TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Pharmaceutical costs

Introduction

The burden of schizophrenia includes direct costs, indirect costs, and intangible costs. Direct costs are estimated by the amount of services used and the price of treatment. Indirect costs are estimated by the averaged reduced future earnings of both patients and caregivers. Intangible costs are those that may be associated with the illness, such as trauma and depression.

This topic presents evidence on direct pharmaceutical costs, including cost of drug treatments and related mental health care services. For more information on the global costs of schizophrenia, please see the Population Burden topic.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight systematic reviews met our inclusion criteria[3-10].

Clozapine

- Moderate quality evidence suggests costs may be lower for clozapine compared to first generation antipsychotics including haloperidol and chlorpromazine.
- Moderate quality evidence suggests the mental healthcare and total healthcare costs

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for clozapine may be higher than risperidone.

Olanzapine

- Moderate quality evidence suggests costs may be lower for olanzapine compared to haloperidol.
- Moderate quality evidence suggests the drug acquisition costs of olanzapine may be higher than risperidone. However, moderate to low quality evidence suggests no apparent difference in mental healthcare or total costs.

Risperidone

- Moderate quality evidence suggests costs may be lower for risperidone compared to fluphenazine.
- Moderate to low quality evidence suggests risperidone may cost less than haloperidol and mean monthly costs of treatment may decrease post-treatment with risperidone.
- Moderate to low quality evidence suggests costs may be lower for risperidone compared to other first-generation antipsychotics.

Trifluoperazine

- Moderate to low quality evidence suggests total direct costs may be lower for patients receiving trifluoperazine alone or in addition to individual psychotherapy compared with electroshock or milieu treatments.

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Amos, A

Assessing the cost of early intervention in psychosis: A systematic review

Australian and New Zealand Journal of Psychiatry 2012; 46: 719

View review abstract online

Comparison	**Resource utilisation and costs of early intervention programs vs. treatment as usual.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, direct, unable to assess consistency or precision) is unable to determine the cost-effectiveness of early intervention programs.**

Economic and clinical outcomes

1 RCT (N = 144) assessed early intervention vs. treatment as usual over 18 months and found no differences in inpatient or outpatient costs, vocational recovery or hospitalisation rates.

1 RCT (N = 41) compared prophylactic treatment in people with at-risk mental states (ARMS) with treatment as usual and found no differences in total costs, but greater outpatient costs during prophylactic treatment, and lower outpatient costs after prophylactic treatment. There were no differences in clinical ratings.

1 case-control study (N = 65) assessed outcomes before and after the introduction of an early intervention program, comparing it to historical/regional treatment-as-usual controls. The study reported emergency department annual costs of AUD$3,445 with early intervention, and AUD$9,503 with historical controls, which was significantly different ($p < 0.01$). This study also reports better clinical ratings with the early intervention program.

1 case review (N = 305) compared outcomes of first-episode psychosis patients before and after the introduction of an early intervention program over a 3-year period. Total inpatient costs reduced significantly from CAD$4,323,590 to CAD$3,415,174 ($p < 0.01$), however there were no changes in bed numbers or occupancy. Early intervention also reduced prehospitalisation injury, but there were no differences in the number of suicide attempts, aggression, or legal involvement.

1 case-control study (N = 127) compared early intervention with historical/regional treatment-as-usual controls over a 3-year period. The study reported significantly reduced inpatient costs with early intervention compared to treatment as usual at 1 year (SEK$9,895 vs. SEK$23,090, $p < 0.05$), however outpatient early intervention costs were higher at 1 year with early intervention (SEK $2,133 vs. SEK$474, $p < 0.05$). There were no differences in costs at years 2 or 3, nor were there differences on any clinical measure at any time point.

1 case-control study (N = 130) compared early intervention with an historical control group over a 2-

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year period. There were no differences in total costs or hospital costs, however outpatient costs were higher with early intervention than with treatment as usual (HKD$12,792 vs. HKD$10,588, $p < 0.05$). Medication costs were also higher with early intervention (HKD$7,542 vs. HKD$231, $p < 0.01$). There were no differences in PANSS positive or general clinical ratings, but PANSS negative rating was better with early intervention. 1 case-control study (N = 46) compared early intervention with treatment as usual over a 5-year period and reported no differences in inpatient or residential costs, but outpatient costs were higher with early intervention (EURO€30,701 vs. EURO€25,292, no *p* value reported). There were no differences in clinical ratings at 5 years. 2 modelling studies reported that prophylactic intervention reduces conversion to psychosis and preserves function such as ability to work, and that inpatient costs are greater with treatment as usual, but outpatient costs are greater with early intervention.

Consistency in results‡	Unable to assess, no measure of consistency is reported.
Precision in results§	Unable to assess, no measure of precision is reported.
Directness of results‖	Direct

Barbui C, Lintas C, Percudani M

Head-To-Head Comparison of the Costs of Atypical Antipsychotics. A Systematic Review

CNS Drugs 2005; 19(11): 935-950

View review abstract online

Comparison 1	**Economic evaluation of olanzapine vs. risperidone.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests the drug acquisition costs of olanzapine may be higher than risperidone. However, moderate to low (appears inconsistent) suggests no apparent difference in mental healthcare or total costs.**

Economic outcomes

16 studies (N = 22,643) compared olanzapine to risperidone.

Drug acquisition costs

13 studies reported the drug cost of olanzapine to be higher than risperidone over 1 to 12 months,

and 1 study reported the drug cost to be the same. 2 studies did not report on drug costs. Mental healthcare costs (inpatient and outpatient mental health treatment) 4 studies reported the mental healthcare costs of olanzapine to be lower than risperidone, 1 reported higher costs of olanzapine than risperidone, and 4 studies reported mental healthcare costs to be the same. 7 studies did not report on mental healthcare costs. Total healthcare costs (all healthcare services) 3 studies reported the healthcare cost of olanzapine to be lower than risperidone, 3 studies reported the healthcare cost to be the same, and 1 study reported the healthcare of olanzapine to be higher than risperidone. 8 studies did not report on total healthcare costs.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 2	**Economic evaluation of clozapine vs. olanzapine vs. risperidone.**
Summary of evidence	**Moderate to low quality evidence (small to medium sample, direct, appears inconsistent, unable to assess precision) is unclear of cost differences between clozapine, risperidone and olanzapine.**
Economic outcomes	
2 studies (N = 171) compared clozapine, olanzapine and risperidone over 10 to 24 months. Drug acquisition costs 1 study reported the drug cost of clozapine and olanzapine to be similar, but higher than risperidone, and 1 study reported the drug cost of risperidone and olanzapine to be similar, but lower than clozapine. Mental healthcare costs (inpatient and outpatient treatment) 1 study reported the mental healthcare costs of clozapine and olanzapine to be similar, but higher than risperidone, and 1 study did not report on mental healthcare costs. Total healthcare costs (all healthcare services) 1 study reported the total healthcare costs of clozapine, risperidone and olanzapine to be similar and 1 study did not report on total healthcare costs.	
Consistency in results	Unable to assess, no measure of consistency is reported.

Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 3	**Economic evaluation of clozapine vs. risperidone.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision) suggests the mental healthcare and total healthcare costs for clozapine may be higher than for risperidone.**
Economic outcomes	
1 study (N = 927) compared clozapine to risperidone over 12 months. Mental healthcare costs (inpatient and outpatient treatment) Mental healthcare costs of clozapine were higher than risperidone. Total healthcare costs (use of healthcare services) Total healthcare costs of clozapine were higher than risperidone.	
Consistency in results	Not applicable; 1 study.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Basu A

Cost-effectiveness analysis of pharmacological treatments in schizophrenia: critical review of results and methodological issues

Schizophrenia Research 2004; 71: 445-462

View review abstract online

Comparison 1	**Economic evaluation of clozapine vs. first generation antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests clozapine may produce greater cost-savings (particularly for inpatients) when**

	compared to haloperidol and other first-generation antipsychotics.
Economic outcomes	
2 studies compared clozapine to haloperidol; 1 RCT (N = 423) reports that one-year total clozapine costs are USD$2,773 lower than haloperidol, including USD$7,440 lower inpatient costs, but USD$5,000 higher outpatient treatment costs for patients with treatment refractory schizophrenia. 1 simulation study reports that clozapine may produce a cost saving of CAD$38,879 per year and produce better outcomes when compared to haloperidol and chlorpromazine. *4 studies compared clozapine to other first-generation antipsychotics in patients with treatment refractory schizophrenia;* 1 cohort study (N = 184) reports that clozapine produces lower BPRS scores and averages USD$1,029 lower total costs over two years than other first-generation antipsychotics, and incremental costs favoured clozapine by USD$15,000, if the length of the initial hospital stay is reduced to 14 days. 1 retrospective pre/post cohort study (N = 47) reports that clozapine produces better outcomes (BPRS positive: p = 0.04, CGI: p = 0.01, QLS: p = 0.008), and a 2-year cost saving of USD$45,872 for patients who continued on clozapine, while patients who dropped out incurred an additional USD$5,226. 1 retrospective pre/post cohort study (N = 21) reports that clozapine produces better outcomes, but costs more over 18 months, with an incremental cost-effectiveness ratio of USD$5,600 per improved patient, USD$4,400 per percentage of improved symptoms (based on CGI), and USD$4,900 per percentage of improved social function (SFS). 1 simulation study reports that clozapine may produce favourable outcomes equivalent to an annual cost saving of GBP£91 and a lifetime saving of GBP£1333. *1 study compared clozapine to other first-generation antipsychotics in patients with chronic schizophrenia;* 1 retrospective pre/post cohort study (N = 26) reports clozapine produces a cost savings of GBP£3768 per annum and significant improvement in clinical ratings over a 3-year period.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 2	**Economic evaluation of olanzapine vs. first generation (haloperidol) or second generation (risperidone).**

Pharmaceutical costs

Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests olanzapine should produce greater cost-savings compared to haloperidol. Low quality evidence (small sample, appears inconsistent) is unable to ascertain differences in cost when compared to risperidone.**
Economic outcomes	
3 studies compared olanzapine to haloperidol; 1 RCT (N = 1,996) reports that olanzapine produces per patient cost savings of USD$388 over the first 6 weeks of treatment and about USD$636 over the next 46 weeks. After 6 weeks of treatment, more patients on olanzapine than haloperidol demonstrate a favourable response to treatment (p = 0.002), and greater improvements in quality of life (QLS: p = 0.09). 1 simulation study reports that olanzapine produces cost-saving of USD$1,539 over 5 years and a 6.8 month gain in disability-free state, 2.3 months gain in QALYs and 13% less chance of relapse. 1 simulation study reports cost-equivalence between olanzapine and haloperidol. *3 studies compared olanzapine to risperidone;* 1 RCT (N = 150) reports that per patient medical costs were USD$2,843 lower for olanzapine, but this difference was not significant (p = 0.341). There were no significant differences in the proportion of patients demonstrating a favourable response based on PANSS total scores, however, olanzapine patients are more likely to maintain this response at follow-up than patients on risperidone (p = 0.048). 1 simulation study reports that olanzapine produces cost-saving of USD1,875 over 5-years and 1.6 weeks gain in disability free state, 0.8 months gain in QALYs and 2% less chance of relapse. 1 simulation study reports cost-equivalence, but suggested olanzapine saved GBP£1,000 over 5 years compared to risperidone or haloperidol.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 3	**Economic evaluation of risperidone vs. first generation haloperidol or second-generation olanzapine.**
Summary of evidence	**Moderate to low quality evidence (small samples, direct, unable to assess precision or consistency) is unable to ascertain difference in costs between risperidone and any other treatments.**

Economic outcomes	
4 studies compared risperidone to any other treatment; 1 cohort study (N = 112) reported no difference between risperidone and the comparison group in costs or GAF scores after controlling for age, sex, ethnicity, marital status, medication clinic site and number of psychiatric emergency visits in the year before patients entered risperidone treatment. 1 retrospective pre/post cohort study (N = 57) reported risperidone treatment produced an annual cost saving of USD$147,962 pre- to post-treatment, with hospitalisation rates declining by 43% in patients who responded to risperidone therapy and by 1.3% in those who did not respond. 1 RCT (N = 43) found the incremental cost-effectiveness ratio for risperidone compared to haloperidol was CAD$24,250 per QALY. 1 simulation study reported that risperidone costs less with more favourable outcomes (significance not reported). 1 simulation study reported cost-equivalence between risperidone and haloperidol.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Hudson T, Sullivan G, Feng W, Owen R, Thrush C

Economic evaluations of novel antipsychotic medications: a literature review

Schizophrenia Research 2003; 60: 199-218

View review abstract online

Comparison 1	**Economic evaluation of risperidone or clozapine vs. first generation antipsychotics.**
Summary of evidence	**Low quality evidence (very small sample, direct, unable to assess precision) is unable to ascertain any differences between clozapine and first-generation antipsychotics.**
Economic outcomes	

1 study compared clozapine to first generation antipsychotics; 1 study (N = 37) reported that medication costs increased significantly in subjects receiving risperidone or clozapine ($p < 0.001$), while total cost of care was US$3,000 lower per patient per year compared to first generation antipsychotics.	
Consistency in results	Not applicable, 1 study.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 2	**Economic evaluation of olanzapine vs. haloperidol;**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests olanzapine was associated with lower total costs in the acute phase, driven by lower mental health care costs, compared to haloperidol.**
Economic outcomes	
3 studies compared olanzapine to haloperidol; 1 RCT (N = 1,996) reported total treatment costs were lower for olanzapine, but only in the acute phase of the trial ($p = 0.03$). Improvements in symptoms were greater in the olanzapine group (BPRS: $p = 0.002$), and quality of life measures showed a trend effect (QLS: $p = 0.094$). Medication costs were significantly higher in the olanzapine group ($p < 0.001$), but inpatient and outpatient costs were significantly lower (inpatient: $p = 0.0044$, outpatient: $p = 0.038$). Incremental cost–effectiveness ratio for olanzapine indicated a savings of US$1,632.50 per unit of improvement on quality of life measures (SF-36 physical health composite) and savings of US$5,654.74 per unit of improvement in the mental health and functioning composite. 1 simulation study reports olanzapine resulted in an additional 6.8 months of a disability free state compared to haloperidol. 1 simulation study reports cost-equivalence between olanzapine and haloperidol. *1 study compared olanzapine to risperidone;* 1 simulation study reports olanzapine resulted in an additional 1.6 weeks of a disability free state compared to risperidone. *1 study compared olanzapine to sertindole;* 1 simulation study reports that the use of sertindole was associated with a saving of US$6,683, and a relative risk of relapse of 1.2, compared with olanzapine.	
Consistency in results	Unable to assess, no measure of consistency is reported.

Pharmaceutical costs

Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 3	**Economic evaluation of risperidone vs. first generation antipsychotics (including haloperidol), or pre-post risperidone treatment.**
Summary of evidence	**Moderate to low quality evidence (small to medium samples, direct, unable to assess precision or consistency) suggests the total cost of risperidone may be lower than haloperidol and mean total costs of treatment may decrease following risperidone treatment.**
Economic outcomes	
5 studies compared risperidone to haloperidol; 1 RCT (N = 135) reported an incremental cost utility of US$21,333 per QALY advantage for risperidone. 1 case-control study (N = 60) reported the estimated mean total monthly costs of US$123.34 lower per patient for risperidone than haloperidol, but this was not statistically significant (p = 0.4693). Medication costs were higher (p = 0.004) and hospitalisation rates lower (p = 0.005) in the risperidone group. Patients treated with risperidone visited the physician more frequently (p = 0.0005). 1 simulation study reports that the total cost per patient per year was US$1,850 lower for risperidone, with a 19.7% greater response rate at the end of 2 years. Total cost per patient: risperidone US$14,599, haloperidol US$23,040. 1 simulation study reports that cost per favourable outcome (patient in clinical response phase) was US$19,709 for risperidone vs. US$31,104 for haloperidol. 1 simulation study reports cost-equivalence between risperidone and haloperidol. *1 study compared risperidone to olanzapine;* 1 simulation study reports olanzapine resulted in an additional 1.6 weeks of a disability free state compared to risperidone *6 studies assessed pre-post risperidone compared to pre-post first generation antipsychotics;* 1 study (N = 150) reported that in the risperidone group, mean monthly medication costs increased (p < 0.05) while total cost, physician cost, and hospital costs all decreased (p < 0.05). In the first-generation antipsychotic group, only the mean monthly physician costs decreased (p < 0.05). 1 study (N = 51) reported total monthly treatment (p = 0.005) and medications costs increased (p = 0.0001) following risperidone.	

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1 study (N = 112) reported total treatment costs did not vary significantly (p = 0.08), however, costs for monthly medication (p < 0.001) and outpatient medication visits (p = 0.02) increased following risperidone. Controlling for baseline GAF scores, there was no significant difference in effectiveness between risperidone and first-generation antipsychotics. 1 study (N = 31) reported that mean total costs decreased from GBP £22,362 at baseline to GBP £21,174 in year 1 (N = 31), and from GBP £19,828 in year 1, to GBP £12,402 in year 2 (N = 18). Significant improvements in symptoms were reported (PANSS total, year 1, p < 0.0001; year 2, p < 0.0002). 1 study (N = 57) reported that risperidone was associated with a significant reduction of symptom severity or service utilisation in both responders (p = 0.001) and non-responders (p = 0.015) and resulted in net savings of US$147. 1 study (N = 37) reported that medication costs increased significantly in subjects receiving risperidone or clozapine (p < 0.001), while total cost of care was US$3,000 lower per client per year compared to first generation antipsychotics. *3 studies assessed pre- post-risperidone treatment with no comparison group;* 1 study (N = 146) reported an overall cost saving of CAD$7,925 per patient per year, with hospital admissions, inpatient length of stay, physician visits and outpatient mental health services decreasing after initiation of risperidone, but with cost of antipsychotic medications increasing. 1 study (N = 139) reported increased pharmaceutical use and decreased clinician services but no different in total cost. 1 study (N = 61) reported a non-significant decrease in service utilisation and a non-significant increase in total monthly treatment costs (US$305), with a significant increase in medication costs (p < 0.001).

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 4	**Economic evaluation of quetiapine pre-post treatment.**
Summary of evidence	**Low quality evidence (very small sample, direct, unable to assess consistency or precision) is unable to ascertain cost differences pre- to post-quetiapine treatment.**

Economic outcomes
1 study (N = 21) reported a non-significant reduction in inpatient days, inpatient hospitalisation costs and inpatient treatment costs after initiation of quetiapine. By 1 year, there were significant improvements in symptoms (BPRS, p < 0.001), clinical ratings (CGI, p < 0.001), involuntary

movement (AIMS, $p < 0.001$), and extrapyramidal side effects (Simpson–Angus scale, $p < 0.005$).	
Consistency in results	Not applicable, 1 study.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 5	**Economic evaluation of sertindole vs. haloperidol.**
Summary of evidence	**Low quality evidence (direct, unable to assess consistency or precision) is unable to ascertain cost differences between sertindole and haloperidol.**
Economic outcomes	
1 simulation study reports that the use of sertindole was associated with a saving of US$6500 and a relative risk of relapse of 1.4 compared with haloperidol.	
Consistency in results	Not applicable, 1 study.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 6	**Economic evaluation of first generation vs. second generation antipsychotics (unspecified).**
Summary of evidence	**Low quality evidence (direct, unable to assess consistency or precision) is unclear as to the most cost-effective option between first- and second-generation antipsychotics.**
Economic outcomes	
1 simulation study reports that depot first generation antipsychotics were the most cost-effective option in the year following discharge. Second generation medications were only cost-effective if 80% compliance was achieved with a 25% reduction in wholesale cost.	
Consistency in results	Not applicable, 1 study.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Liu G, Sun S, Christensen D, Luo X

Cost Comparisons of Olanzapine and Risperidone in Treating Schizophrenia

The Annals of Pharmacotherapy 2004; 38: 134-141

View review abstract online

Comparison 1	**Economic evaluation of risperidone vs. first generation antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess precision or consistency) suggests costs may be lower for risperidone compared to first generation antipsychotics.**

Economic outcomes

15 studies (N = 2,010) compared risperidone to first generation antipsychotics.

8 studies reported reduced healthcare costs for risperidone;

1 study reported a saving of USD$2,458 for risperidone, and an increase of USD$1,928 for first generation antipsychotics, with this difference between groups being significant ($p = 0.0048$).

1 study reported a decrease in total mental health care costs of USD$2,160, but an increase in the antipsychotic drug cost by USD$1,536, which resulted in an annual total cost savings of USD$624 with risperidone ($p < 0.05$).

1 study reported a median savings in total annual costs per patient of USD$2,659 ($p < 0.05$).

1 study reported a reduction of USD$2,596 ($p$ not reported).

1 study reported a reduction of USD$2,421 ($p$ not reported).

1 study reported a reduction of CAD$7,925 per patient ($p$ not reported).

1 study reported a reduction of CAD$3,314 per patient ($p$ not reported).

1 study reported a reduction of GBP£1,188 per patient during the first year of risperidone treatment and a further reduction of GBP£8,772 during the second year (p not reported).

2 studies reported increased healthcare costs for risperidone;

1 study reported the mean annual cost was USD$8,858 higher than haloperidol ($p < 0.001$).

1 study (N = 31) reported an increase of USD$5,617 ($p = 0.005$) in total yearly health care costs per patient.

5 studies reported no differences between groups.

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 2	**Economic evaluation of olanzapine vs. first generation antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess precision or consistency) suggests olanzapine may reduce the total cost of treatment compared to haloperidol, particularly in the acute phase.**
Economic outcomes	
4 studies (N = 385) compared olanzapine to first generation antipsychotics. *2 studies reported reduced healthcare costs for olanzapine;* 1 study (N = 817) reported total costs per patient were USD$388 lower in the olanzapine group compared to haloperidol during the first 6-week acute treatment phase (*p* = 0.033), and were USD$636 lower during the 46-week maintenance phase (*p* = 0.128), total annual cost reduced by USD$1,024 per patient. 1 study reported a mean annual total cost per patient saving of USD$9387 with olanzapine (*p* not reported). 2 further studies reported no differences compared to first generation antipsychotics.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 3	**Economic evaluation of risperidone vs. olanzapine.**
Summary of evidence	**Moderate to low quality evidence (large samples, direct, unable to assess precision or consistency) suggests the cost of risperidone may be lower than olanzapine.**
Economic outcomes	
5 studies (N = 5,038) compared risperidone to olanzapine. *3 studies reported significantly reduced costs with risperidone (adjusted for confounders);*	

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1 study reported the annual cost reduction per patient was USD$1,834 ($p < 0.05$). 1 study reported the annual cost reduction per patient was USD$693 ($p = 0.03$). 1 study reported the annual cost reduction per patient was USD$5,752 ($p = 0.009$). *2 studies reported non-significant reductions in cost with risperidone (adjusted for confounders);* 1 study reported the annual cost reduction per patient was USD$6,792 ($p = 0.3062$). 1 study reported the annual cost reduction per patient was USD$4,496 ($p = 0.212$).

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Oh P, Iskedjain M, Addis A, Langtot K, Einarson T

Pharmacoeconomic evaluation of clozapine in treatment resistant schizophrenia: a cost-utility analysis

Canadian Journal of Clinical Pharmacology 2001; 8(4): 199-206

View review abstract online

Comparison	**Economic evaluation of clozapine vs. haloperidol or chlorpromazine.**
Summary of evidence	**Moderate to low quality evidence (small to medium sample, direct, unable to assess precision or consistency) suggests costs may be lower for clozapine compared to haloperidol or chlorpromazine.**

Economic outcomes

3 studies (N = 157) compared clozapine to either haloperidol or chlorpromazine, and found clozapine showed higher drug acquisition costs (CAD$6,541 vs. CAD$194), but lower non-drug costs (CAD$84,186 vs. CAD$129,413). Overall, clozapine was cheaper (CAD$90,727 vs. CAD$129,607).

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.

Directness of results	Direct

Oh P, Langtot K, Mittmann N, Iskedjain M, Einarson T

Cost-utility of risperidone compared with standard conventional antipsychotics in chronic schizophrenia

Journal of Medical Economics 2001; 4: 137-156

View review abstract online

Comparison	**Economic evaluation of risperidone vs. haloperidol or fluphenazine.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess precision or consistency) suggests costs may be lower for risperidone compared to haloperidol or fluphenazine.**
Economic outcomes	
14 studies (N = 2,308) compared risperidone to haloperidol or fluphenazine and overall costs were lower for risperidone; Risperidone CAD$69,855 Haloperidol CAD$76,365 Haloperidol decanoate CAD$78,388 Fluphenazine decanoate CAD$82,264	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Sevy S, Visweswaraiah H, Mentschel C, Leucht S, Schooler N

Relationship Between Costs and Symptoms in Schizophrenia Patients

treated With Antipsychotic Medication: A Review **Journal of Clinical Psychiatry 2004; 65: 756-765** View review abstract online	
Comparison	**Economic evaluation of all treatment costs.**
Summary of evidence	**Moderate to low quality evidence (mixed sample sizes, direct, unable to assess precision or consistency) suggests direct treatment costs may be lower for clozapine compared to first generation antipsychotics. Treatment with olanzapine may be more cost-effective than haloperidol. Total direct costs may be lower for patients receiving trifluoperazine alone or in addition to individual psychotherapy compared with electroshock or milieu treatments.** **No conclusions can be made for risperidone or quetiapine.**

Economic outcomes

Clozapine

1 RCT (N = 423) reported treatment-refractory patients receiving clozapine for 1 year had lower inpatient costs and higher costs for medication and outpatient services (no significant change in total costs) than patients receiving haloperidol. In high hospital users, clozapine lowered hospitalisation costs and total health care costs. In low hospital users (i.e. inpatient costs less than $60,000 per year), clozapine increased total health care costs due to medication costs.

1 RCT (N = 227) reported that clozapine was more cost-effective than first generation antipsychotics (stats not reported).

1 study (N = 184) reported that clozapine patients had lower hospitalisation costs and lower direct costs than patients taking first generation antipsychotics after 2 years of treatment.

1 study (N = 47) reported treatment-refractory patients receiving clozapine for 2 years had higher outpatient costs but lower hospitalisation costs compared to patients who dropped out of the trial, resulting in an overall decrease in total costs.

1 study (N = 33) of treatment-refractory patients with schizophrenia reported lower direct health care costs compared with the 16 patients who discontinued clozapine.

1 study (N = 26) of treatment-refractory patients with schizophrenia reported no significant difference between pre- and post-clozapine on total costs.

1 study (N = 91) of clozapine vs. olanzapine vs. risperidone reported total mean costs per month were highest for the clozapine group and lowest for the risperidone group.

Olanzapine

1 RCT (N = 817) reported olanzapine resulted in greater symptom improvement (BPRS) and quality of life (QLS) scores and lower inpatient and outpatient costs compared to haloperidol in the acute phase. During the maintenance phase, the olanzapine group had lower mean inpatient/outpatient costs and lower total costs (despite higher mean medication costs).

1 RCT (N = 275) reported the olanzapine group had lower hospitalisation costs than the haloperidol group. There was no difference between groups for other service costs.

1 RCT (N = 812) reported hospitalisation costs were lower in the olanzapine group compared to haloperidol. There was also increased improvement on SF-36 physical and mental health factor scores. A change of 1 point in the SF-36 mental health factor score resulted in a savings of USD$5655.

1 RCT (N = 150) reported that patients receiving olanzapine had lower inpatient/outpatient service costs compared with patients receiving risperidone, with no significant differences in clinical scores, however, the olanzapine-treated patients were more likely to maintain response.

1 RCT (N = 108) reported medication costs and total mental health care costs were higher for the risperidone and olanzapine groups compared with the first generation antipsychotic group. There was also a significant decrease over time of PANSS negative and positive subscale scores, BPRS total scores, substance abuse symptoms, and side effects. There was a significant increase over time of depression/mania symptoms, role functioning, and client satisfaction.

1 RCT (N = 65) reported no differences in costs between groups. Greater improvements in PANSS total and subscale scores, BPRS scores, and quality of life (QLS and SF-36) were reported in patients treated with olanzapine compared with risperidone. Both groups had a decrease in hospital days and use of community crisis teams, but an increase in home visits.

Trifluoperazine

1 RCT (N = 228) reported that after 1-year, total direct costs were lower and clinical improvement higher for the groups that received trifluoperazine alone or in addition to individual psychotherapy compared with electroshock or milieu treatment.

Risperidone

1 study (N = 32) reported that after 2 years of risperidone treatment, patients had decreased number of inpatient days and increased days spent in treatment homes.

1 study (N = 31) reported that after 2 years of risperidone treatment, patients had decreased hospitalisation costs and increased residential costs.

Quetiapine

1 study (N = 21) reported a decrease in hospitalisation costs following the initiation of quetiapine.

Relationship with symptoms

1 study (N = 258) reported that an increase of 1 point in the 24-item BPRS total score would lead to an increase of 12-month costs by German Deutsche Mark 14,112.60 (approximately USD$7000 [as reported in 2004]).

1 study (N = 307) reported a significant effect of increased PANSS total score increasing direct

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Pharmaceutical costs

costs.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

AIMS = Abnormal Involuntary Movement Scale, ARMS = at-risk mental state, AUD = Australian dollar, BPRS = Brief Psychiatric Rating Scale, CAD = Canadian dollars, CGI = Clinical Global Index, CI = Confidence Interval, GAF = Global Assessment of Functioning, GBP = British pound, HKD = Hong Kong dollar, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, QALY = quality-adjusted life year, QLS = Quality of Life Scale, SEK = Swedish Krona, SFS = Social Functioning Scale, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[11].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[11].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardized (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[11];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[13].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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