Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

Summary

Background Because of the debate about whether second-generation antipsychotic drugs are better than first-generation antipsychotic drugs, we did a meta-analysis of randomised controlled trials to compare the effects of these two types of drugs in patients with schizophrenia.

Methods We compared nine second-generation antipsychotic drugs with first-generation drugs for overall efficacy (main outcome), positive, negative and depressive symptoms, relapse, quality of life, extrapyramidal side-effects, weight gain, and sedation.

Findings We included 150 double-blind, mostly short-term, studies, with 21,533 participants. We excluded open studies because they systematically favoured second-generation drugs. Four of these drugs were better than first-generation antipsychotic drugs for overall efficacy, with small to medium effect sizes (amisulpride −0.31 [95% CI −0.44 to −0.19, p<0.0001], clozapine −0.52 [−0.75 to −0.29, p<0.0001], olanzapine −0.28 [−0.38 to −0.18, p<0.0001], and risperidone −0.13 [−0.22 to −0.05, p=0.002]). The other second-generation drugs were not more efficacious than the first-generation drugs, except for negative symptoms. Therefore efficacy on negative symptoms cannot be a core component of atypicality. Second-generation antipsychotic drugs induced fewer extrapyramidal side-effects than did haloperidol (even at low doses). Only a few have been shown to induce fewer extrapyramidal side-effects than low-potency first-generation antipsychotic drugs. With the exception of aripiprazole and ziprasidone, second-generation antipsychotic drugs induced more weight gain, in various degrees, than did haloperidol but not than low-potency first-generation drugs. The second-generation drugs also differed in their sedating properties. We did not note any consistent effects of moderator variables, such as industry sponsorship, comparator dose, or prophylactic antiparkinsonian medication.

Interpretation Second-generation antipsychotic drugs differ in many properties and are not a homogeneous class. This meta-analysis provides data for individualised treatment based on efficacy, side-effects, and cost.

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Introduction

The high costs of second-generation (atypical) antipsychotic drugs, with $7·5 billion sales in the USA in 2003,1 has led to a continuing debate about their benefits compared with first-generation compounds. Limitations of previous reviews2 were that they analysed only one global efficacy outcome, even though the main advantage of second-generation antipsychotic drugs is claimed to be their broad efficacy spectrum. In particular, these drugs are thought to improve negative symptoms, depression, and quality of life more than do conventional antipsychotic drugs. Improved efficacy for these problems is thought to be a major characteristic of the atypicality of second-generation antipsychotic drugs, in addition to a reduction in extrapyramidal side-effects. In previous meta-analyses (apart from Cochrane reviews), side-effects were not assessed thoroughly, even though they are important criteria in drug choice. Furthermore, the number of randomised controlled trials in which antipsychotic drugs were assessed is continually increasing, making new meta-analyses necessary. We present a meta-analysis of randomised controlled trials to compare the effects of second-generation antipsychotic drugs with first-generation antipsychotic drugs on several outcomes in patients with schizophrenia.

Methods

Search

We searched (without language restrictions) the register of the Cochrane Schizophrenia Group,1 US Food and Drugs Administration website, and previous reviews2−4 for randomised controlled trials in which oral formulations of second-generation antipsychotic drugs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine) were compared with first-generation antipsychotic drugs for the treatment of schizophrenia or related disorders (schizoaffective, schizoaffectivform, or delusional disorder, and irrespective of the diagnostic criterion used). We started the search in August, 2005, and searched Medline up to October, 2006. The Cochrane Schizophrenia Group register is compiled with regular methodical searches of ten electronic databases, and supplemented with manual searching of relevant journals and conference proceedings.4 We included only those studies meeting quality criteria A (adequate randomisation) and B (usually...
stated as randomised without details) according to the Cochrane handbook.1 For fixed-dose studies, we selected only those with optimum doses of second-generation antipsychotic drugs as reported in dose-finding studies ( amisulpride 50–300 mg per day for predominantly negative symptoms and 400–800 mg per day for positive symptoms, aripiprazole 10–30 mg per day, olanzapine 10–20 mg per day, quetiapine >250 mg per day, risperidone 4–6 mg per day, sertindole 16–24 mg per day, and ziprasidone 120–160 mg per day). Note that if we had used an increased threshold dose of quetiapine, the efficacy would have been reduced because 750 mg per day was the least effective dose in the only relevant study. For the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,7 we used the Positive and Negative Syndrome Scale (PANSS) total score and quality-of-life score, since these alone were available for all patients without tardive dyskinesia.8 We included studies in which medications were allowed to be switched between groups.9–12 Inclusion or exclusion of these studies and other CATIE results had no important effect on the outcomes.

Data extraction and outcome variables
Two reviewers (DA, CL, SL) independently extracted all data. We contacted first authors (if address was available) and all second-generation antipsychotic drug manufacturers for missing data. We assessed the mean overall change in symptoms, with the following order: change in PANSS total score from baseline, if not available then the change in the Brief Psychiatric Rating Scale (BPRS), and then values of these scales at study endpoint, all based on intention-to-treat datasets whenever available. We similarly analysed negative, positive, and depressive symptoms, and overall quality of life; and we analysed dichotomous-outcome responder rates for number needed to treat (NNT), number needed to harm (NNH), and relapse rates. A 50% reduction from baseline in PANSS or BPRS scores, or a score of much improved on the Clinical Global Impression Scale, were the a-priori chosen cutoffs,8,9 However, when these were not available, we applied the authors’ definitions of response. We analysed weight gain and sedation. For extrapyramidal side-effects, the main outcome was use of antiparkinsonian medication; in comparisons with low-potency first-generation antipsychotic drugs, use of antiparkinsonian medication was so rarely reported so we used at least one extrapyramidal side-effect as the outcome in such studies. In meta-regression analyses, in which we assessed the effect of prophylactic antiparkinsonian medication on differences in extrapyramidal side-effects, the results of the extrapyramidal side-effect rating scales were the dependent variable.

Meta-analytical calculations
For continuous data, we used the standardised mean difference Hedges’ adjusted g. Unreported SD values were calculated from other statistics or from the average of the other studies. Standard inverse of the variance weighting was used when we pooled the studies. We did not apply weighting for study quality, because determination of how much weight to assign to different quality criteria has no empirical basis.13 For dichotomous data, we applied a once randomised-analysed endpoint assessment, calculating relative risks (RR) primarily, risk differences, and NNT or NNH. Since considerable heterogeneity exists in some analyses according to the I² statistics,14 we applied the Der-Simionan and Laird random-effects model throughout.

We compared double-blind studies with open-label or single-blind studies and noted that the open-label and single-blind studies systematically favoured the second-generation antipsychotic drugs. We therefore based all subsequent analyses on double-blind studies. With random-effect restricted maximum-likelihood meta-regression or sensitivity analyses, or both, we assessed industry sponsorship, chronicity, study duration, western versus Oriental (mainly Chinese) studies, comparator dose, differences in extrapyramidal side-effects between second-generation and first-generation antipsychotic
Figure 2: Second-generation versus first-generation antipsychotic drugs—efficacy in various domains.

Data are Hedges' g (95% CI). Note that the results are significant at p<0.05 if the 95% CIs do not overlap the x-axis. SGA=second-generation antipsychotic drug.
or single-blind studies were excluded after the absence of double blind was detected as a bias.

We included a total of 239 publications of 130 double-blind studies with 21,533 participants. Haloperidol was the comparator drug in 95 studies, chlorpromazine in 28, perphenazine in five, fluphenazine in four, flupenthixol and perazine in three each, thioridazine and levomepromazine in two each, and all other drugs (clozapine, risperidone, clopenthixol, loxapine, tiotixene, clozapine, trifluoperazine, pericazine, and any first-generation antipsychotic drugs) in one each. 35 studies were of Orient or g in five studies, the first episode of schizophrenia was assessed; 121 (81%) studies lasted 12 weeks or less; 17 (11%) lasted up to 6 months; and 12 (8%) were longer than 6 months. The mean duration of illness was 11-8 years (SD 7-7) and mean age of patients was 36-2 years (7-7; webtable 1).

### Outcomes

Figures 1-7 and tables 1-7 summarise the findings. Webtables 2-4 show detailed statistics, meta-regressions, and sensitivity analyses; webfigures 1-10 show forest-plots; webfigure 11 shows the funnel-plots, webtable 5 shows further results and discussions on comparator dose; webtable 6 shows prophylactic antiparkinsonian medications; webtable 7 shows industry-sponsorship; and webtable 8 shows efficacy versus effectiveness research.

### Effects of blinding

Open-label and single-blind studies yielded significantly higher effect sizes than did double-blind studies in several domains of efficacy and tolerability (figure 1; table 1). Further, effects of the absence of masking were noted for single second-generation drugs—eg, in the overall efficacy of olanzapine (p=0.040) and quetiapine (p=0.009).

### Overall efficacy

Five second-generation antipsychotic drugs (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were not significantly different from first-generation antipsychotic drugs in their effects on overall symptoms (figure 2; table 2). Four second-generation antipsychotic drugs—ie, amisulpride, clozapine, olanzapine, and risperidone—were more efficacious (Hedges' g -0.13 to -0.52) than first-generation drugs (figure 2; table 2). The NNT for one additional responder was between 6 (95% CI 4-10) for amisulpride and 13 (9-36) for risperidone (webtable 4).

### Specific psychopathology

These four second-generation antipsychotic drugs were also more efficacious than first-generation drugs for treatment of positive and negative symptoms (figure 2; table 2).

Importantly for the notion of atypicality, the other five second-generation antipsychotic drugs (ie, aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were not more effective than first-generation drugs for treatment of negative symptoms. The drugs were also no more efficacious than first-generation antipsychotic drugs for positive symptoms, and quetiapine was less efficacious.
The pattern for depression was somewhat different—i.e., amisulpride, clozapine, olanzapine, and aripiprazole and quetiapine, were significantly better than first-generation drugs, whereas risperidone was not.

Relapse
Relapse was reported in only 14 long-term studies. Olanzapine (four studies, 1008 participants, RR 0.67 [0.49–0.92], NNT 17 [8–100]), risperidone (5, 1174, 0.74 [0.63–0.87], 11 [7–33]), and sertindole (1, 282, 0.17 [0.04–0.73], 14 [8–50]) proved to be significantly better than first-generation antipsychotic drugs; amisulpride, aripiprazole, and clozapine showed no significant difference (webtable 2). No studies were available for the other second-generation antipsychotic drugs. For quetiapine, in a large unpublished study, no difference compared with haloperidol (n=301) was reported, but the data necessary for meta-analytical calculations were not presented.

Quality of life
Quality of life was reported in only 17 studies. Only amisulpride, clozapine, and sertindole were better than first-generation antipsychotic drugs (figure 3; table 3). In three further olanzapine studies, no significant difference was reported for the related idea of patients’ attitude towards treatment (n=171, -0.36 [95% CI -0.90 to 0.21, p=0.21]).

Side-effects
According to textbooks, high-potency and low-potency first-generation antipsychotic drugs are equally efficacious, but differ in side-effects. Therefore, we have presented the tolerability results separately for haloperidol and low-potency comparator drugs.

Extrapyramidal side-effects
All second-generation antipsychotic drugs were associated with much fewer extrapyramidal side-effects than haloperidol. NNT was between 2 for clozapine and 5 for zotepine (figure 4; table 4). However, with the exception of clozapine, olanzapine, and risperidone, second-generation drugs have not been shown to be better than low-potency first-generation antipsychotic drugs, and we noted a robust superiority based on more than two studies only for clozapine (figure 4; table 4).

Weight gain
Amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine were associated with significantly more weight gain than was haloperidol, whereas aripiprazole and ziprasidone were not (figure 5; table 5). We did not note a significant difference between second-generation antipsychotic drugs and low-potency first-generation drugs (figure 5; table 5).

Sedation
Clozapine (NNH 5 [3–14]), quetiapine (13 [8–20]), and zotepine (NNH not significant) were significantly more sedating than was haloperidol, whereas aripiprazole (33 [20–101]) was significantly less sedating (figure 6; table 6). By contrast, compared with low-potency first-generation antipsychotic drugs, only clozapine (13 [7–220]) was significantly more sedating (figure 6; table 6).

Effects of comparator dose
We did not note a clear pattern of comparator-drug dose affecting the efficacy of second-generation antipsychotic drugs, and the few significant differences between studies with haloperidol at more or less than 12 mg per day or 7.5 mg per day (or chlorpromazine 600 mg equivalents for low-potency first-generation drugs) were contradictory. Figure 7 and table 7 show results based on the haloperidol cutoff of 12 mg per day. Haloperidol was given to participants at less than or equal to 7.5 mg per day in only 12 studies (webtable 5).

Higher haloperidol doses usually induced more extrapyramidal side-effects than did lower doses, but the effects...
were small and not always consistent (figure 7; table 7; webtable 5). Only higher doses of low-potency first-generation antipsychotic drugs than 600 mg per day produced more extrapyramidal side-effects than did clozapine, the only drug with enough studies for assessment.

**Prophylactic antiparkinsonian medication**

In 11 studies of clozapine, olanzapine, or risperidone, prophylactic antiparkinsonian medications were used by participants in the first-generation antipsychotic drugs’ groups. Only one meta-regression analysis (clozapine for negative symptoms) was significant (webtable 3). The efficacy effect sizes were in the same range as those in the overall analysis, but the statistical significance was inconsistent and absent for risperidone. Clozapine and olanzapine induced significantly fewer extrapyramidal side-effects than did first-generation antipsychotic drugs despite prophylactic antiparkinsonian medication, but the effect size was relatively small. Risperidone showed no difference in these side-effects compared with first-generation antipsychotic drugs combined with prophylactic antiparkinsonian medication (webtable 6).

**Industry sponsorship**

There were enough non-industry sponsored studies for only clozapine, olanzapine, quetiapine, and risperidone. The only significant difference between sponsored and non-sponsored studies was noted for the effect of clozapine on positive symptoms (webtable 3). Nevertheless, when industry-sponsored studies were excluded in a sensitivity analysis, the efficacy of this drug was reduced (eg, an effect size of -0.22 for overall symptoms compared with -0.52 when all studies were included) but still significant. Risperidone was not significantly more efficacious than first-generation antipsychotic drugs for the overall change in symptoms when industry-sponsored studies were excluded. The results for olanzapine and quetiapine were unchanged by sponsorship (webtable 2; webtable 7).

Other moderators did not affect the results in a uniform direction, and most sensitivity analyses were consistent with the main results (webtable 2; webtable 3). Funnel plots did not show a potential publication bias (webfigure 11). Webtable 8 compares the results of efficacy and effectiveness studies.

**Discussion**

Four second-generation antipsychotic drugs—amisulpride, clozapine, olanzapine, and risperidone—were more efficacious than first-generation drugs in the main domains (overall change in symptoms, and positive and negative symptoms). The other five second-generation antipsychotic drugs were only as efficacious as first-generation antipsychotic drugs, even in terms of negative symptoms. Second-generation antipsychotic drugs caused fewer extrapyramidal side-effects than did haloperidol, even
when the haloperidol dose was less than 7.5 mg per day; however, a difference between most second-generation antipsychotic drugs and low-potency first-generation antipsychotics has not been shown. Most second-generation drugs (except aripiprazole and ziprasidone) induced more weight gain than did high-potency but not low-potency first-generation antipsychotic drugs.

Many companies claimed that improved efficacy in negative symptoms is a core characteristic of atypicality. Our meta-analysis does not confirm this common notion because the effects of some second-generation antipsychotic drugs were not significant compared with those of first-generation drugs. The most efficacious drugs were better in all efficacy domains, whereas the others ones were only as efficacious as first-generation antipsychotics, although the effect sizes for negative symptoms were often larger than those for positive symptoms. The findings for depression were different; risperidone did not seem to be better than first-generation drugs, whereas aripiprazole and quetiapine were, consistent with evidence of their effectiveness in major depression.

Quality of life was reported in only very few studies; if a superiority of second-generation antipsychotic drugs was noted, the effect size was in the same range as that for efficacy. In another meta-analysis, second-generation antipsychotic drugs were better for global cognitive functioning (effect size -0.24). Clozapine has been shown to reduce suicidality more than does olanzapine.

With respect to the magnitude of the efficacy effect sizes, the superiority of the more efficacious second-generation antipsychotic drugs was only small to medium according to Cohen's classification. For perspective, the pooled effect size in another review comparing second-generation antipsychotic drugs with placebo was -0.51 and the NNT was 6. Differences, such as higher dropout rates in the placebo-controlled trials than in the active-comparator-drug-controlled trials make it impossible for us to say that the efficacy of clozapine doubles the efficacy compared with placebo (ie, the effect size of antipsychotic drugs vs placebo is 0.51 and the effect size of clozapine vs first-generation antipsychotic drugs is 0.52). However, schizophrenia usually affects patients for life and even a small benefit could be important.

In this study, second-generation antipsychotic drugs induced fewer extrapyramidal side-effects than did haloperidol, and most of them even when haloperidol was used at doses less than 7.5 mg per day. In individual

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Mean weight-gain difference (kg; 95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>SGA versus haloperidol</strong></td>
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<td>Amisulpride</td>
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<td>373</td>
<td>0.9 (0.2 to 1.6)</td>
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<td>1998</td>
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<td>3.4 (2.0 to 4.9)</td>
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<td>3.2 (2.2 to 4.4)</td>
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<td>321</td>
<td>2.7 (2.2 to 3.3)</td>
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<td><strong>SGA versus low-potency FGA</strong></td>
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FGA=first-generation antipsychotic drug. SGA=second-generation antipsychotic drug.
SGA versus haloperidol: number of patients with sedation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of studies</th>
<th>Number of patients with sedation</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
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<td>1.70 (1.32-2.19)</td>
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<td>0.80 (0.69-0.92)</td>
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<td>Ziprasidone</td>
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<td>302</td>
<td>1.80 (1.03-3.08)</td>
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</table>

SGA versus low-potency FGA: number of patients with sedation

<table>
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<th>Drug</th>
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<td>Zotepine</td>
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FGA=first-generation antipsychotic drug. SGA=second-generation antipsychotic drug.

Table 6: Sedation

The fact that absence of masking can bias the results is important because previous meta-analyses included both open-label and double-blind studies (all Cochrane reviews and others). We did not note a consistent pattern of other moderators affecting the results. This inconsistency supports the notion that the second-generation antipsychotic drugs are a heterogeneous group of drugs. However, the meta-regressions and sensitivity analyses were hampered by missing data in the predictor matrix (rarely were all outcomes in a study reported) and often by the small numbers of studies. Although the comparator-drug dose had some effects on extrapyramidal side-effects, a consistent effect on efficacy was not noted. The optimum haloperidol dose is still not known, which is a problem when it is used. In one study, about 3 mg per day was sufficient, whereas in another study the efficacy increased with doses up to 20 mg per day, and the American Psychiatric Association guideline recommends a broad range of 5–20 mg per day. Use of low-potency first-generation antipsychotic drugs does not solve all problems, because these drugs induce weight gain and cause sedation.

Whether prophylactic antiparkinsonian medication can reverse the superiority in efficacy of second-generation drugs cannot be shown with certainty. The effects were inconsistent, and prophylactic antiparkinsonian medication was used in only 11 studies with three second-generation antipsychotic drugs. Although the prophylactic antiparkinsonian drug reduced the differences in extrapyramidal effects, significance was maintained for clozapine and olanzapine. Use of prophylactic antiparkinsonian drugs warrants further investigation; guidelines about their use are ambivalent.

The advantages of these drugs are the avoidance of extrapyramidal side-effects that can also mimic negative symptoms; disadvantages are that many patients will not have these side-effects, and antiparkinsonian drugs cause anticholinergic side-effects.
We could not find a consistent effect on efficacy of sponsoring by industry because the results of olanzapine and quetiapine were largely unchanged. The reasons for possible sponsorship effects in clozapine and risperidone studies need to be assessed in more detail. They could relate to differences in questions addressed, flawed or different designs, or selective publication of positive studies by industry. We have noted systematic bias in the reporting of results by industry with masked ratings of abstracts.

We discuss our results in the context of the effectiveness studies CATIE and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS). In phase I of the CATIE study, olanzapine treatment resulted in the lowest discontinuation rate (all-cause and inefficacy) but the largest weight gain. In phase II, clozapine was more effective than the other second-generation antipsychotic drugs. Treatment with the first-generation antipsychotic drug perphenazine resulted in the highest discontinuation rate because of extrapyramidal side-effects, but was not different in scale-derived extrapyramidal side-effects. The effects of second-generation drugs were not better than those of perphenazine on PANS total score, cognition, cost, quality of life, and psychosocial functioning. Although some of the CATIE results are compatible with our findings (a detailed comparison is provided in...
CUTLASS\(^5\) and CATIE\(^5\) addressed different questions with different designs. Most previous studies addressed pure efficacy and safety, whereas in the CATIE\(^5\) and CUTLASS\(^5\) studies the investigators focused on real-world effectiveness. In these studies, broader inclusion criteria were applied and use of more concomitant medication was allowed than in efficacy studies; in the CUTLASS\(^5\) study, the doctors could choose from among the different first-generation and second-generation antipsychotic drugs, and even switch between drug groups. Both study types have strengths and weaknesses. A strength of CATIE\(^5\) and CUTLASS\(^5\) was the use of comparator drugs that are less potent than haloperidol. Sulpiride, initially used by 50% of the participants in the CUTLASS\(^5\) study's first-generation antipsychotic drug group, might induce fewer extrapyramidal side-effects than other first-generation drugs.\(^6\) A major limitation of our meta-analysis is that haloperidol was the comparator drug in most of the studies, and the number of studies of mid-potency first-generation drugs was insufficient. Results of the CATIE\(^5\) and CUTLASS\(^5\) studies suggest that mid-potency first-generation drugs would have been more appropriate, because they are less likely to cause extrapyramidal side-effects (early work has suggested that perphenazine causes fewer dystonias than does fluphenazine),\(^9\) and they are not associated with sedation or weight gain. In our database, we did not note a difference in the use of antiparkinsonian medication between patients given thiothixene and zotepine in the only available study,\(^9\) and in one of two perphenazine-controlled studies (high-dose risperidone 5–15 mg).\(^9\)

In the other perphenazine-controlled study, only a 10% difference in use of antiparkinsonian medication compared with aripiprazole was noted.\(^6\) But to conclude from CATIE and CUTLASS that all antipsychotics are the same and thus to let psychiatrists revert to old bad habits, such as the widespread use of high-dose haloperidol (and not sulpiride or perphenazine) as the primary first-generation antipsychotic drug in many industrialised countries\(^6\) would not help patients, and there are problems with low-potency first-generation drugs as well. The second-generation drugs are expensive, and cost-effectiveness has not been proven.\(^6\)

Public institutions could save costs by funding studies to accurately define selected old compounds, because they were not rigorously studied when the time they were introduced.\(^6\)

Because the second-generation antipsychotic drugs differ in many properties, including efficacy, side-effects, cost (some are now generic), and pharmacology (amisulpride is not a serotonin receptor blocker), they do not form a homogeneous class and neither do first-generation antipsychotic drugs. Improper generalisation creates confusion and as a result the classification might be abandoned.

This meta-analysis provides data that clinicians could use for individualised treatment of patients with schizophrenia based on efficacy, side-effects, and cost of antipsychotic drugs.

**Contributors**

SL contributed to designing the study, quality assessment of single-drug studies, data extraction, statistical analysis, and writing of the report. CC contributed to statistical analysis and writing of the report. DA contributed to quality assessment of single-drug studies, data extraction, and writing of the report. RE and JD contributed to designing the study, statistical analysis, and writing of the report. CI contributed to quality assessment of single-drug studies and data extraction.

**Conflict of interest statement**

SL has received speaker and consultancy honoraria from Sanofi-Aventis, BMS, Lilly, Janssen, Lundbeck, and Pfizer. The other authors declare that they have no conflict of interest.

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