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 versus 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 heterogeneous 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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METHODS

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.
## 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‡ | Moderate |
| 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-I | | | | | | | |
| 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-S | | | | | | | |
| 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 |
| Haloperidol vs. olanzapine | 6 (2639) | Medium | Consistent | Precise | 2.46 (1.78 to 3.14)† | Olanzapine | Moderate |

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of illness (positive and negative symptoms and general psychopathology) and 4 adverse events specified a priori. Secondary outcomes included 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, \( -78.70 (-119.34 \text{ to } -38.06) \)† |
| Perphenazine vs. risperidone | 48 221               | MD, \(-33.40 (-75.18 \text{ to } 8.38) \)  |
| **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)  |
| Haloperidol vs. olanzapine | 747/1606 1312/2493 | RR, 1.12 (0.86 to 1.46)  |
| 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. olanzapine | 49/115 115/220     | RR, 0.82 (0.64 to 1.04)  |
| Haloperidol vs. risperidone | 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. 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, \(-7.10 (-19.02 \text{ to } 4.82) \) |
| Haloperidol vs. olanzapine | 150 159           | MD, \(-7.10 (-20.95 \text{ to } 6.75) \) |
| **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, \(-12.12 (-22.06 \text{ to } -2.17) \)† |
| Haloperidol vs. olanzapine | 103 227          | MD, \(-2.62 (-6.39 \text{ to } 1.15) \) |
| Haloperidol vs. risperidone | 30 33            | MD, \(-0.10 (-0.17 \text{ to } 0.37) \) |
| Perphenazine vs. olanzapine | 261 336          | MD, \(-0.00 (-0.16 \text{ to } 0.16) \) |
| Perphenazine vs. quetiapine | 261 337          | MD, \(-0.10 (-0.07 \text{ to } 0.27) \) |
| Perphenazine vs. risperidone | 261 341         | MD, \(-0.07 (-0.24 \text{ to } 0.10) \) |
| Perphenazine vs. ziprasidone | 261 185         | MD, \(-0.07 (-0.27 \text{ to } 0.13) \) |

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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.

### Table 2—Continued

| Variable and Comparison | Events/Participants, n/N* | FGAs | SGA, Effect Estimate (95% CI) |
|-------------------------|-------------------------|------|--------------------------------|
| **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) |
| **QLP**                 |                         |      |                                |
| 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 | 7/11/3/13              | 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).
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), although there was substantial heterogeneity (I² = 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

| 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)                       | –                         | –                         | –.04 (-.14 to .06)        | 0.33 (0.01 to 7.81)  |
|                            | RCT         | 208 wk         | 1 (50)                        | 0/25                      | 1/25                      | –.01 (-.02 to .05)        | 2.93 (0.12 to 70.85) |
|                            | RCT         | 12 mo          | 1 (164)                       | 1/83                      | 0/81                      | –                        |                     |
| 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                     | –.01 (-.03 to .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                      | –.02 (-.17 to .13)        | 0.82 (0.24 to 2.82)  |
|                            | RCT         | 6 wk           | 1 (66)                        | 1/31                      | 9/35                      | –.22 (-.38 to -.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.
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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Cognitive effects of antipsychotic drugs in first-episode schizophrenia

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| 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 | Oral Intramuscular                           | 2.5 to 10 mg/d          | Approved in 1960 | Schizophrenia and BD                 | 0.26/2.5 mg                         |
| Fluphenazine hydrochloride |              |                                                | 2.5 to 10 mg/dose       |                |                                      |                                     |
| Haloperidol        | Haldol              | Oral Intramuscular                            | 4 to 12 mg/d            | Approved in 1986 | Schizophrenia                        | 0.44/4 mg                           |
| Droperidol decanoate |                    |                                                |                         |                |                                      |                                     |
| 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                          |
| Loxapine decanoate |                     |                                               |                         |                |                                      |                                     |
| Pimozide           | Orap                | Oral                                           | 7 to 10 mg/d            | Approved in 1984 | Schizophrenia                        | 6.40/7 mg                           |
| Prochlorperazine   | Compro              | Oral                                           | 15 to 40 mg/d           | Approved in 1966 | Schizophrenia                        | 1.40/15 mg                          |
| Prochlorperazine edisylate |         | Intramuscular                                  | 15 to 40 mg/d           | Approved in 1956 | Schizophrenia                        | 1.90/15 mg                          |
| Prochlorperazine maleate |          | Intravenous                                    | 7.5 to 40 mg/d          |                |                                      |                                     |
| 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 | Schizophrenia                        | 6.56/10 mg                          |
| Asenapine          | Saphouris           | Oral                                           | Schizophrenia, 5 mg BD, 10 mg | Approved in 2004 | 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 BD L, 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 | Schizophrenia                        | 2.78/150 mg                         |
| Risperidone        | Risperdal           | Oral; intramuscular injection                  | Schizophrenia, 4 to 8 mg BD L, 1 to 6 mg/d | Approved in 1997 | Schizophrenia                        | 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.
|   |                                                                                       |
|---|----------------------------------------------------------------------------------------|
| 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$.mp.                                                                        |
| 10| (dementia adj (praecox or precoc)).tw.                                                  |
| 11| (delusional adj2 disorder*).tw.                                                         |
| 12| (negative or positive) adj syndrome*.tw.                                                 |
| 13| hebephrenia.tw.                                                                         |
| 14| exp Bipolar Disorder/                                                                   |
| 15| (((bipolar or manic) adj2 (I or II or illness or disorder or psychosis or depress$)) or mania*).tw. |
| 16| (BP 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).                                                                     |
| 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| (Aminizin or Aminazine or Ampliact or BC 135 or Chlorpromazine or Chlorpromazinum or Chlorpromazina or Chlor-Promaryl or Chlorpromados or Chloroderan or Chlorpromazin or Contomin or Elmarin or Esnind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largacthiazine or Megaphen or Largactyl or Klooprampatsiini or Kloprampzin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Prima or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazin or Torazina or Winterini).mp. |
| 33| Droperidol/                                                                            |
| 34| 548-73-2.rn.                                                                           |
| 35| (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Dropeptan or Droperidol or Droperidol or Droperidol or Droperidolum or Disifelt or Halkan or Inapsin or Inapsine or Inopin or Thalamonal or Nilperidon or Properinol or Sintodril or Vetkalm).mp. |
| 36| fluphenazine/                                                                           |
| 37| 69-23-8.rn.                                                                            |
| 38| (Dapolum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluphenazinum or Ftorphenazine or Meditmen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespame).mp. |
| 39| haloperidol/                                                                           |
| 40| 52-86-8.rn.                                                                            |
| 41| (Aldo or Alopeirdin or Aloperidol or Aloperidolo or Bootopron or Dazic or Einalon S or Eukystol or Fortunol or Galoperidol or Haldol or Halozut or Haloperidol or Haloperidol or Haloperidolon or Haloperidol or Serenace or Haloperidol or Haloper or Halopen or Keselan or Lealgin or Lintol or Mixidol or Peeluca or Permx or Serence or Sereneff or Sernas or Sernel or Serenda or Ullolind or Uliolind or Vesalium).mp. |
| 42| loxapine/                                                                              |
| 43| 1977-10-2.m.                                                                           |
| 44| (Clozaepine or CL 62362 or Dibenacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Oxilapina or Oxilapac or Loxtane or Desconex).mp. |
| 45| perphenazine/                                                                           |
| 46| 58-39-9.m.                                                                             |
| 47| (Chlorperphenazine or Chlorpizaprin or Decenant or Emsinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfanina or Perfanzena or Perfazanazina or Perfenazina or Perphenazina or Perphenazinum or Perpirtyn or Sch 3940 or Thilatazin or Tranquisan or Trilaron or Trilafon or Trifan or Triptafen or Triphenat or Triavl).mp. |
| 48| Pimozide/                                                                              |
| 49| 2062-78-4.m.                                                                           |
| 50| (Antollon or Opian or Orap or Pimotsidi or Pimozid or Pimoza or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp. |
| 51| Prochlorperazine/                                                                       |
| 52| 58-38-8.m.                                                                             |
| 53| (Apo-Prochlorazine or Capazine or Chlormethazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazene or Mitil or Prochlpomazine or Prochlorperazine or Proclorperazina or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothazine or Serall or Stemetil or Tementil or Temetid).mp. |
| 54| thiotoxine/                                                                             |
| 55| 5591-45-7.m.                                                                           |
| 56| (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotxen or Tiotixeno or Tiotexen or Thixit or Tiotixene).mp. |
### Appendix Table 2—Continued

|   |   |
|---|---|
| 57 | trifluoperazine/ |
| 58 | 117-89-5.rn. |
| 59 | (Cuart D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or trifftazin 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 Meleral or Mellerets or Melleretten or Melleril or Sonapax or Thoridazin or Thoridazine or Thoridazinium or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp. |
| 63 | methotrimeprazine/ |
| 64 | 60-99-1.rn. |
| 65 | (Dedoran or Himamin or Himamine or Levomepromazine or Levomepromazin or Levopromazine or Levopromazinum or Levoxpro or Levoxpromazine or Neurocil or Neozine or Nirvan or Nojivan or Nozikan or Nozizane or Sinogan or Levomol or Nozian or Sinogina or Tisercin or Veractil).mp. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects] |
| 66 | Butyrophenones/ad, to, tu, ct, po, ae |
| 67 | thioxanthenes/ad, to, tu, ct, po, ae |
| 68 | Dibenzoxazepines/ad, to, tu, ct, po, ae |
| 69 | Indoles/ad, to, tu, ct, po, ae |
| 70 | or/29-70 |
| 71 | atypical antipsychotic$\cdot$tw. |
| 72 | ((second or 2nd) adj generation adj antipsychotic*).tw. |
| 73 | ((third or 3rd) adj generation adj antipsychotic*).tw. |
| 74 | Asenapine/ |
| 75 | 65576-45-6.rn. |
| 76 | (Asenapine or EINECS 265-829-4).mp. |
| 77 | clozapine/ |
| 78 | 5786-21-0.rn. |
| 79 | (Clozapin or Clozapina or Clozapinium or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp. |
| 80 | risperdone/ |
| 81 | 106266-06-2.rn. |
| 82 | (Apexdione or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperlept or Rispolin or Spiron).mp. |
| 83 | olanzapine.mp. |
| 84 | 132539-06-1.rn. |
| 85 | (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera or Symbax).mp. |
| 86 | quetiapine.mp. |
| 87 | (111974-69-7 or 111974-72-2).rn. |
| 88 | (Co-Quetiapine or HSD8 7557 or Seroquel).mp. |
| 89 | ziprasidone.mp. |
| 90 | 146939-27-7.rn. |
| 91 | (Zeldox or zeldrox or geodon).mp. |
| 92 | aripiprazole.mp. |
| 93 | 129722-12-9.rn. |
| 94 | (Abilittat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp. |
| 95 | paliperidone.mp. |
| 96 | 144598-75-4.rn. |
| 97 | (9-Hydroxypiperidone or Invega or R 76477 or RO76477).mp. |
| 98 | iloperidone/ |
| 99 | 133454-47-4.rn. |
| 100 | (Fanapt or iloperidone or HP 873 or Zomaril).mp. |
| 101 | Isoxazoles/ad, to, tu, ct, po, ae |
| 102 | Dibenazepines/ad, to, tu, ct, po, ae |
| 103 | Pyrimidiones/ad, to, tu, ct, po, ae |
| 104 | Piperidines/ad, to, tu, ct, po, ae |
| 105 | Dibenzothiazepines/ad, to, tu, ct, po, ae |
| 106 | Piperazines/ad, to, tu, ct, po, ae |
| 107 | Pirenzipine/tu, ad, to, ct, po, ae |
| 108 | Thiazoles/ad, th, ct, po, to, ae |
| 109 | Quinolones/to, po, ct, ad, tu, ae |
| 110 | or/72-110 |
| 111 | and/71,111 |
| 112 | and/28,71,111 |
| 113 | or/112-113 |
| 114 | randomized controlled trial.pt. |
| 115 | controlled clinical trial.pt. |
| 116 | randomi?ed.ab. |
| 117 | placebo*.ab. |
| 118 | drug therapy.fs. |
| 119 | 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 cohort$ or control$ or volunteer$ or evaluat$ or compar$ or longitudinal or long term or long-term 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       | Direct      | Imprecise  |           | 0.16 (−1.22 to 1.54)     | –             | Insufficient          |
| Perphenazine vs. olanzapine | 1 (597)                        | Medium       | Direct      | Precise   | 1.47 (0.55 to 2.40)*     | Olanzapine     | Insufficient          |
| Perphenazine vs. quetiapine | 1 (598)                        | Medium       | Direct      | Imprecise  |           | −0.92 (−1.93 to 0.05)    | –             | Insufficient          |
| Perphenazine vs. risperidone | 1 (602)                       | Medium       | Direct      | Imprecise  |           | −0.06 (−1.04 to 0.93)    | –             | Insufficient          |
| Perphenazine vs. ziprasidone | 1 (446)                       | Medium       | 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       | Direct      | Imprecise  |           | 0.39 (−0.72 to 1.51)     | –             | Insufficient          |
| Perphenazine vs. olanzapine | 1 (597)                        | Medium       | Direct      | Imprecise  |           | 0.43 (−0.55 to 1.41)     | –             | Insufficient          |
| Perphenazine vs. quetiapine | 1 (598)                        | Medium       | Direct      | Imprecise  |           | −0.70 (−1.66 to 0.25)    | –             | Insufficient          |
| Perphenazine vs. risperidone | 1 (602)                       | Medium       | Direct      | Imprecise  |           | −0.87 (−1.85 to 0.11)    | –             | Insufficient          |
| Perphenazine vs. ziprasidone | 1 (446)                       | Medium       | Direct      | Imprecise  |           | −0.97 (−2.06 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. aripiprazole | 1 (300)                      | Medium       | Direct      | Precise   |           | −4.59 (−7.42 to −1.77)*  | Perphenazine   | Insufficient          |
| Perphenazine vs. olanzapine | 1 (597)                        | Medium       | Direct      | Imprecise  |           | −0.70 (−5.61 to 4.21)    | –             | Insufficient          |
| Perphenazine vs. quetiapine | 1 (598)                        | Medium       | Direct      | Imprecise  |           | 1.52 (1.36 to 4.41)      | –             | Insufficient          |
| Perphenazine vs. risperidone | 1 (602)                       | Medium       | Direct      | Imprecise  |           | 0.17 (−2.84 to 3.19)     | –             | Insufficient          |
| Perphenazine vs. ziprasidone | 1 (446)                       | Medium       | 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       | Direct      | Imprecise  |           | 0.26 (−1.59 to 2.10)     | –             | Insufficient          |
| Perphenazine vs. olanzapine | 1 (597)                        | Medium       | Direct      | Imprecise  |           | 2.17 (0.66 to 3.68)*     | Olanzapine     | Insufficient          |
| Perphenazine vs. ziprasidone | 1 (446)                       | Medium       | Direct      | Imprecise  |           | −1.92 (−3.69 to −0.15)*  | Perphenazine   | Insufficient          |
| Perphenazine vs. quetiapine | 1 (598)                        | Medium       | Direct      | Imprecise  |           | −0.54 (−2.09 to 1.01)    | –             | Insufficient          |
| Perphenazine vs. risperidone | 1 (602)                       | Medium       | 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) | Total | Olanzapine Mean (SD) | Total | Mean Difference Weight, % 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)            | 55    | 58.2 (15.2)           | 32    | 9.3 -2.50 (-8.30 to 3.30)                  |
| Subtotal                | 91                    | 87    | 100.0                 | 87    | -3.14 (-4.90 to -1.37)                     |

Heterogeneity: $\chi^2 = 0.00; \phi^2 = 0.05 (P = 0.82); I^2 = 0%$

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) | Total | Olanzapine Mean (SD) | Total | Mean Difference Weight, % IV, Random (95% CI) |
|-------------------------|-----------------------|-------|-----------------------|-------|---------------------------------------------|
| PANSS                   |                       |       |                       |       |                                             |
| 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 (6.4)           | 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: $\chi^2 = 0.30; \phi^2 = 17.91 (P = 0.16); I^2 = 27%$

Test for overall effect: $Z = 3.44 (P < 0.001)$

SANS

| Study, Year (Reference) | Haloperidol Mean (SD) | Total | Olanzapine Mean (SD) | Total | Mean Difference Weight, % IV, Random (95% CI) |
|-------------------------|-----------------------|-------|-----------------------|-------|---------------------------------------------|
| 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: $\chi^2 = 0.82; \phi^2 = 5.28 (P = 0.26); I^2 = 24%$

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) | PANSS | Haloperidol | Olanzapine | Mean Difference | Mean Difference |
|-------------------------|-------|-------------|------------|----------------|----------------|
|                         |       | Mean (SD)   | Mean (SD)  | Total           | Total           |
| Beasley et al, 1997 (41)|       | –20 (25.9)  | –21.91 (26.9) | 350             | 6.2             | 1.91 (4.40 to 8.22) |
| Tollefsen et al, 1997 (135)|   | –13.4 (20.6) | –17.7 (21.8) | 1336          | 17.4           | 4.30 (2.34 to 6.26) |
| Ishigooka et al, 2001 (85)|   | –7.94 (21.85) | –11.84 (17.42) | 93             | 7.1             | 3.90 (–1.86 to 9.66) |
| Bernardo et al, 2001 (42)|   | 62.7 (20.7) | 68.23 (23.3) | 14             | 1.2             | –5.30 (–21.90 to 11.30) |
| Altamura et al, 2002 (32)|   | 74.43 (5.42) | 75.08 (5.65) | 13             | 10.5           | –0.65 (–4.77 to 3.47) |
| Volavka et al, 2002 (138)|   | 88.7 (16.6) | 81.9 (21.8) | 39             | 3.8             | 6.80 (–1.88 to 15.48) |
| de Haan et al, 2003 (68)|   | –11.4 (19.5) | –7.2 (31.9) | 12             | 0.8             | –4.20 (–25.35 to 16.95) |
| Rosenheck et al, 2003 (124)| | 75 (19) | 73 (21) | 159           | 9.7             | 2.00 (–2.46 to 6.46) |
| Lieberman et al, 2003 (106)| | 50 (29.9) | 50 (28.78) | 131           | 5.3             | 0.00 (–7.09 to 7.09) |
| Krakowski et al, 2006 (102)| | 0.58 (15.2) | 4.83 (9.7) | 37             | 6.9             | –4.25 (–10.12 to 1.62) |
| Kongsakon et al, 2006 (101)| | –36.7 (29.9) | –44.6 (28.78) | 144            | 5.4             | 7.90 (0.96 to 14.84) |
| Keele et al, 2006 (98) |       | –7.6 (16.3) | –12.4 (16) | 159           | 10.6           | 4.80 (0.71 to 8.89) |
| Boulay et al, 2007 (45) |       | 56.1 (12.97) | 62 (12.84) | 14             | 2.9             | –5.90 (–16.10 to 4.30) |
| Lindenmayer et al, 2007 (107) | | 67.58 (17.7) | 57.25 (11.73) | 16             | 3.1             | 10.33 (0.51 to 20.15) |
| Kahn et al, 2008 (88)   |       | 53.3 (17.25) | 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: $\tau^2 = 4.22; \psi^2 = 22.25$ ($P \geq 0.07$); $I^2 = 37\%$
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) | PANSS | Haloperidol | Risperidone | Mean Difference | Mean Difference |
|-------------------------|-------|-------------|------------|----------------|----------------|
|                         |       | Mean (SD)   | Mean (SD)  | Total           | Total           |
| Beasley et al, 1997 (41)|       | –20 (25.9)  | –21.91 (26.9) | 350             | 6.2             | 1.91 (4.40 to 8.22) |
| Tollefsen et al, 1997 (135)|   | –13.4 (20.6) | –17.7 (21.8) | 1336          | 17.4           | 4.30 (2.34 to 6.26) |
| Ishigooka et al, 2001 (85)|   | –7.94 (21.85) | –11.84 (17.42) | 93             | 7.1             | 3.90 (–1.86 to 9.66) |
| Bernardo et al, 2001 (42)|   | 62.7 (20.7) | 68.23 (23.3) | 14             | 1.2             | –5.30 (–21.90 to 11.30) |
| Altamura et al, 2002 (32)|   | 74.43 (5.42) | 75.08 (5.65) | 13             | 10.5           | –0.65 (–4.77 to 3.47) |
| Volavka et al, 2002 (138)|   | 88.7 (16.6) | 81.9 (21.8) | 39             | 3.8             | 6.80 (–1.88 to 15.48) |
| de Haan et al, 2003 (68)|   | –11.4 (19.5) | –7.2 (31.9) | 12             | 0.8             | –4.20 (–25.35 to 16.95) |
| Rosenheck et al, 2003 (124)| | 75 (19) | 73 (21) | 159           | 9.7             | 2.00 (–2.46 to 6.46) |
| Lieberman et al, 2003 (106)| | 50 (29.9) | 50 (28.78) | 131           | 5.3             | 0.00 (–7.09 to 7.09) |
| Krakowski et al, 2006 (102)| | 0.58 (15.2) | 4.83 (9.7) | 37             | 6.9             | –4.25 (–10.12 to 1.62) |
| Kongsakon et al, 2006 (101)| | –36.7 (29.9) | –44.6 (28.78) | 144            | 5.4             | 7.90 (0.96 to 14.84) |
| Keele et al, 2006 (98) |       | –7.6 (16.3) | –12.4 (16) | 159           | 10.6           | 4.80 (0.71 to 8.89) |
| Boulay et al, 2007 (45) |       | 56.1 (12.97) | 62 (12.84) | 14             | 2.9             | –5.90 (–16.10 to 4.30) |
| Lindenmayer et al, 2007 (107) | | 67.58 (17.7) | 57.25 (11.73) | 16             | 3.1             | 10.33 (0.51 to 20.15) |
| Kahn et al, 2008 (88)   |       | 53.3 (17.25) | 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: $\tau^2 = 4.22; \psi^2 = 22.25$ ($P \geq 0.07$); $I^2 = 37\%$
Test for overall effect: $Z = 2.42$ ($P = 0.02$)

IV = inverse variance; PANSS = Positive and Negative Syndrome Scale.
### Appendix Figure 5. Global rating and total symptom score improvement (PANSS): haloperidol versus risperidone (outlier removed).

| Study, Year (Reference) | Haloperidol | Risperidone | Mean Difference | Mean Difference |
|-------------------------|-------------|-------------|-----------------|----------------|
|                         | Mean (SD)   | Total       | Mean (SD)       | Total          | Weight, % IV, Random (95% CI) | Mean Difference IV, Random (95% CI) |
| 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                       | -8.30 (-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)    | -15.2 (19.95)| 226         | -16.52 (22.97)  | 1136           | 13.6                      | 1.52 (-1.64 to 4.67)                |
| Bliu et al, 1996 (43)   | -26.4 (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 (-0.51 to 8.81)                |
| Liu et al, 2000 (108)   | -31.6 (20.6)| 28          | -24.7 (15.7)    | 28             | 2.6                       | -9.90 (-16.69 to 2.69)              |
| Shrivastava and Gupta, 2000 (130) | 37.1 (3.6) | 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 (10.6)     | 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                       | 5.05 (-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)               |
| Abdallahian, 2004 (31)  | 86.1 (27.7) | 30          | 71.3 (30.6)     | 35             | 1.3                       | 14.80 (0.62 to 28.38)               |
| Apiqian et al, 2008 (33) | -33.3 (7.7) | 10          | -35.6 (16.9)    | 10             | 1.9                       | 2.30 (-9.21 to 13.81)               |
| Falha et al, 2008 (73)  | 57.27 (12.92)| 15         | 54.7 (9.5)      | 15             | 3.5                       | 2.57 (-5.55 to 10.69)               |
| Müller et al, 2008 (115) | 57.5 (22.2) | 146         | 56.6 (19.7)     | 143            | 8.0                       | 0.30 (-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: $\chi^2 = 2.44$; $\phi^2 = 24.83$ ($P = 0.21$); $I^2 = 19$

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 | Clozapine | Mean Difference | Mean Difference |
|-------------------------|---------------|-----------|-----------------|----------------|
|                         | Mean (SD)     | Total     | Mean (SD)       | Total          | Weight, % IV, Random (95% CI) | Mean Difference IV, Random (95% CI) |
| BPDS (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)            |
| Riniers et al, 1980 (123) | 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)              |
| Kan 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: $\chi^2 = 1.95$; $\phi^2 = 6.27$ ($P = 0.28$); $I^2 = 20$

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) | Total | Olanzapine Mean (SD) | Total | Mean Difference Weight, % IV, Random (95% CI) | Mean Difference IV, Random (95% CI) |
|------------------------|-----------------------|-------|----------------------|-------|-----------------------------------------------|-------------------------------------|
| 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 | |

Heterogeneity: τ² = 0.00; χ² = 4.27 (P = 0.51); I² = 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 | 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.