FDA-approved FGA	Unavailable or non–FDA-approved FGA or other interventions
Comparators	Any available FDA-approved SGA	Unavailable or non–FDA-approved SGA, placebo, or other interventions
Outcomes	Outcomes listed in the KQ; cohort studies reporting on ≥1 SAE	No a priori–identified outcomes available from the trial report or communication with the study's corresponding author
Timing	All follow-up periods for trials; cohort studies with ≥2-y follow-up	Cohorts with <2-y follow-up
Setting	All settings	–

FDA = U.S. Food and Drug Administration; FGA = first-generation antipsychotic; KQ = key question; RCT = randomized, controlled trial; SAE = serious adverse event; SGA = second-generation antipsychotic.

Appendix Table 4. Examples of Core Symptoms*

Symptom Domain	Example
Negative	Delusions
	Conceptual disorganization
	Hallucinatory behavior
Positive	Blunted affect
	Emotional withdrawal
	Poor rapport
	Passive/apathetic social withdrawal
General	Anxiety
	Depression
	Motor retardation
	Disorientation
	Poor attention
	Disturbance of volition
	Active social avoidance

* Based on the Positive and Negative Syndrome Scale (159).

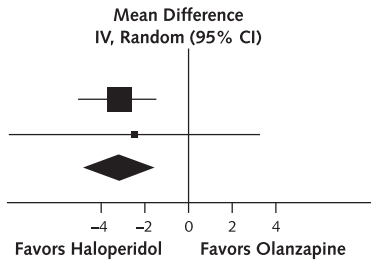
Appendix Table 5. Summary of Insufficient Strength of Evidence for Core Illness Symptoms When the PANSS Was Used

Variable and Comparison	Studies (Participants), *n (n)*	Risk of Bias	Consistency	Directness	Precision	Effect Estimate (95% CI)	Favored Drug	Strength of Evidence
Positive symptoms								
Chlorpromazine vs. clozapine	1 (40)	Medium	Unknown	Direct	Imprecise	2.00 (−0.79 to 4.79)	–	Insufficient
Fluphenazine vs. olanzapine	1 (60)	Medium	Unknown	Direct	Precise	5.10 (0.57 to 9.63)*	Olanzapine	Insufficient
Haloperidol vs. asenapine	1 (335)	Medium	Unknown	Direct	Imprecise	0.16 (−1.22 to 1.54)	–	Insufficient
Perphenazine vs. olanzapine	1 (597)	Medium	Unknown	Direct	Precise	1.47 (0.55 to 2.40)*	Olanzapine	Insufficient
Perphenazine vs. quetiatpine	1 (598)	Medium	Unknown	Direct	Imprecise	−0.92 (−1.93 to 0.05)	–	Insufficient
Perphenazine vs. risperidone	1 (602)	Medium	Unknown	Direct	Imprecise	−0.06 (−1.04 to 0.93)	–	Insufficient
Perphenazine vs. ziprasidone	1 (446)	Medium	Unknown	Direct	Imprecise	−0.85 (−2.05 to 0.35)	–	Insufficient
Negative symptoms								
Fluphenazine vs. olanzapine	1 (60)	Medium	Unknown	Direct	Imprecise	3.00 (−1.00 to 7.00)	–	Insufficient
Haloperidol vs. asenapine	1 (335)	Medium	Unknown	Direct	Imprecise	0.39 (−0.72 to 1.51)	–	Insufficient
Perphenazine vs. olanzapine	1 (597)	Medium	Unknown	Direct	Imprecise	0.43 (−0.55 to 1.41)	–	Insufficient
Perphenazine vs. quetiapine	1 (598)	Medium	Unknown	Direct	Imprecise	−0.70 (−1.66 to 0.25)	–	Insufficient
Perphenazine vs. risperidone	1 (602)	Medium	Unknown	Direct	Imprecise	−0.87 (−1.85 to 0.11)	–	Insufficient
Perphenazine vs. ziprasidone	1 (446)	Medium	Unknown	Direct	Imprecise	−0.97 (−2.05 to 0.10)	–	Insufficient
Total score								
Chlorpromazine vs. clozapine	1 (40)	Medium	Unknown	Direct	Imprecise	12.00 (−4.48 to 28.5)	–	Insufficient
Fluphenazine vs. olanzapine	1 (60)	Medium	Unknown	Direct	Precise	16.20 (1.22 to 31.18)*	Olanzapine	Insufficient
Haloperidol vs. asenapine	1 (335)	Medium	Unknown	Direct	Imprecise	0.23 (−2.50 to 2.95)	–	Insufficient
Perphenazine vs. olanzapine	1 (597)	Medium	Unknown	Direct	Precise	−4.59 (−7.42 to −1.77)*	Perphenazine	Insufficient
Perphenazine vs. aripiprazole	1 (300)	Medium	Unknown	Direct	Imprecise	−0.70 (−5.61 to 4.21)	–	Insufficient
Perphenazine vs. quetiapine	1 (598)	Medium	Unknown	Direct	Imprecise	1.52 (−1.36 to 4.41)	–	Insufficient
Perphenazine vs. risperidone	1 (602)	Medium	Unknown	Direct	Imprecise	0.17 (−2.84 to 3.19)	–	Insufficient
Perphenazine vs. ziprasidone	1 (446)	Medium	Unknown	Direct	Imprecise	2.23 (−1.15 to 5.61)	–	Insufficient
General psychopathology								
Chlorpromazine vs. clozapine	1 (40)	Medium	Unknown	Direct	Imprecise	5.00 (−3.68 to 13.68)	–	Insufficient
Fluphenazine vs. olanzapine	1 (60)	Medium	Unknown	Direct	Precise	8.20 (0.83 to 15.57)*	Olanzapine	Insufficient
Haloperidol vs. aripiprazole	1 (99)	Medium	Unknown	Direct	Imprecise	−1.60 (−5.28 to 2.08)	–	Insufficient
Haloperidol vs. asenapine	1 (335)	Medium	Unknown	Direct	Imprecise	0.26 (−1.59 to 2.10)	–	Insufficient
Perphenazine vs. olanzapine	1 (597)	Medium	Unknown	Direct	Precise	2.17 (0.66 to 3.68)*	Olanzapine	Insufficient
Perphenazine vs. ziprasidone	1 (446)	Medium	Unknown	Direct	Precise	−1.92 (−3.69 to −0.15)*	Perphenazine	Insufficient
Perphenazine vs. quetiapine	1 (598)	Medium	Unknown	Direct	Imprecise	−0.54 (−2.09 to 1.01)	–	Insufficient
Perphenazine vs. risperidone	1 (602)	Medium	Unknown	Direct	Imprecise	0.24 (−1.38 to 1.86)	–	Insufficient

PANSS = Positive and Negative Syndrome Scale.
* Statistically significant result.

Appendix Figure 1. **Positive symptoms (SAPS): haloperidol versus olanzapine.**

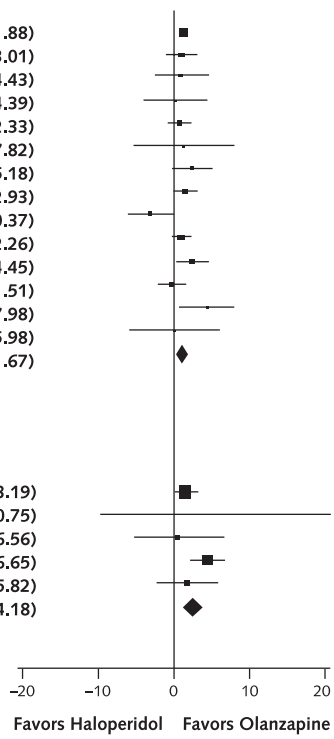
Study, Year (Reference)	Haloperidol Mean (SD)	Haloperidol Total	Olanzapine Mean (SD)	Olanzapine Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
SAPS						
Crespo-Facorro et al, 2012 (62)	–12.1 (2.9)	56	–8.9 (6.4)	55	90.7	–3.20 (–5.05 to –1.35)
Kim et al, 2010 (99)	55.7 (7.3)	35	58.2 (15.2)	32	9.3	–2.50 (–8.30 to 3.30)
Subtotal		91		87	100.0	–3.14 (–4.90 to –1.37)
Heterogeneity: $\tau^2 = 0.00$; $\psi^2 = 0.05$ ($P = 0.82$); $I^2 = 0\%$						
Test for overall effect: $Z = 3.48$ ($P < 0.001$)						



IV = inverse variance; SAPS = Scale for the Assessment of Positive Symptoms.

Appendix Figure 2. **Negative symptoms (PANSS and SANS): haloperidol versus olanzapine.**

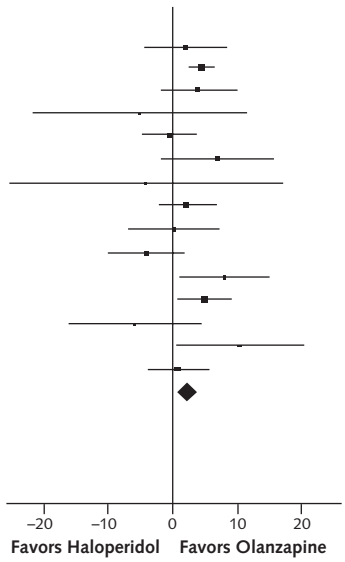
Study, Year (Reference)	Haloperidol Mean (SD)	Haloperidol Total	Olanzapine Mean (SD)	Olanzapine Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
PANSS	–3.2 (6.1)	660	–4.5 (6.3)	1336	24.5	1.30 (0.72 to 1.88)
Tollefson et al, 1997 (135)	–4.4 (8.2)	81	–5.47 (7.2)	350	7.4	1.07 (–0.87 to 3.01)
Beasley et al, 1997 (41)	–1.74 (5.72)	23	–2.76 (5.81)	21	2.9	1.02 (–2.39 to 4.43)
Purdon et al, 2000 (120)	18 (5.6)	13	17.8 (5.5)	14	2.0	0.20 (–3.99 to 4.39)
Bernardo et al, 2001 (42)	–2.94 (5.65)	89	–3.76 (4.65)	93	10.7	0.82 (–0.69 to 2.33)
Ishigooka et al, 2001 (85)	16.86 (8.71)	10	15.62 (7.93)	17	0.8	1.24 (–5.34 to 7.82)
Avasthi et al, 2001 (39)	22.6 (5.6)	37	20.1 (6.3)	39	4.4	2.50 (–0.18 to 5.18)
Volavka et al, 2002 (138)	17.56 (5.95)	132	16.07 (6)	131	11.3	1.49 (0.05 to 2.93)
Lieberman et al, 2003 (106)	19 (3.5)	15	22.2 (4.5)	16	4.0	–3.20 (–6.03 to –0.37)
Smelson et al, 2006 (132)	–1.5 (4.8)	97	–2.5 (5.3)	159	13.3	1.00 (–0.26 to 2.26)
Keefe et al, 2006 (98)	–8.6 (8.792)	132	–11 (8.57)	144	6.8	2.40 (0.35 to 4.45)
Kongsakon et al, 2006 (101)	0.44 (4.6)	36	0.72 (3)	37	8.4	–0.28 (–2.07 to 1.51)
Krakowski et al, 2006 (102)	22.58 (6.54)	19	18.25 (4.42)	16	2.5	4.33 (0.68 to 7.98)
Lindenmayer et al, 2007 (107)	17.9 (7.84)	11	17.79 (6.89)	14	1.0	0.11 (–5.76 to 5.98)
Boulay et al, 2007 (45)		1355		2387	100.0	1.06 (0.46 to 1.67)
Subtotal						
Heterogeneity: $\tau^2 = 0.30$; $\psi^2 = 17.91$ ($P = 0.16$); $I^2 = 27\%$						
Test for overall effect: $Z = 3.44$ ($P < 0.001$)						
SANS						
Beasley et al, 1996 (40)	–2.7 (5.9)	69	–4.26 (6.11)	198	44.9	1.56 (–0.08 to 3.19)
Avasthi et al, 2001 (39)	27.43 (19.43)	10	21.87 (19.47)	17	1.1	5.56 (–9.63 to 20.75)
Buchanan et al, 2005 (49)	30.2 (11.6)	34	29.6 (12.4)	29	6.7	0.60 (–5.36 to 6.56)
Crespo-Facorro et al, 2012 (62)	0.1 (6.3)	56	–4.4 (5.2)	55	33.7	4.50 (2.35 to 6.65)
Kim et al, 2010 (99)	56.6 (4.4)	35	54.8 (10.8)	32	13.5	1.80 (–2.22 to 5.82)
Subtotal		204		331	100.0	2.56 (0.94 to 4.18)
Heterogeneity: $\tau^2 = 0.82$; $\psi^2 = 5.28$ ($P = 0.26$); $I^2 = 24\%$						
Test for overall effect: $Z = 3.11$ ($P = 0.002$)						



IV = inverse variance; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms.

Appendix Figure 3. **Global rating and total symptom score improvement (PANSS): haloperidol versus olanzapine.**

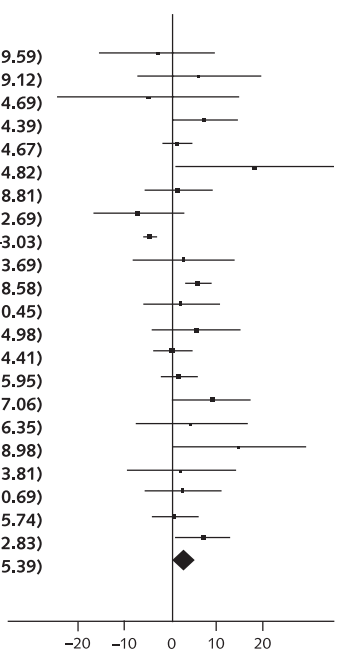
Study, Year (Reference)	Haloperidol Mean (SD)	Haloperidol Total	Olanzapine Mean (SD)	Olanzapine Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
PANSS						
Beasley et al, 1997 (41)	–20 (25.9)	81	–21.91 (26.9)	350	6.2	1.91 (–4.40 to 8.22)
Tollefson et al, 1997 (135)	–13.4 (20.6)	660	–17.7 (21.8)	1336	17.4	4.30 (2.34 to 6.26)
Ishigooka et al, 2001 (85)	–7.94 (21.85)	89	–11.84 (17.42)	93	7.1	3.90 (–1.86 to 9.66)
Bernardo et al, 2001 (42)	62.7 (20.7)	13	68 (23.3)	14	1.2	–5.30 (–21.90 to 11.30)
Altamura et al, 2002 (32)	74.43 (5.42)	15	75.08 (5.65)	13	10.5	–0.65 (–4.77 to 3.47)
Volavka et al, 2002 (138)	88.7 (16.6)	37	81.9 (21.8)	39	3.8	6.80 (–1.88 to 15.48)
de Haan et al, 2003 (68)	–11.4 (19.5)	12	–7.2 (31.9)	12	0.8	–4.20 (–25.35 to 16.95)
Rosenheck et al, 2003 (124)	75 (19)	150	73 (21)	159	9.7	2.00 (–2.46 to 6.46)
Lieberman et al, 2003 (106)	50 (29.9)	132	50 (28.78)	131	5.3	0.00 (–7.09 to 7.09)
Krakowski et al, 2006 (102)	0.58 (15.2)	36	4.83 (9.7)	37	6.9	–4.25 (–10.12 to 1.62)
Kongsakon et al, 2006 (101)	–36.7 (29.9)	132	–44.6 (28.78)	144	5.4	7.90 (0.96 to 14.84)
Keefe et al, 2006 (98)	–7.6 (16.3)	97	–12.4 (16)	159	10.6	4.80 (0.71 to 8.89)
Boulay et al, 2007 (45)	56.1 (12.97)	11	62 (12.84)	14	2.9	–5.90 (–16.10 to 4.30)
Lindenmayer et al, 2007 (107)	67.58 (17.7)	19	57.25 (11.73)	16	3.1	10.33 (0.51 to 20.15)
Kahn et al, 2008 (88)	53.3 (17.25)	103	52.4 (17.42)	105	9.1	0.90 (–3.81 to 5.61)
Subtotal		1587		2622	100.0	2.31 (0.44 to 4.18)
Heterogeneity: $\tau^2 = 4.22$; $\psi^2 = 22.25$ ($P = 0.07$); $I^2 = 37\%$						
Test for overall effect: $Z = 2.42$ ($P = 0.02$)						



IV = inverse variance; PANSS = Positive and Negative Syndrome Scale.

Appendix Figure 4. **Global rating and total symptom score improvement (PANSS): haloperidol versus risperidone (with outlier).**

Study, Year (Reference)	Haloperidol Mean (SD)	Haloperidol Total	Risperidone Mean (SD)	Risperidone Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
PANSS						
Claus et al, 1992 (56)	74.3 (20.16)	21	76.9 (20.16)	21	2.9	–2.60 (–14.79 to 9.59)
Chouinard et al, 1993 (53)	–9.3 (27.7)	21	–15.31 (27.55)	92	2.6	6.01 (–7.11 to 19.12)
Min et al, 1993 (114)	–21.9 (27.7)	19	–17.1 (30.6)	16	1.4	–4.80 (–24.29 to 14.69)
Marder and Meibach, 1994 (111)	88.8 (26.4)	66	81.54 (26.13)	256	5.0	7.26 (0.13 to 14.39)
Peuskens, 1995 (116)	–15 (21.95)	226	–16.52 (22.97)	1136	7.3	1.52 (–1.64 to 4.67)
Blin et al, 1996 (43)	–26.6 (27.6)	20	–44.7 (27)	21	1.8	18.10 (1.38 to 34.82)
Emsley, 1999 (71)	–29.3 (24.75)	84	–30.9 (24.87)	99	5.0	1.60 (–5.61 to 8.81)
Liu et al, 2000 (108)	–31.6 (20.6)	28	–24.7 (15.7)	28	3.8	–6.90 (–16.49 to 2.69)
Shrivastava and Gopa, 2000 (130)	37.1 (3.4)	50	41.5 (3.6)	50	8.0	–4.40 (–5.77 to –3.03)
Zhang et al, 2001 (143)	64.7 (16.6)	37	61.8 (30.6)	41	3.3	2.90 (–7.89 to 13.69)
Csernansky et al, 2002 (63)	2.69 (15.63)	188	–3.17 (10.51)	177	7.5	5.86 (3.14 to 8.58)
Volavka et al, 2002 (138)	88.7 (16.6)	37	86.4 (20.1)	41	4.5	2.30 (–5.85 to 10.45)
Yen et al, 2004 (142)	66.2 (16)	20	60.7 (14.9)	21	3.9	5.50 (–3.98 to 14.98)
Schooler et al, 2005 (127)	–20.6 (23.8)	277	–21 (24.34)	278	6.8	0.40 (–3.61 to 4.41)
Keefe et al, 2006 (98)	–7.6 (16.3)	97	–9.5 (15.5)	158	6.8	1.90 (–2.15 to 5.95)
Tamrakar et al, 2006 (134)	–43.17 (12.64)	18	–52.11 (12.2)	18	4.5	8.94 (0.82 to 17.06)
Lee et al, 2007 (104)	68.1 (15.81)	10	63.6 (10.75)	10	3.0	4.50 (–7.35 to 16.35)
Abdollahian, 2004 (31)	86.1 (27.7)	30	71.3 (30.6)	35	2.3	14.80 (0.62 to 28.98)
Apiquian et al, 2008 (35)	–33.3 (7.7)	10	–35.6 (16.9)	10	3.1	2.30 (–9.21 to 13.81)
Fakra et al, 2008 (73)	57.27 (12.92)	15	54.7 (9.5)	15	4.5	2.57 (–5.55 to 10.69)
Möller et al, 2008 (115)	57.5 (22.2)	146	56.6 (19.7)	143	6.3	0.90 (–3.94 to 5.74)
Ghaleiha et al, 2011 (76)	59.81 (8.5)	17	52.81 (8.84)	17	5.7	7.00 (1.17 to 12.83)
Subtotal		1437		2683	100.0	2.82 (0.25 to 5.39)
Heterogeneity: $\tau^2 = 21.06$; $\psi^2 = 87.86$ ($P < 0.001$); $I^2 = 76\%$						
Test for overall effect: $Z = 2.15$ ($P = 0.03$)						

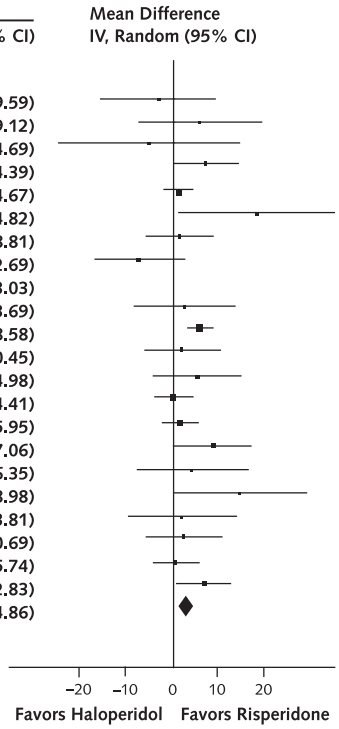


IV = inverse variance; PANSS = Positive and Negative Syndrome Scale.

Appendix Figure 5. **Global rating and total symptom score improvement (PANSS): haloperidol versus risperidone (outlier removed).**

Study, Year (Reference)	Haloperidol Mean (SD)	Haloperidol Total	Risperidone Mean (SD)	Risperidone Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
PANSS						
Claus et al, 1992 (56)	74.3 (20.16)	21	76.9 (20.16)	21	1.7	–2.60 (–14.79 to 9.59)
Chouinard et al, 1993 (53)	–9.3 (27.7)	21	–15.31 (27.55)	92	1.5	6.01 (–7.11 to 19.12)
Min et al, 1993 (114)	–21.9 (27.7)	19	–17.1 (30.6)	16	0.7	–4.80 (–24.29 to 14.69)
Marder and Meibach, 1994 (111)	88.8 (26.4)	66	81.54 (26.13)	256	4.4	7.26 (0.13 to 14.39)
Peuskens, 1995 (116)	–15 (21.95)	226	–16.52 (22.97)	1136	13.6	1.52 (–1.64 to 4.67)
Blin et al, 1996 (43)	–26.6 (27.6)	20	–44.7 (27)	21	0.9	18.10 (1.38 to 34.82)
Emsley, 1999 (71)	–29.3 (24.75)	84	–30.9 (24.87)	99	4.3	1.60 (–5.61 to 8.81)
Liu et al, 2000 (108)	–31.6 (20.6)	28	–24.7 (15.7)	28	2.6	–6.90 (–16.49 to 2.69)
Shrivastava and Gopa, 2000 (130)	37.1 (3.4)	50	41.5 (3.6)	50	0.0	–4.40 (–5.77 to –3.03)
Zhang et al, 2001 (143)	64.7 (16.6)	37	61.8 (30.6)	41	2.1	2.90 (–7.89 to 13.69)
Csernansky et al, 2002 (63)	2.69 (15.63)	188	–3.17 (10.51)	177	15.7	5.86 (3.14 to 8.58)
Volavka et al, 2002 (138)	88.7 (16.6)	37	86.4 (20.1)	41	3.5	2.30 (–5.85 to 10.45)
Yen et al, 2004 (142)	66.2 (16)	20	60.7 (14.9)	21	2.7	5.50 (–3.98 to 14.98)
Schooler et al, 2005 (127)	–20.6 (23.8)	277	–21 (24.34)	278	10.4	0.40 (–3.61 to 4.41)
Keefe et al, 2006 (98)	–7.6 (16.3)	97	–9.5 (15.5)	158	10.2	1.90 (–2.15 to 5.95)
Tamrakar et al, 2006 (134)	–43.17 (12.64)	18	–52.11 (12.2)	18	3.5	8.94 (0.82 to 17.06)
Lee et al, 2007 (104)	68.1 (15.81)	10	63.6 (10.75)	10	1.8	4.50 (–7.35 to 16.35)
Abdollahian, 2004 (31)	86.1 (27.7)	30	71.3 (30.6)	35	1.3	14.80 (0.62 to 28.98)
Apiquian et al, 2008 (35)	–33.3 (7.7)	10	–35.6 (16.9)	10	1.9	2.30 (–9.21 to 13.81)
Fakra et al, 2008 (73)	57.27 (12.92)	15	54.7 (9.5)	15	3.5	2.57 (–5.55 to 10.69)
Möller et al, 2008 (115)	57.5 (22.2)	146	56.6 (19.7)	143	8.0	0.90 (–3.94 to 5.74)
Ghaleiha et al, 2011 (76)	59.81 (8.5)	17	52.81 (8.84)	17	6.1	7.00 (1.17 to 12.83)
Subtotal		1387		2633	100.0	3.24 (1.62 to 4.86)

Heterogeneity: $\tau^2 = 2.44$; $\psi^2 = 24.83$ ($P = 0.21$); $I^2 = 19\%$
Test for overall effect: $Z = 3.91$ ($P < 0.001$)

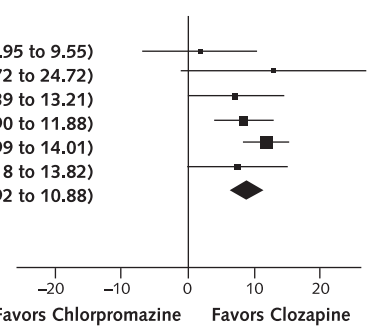


IV = inverse variance; PANSS = Positive and Negative Syndrome Scale.

Appendix Figure 6. **Global rating and total symptom score improvement (BPRS): chlorpromazine versus clozapine.**

Study, Year (Reference)	Chlorpromazine Mean (SD)	Chlorpromazine Total	Clozapine Mean (SD)	Clozapine Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
BPRS (on medication)						
Singer and Law, 1974 (131)	22.3 (12)	20	20.5 (13)	20	9.1	1.80 (–5.95 to 9.55)
Gelenberg and Doller, 1979 (75)	39 (12)	8	27 (13)	7	3.6	12.00 (–0.72 to 24.72)
Rinieris et al, 1980 (122)	33.4 (9.7)	16	26.6 (4.9)	5	12.6	6.80 (0.39 to 13.21)
Claghorn et al, 1987 (55)	–14.64 (12)	76	–22.53 (13)	75	26.2	7.89 (3.90 to 11.88)
Kane et al, 1988 (91)	56 (12)	142	45 (13)	126	37.1	11.00 (7.99 to 14.01)
Hong et al, 1997 (84)	52 (10)	19	45 (12)	21	11.4	7.00 (0.18 to 13.82)
Subtotal		281		254	100.0	8.40 (5.92 to 10.88)

Heterogeneity: $\tau^2 = 1.95$; $\psi^2 = 6.27$ ($P = 0.28$); $I^2 = 20\%$
Test for overall effect: $Z = 6.65$ ($P = 0.001$)

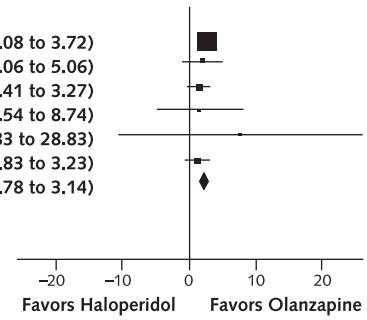


BPRS = Brief Psychiatric Rating Scale; IV = inverse variance.

Appendix Figure 7. **General psychopathology (MADRS): haloperidol versus olanzapine.**

Study, Year (Reference)	Haloperidol Mean (SD)	Haloperidol Total	Olanzapine Mean (SD)	Olanzapine Total	Mean Difference Weight, %	Mean Difference IV, Random (95% CI)
MADRS						
Tollefson et al, 1997 (135)	–3.1 (8.8)	660	–6 (8.7)	1336	69.3	2.90 (2.08 to 3.72)
Avasthi et al, 2001 (39)	5 (4.58)	10	3 (2.42)	17	4.9	2.00 (–1.06 to 5.06)
Lieberman et al, 2003 (106)	8.38 (8.21)	132	6.95 (7.01)	131	13.6	1.43 (–0.41 to 3.27)
de Haan et al, 2003 (68)	–1.2 (3.6)	12	–2.8 (12.1)	12	0.9	1.60 (–5.54 to 8.74)
Krakowski et al, 2006 (102)	43.6 (53.4)	36	35.1 (32.4)	37	0.1	8.50 (–11.83 to 28.83)
Keefe et al, 2006 (98)	–1.7 (7.9)	97	–2.9 (8.3)	159	11.2	1.20 (–0.83 to 3.23)
Subtotal		947		1692	100.0	2.46 (1.78 to 3.14)

Heterogeneity: $\tau^2 = 0.00$; $\psi^2 = 4.27$ ($P = 0.51$); $I^2 = 0\%$
Test for overall effect: $Z = 7.09$ ($P = 0.001$)



IV = inverse variance; MADRS = Montgomery–Asberg Depression Rating Scale.

Appendix Table 6. **Summary of Results for 4 Key Adverse Events With Insufficient Strength of Evidence**

Adverse Event and Comparison	Study Design	Study Duration	Events/ Participants, *n/N*	Events/ Participants, *n/N*	Risk Difference (95% CI)	Risk Ratio (95% CI)	Risk of Bias	Consistency	Directness	Precision	Favored Drug
Diabetes mellitus											
Haloperidol vs. olanzapine	RCT	6 wk	3/31	4/35	−0.02 (−0.17 to 0.13)	0.85 (0.21 to 3.49)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. olanzapine	RCT	18 mo	17/261	27/336	−0.02 (−0.06 to 0.03)	0.81 (0.45 to 1.45)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. quetiapine	RCT	18 mo	17/261	14/337	0.02 (−0.01 to 0.06)	1.57 (0.79 to 3.12)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. risperidone	RCT	18 mo	17/261	21/341	0.00 (−0.04 to 0.04)	1.06 (0.57 to 1.96)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. ziprasidone	RCT	18 mo	17/261	12/185	0.00 (−0.05 to 0.05)	1.00 (0.49 to 2.05)	Medium	Unknown	Direct	Imprecise	–
The metabolic syndrome											
Haloperidol vs. clozapine	RCT	12 wk	4/36	15/37	−0.29 (−0.48 to −0.11)*	0.27 (0.10 to 0.75)*	Medium	Unknown	Direct	Precise	Haloperidol
Perphenazine vs. olanzapine	RCT	18 mo	49/261	72/336	−0.03 (−0.09 to 0.04)	0.88 (0.63 to 1.21)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. quetiapine	RCT	18 mo	49/261	53/337	0.03 (−0.03 to 0.09)	1.19 (0.84 to 1.70)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. risperidone	RCT	18 mo	49/261	45/341	0.06 (−0.00 to 0.12)	1.42 (0.98 to 2.06)	Medium	Unknown	Direct	Imprecise	–
Perphenazine vs. ziprasidone	RCT	18 mo	49/261	23/185	0.06 (−0.00 to 0.13)	1.51 (0.96 to 2.39)	Medium	Unknown	Direct	Imprecise	–
Death											
Chlorpromazine vs. ziprasidone	RCT	12 wk	0/154	0/152	0.00 (−0.01 to 0.01)	NE	Medium	Unknown	Direct	Imprecise	–
Haloperidol vs. clozapine	Cohort	Duration of prescription	235/41 295	24/8330	0.00 (0.00 to 0.00)	1.98 (1.30 to 3.00)*	Medium	Unknown	Direct	Imprecise	Clozapine
Haloperidol vs. risperidone	Cohort	Duration of prescription	235/41 295	74/22 057	0.00 (0.00 to 0.00)	1.70 (1.31 to 2.20)*	Medium	Unknown	Direct	Imprecise	Risperidone
Haloperidol vs. ziprasidone	RCT	2 to 3 d	0/27	0/31	0.00 (−0.07 to 0.07)	NE	Medium	Unknown	Direct	Imprecise	–
Thioridazine vs. clozapine	Cohort	Duration of prescription	146/23 950	24/8330	0.00 (0.00 to 0.00)	2.12 (1.38 to 3.26)*	Medium	Unknown	Direct	Imprecise	Clozapine
Thioridazine vs. risperidone	Cohort	Duration of prescription	146/23 950	74/22 057	0.00 (0.00 to 0.00)	1.82 (1.37 to 2.40)*	Medium	Unknown	Direct	Imprecise	Risperidone
Tardive dyskinesia											
Chlorpromazine vs. ziprasidone	RCT	12 wk	16/154	13/152	0.02 (−0.05 to 0.08)	1.21 (0.61 to 2.44)	Medium	Unknown	Direct	Imprecise	–
Haloperidol vs. clozapine	Cohort	22 y	14/152	0/181	0.09 (0.05 to 0.14)*	34.50 (2.07 to 573.55)*	Medium	Unknown	Direct	Precise	Clozapine
Haloperidol vs. olanzapine	RCT	12 wk	5/219	0/234	0.02 (0.00 to 0.04)	11.75 (0.65 to 211.26)	Medium	Unknown	Direct	Imprecise	–
Haloperidol vs. ziprasidone	RCT	28 wk	2/153	0/148	0.01 (−0.01 to 0.04)	4.84 (0.23 to 99.93)	Medium	Unknown	Direct	Imprecise	–

NE = not estimable; RCT = randomized, controlled trial.
* Statistically significant result.