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, even 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.

Funding National Institute of Mental Health.

Lancet 2009; 373: 31–41
Published Online December 5, 2008
DOI:10.1016/S0140-6736(08)61764-X

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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 reviews[2,3] 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,[4] US Food and Drugs Administration website, and previous reviews[2–4] 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, schizophreniform, 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

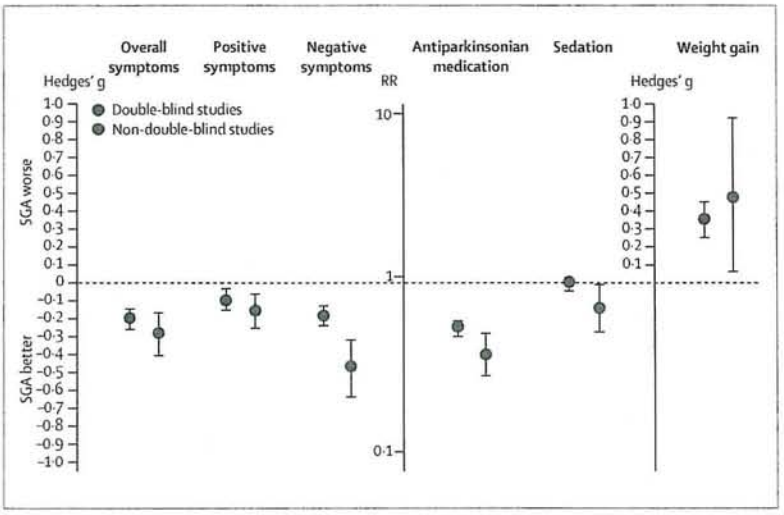

Figure 1: **Non double-blind studies favour second-generation antipsychotic drugs**
Data are Hedges' g (95% CI) and relative risk (RR; 95% CI). Similar results were obtained after correction for differences in efficacy and side-effects of the drugs. SGA=second-generation antipsychotic drug.

	Number of double-blind studies	Number of open-label/single-blind studies	Q	p value*
Overall symptoms	127	49	1·57	0·2110
Positive symptoms	81	36	1·37	0·2414
Negative symptoms	101	41	11·98	0·0005
Antiparkinsonian medication	87	17	5·48	0·0192
Sedation	69	18	4·05	0·0441
Weight gain	44	6	0·38	0·540

*For difference between double-blind and open-label or single-blind studies.

Table 1: **Non double-blind studies favour second-generation antipsychotic drugs**

stated as randomised without details) according to the Cochrane handbook.[5] 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[6] 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.[8,9] We included studies in which medications were allowed to be switched between groups.[10–12] Inclusion or exclusion of these studies and other CATIE[7] 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;[4,13] 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.[5] 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 I^2 statistics,[14] we applied the Der-Simonian and Laird[15] 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

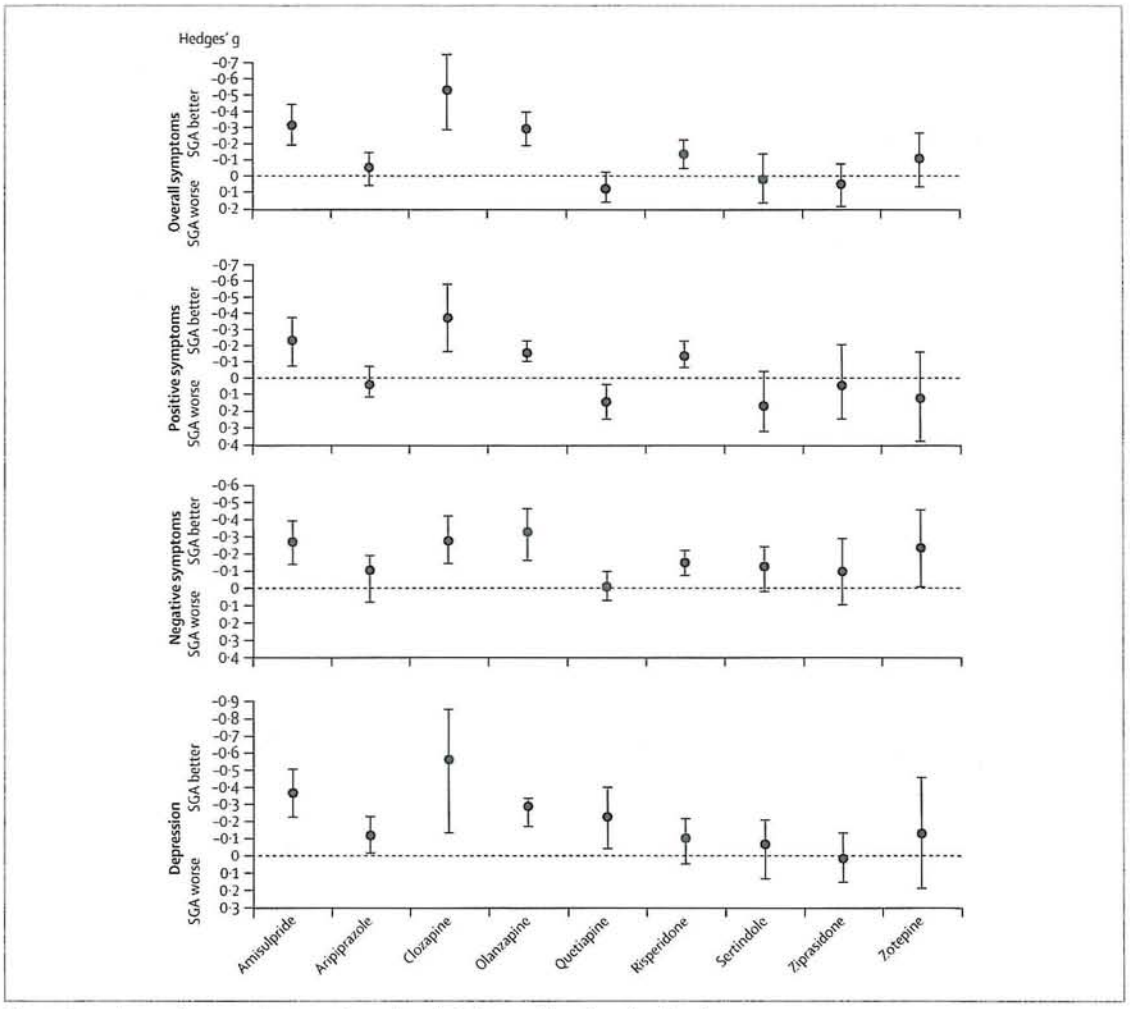

Figure 2: **Second-generation versus first-generation antipsychotic drugs—efficacy in various domains**
Data are Hedges' g (95% CI). Note that the results are significant at p<0·05 if the 95% CIs do not overlap the x axis. SGA=second-generation antipsychotic drug.

drugs, prophylactic antiparkinsonian medication, and haloperidol versus low-potency comparator drug (defined as less or equipotent to chlorpromazine) as potential moderators.[16] With the last four moderators, we tested the hypothesis that extrapyramidal side-effects induced by first-generation antipsychotic drugs might mimic symptoms of schizophrenia and falsely suggest that second-generation drugs are better.[1,2,17] We analysed the effects of comparator-drug dose with the following cutoffs: haloperidol 12 mg per day[2,16] or 7·5 mg per day (an adequate dose according to a Cochrane review),[18] and, for low-potency first-generation antipsychotic drugs, 600 mg per day[17] chlorpromazine equivalents.[16,17]

We assessed publication bias with funnel plots.[5] We did calculations with Comprehensive Meta-Analysis (version 2.2.034)[19] and Stata (version 7.0). Two-sided α was set at p<0·05. We did not adjust significance levels for multiple testing. Note that we did the sensitivity analyses to assess the robustness of results and not to gather significant results.

Role of the funding source

The sponsor had no influence on design, analysis, interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Search

Our search yielded 4166 citations. Of 411 inspected, we excluded 107 studies for reasons of inadequate randomisation (n=50), no appropriate intervention or control group (n=29), inappropriate participants (n=2), no usable data (n=24), presentation of a subgroup only (n=1), and very short duration (ie, 5 days; n=1). Another 65 open

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 150 double-blind studies with 21533 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 (clopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciacine, and any first-generation antipsychotic drugs) in one each. 35 studies were of Oriental origin; 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 (7·1; webtable 1).

See Online for webtables 1–8 and webfigures 1–11

	Number of studies	Number of participants	Hedges' g (95% CI)	p value
Amisulpride				
Overall symptoms	13	1017	−0·31 (−0·44 to −0·19)	<0·0001
Positive symptoms	4	703	−0·22 (−0·37 to −0·06)	0·005
Negative symptoms	10	929	−0·27 (−0·40 to −0·14)	0·0001
Depression	9	900	−0·37 (−0·51 to −0·24)	<0·0001
Aripiprazole				
Overall symptoms	5	2049	−0·05 (−0·14 to 0·05)	0·326
Positive symptoms	4	1983	0·03 (−0·06 to 0·12)	0·508
Negative symptoms	5	2049	−0·09 (−0·19 to 0·01)	0·079
Depression	1	1278	−0·12 (−0·24 to −0·01)	0·040
Clozapine				
Overall symptoms	23	1997	−0·52 (−0·75 to −0·29)	<0·0001
Positive symptoms	10	1080	−0·36 (−0·56 to −0·16)	<0·0001
Negative symptoms	17	1603	−0·27 (−0·42 to −0·13)	<0·0001
Depression	6	426	−0·51 (−0·87 to −0·14)	0·006
Olanzapine				
Overall symptoms	28	4966	−0·28 (−0·38 to −0·18)	<0·0001
Positive symptoms	24	4189	−0·15 (−0·21 to −0·09)	<0·0001
Negative symptoms	24	4187	−0·32 (−0·47 to −0·16)	<0·0001
Depression	12	2893	−0·27 (−0·35 to −0·19)	<0·0001
Quetiapine				
Overall symptoms	11	2412	0·04 (−0·04 to 0·12)	0·308
Positive symptoms	9	1742	0·14 (0·03 to 0·26)	0·013
Negative symptoms	10	1926	0 (−0·09 to 0·09)	0·928
Depression	4	442	−0·23 (−0·41 to −0·04)	0·016
Risperidone				
Overall symptoms	34	4173	−0·13 (−0·22 to 0·05)	0·002
Positive symptoms	28	3286	−0·13 (−0·20 to −0·05)	0·001
Negative symptoms	30	3455	−0·13 (−0·21 to −0·06)	<0·0001
Depression	11	1611	−0·10 (−0·23 to 0·03)	0·145
Sertindole				
Overall symptoms	4	1344	0·02 (−0·13 to 0·16)	0·836
Positive symptoms	3	1145	0·17 (−0·03 to 0·36)	0·089
Negative symptoms	4	1198	−0·11 (−0·22 to 0·01)	0·068
Depression	2	574	−0·04 (−0·22 to 0·14)	0·680
Ziprasidone				
Overall symptoms	5	980	0·04 (−0·08 to 0·17)	0·483
Positive symptoms	4	728	0·03 (−0·20 to 0·26)	0·813
Negative symptoms	3	691	−0·09 (−0·29 to 0·11)	0·384
Depression	3	691	0·01 (−0·14 to 0·16)	0·910
Zotepine				
Overall symptoms	15	1125	−0·10 (−0·27 to 0·06)	0·212
Positive symptoms	2	192	0·12 (−0·16 to 0·40)	0·409
Negative symptoms	5	450	−0·23 (−0·46 to 0)	0·050
Depression	2	134	−0·14 (−0·48 to 0·20)	0·413

Table 2: **Second-generation versus first-generation antipsychotic drugs—efficacy in various domains**

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 15 (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—ie, 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)[20] 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.[21] 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 [20–1011]) 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

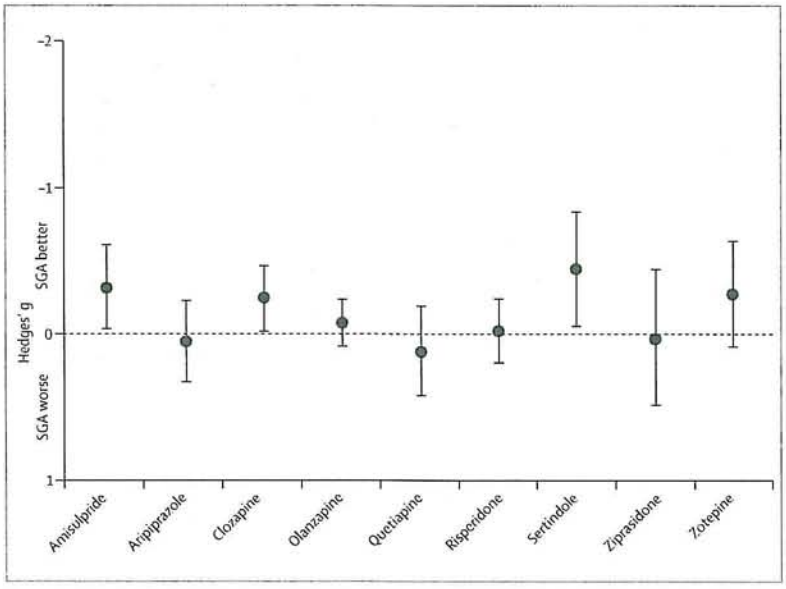

Figure 3: **Quality of life**
Data are Hedges' g (95% CI). SGA=second-generation antipsychotic drug.

	Number of studies	Number of participants	Hedges' g (95% CI)	p value
Amisulpride	1	194	−0·31 (−0·60 to −0·03)	0·030
Aripiprazole	1	206	0·06 (−0·22 to 0·33)	0·683
Clozapine	1	311	−0·24 (−0·46 to −0·01)	0·039
Olanzapine	5	1450	−0·07 (−0·23 to 0·09)	0·398
Quetiapine	2	166	0·12 (−0·18 to 0·43)	0·432
Risperidone	4	330	−0·02 (−0·23 to 0·20)	0·887
Sertindole	1	105	−0·44 (−0·83 to −0·05)	0·027
Ziprasidone	1	72	0·03 (−0·43 to 0·49)	0·905
Zotepine	1	122	−0·27 (−0·63 to 0·09)	0·138

Table 3: **Quality of life**

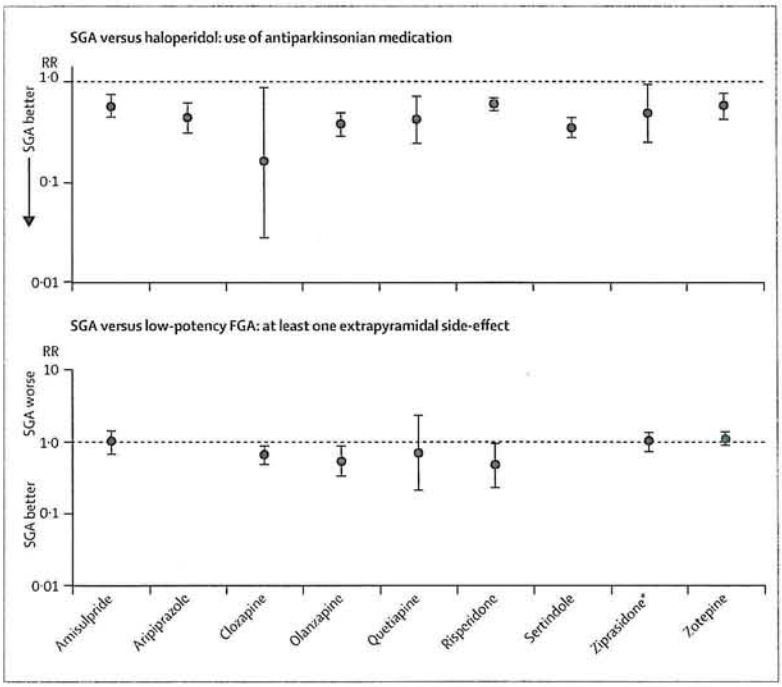

Figure 4: **Extrapyramidal side-effects**
Data are relative risk (RR; 95% CI). SGA=second-generation antipsychotic drug. FGA=first-generation antipsychotic drug. *Use of antiparkinsonian medication.

	Number of studies	Number of participants	Relative risk (95% CI)	p value
SGA versus haloperidol*				
Amisulpride	8	783	0·58 (0·45–0·76)	<0·0001
Aripiprazole	4	1794	0·45 (0·32–0·64)	<0·0001
Clozapine	3	162	0·17 (0·03–0·88)	0·035
Olanzapine	12	3670	0·39 (0·30–0·51)	<0·0001
Quetiapine	5	1167	0·43 (0·25–0·74)	0·002
Risperidone	21	2738	0·61 (0·52–0·72)	<0·0001
Sertindole	4	1472	0·36 (0·29–0·45)	<0·0001
Ziprasidone	3	501	0·50 (0·26–0·96)	0·037
Zotepine	4	398	0·59 (0·44–0·79)	<0·0001
SGA versus low-potency FGA†				
Amisulpride	1	30	1·00 (0·70–1·43)	1·000
Aripiprazole	..	..	..	..
Clozapine	11	775	0·66 (0·48–0·91)	0·010
Olanzapine	2	152	0·53 (0·32–0·89)	0·016
Quetiapine	2	422	0·66 (0·19–2·23)	0·503
Risperidone	2	108	0·47 (0·22–0·99)	0·046
Sertindole	..	..	..	..
Ziprasidone*	1	306	1·13 (0·91–1·41)	0·252
Zotepine	5	322	1·04 (0·76–1·42)	0·801

SGA=second-generation antipsychotic drug. FGA=first-generation antipsychotic drug. *Use of antiparkinsonian medication. †At least one extrapyramidal side-effect.

Table 4: **Extrapyramidal side-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.[22] 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 antipsychotic drugs, 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.[23,24] Quality of life was reported in only very few studies; if a superiority of second-generation 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).[25] Clozapine has been shown to reduce suicidality more than does olanzapine.[26]

	Number of studies	Number of participants	Mean weight-gain difference (kg; 95% CI)	p value
SGA versus haloperidol				
Amisulpride	2	373	0·9 (0·2 to 1·6)	0·012
Aripiprazole	2	1598	0·6 (−0·1 to 1·2)	0·071
Clozapine	3	170	3·4 (2·0 to 4·9)	<0·0001
Olanzapine	9	2952	3·3 (2·2 to 4·4)	<0·0001
Quetiapine	3	945	1·4 (0·7 to 2·1)	<0·0001
Risperidone	9	1366	1·7 (0·9 to 2·4)	<0·0001
Sertindole	2	779	3·3 (0·2 to 6·4)	0·040
Ziprasidone	1	301	0·1 (−1·2 to 1·3)	0·887
Zotepine	3	321	2·7 (1·7 to 3·7)	<0·0001
SGA versus low-potency FGA				
Amisulpride	1	30	0·3 (−3·6 to 4·2)	0·881
Aripiprazole	..	..	..	..
Clozapine	3	232	0·3 (−1·6 to 2·2)	0·753
Olanzapine	..	..	..	..
Quetiapine	1	201	0·5 (−1·0 to 2·0)	0·518
Risperidone	..	..	..	..
Sertindole	..	..	..	..
Ziprasidone	1	307	−1·1 (−2·3 to 0·2)	0·087
Zotepine	1	106	1·0 (−0·9 to 2·9)	0·306

FGA=first-generation antipsychotic drug. SGA=second-generation antipsychotic drug.

Table 5: **Weight gain**

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.[27] For perspective, the pooled effect size in another review comparing second-generation antipsychotic drugs with placebo was −0·51 and the NNT was 6.[28] Differences, such as higher dropout rates in the placebo-controlled trials[29] 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[28] and the effect size of clozapine *vs* first-generation antipsychotic drugs is 0·52). However, schizophrenia usually afflicts 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

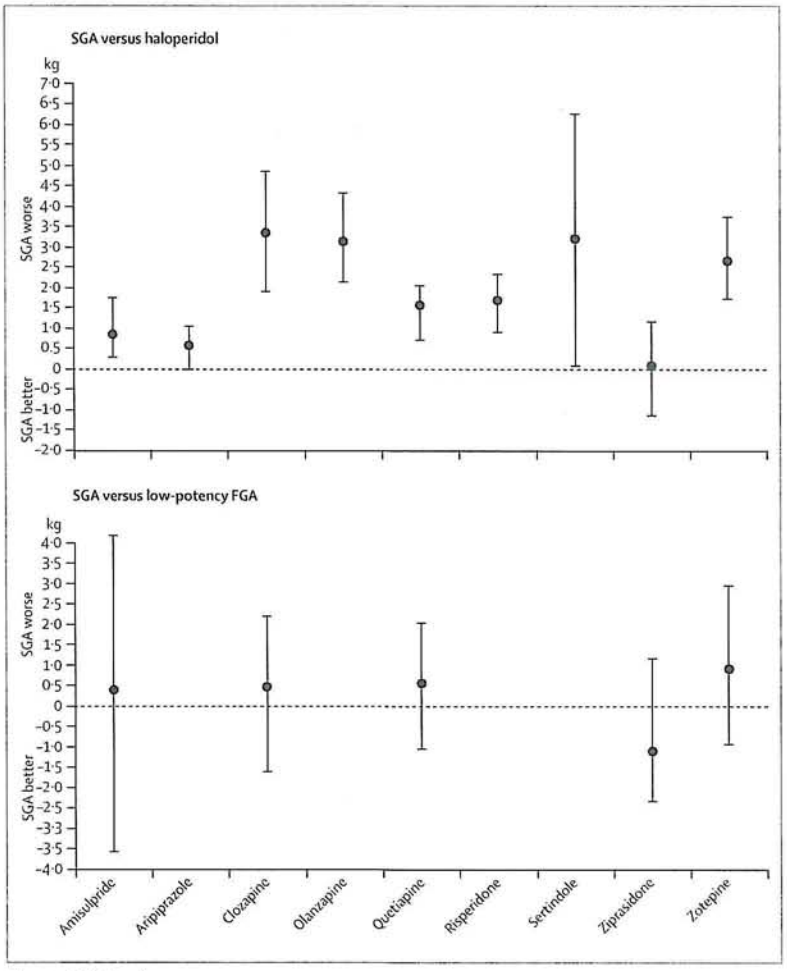

Figure 5: **Weight gain**
Data are mean weight-gain difference (kg; 95% CI). FGA=first generation antipsychotic drug. SGA=second-generation antipsychotic drug.

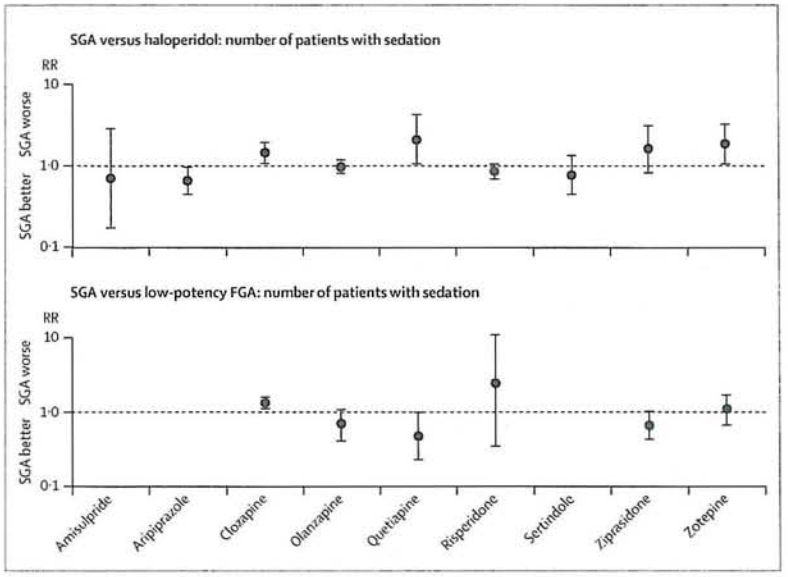

Figure 6: **Sedation**
Data are relative risk (RR; 95% CI). FGA=first-generation antipsychotic drug. SGA=second-generation antipsychotic drug.

	Number of studies	Number of patients with sedation	Relative risk (95% CI)	p value
SGA versus haloperidol				
Amisulpride	4	490	0·69 (0·15–3·13)	0·634
Aripiprazole	2	1602	0·65 (0·45–0·95)	0·024
Clozapine	6	655	1·50 (1·01–2·23)	0·043
Olanzapine	6	2767	0·95 (0·82–1·10)	0·507
Quetiapine	4	970	2·07 (1·01–4·27)	0·047
Risperidone	15	2194	0·86 (0·70–1·05)	0·137
Sertindole	3	1127	0·77 (0·44–1·34)	0·360
Ziprasidone	1	301	1·59 (0·82–3·08)	0·169
Zotepine	3	221	1·86 (1·04–3·33)	0·037
SGA versus low-potency FGA				
Amisulpride	..	..	..	..
Aripiprazole	..	..	..	..
Clozapine	9	928	1·32 (1·10–1·59)	0·003
Olanzapine	1	84	0·68 (0·41–1·12)	0·132
Quetiapine	3	659	0·49 (0·23–1·03)	0·061
Risperidone	2	108	2·59 (0·29–22·94)	0·393
Sertindole	..	..	..	..
Ziprasidone	1	306	0·67 (0·44–1·01)	0·055
Zotepine	2	146	1·09 (0·69–1·73)	0·719

FGA=first-generation antipsychotic drug. SGA=second-generation antipsychotic drug.

Table 6: **Sedation**

studies, treatment with haloperidol 3–4 mg per day resulted in more extrapyramidal side-effects than with risperidone and sertindole.[10,11] Only a few second-generation antipsychotic drugs have been shown to be better than low-potency first-generation antipsychotic drugs.[17] A limitation of all comparisons with low-potency first-generation drugs is the smaller evidence base than that for high-potency first-generation drugs.

Compared with haloperidol (but not low-potency first-generation antipsychotic drugs), clozapine, olanzapine, sertindole, and zotepine induced the most weight gain, quetiapine and risperidone caused intermediate weight gain, amisulpride had little effect, and aripiprazole and ziprasidone had no significant effect. Weight gain is time dependent but most studies were short-term. Nevertheless, the hierarchy is similar to that reported by Allison and colleagues.[12]

Clozapine, quetiapine, and zotepine were more sedating, and aripiprazole was less sedating than was haloperidol, whereas some second-generation drugs might be less sedating than are low-potency first-generation drugs. Concomitant use of benzodiazepines in the studies should not be ignored. Although sedation is sometimes transient, it is an important side-effect, and more data are needed.

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[4] and others[2,3,11]). 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,[34] whereas in another study the efficacy increased with doses up to 20 mg per day;[35] and the American Psychiatric Association guideline recommends a broad range of 5–20 mg per day.[36] 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.[16,36] 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.

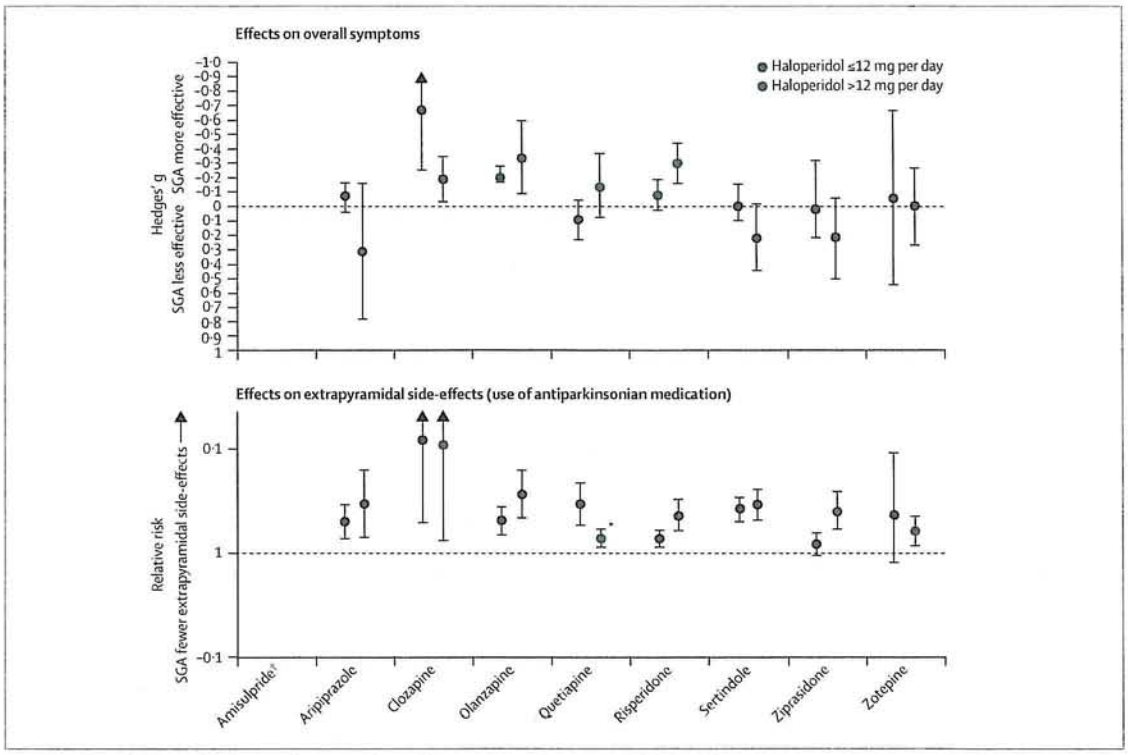

Figure 7: **Effects of haloperidol dose on effect sizes of overall symptoms and extrapyramidal side-effects**
Data are Hedge's g (95% CI) or relative risk (95% CI). SGA=second-generation antipsychotic drug. >12 mg per day=mean effect size of studies with haloperidol dose greater than 12 mg per day. ≤12 mg per day=mean effect size of studies with haloperidol dose less than or equal to 12 mg per day. *The reversed dose effect on extrapyramidal side-effects in the quetiapine studies can be explained by two outliers (for explanation see webtable 5). †All studies had haloperidol dose more than 12 mg per day.

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.[17] We have noted systematic bias in the reporting of results by industry with masked ratings of abstracts.[18]

We discuss our results in the context of the effectiveness studies CATIE[7] and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS).[12] In phase I of the CATIE study,[7] 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.[19] 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.[19] The effects of second-generation drugs were not better than those of perphenazine on PANSS total score,[8] cognition,[40] cost,[8] quality of life,[9] and psychosocial functioning.[9] Although some of the CATIE[7] results are compatible with our findings (a detailed comparison is provided in

	Haloperidol >12 mg per day	Haloperidol ≤12 mg per day	p value*
Overall symptoms (Hedges' g, 95% CI)			
Amisulpride†	..	..	..
Aripiprazole	0·30 (−0·18 to 0·78)	−0·08 (−0·18 to 0·02)	0·14
Clozapine	−0·20 (−0·36 to −0·04)	−0·67 (−1·06 to −0·27)	0·0053
Olanzapine	−0·35 (−0·60 to −0·10)	−0·21 (−0·29 to −0·14)	0·30
Quetiapine	−0·15 (−0·38 to 0·07)	0·08 (−0·06 to 0·22)	0·08
Risperidone	−0·31 (−0·45 to −0·17)	−0·09 (−0·19 to 0·01)	0·0124
Sertindole	0·21 (−0·02 to 0·43)	−0·04 (−0·17 to 0·09)	0·06
Ziprasidone	0·21 (−0·07 to 0·49)	−0·06 (−0·32 to 0·20)	0·16
Zotepine	−0·01 (−0·28 to 0·26)	−0·07 (−0·67 to 0·52)	0·85
Extrapyramidal side-effects (use of antiparkinsonian medication; relative risk, 95% CI)			
Amisulpride	..	..	..
Aripiprazole	0·32 (0·14 to 0·69)	0·48 (0·32 to 0·72)	0·35
Clozapine	0·05 (0 to 0·75)	0·07 (0·01 to 0·49)	0·81
Olanzapine	0·25 (0·14 to 0·44)	0·47 (0·34 to 0·65)	0·05
Quetiapine	0·75 (0·60 to 0·95)	0·33 (0·20 to 0·55)	0·0040
Risperidone	0·43 (0·29 to 0·63)	0·74 (0·67 to 0·81)	0·0080
Sertindole	0·34 (0·23 to 0·49)	0·37 (0·27 to 0·51)	0·72
Ziprasidone	0·36 (0·23 to 0·57)	0·79 (0·62 to 1·02)	0·0034
Zotepine	0·60 (0·42 to 0·85)	0·40 (0·09 to 1·75)	0·60

*For comparison of the effect sizes of studies with haloperidol dose less than and more than 12 mg per day.

Table 7: **Effects of haloperidol dose on the effect sizes of overall symptoms and extrapyramidal side-effects**

webtable 8), those of the CUtLASS[12] did not show any differences between second-generation and first-generation drugs.[41]

CATIE[7] and CUtLASS[12] addressed different questions with different designs. Most previous studies addressed pure efficacy and safety, whereas in the CATIE[7] and CUtLASS[12] 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[12] 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[7] and CUtLASS[12] was the use of comparator drugs that are less potent than haloperidol. Sulpiride, initially used by 50% of the participants in the CUtLASS[12] study's first-generation antipsychotic drug group, might induce fewer extrapyramidal side-effects than do other first-generation drugs.[42] 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[7] and CUtLASS[12] 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),[43] 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,[44] and in one of two perphenazine-controlled studies (with high-dose risperidone 5–15 mg).[45] In the other perphenazine-controlled study, only a 10% difference in use of antiparkinsonian medication compared with aripiprazole was noted.[46] 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[47–49] 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.[8,41,50] Public institutions could save costs by funding studies to accurately define selected old compounds, because they were not rigorously studied at the time they were introduced.[51]

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. CL 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.

Acknowledgments

A small proportion of JMD's work was supported by a National Institute of Mental Health grant (1-P01MH68580-01-CFDA-#93.242); the authors did most of the work in their own time.We are greatly indebted to the Cochrane Schizophrenia Group; without access to their register of randomised controlled trials, this review would not have been possible. We thank Köksal Alptekin, Michael Berk, Robert Buchanan, Chen Jindong, Robert Conley, Nancy Covell, Lieuwe de Haan, Eduardo Ponde de Sena, Robin Emsley, Susan Essock, Bernd Gallhofer, Alan Gelenberg, Jes Gerlach, Donald Goff, Adolph Heck, Chen-Jee Hong, Matti Huttunen, Marek Jarema, Jeanette Jerrell, Deanna Kelly, Eckhard Klieser, Li Zhongyi, Nicolai Malykhin, Sung Kil Min, Ann Mortimer, Robert Rosenheck, Ronald See, Bilgen Taneli, Donna Wirshing, and Zhang Hong Yan for sending us further information on their studies; AstraZeneca, Astellas, Bristol-Myers Squibb, Eli Lilly, Lundbeck, and Sanofi-Aventis for providing unpublished data; and Michiaki Taniguchi, Makoto Wada, Toshiyuki Watanabe, and Rong Xie for translating Japanese and Chinese articles.

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