Introduction

Cognitive symptoms have been found in all cognitive domains, including executive function, memory, and attention, and often develop prior to the other symptoms of schizophrenia. They are highly disabling and predict poor functional outcomes. This topic assesses the treatments that are available for the cognitive symptoms of schizophrenia.

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. Those with pooled data are given priority for inclusion. 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.

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. Reviews were assigned a low, medium or high possibility of reporting bias depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. 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 (RCT) may be downgraded to moderate, low or very 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). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.
Results
We found eleven systematic reviews that met inclusion criteria\(^3\)\(^{13}\).

Click on review ID for a link to the review’s abstract.

See PRISMA checklists for assessment of review quality.

Conclusions

• Moderate to high quality evidence shows second generation antipsychotics in general are associated with small improvements in processing speed, verbal fluency, learning, motor skills, and global cognition when compared to first generation antipsychotics, but have no benefit over first generation antipsychotics for improving attention, cognitive flexibility, working memory, delayed recall, visuospatial processing.

• Moderate quality evidence suggests small benefits of second-generation antipsychotics over first-generation antipsychotics for improving long-term memory.

• Moderate quality evidence shows small benefits of first-generation antipsychotics for improving general cognitive function relative to placebo.

• Moderate to high quality evidence shows haloperidol was associated with small improvements in global cognition (low haloperidol dose only), verbal learning (low and high dose), delayed recall (low and high dose), and attention (low dose only), when compared to second generation antipsychotics, with no differences for executive function, verbal fluency, motor skills, or processing speed.

• Moderate to low quality evidence suggests sertindole may be more superior than clozapine, quetiapine, and first generation antipsychotics for general cognitive ability, and more superior than clozapine, quetiapine, and olanzapine for memory, more superior than clozapine, quetiapine, olanzapine and ziprasidone for executive functioning, and more superior than quetiapine for processing speed. Olanzapine may be more superior than clozapine and first generation antipsychotics for visuospatial skills and verbal fluency.

• Moderate to high quality evidence suggests small benefits of antidepressants over placebo for global cognition and executive functioning. Authors state that these findings were not clinically significant.
Symptom domains of schizophrenia: the role of atypical antipsychotic agents.


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effectiveness of second generation antipsychotics vs. various control conditions.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>Low quality evidence (small samples, unable to assess consistency or precision) is unclear as to specific benefits among second-generation antipsychotics for improving cognition.</td>
</tr>
</tbody>
</table>

**General cognitive ability**

*Clozapine*

10 studies (N not reported) have studied any effects of clozapine on cognitive ability, authors report consistent improvements in a range of cognitive functions (verbal fluency, attention span, reaction time). Some (less consistent) benefits were also reported for executive function, perceptual processing and set shifting.

*Risperidone*

7 studies (N not reported) reported benefits of risperidone for perceptual processing, reaction time, executive function, working memory, verbal learning and motor function.

1 RCT (N = 324) found that long-acting risperidone was associated with improvements in motor speed, attention, executive function, and memory.

3 RCT (N = 323) found benefits of long-acting risperidone for attention, working memory, verbal learning and executive function.

*Olanzapine*

1 study (N = 101) found that both olanzapine and risperidone showed improvements in cognitive function relative to haloperidol, \( p < 0.02 \). A second study (N = 65) found olanzapine (5-20mg/day) conferred cognitive benefits over both risperidone (4-10mg/day) and haloperidol (5-20mg/day).

1 study (N = 48) found olanzapine was equally effective as clozapine for improving verbal fluency (\( p = 0.01 \)), verbal learning (\( p < 0.001 \)) and verbal memory.
Quetiapine

1 study (N = 58) found greater cognitive improvements in patients following quetiapine (600mg/day) compared to haloperidol (12mg/day). An open-label study (N not reported) found significant improvements in neurocognitive skills following quetiapine.

1 RCT (N not reported) found cognitive improvements in both risperidone (4-8mg/day) and quetiapine (400-800mg/day), with greater benefits of quetiapine for memory.

Ziprasidone

1 RCT (N not reported) found that ziprasidone is as effective as olanzapine for improving attention, working memory, executive function, and motor speed.

1 open-label study (N = 185) found that switching to ziprasidone from other antipsychotics was associated with improved cognition.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>


Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis

European Journal of Clinical Pharmacology 2014; 70:127-134

View review abstract online

Comparison | Effectiveness of individual antipsychotics.
Summary of evidence | Moderate to low quality evidence (large samples, consistent, unable to assess precision, direct and indirect) suggests that quetiapine and olanzapine had the most positive effects on cognition, followed by risperidone, then ziprasidone, amisulpride, and haloperidol.

General cognitive ability
Treatments – For Cognitive Symptoms

9 RCTs, N = 1540

*Greater improvement was found with quetiapine than:*
- Amisulpride: MD 0.27, 95%CI 0.10 to 0.44, *p* < 0.05
- Haloperidol: MD 0.27, 95%CI 0.13 to 0.41, *p* < 0.05

*Greater improvement was found with olanzapine than:*
- Amisulpride: MD 0.20, 95%CI 0.04 to 0.37, *p* < 0.05
- Haloperidol: MD 0.21, 95%CI 0.10 to 0.32, *p* < 0.05

*Greater improvement was found with risperidone than:*
- Haloperidol: MD 0.16, 95%CI 0.02 to 0.30, *p* < 0.05

### Memory

*Greater improvement was found with ziprazidone than:*
- Amisulpride: MD 0.28, 95%CI 0.02 to 0.54, *p* < 0.05
- Haloperidol: MD 0.32, 95%CI 0.09 to 0.55, *p* < 0.05

*Greater improvement was found with olanzapine than:*
- Haloperidol: MD 0.19, 95%CI 0.04 to 0.34, *p* < 0.05

### Attention and processing speed

*Greater improvement was found with quetiapine than:*
- Ziprasidone: MD 0.18, 95%CI 0.09 to 0.28, *p* < 0.05
- Olanzapine: MD 0.21, 95%CI 0.16 to 0.27, *p* < 0.05
- Amisulpride: MD 0.27, 95%CI 0.20 to 0.34, *p* < 0.05
- Risperidone: MD 0.32, 95%CI 0.24 to 0.39, *p* < 0.05
- Haloperidol: MD 0.38, 95%CI 0.30 to 0.46, *p* < 0.05

*Greater improvement was found with ziprasidone than:*
- Amisulpride: MD, 95%CI 0.09 0.00 to 0.18, *p* < 0.05
- Risperidone: MD, 95%CI 0.13 0.02 to 0.25, *p* < 0.05
- Haloperidol: MD, 95%CI 0.20 0.10 to 0.30, *p* < 0.05

*Greater improvement was found with olanzapine than:*
- Amisulpride: MD, 95%CI 0.06 0.00 to 0.11, *p* < 0.05
Risperidone: MD, 95%CI 0.10 0.02 to 0.18, \( p < 0.05 \)
Haloperidol: MD, 95%CI 0.17 0.10 to 0.24, \( p < 0.05 \)

**Greater improvement was found with amisulpride than:**
Haloperidol: MD, 95%CI 0.11 0.03 to 0.19, \( p < 0.05 \)

**Executive functioning**

**Greater improvement was found with quetiapine than:**
Amisulpride: MD, 95%CI 0.20 0.02 to 0.38, \( p < 0.05 \)

**Greater improvement was found with olanzapine than:**
Amisulpride: MD, 95%CI 0.19 0.01 to 0.36, \( p < 0.05 \)

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Authors state that data are consistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess (not standardised MD)</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct and indirect comparisons combined</td>
</tr>
</tbody>
</table>

**Jainer AK, Campbell C, Srivastava S**

**Atypical antipsychotic drugs and cognitive deficits in schizophrenia: a review of double-blind randomised controlled trials**

*International Medical Journal 2003; 10(4): 243-7*

[View review abstract online](#)

**Comparison**

Effectiveness of second generation antipsychotics vs. various control conditions.

**Summary of evidence**

Low quality evidence (small samples, unable to assess consistency or precision) is unclear as to the benefits of second-generation antipsychotics.

**General cognitive ability**
Treatments – For Cognitive Symptoms

5 RCTs (N = 173) assessed the use of second-generation antipsychotics for improving cognitive deficits in people with schizophrenia. Two of these studies examined a sample of treatment-resistant schizophrenia. The studies examined second-generation antipsychotics clozapine (200-600mg/day), zotepine (150-450mg/day), risperidone (4-10mg/day), quetiapine (330mg/day), and olanzapine (5-20mg/day), compared to haloperidol (5-30mg/day) or to another second-generation medication. All 5 studies reported improvement in cognitive functioning in the test group, observed within the first month of treatment in three studies.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Mishara AL, Goldberg TE

A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book

Biological Psychiatry 2004; 55: 1013-1022

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effectiveness of first generation antipsychotics vs. placebo or wash-out period (min 2 weeks).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (consistent, precise, direct, large samples, some studies were naturalistic, open-label studies) suggests small benefits of first-generation antipsychotics for improving general cognitive function.</td>
</tr>
<tr>
<td>General cognitive ability</td>
<td></td>
</tr>
</tbody>
</table>

A small, significant effect of improved general cognitive function with first-generation antipsychotics

34 studies, N = 1026, $d = 0.22$, 95%CI 0.19 to 0.34, $p = 0.0005$, $Q = 38.69$, $p = 0.22$

Subgroup analysis of within-subject studies (n = 15 with wash-out periods) and between-subject studies (n = 19 with a placebo arm) found a higher mean effect size in the between-subject studies.
(\(d = 0.25\), 95%CI 0.09 to 0.41, \(p = 0.002\), \(Q = 19.52, p > 0.35\) vs. \(d = 0.18\), 95%CI -0.01 to 0.37, \(p = 0.03\), \(Q = 18.67, p > 0.17\))

Meta-regression found no significant associations according to study quality, dose, symptom severity, year of publication, length of illness, age, or sex (all \(r < 0.20\), \(p > 0.10\))

Examining the cognitive domains separately: a large effect size (\(d > 0.80\)) was reported for learning automaticity (\(N = 46\), 95%CI 0.34 to 1.62); a medium effect size (\(d > 0.50\)) was reported for perceptual processing (\(N = 87\), 95%CI 0.08 to 1.0); and small to medium effect sizes (\(d > 0.20\)) were reported for attention (\(N = 509\), 95%CI 0.10 to 0.40), language (\(N = 292\), 95%CI 0.06 to 0.51), and memory (\(N = 159\), 95%CI -0.13 to 0.75)

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise for overall effect, attention, and language</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct for subgroup analysis</td>
</tr>
</tbody>
</table>

Nielsen RE, Levander S, Kjaersdam Tell_eus G, Jensen SOW, Østergaard Christensen T, Leucht S

Second-generation antipsychotic effect on cognition in patients with schizophrenia - a meta-analysis of randomized clinical trials

Acta Psychiatrica Scandinavica 2015; 131: 185-196

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effectiveness of second generation antipsychotics vs. other antipsychotics or placebo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate to low quality evidence (large samples, consistent, some imprecision, direct and indirect) suggests sertindole may be more superior than clozapine, quetiapine, and first generation antipsychotics for general cognitive ability, and more superior than clozapine, quetiapine, and olanzapine for memory, clozapine, quetiapine, and olanzapine and ziprasidone for executive functioning and more superior than quetiapine for processing speed. Olanzapine may be more superior than clozapine and first generation antipsychotics for visuospatial skills and verbal fluency.</td>
</tr>
</tbody>
</table>
# General cognitive ability

37 RCTs, N = 3526

*Large effects of greater improvement with sertindole than:*

- Clozapine: $d = 0.87$, 95% CI 0.12 to 1.63, $p < 0.05$
- Quetiapine: $d = 0.75$, 95% CI 0.00 to 1.49, $p < 0.05$

First generation antipsychotics combined: $d = 0.89$, 95% CI 0.14 to 1.64, $p < 0.05$

Authors report no effect of possible confounders (publication year, duration of illness, study duration, gender, sponsorship of study, blinding, and number of patients)

## Memory

*Small to medium effects of greater improvement in verbal working memory with sertindole than:*

- Clozapine: $d = 0.37$, 95%CI 0.00 to 0.74, $p < 0.05$
- Olanzapine: $d = 0.31$, 95%CI 0.02 to 0.59, $p < 0.05$
- Quetiapine: $d = 0.34$, 95% CI 0.03 to 0.64, $p < 0.05$

First generation antipsychotics combined: $d = 0.51$, 95% CI 0.18 to 0.83, $p < 0.05$

*Small effect of greater improvement in verbal working memory with risperidone than:*

First generation antipsychotics combined: $d = 0.31$, 95%CI 0.04 to 0.58, $p < 0.05$

*Medium effect of greater improvement in long-term verbal working memory with olanzapine than:*

- Clozapine: $d = 0.41$, 95%CI 0.06 to 0.76, $p < 0.05$

## Executive functioning

*Large effects of greater improvement in executive functioning with sertindole than:*

- Clozapine: $d = 0.82$, 95%CI 0.06 to 1.58, $p < 0.05$
- Olanzapine: $d = 0.81$, 95%CI 0.07 to 1.55, $p < 0.05$
- Quetiapine: $d = 0.76$, 95%CI 0.02 to 1.51, $p < 0.05$
- Ziprasidone: $d = 0.90$, 95%CI 0.14 to 1.67, $p < 0.05$

First generation antipsychotics combined: $d = 0.83$, 95%CI 0.08 to 1.58, $p < 0.05$

## Processing speed

*Medium to large effects of greater improvement in processing speed with sertindole than:*

First generation antipsychotics combined: $d = 0.97$, 95%CI 0.02 to 1.91, $p < 0.05$
Treatments – For Cognitive Symptoms

Quetiapine: $d = 0.36$, 95%CI 0.01 to 0.72, $p < 0.05$

<table>
<thead>
<tr>
<th>Visuospatial skill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium effects of greater improvement in visuospatial skill with olanzapine than:</td>
</tr>
<tr>
<td>First generation antipsychotics combined: $d = 0.41$; 95%CI 0.04 to 0.78, $p &lt; 0.05$</td>
</tr>
<tr>
<td>Clozapine: $d = 0.44$, 95%CI 0.05 to 0.83, $p &lt; 0.05$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal fluency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small to medium effect of greater improvement in verbal fluency with olanzapine than:</td>
</tr>
<tr>
<td>First generation antipsychotics combined: $d = 0.26$, 95%CI 0.01 to 0.50, $p &lt; 0.05$</td>
</tr>
<tr>
<td>Clozapine: $d = 0.44$, 95%CI 0.06 to 0.81, $p &lt; 0.05$</td>
</tr>
</tbody>
</table>

### Consistency in results
Authors state that data are consistent

### Precision in results
Imprecise for general cognitive ability and executive functioning

### Directness of results
Direct and indirect

---

**So S, Garety P, Peters E, Kapur S**

**Do antipsychotics improve reasoning biases? A review**

*Psychosomatic Medicine* 2010; 72: 681-93

[View review abstract online](#)

### Comparison
Effectiveness of unspecified antipsychotics for reasoning biases.

### Summary of evidence
Low quality evidence (small samples, unable to assess consistency or precision) is unclear as to any the benefit of antipsychotic treatments for reasoning biases.

### Reasoning biases

6 studies investigate the effects of antipsychotic treatment (unspecified) on reasoning biases

1 study (N = 17) assessed medicated patients pre- and post-remission and found that on remission of psychosis, reasoning bias persisted (jumping to conclusions, JTC). They also found that a
subsample of actively deluded patients had a depressive attributional style, which was normalised upon achieving remission from delusions

1 study (N = 19) found that JTC biases improved initially but plateaued, despite continued improvement in psychosis over 4 weeks of atypical antipsychotic treatment

1 study (N = 19) found that over 12 weeks, 15 medicated patients had decreasing delusions. There was also an increase in jumping to conclusions, but the authors attribute this to a task practice effect

1 study (N = 95) found that patients achieving remission from delusions following treatment also showed improved flexibility of beliefs and did not differ from controls or patients with anxiety

1 study (N = 17) found that a session of reasoning training was not significantly better than attention control training for increasing belief flexibility

1 study (N = 17) found that over 6 weeks of antipsychotic treatment, symptom severity reduced but attributional style did not significantly change; and theory of mind performance improved, but did not correlate with any changes in symptoms

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Thornton AE, Van Snellenberg JX, Sepehry AA, Honer WG

The impact of atypical antipsychotic medications on long-term memory dysfunction in schizophrenia spectrum disorder: a quantitative review

Journal of Psychopharmacology 2006; 20(3): 335-346

Comparison | Effectiveness of second generation vs. first generation antipsychotics for long term memory.

Summary of evidence | Moderate quality evidence (precise, unable to assess consistency, direct, large samples) suggests small benefits of second-generation antipsychotics over first-generation antipsychotics for improving long-term memory performance.
Long-term memory

Small, significant effect suggests patients receiving second-generation antipsychotics showed better long-term memory performance than patients receiving first-generation antipsychotics

17 studies (not all were RCTs), \( N = 939, g = 0.17, 95\% CI 0.04 \text{ to } 0.31, p = 0.01 \)

*This effect was retained when only randomized studies were included*

12 studies, \( N = 722, g = 0.159, 95\% CI 0.01 \text{ to } 0.31, p < 0.05 \)

*And when verbal memory tasks were considered alone*

15 studies, \( N = 732, g = 0.179, 95\% CI 0.02 \text{ to } 0.33, p < 0.05 \)

*There was no difference between groups for non-verbal memory tasks*

9 studies, \( N = 393, g = 0.144, 95\% CI -0.07 \text{ to } 0.36, p > 0.1 \)

When comparing specific medications, only olanzapine showed a significant but small benefit over unspecified first-generation antipsychotics for improving long-term memory overall

Olanzapine vs. first-generation: 6 studies, \( N = 367, g = 0.285, 95\% CI 0.08 \text{ to } 0.49, p < 0.05 \)

Clozapine vs. first-generation: 5 studies, \( N = 188, g = -0.064, 95\% CI -0.35 \text{ to } 0.23, p > 0.1 \)

Risperidone vs. first-generation: 7 studies, \( N = 295, g = 0.203, 95\% CI -0.03 \text{ to } 0.44, p < 0.1 \) (trend)

Quetiapine vs. first-generation: 3 studies, \( N = 111, g = 0.259, 95\% CI -0.15 \text{ to } 0.66, p > 0.1 \)

Risperidone vs. Clozapine: 4 studies, \( N = 118, g = 0.318, 95\% CI -0.05 \text{ to } 0.69, p < 0.1 \) (trend)

Olanzapine vs. Clozapine: 2 studies, \( N = 80, g = 0.260, 95\% CI -0.19 \text{ to } 0.71, p > 0.1 \)

*Olanzapine vs. Risperidone: 7 studies, \( N = 618, g = 0.005, 95\% CI -0.15 \text{ to } 0.16, p > 0.1 \)*

Olanzapine and Risperidone vs. Clozapine: 5 studies, \( N = 174, g = 0.277, 95\% CI -0.04 \text{ to } 0.59, p < 0.1 \) (trend)

*Only olanzapine and risperidone showed significant benefits over clozapine for improving verbal memory*

Risperidone vs. Clozapine: 4 studies, \( N = 118, g = 0.491, 95\% CI 0.11 \text{ to } 0.87, p < 0.05 \)

Olanzapine and Risperidone vs. Clozapine: 5 studies, \( N = 174, g = 0.357, 95\% CI 0.04 \text{ to } 0.67, p < 0.05 \)
Authors state that the antipsychotics that induced improvements in long-term memory were those associated with reduced anticholinergic activity of the medications. Antipsychotics with higher anticholinergic ‘load’ were associated with smaller or no improvements in long-term memory.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Vernon JA, Grudnikoff E, Seidman AJ, Frazier TW, Vemulapalli MS, Pareek P, Goldberg TE, Kane JM, Correll CU

**Antidepressants for cognitive impairment in schizophrenia – A systematic review and meta-analysis**

*Schizophrenia Research* 2014; 159: 385–394

[View review abstract online](#)

**Comparison**

Effectiveness of adjunctive antidepressants vs. adjunctive placebo.

**Summary of evidence**

Moderate to high quality evidence (consistent, precise, direct, medium to large samples) suggests small benefits of antidepressants over placebo for global cognition and executive functioning. Authors state that these findings were not clinically significant.

**Global cognition**

*Small, significant effect of greater improvement in the antidepressant group*

11 RCTs, N = 501, $g = 0.09$, 95%CI 0.02 to 0.17, $p = 0.012$, $I^2$ 45%

**Executive functioning**

*Small, significant effect of greater improvement in the antidepressant group*

8 RCTs, N = 259, $g = 0.17$, 95%CI 0.02 to 0.31, $p = 0.02$, $I^2$ 47%
## Memory

*No significant differences between groups*

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>g</th>
<th>95%CI</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global memory</td>
<td>9</td>
<td>0.077</td>
<td>−0.038 to 0.19</td>
<td>0.19</td>
<td>46%</td>
</tr>
<tr>
<td>Auditory verbal long-term memory</td>
<td>4</td>
<td>0.06</td>
<td>−0.20 to 0.31</td>
<td>0.66</td>
<td>41%</td>
</tr>
<tr>
<td>Visuospatial long-term memory</td>
<td>4</td>
<td>0.07</td>
<td>−0.45 to 0.59</td>
<td>0.79</td>
<td>66%</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>7</td>
<td>0.11</td>
<td>−0.18 to 0.40</td>
<td>0.45</td>
<td>45%</td>
</tr>
<tr>
<td>Auditory verbal working memory</td>
<td>4</td>
<td>0.11</td>
<td>−0.12 to 0.34</td>
<td>0.34</td>
<td>0%</td>
</tr>
<tr>
<td>Visuospatial working memory</td>
<td>4</td>
<td>0.06</td>
<td>−0.18 to 0.31</td>
<td>0.61</td>
<td>7%</td>
</tr>
<tr>
<td>Working memory</td>
<td>8</td>
<td>0.07</td>
<td>−0.087 to 0.24</td>
<td>0.37</td>
<td>0%</td>
</tr>
<tr>
<td>Auditory verbal memory</td>
<td>5</td>
<td>0.08</td>
<td>−0.081 to 0.25</td>
<td>0.32</td>
<td>20%</td>
</tr>
<tr>
<td>Visuospatial memory</td>
<td>5</td>
<td>0.06</td>
<td>−0.16 to 0.29</td>
<td>0.57</td>
<td>0%</td>
</tr>
</tbody>
</table>

## Attention

*No significant differences between groups*

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>g</th>
<th>95%CI</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 RCTs, N = 321, g = 0.02, 95%CI −0.19 to 0.23, p = 0.84, I² 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Processing speed

*No significant differences between groups*

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>g</th>
<th>95%CI</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 RCTs, N = 344, g = 0.09, 95%CI −0.031 to 0.21, p = 0.15, I² 16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Visuospatial processing

*No significant differences between groups*

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>g</th>
<th>95%CI</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 RCTs, N = 94, g = 0.14, 95%CI −0.73 to 1.00, p = 0.76, I² 78%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatments – For Cognitive Symptoms

Verbal fluency

No significant differences between groups

5 RCTs, N = 327, g = 0.019, 95%CI –0.14 to 0.18, p = 0.81, I² 0%

Consistency in results
Inconsistent for visuospatial long-term memory and processing

Precision in results
Imprecise for visuospatial processing

Directness of results
Direct

Woodward ND, Purdon SE, Meltzer HY, Zald DH

A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia

International Journal of Neuropsychopharmacology 2005; 8: 457-472

View review abstract online

Comparison
Effectiveness first generation vs. second generation antipsychotics for neuropsychological function.

Summary of evidence
Moderate to high quality evidence (precise, consistent, direct, medium to large samples) shows second generation antipsychotics were associated with small improvements in global cognition, processing speed, verbal fluency, learning, motor skills, but had no benefit over first generation antipsychotics for improving attention, cognitive flexibility, working memory, delayed recall, or visuospatial processing.

Global cognition

A small, significant effect of improved global cognition with second generation antipsychotics

18 studies, N = 514, g = 0.24, 95%CI 0.114 to 0.37, p < 0.001 (Q: p > 0.05)

Post-treatment, a medium effect size suggests patients second generation antipsychotics improved global cognition
Treatments – For Cognitive Symptoms

Quetiapine: 7 studies, N = 118, g = 0.44, CI not reported, p < 0.05 (Q: p > 0.05)
Olanzapine: 13 studies, N = 690, g = 0.43, CI not reported, p < 0.05 (Q: p > 0.05)
Clozapine: 17 studies, N = 344, g = 0.29, CI not reported, p < 0.05 (Q: p > 0.05)
Risperidone: 13 studies, N = 361, g = 0.28, CI not reported, p < 0.05 (Q: p > 0.05)

<table>
<thead>
<tr>
<th>Processing Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A small, significant effect of improved processing speed with second generation antipsychotics</td>
</tr>
<tr>
<td>15 studies, N = 451, g = 0.21, 95%CI 0.07 to 0.35, p = 0.003 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Post-treatment, a small effect size suggests patients receiving clozapine, olanzapine or risperidone showed improved processing speed</td>
</tr>
<tr>
<td>Clozapine: 16 studies, N = 326, g = 0.35, CI not reported, p &lt; 0.006 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Olanzapine: 12 studies, N = 648, g = 0.43, CI not reported, p &lt; 0.006 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Risperidone: 9 studies, N = 299, g = 0.30, CI not reported, p &lt; 0.006 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>No improvements were reported for patients on quetiapine</td>
</tr>
<tr>
<td>Quetiapine: 6 studies, N = 107, g = 0.35, CI not reported, p &gt; 0.05 (Q: p &gt; 0.05)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal fluency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A small, significant effect of improved verbal fluency with second generation antipsychotics</td>
</tr>
<tr>
<td>15 studies, N = 449, g = 0.16, 95%CI 0.02 to 0.30, p = 0.024 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Post-treatment, medium effect sizes show improved performance in patients receiving olanzapine, clozapine or quetiapine</td>
</tr>
<tr>
<td>Quetiapine: 6 studies, N = 107, g = 0.63, CI not reported, p &lt; 0.006 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Clozapine: 15 studies, N = 319, g = 0.44, CI not reported, p &lt; 0.006 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Olanzapine: 11 studies, N = 651, g = 0.25, CI not reported, p &lt; 0.006 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Patients receiving risperidone showed no significant improvement post medication</td>
</tr>
<tr>
<td>Risperidone: 5 studies, N = 207, g = 0.06, CI not reported, p &gt; 0.05 (Q: p &gt; 0.05)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Learning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A small, significant effect of improved learning with second generation antipsychotics</td>
</tr>
<tr>
<td>14 studies, N = 442, g = 0.24, 95%CI 0.10 to 0.38, p &lt; 0.001 (Q: p &gt; 0.05)</td>
</tr>
<tr>
<td>Post-treatment, a medium effect size shows patients receiving olanzapine, clozapine or risperidone had improved learning</td>
</tr>
</tbody>
</table>
## Treatments – For Cognitive Symptoms

| Olanzapine: 10 studies, N = 625, g = 0.61, CI not reported, p < 0.006 (Q: p < 0.05) |
| Risperidone: 7 studies, N = 251, g = 0.41, CI not reported, p < 0.006 (Q: p > 0.05) |
| Clozapine: 10 studies, N = 210, g = 0.31, CI not reported, p < 0.006 (Q: p > 0.05) |
| Patients receiving quetiapine showed no significant improvement post medication |
| Quetiapine: 6 studies, N = 108, g = 0.24, CI not reported, p > 0.05 (Q: p > 0.05) |

### Motor skills

A small, significant effect of improved motor skills with second generation antipsychotics

9 studies, N = 3226, g = 0.21, 95%CI 0.05 to 0.37, p = 0.010 (Q: p > 0.05)

Post-treatment, medium effect size showed improved performance in patients receiving clozapine

| Clozapine: 4 studies, N = 68, g = 0.64, p < 0.006 (Q: p > 0.05) |

Patients receiving olanzapine, risperidone or quetiapine showed no improvement post medication

| Olanzapine: 5 studies, N = 238, g = 0.25, (CI not reported), p > 0.05 (Q: p > 0.05) |
| Risperidone: 2 studies, N = 65, g = 0.22, (CI not reported), p > 0.05 (Q: p > 0.05) |
| Quetiapine: 2 studies, N = 34, g = 0.20, (CI not reported), p > 0.05 (Q: p > 0.05) |

### Attention

No difference was reported between patients receiving second-generation compared to first-generation

12 studies, N = 316, g = 0.12, 95%CI -0.04 to 0.28, p = 0.152 (Q: p > 0.05)

Post-treatment, a medium effect size suggests improved attention in patients receiving olanzapine or quetiapine

| Olanzapine: 9 studies, N = 512, g = 0.47, (CI not reported), p < 0.006 (Q: p > 0.05) |
| Quetiapine: 5 studies, N = 91, g = 0.82, (CI not reported), p < 0.006 (Q: p > 0.05) |

Patients receiving clozapine or risperidone showed no significant improvement post medication

| Clozapine: 8 studies, N = 152, g = 0.17, (CI not reported), p > 0.05 (Q: p > 0.05) |
| Risperidone: 9 studies, N = 289, g = 0.12, (CI not reported), p > 0.05 (Q: p > 0.05) |

### Cognitive flexibility and abstraction

There was no difference between patients receiving second-generation or first-generation antipsychotics

14 studies, N = 405, g = 0.04, 95%CI -0.10 to 0.18, p = 0.581 (Q: p > 0.05)
### Post-treatment, there were no improvements in cognitive flexibility in patients receiving:

- **Clozapine**: 12 studies, N = 227, $g = 0.25$, CI not reported, $p > 0.05$ (Q: $p > 0.05$)
- **Olanzapine**: 10 studies, N = 471, $g = 0.15$, CI not reported, $p > 0.05$ (Q: $p > 0.05$)
- **Risperidone**: 4 studies, N = 189, $g = 0.10$, CI not reported, $p > 0.05$ (Q: $p > 0.05$)
- **Quetiapine**: 3 studies, N = 50, $g = 0.33$, CI not reported, $p > 0.05$ (Q: $p > 0.05$)

### Working memory

*There was no difference in working memory between patients receiving second-generation or first-generation antipsychotics*

10 studies, N = 286, $g = 0.05$, 95%CI -0.12 to 0.22, $p = 0.546$ (Q: $p > 0.05$)

*Post-treatment, a small effect size shows improved performance in patients receiving olanzapine or risperidone*

- **Olanzapine**: 8 studies, N = 406, $g = 0.24$, (CI not reported), $p < 0.006$ (Q: $p > 0.05$)
- **Risperidone**: 9 studies, N = 281, $g = 0.24$, (CI not reported), $p < 0.006$ (Q: $p > 0.05$)

*Patients receiving clozapine or quetiapine showed no significant improvement post medication*

- **Quetiapine**: 2 studies, N = 27, $g = 0.41$ (CI not reported), $p > 0.05$ (Q: $p > 0.05$)
- **Clozapine**: 8 studies, N = 160, $g = 0.25$, (CI not reported), $p > 0.05$ (Q: $p > 0.05$)

### Delayed recall

*There was no difference in delayed recall between patients receiving second-generation or first-generation antipsychotics*

10 studies, N = 374, $g = 0.13$, 95%CI -0.02 to 0.28, $p = 0.091$ (Q: $p > 0.05$)

*Post-treatment, a small to medium effect size shows improved performance in patients receiving clozapine, olanzapine, or risperidone*

- **Clozapine**: 13 studies, N = 280, $g = 0.25$, CI not reported, $p < 0.006$ (Q: $p > 0.05$)
- **Olanzapine**: 7 studies, N = 460, $g = 0.53$, CI not reported, $p < 0.006$ (Q: $p > 0.05$)
- **Risperidone**: 5 studies, N = 211, $g = 0.46$, CI not reported, $p < 0.006$ (Q: $p > 0.05$)

*Patients receiving quetiapine showed no significant improvement post medication*

- **Quetiapine**: 3 studies, N = 58, $g = 0.30$, (CI not reported), $p > 0.05$ (Q: $p > 0.05$)

### Visuospatial processing
There was no difference in attention between patients receiving second-generation or first-generation antipsychotics

10 studies, N = 253, g = 0.00, 95%CI -0.18 to 0.02, p = 0.988 (Q: p > 0.05)

Post-treatment, a medium effect size showed improved performance in patients receiving olanzapine

Olanzapine: 5 studies, N = 144, g = 0.50, (CI not reported), p > 0.006 (Q: p > 0.05)

Patients receiving clozapine or risperidone or quetiapine showed no significant improvement post-medication

Clozapine: 9 studies, N = 179, g = 0.20, (CI not reported), p > 0.05 (Q: p > 0.05)
Risperidone: 3 studies, N = 65, g = 0.39, (CI not reported), p > 0.05 (Q: p > 0.05)
Quetiapine: 1 studies, N = 11, g = 0.56, (CI not reported), p > 0.05 (Q: p > 0.05)

Consistency in results | Consistent
---|---
Precision in results | Precise
Directness of results | Direct

Woodward ND, Purdon SE, Meltzer HY, Zald DH

A meta-analysis of cognitive changes with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects

Schizophrenia Research 2007; 89: 211-224

View review abstract online

Comparison | Cognitive change over time with low or high dose haloperidol vs. second generation antipsychotics, and vs. healthy controls to assess practice effects.
---|---
Summary of evidence | Moderate to high quality evidence (precise, consistent, direct, medium to large samples) shows haloperidol was associated with small improvements in global cognition (low haloperidol dose only), verbal learning (low and high dose), delayed recall (low and high dose), and attention (low dose only), when compared to second generation antipsychotics, with no
## Global cognition

Small, significant effect suggests improved global cognitive with low dose haloperidol, but not high dose haloperidol compared to second generation antipsychotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>g = 0.18, 95%CI 0.08 to 0.28</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Low dose (&lt; 10mg)</td>
<td>g = 0.20, 95%CI 0.07 to 0.33</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>g = 0.13, 95%CI -0.05 to 0.31</td>
<td>&gt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

The difference in effect sizes was not statically significant (0.20 vs. 0.13; Q_B = 0.36, p = 0.548)

*There was no measure of practice effects for this task*

## Verbal learning

Small, significant effect suggests improved verbal learning with both low and high dose haloperidol compared to second generation antipsychotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>g = 0.32, 95%CI 0.19 to 0.43</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>g = 0.37, 95%CI 0.23 to 0.51</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>g = 0.20, 95%CI 0.00 to 0.40</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

There was no measure of practice effects for this task

## Delayed verbal recall

Small, significant effect suggests improved delayed verbal recall with both low and high dose haloperidol compared to second generation antipsychotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>g = 0.27, 95%CI 0.14 to 0.40</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>g = 0.22, 95%CI 0.05 to 0.39</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>g = 0.28, 95%CI 0.06 to 0.50</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

There was no measure of practice effects for this task

## Attention

Small, significant effect suggests improved Continuous Performance Test scores with low dose haloperidol compared to second generation antipsychotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>g = 0.20, 95%CI 0.05 to 0.35</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>g = 0.22, 95%CI 0.06 to 0.38</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

The differences between groups in executive function, verbal fluency, motor skills, or processing speed.
No differences between groups on Trail Making Test A (TMT-A)

All studies: 6 studies, N = 231, g = 0.15, 95%CI -0.03 to 0.33, p > 0.05
Low dose: 2 studies, N = 151, g = 0.07, 95%CI -0.15 to 0.29, p > 0.05
High dose: 3 studies, N = 53, g = 0.22, 95%CI -0.16 to 0.60, p > 0.05

There were no differences in practice effects on TMT-A between patients taking haloperidol and healthy controls

Processing speed

Small, significant effect of improved performance on digit symbol/modalities test (DSST) when all studies are combined, but no differences between groups in low or high dose analyses

All studies: 9 studies, N = 475, SMD = 0.13, 95%CI 0.01 to 0.25, p < 0.05
Low dose: 5 studies, N = 344, SMD = 0.13, 95%CI -0.02 to 0.28, p > 0.05
High dose: 4 studies, N = 131, SMD = 0.13, 95%CI -0.09 to 0.35, p > 0.05

No differences between groups on Trail Making Test B (TMT-B)

All studies: 11 studies, N = 384, SMD = 0.09, 95%CI -0.04 to 0.23, p > 0.05
Low dose: 4 studies, N = 179, SMD = 0.02, 95%CI -0.18 to 0.22, p > 0.05
High dose: 6 studies, N = 178, SMD = 0.12, 95%CI -0.08 to 0.32, p > 0.05

Practice effects were greater in healthy controls than in patients taking haloperidol for the DSST, but there were no differences on TMT-B

Motor skills

No differences between groups in finger tapping/oscillation

All studies: 4 studies, N = 128, g = -0.05, 95%CI -0.30 to 0.20, p > 0.05
Low dose: 2 studies, N = 92, g = -0.06, 95%CI -0.35 to 0.23, p > 0.05
High dose: 2 studies, N = 36, g = -0.04, 95%CI -0.50 to 0.43, p > 0.05

No differences between groups in grooved pegboard test (GPB)

All studies: 5 studies, N = 196, g = 0.01, 95%CI -0.17 to 0.19, p > 0.05
Low dose: 3 studies, N = 104, g = -0.08, 95%CI -0.34 to 0.18, p > 0.05
High dose: 2 studies, N = 92, g = 0.09, 95%CI -0.17 to 0.35, p > 0.05

There were no differences in practice effects on the GPB between patients taking haloperidol and healthy controls
Executive functioning

No differences between groups on Wisconsin Card Sorting Test (WCST)

- All studies: 10 studies, N = 491, g = 0.02, 95%CI -0.10 to 0.14, p > 0.05
- Low dose: 6 studies, N = 359, g = -0.01, 95%CI -0.16 to 0.13, p > 0.05
- High dose: 4 studies, N = 132, g = 0.12, 95%CI -0.11 to 0.33, p > 0.05

There was no measure of practice effects for this task

Verbal fluency

No differences between groups on Controlled Oral Word Association Test (COWA)

- All studies: 12 studies, N = 553, g = 0.05, 95%CI -0.07 to 0.17, p < 0.05
- Low dose: 6 studies, N = 372, g = 0.04, 95%CI -0.10 to 0.18, p < 0.05
- High dose: 5 studies, N = 154, g = 0.00, 95%CI -0.21 to 0.21, p < 0.05

No differences between groups on Category Instance Generation Test (CIGT)

- All studies: 5 studies, N = 349, g = -0.09, 95%CI -0.24 to 0.06, p < 0.05
- Low dose: 4 studies, N = 330, g = -0.06, 95%CI -0.21 to 0.09, p < 0.05
- High dose: 1 studies, N = 19, g = -0.68, 95%CI -1.33 to 0.05, p < 0.05

Practice effects were greater in healthy controls than in patients taking haloperidol for the COWA, but there were no differences on the CIGT

Consistency in results: Unable to assess, authors report consistent

Precision in results: Precise

Directness of results: Direct

Zhang J, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU

Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2013; 16: 1205-1218
Comparison | First generation vs. second generation antipsychotics for people with first-episode psychosis.
--- | ---
Summary of evidence | Moderate to high quality evidence (large samples, precise, direct, inconsistent) suggests olanzapine and risperidone may improve cognition more than haloperidol.

Moderate to high quality evidence (large samples, precise, direct, inconsistent) suggests less extrapyramidal side effects and akathisia with olanzapine and risperidone compared to haloperidol, although olanzapine and risperidone may cause more weight gain. There is less use of benzodiazepines with olanzapine compared to haloperidol, and moderate quality evidence (imprecise) also suggests less use of anticholinergic medications and beta-blockers with olanzapine, although cholesterol change is higher than haloperidol. For tryglyceride change, amisulpride resulted in greater change than haloperidol.

All other side effects information was rated as low quality due to the small samples involved.

Cognitive function

A *small effect of improved global cognition for second generation antipsychotics compared to first generation antipsychotics*

11 RCTs, N = 1932, $g = 0.25$, 95%CI 0.10 to 0.40, $p < 0.01$

Individually, only olanzapine (4 RCTs, N = 653, $g = 0.27$, 95%CI 0.06 to 0.49, $p < 0.01$) and risperidone (5 RCT, N = 1136, $g = 0.23$, 95%CI 0.04 to 0.43, $p < 0.01$) were superior to haloperidol.

Risks

Overall, second generation antipsychotics resulted in less extrapyramidal side effects (9 RCTs, N = 1338, $g = -0.43$, 95%CI -0.64 to -0.22, $p < 0.01$), which was most evident in individual analyses of olanzapine (4 RCTs, N = 609, $g = -0.69$, 95%CI -1.02 to -0.35, $p < 0.01$), and risperidone (3 RCTs, N = 588, $g = -0.33$, 95%CI -0.51 to -0.16, $p < 0.01$) compared to haloperidol, and in the comparison of clozapine with chlorpromazine (1 RCT, N = 160, $g = -0.72$, 95%CI -1.04 to -0.41, $p < 0.01$). More recent studies had smaller effect sizes for extrapyramidal side effects ($b = 0.04$, $p = 0.02$), and higher patient age was associated with larger effect sizes ($b = -0.04$, $p = 0.006$). Less akathisia was reported with second generation antipsychotics (7
RCTs, N = 998, g -0.48, 95%CI -0.62 to -0.34, p < 0.01), particularly for olanzapine (4 RCTs, N = 611, g -0.61, 95%CI -0.79 to -0.42, p < 0.01), and risperidone (2 RCTs, N = 406, g -0.29, 95%CI -0.52 to -0.06, p < 0.05) compared to haloperidol

Second generation antipsychotics resulted in less use of anticholinergic medications (6 RCTs, N = 999, RR 0.47, 95%CI 0.29 to 0.77, p < 0.01), particularly for olanzapine compared to haloperidol (3 RCTs, N = 445, RR 0.21, 95%CI 0.09 to 0.51, p < 0.01), or molindone (1 RCT, N = 75, RR 0.31, 95%CI 0.13 to 0.76, p < 0.01). Less use of benzodiazepines (5 RCTs, N = 816, RR 0.84, 95%CI 0.75 to 0.95, p < 0.01), particularly for olanzapine compared to haloperidol (3 RCTs, N = 445, RR 0.83, 95%CI 0.71 to 0.96, p < 0.05). Less use of beta-blockers for olanzapine compared to haloperidol (1 RCT, N = 251, RR 0.11, 95%CI 0.03 to 0.40, p < 0.01).

More patients on first generation antipsychotics in open-label studies took anticholinergics than in double-blind studies. Less anticholinergic use with second generation antipsychotics compared to first generation antipsychotics was associated with smaller sample size, younger age, male sex and longer follow-up.

Olanzapine (2 RCTs, N = 362, RR 3.31, 95%CI 1.83 to 5.98, p < 0.01) and risperidone (2 RCTs, N = 485, RR 1.61, 95%CI 1.25 to 2.09, p < 0.01) caused more weight gain than haloperidol (>7% gain). Larger differences in weight gain were associated with shorter follow-up time, smaller sample size, younger age, female sex and schizophrenia diagnosis.

Olanzapine (1 RCT, N = 53, g -1.21, 95%CI -1.79 to -0.63, p < 0.01), risperidone (1 RCT, N = 58, g -1.99, 95%CI -2.61 to -1.36, p < 0.01), and clozapine (1 RCT, N = 59, g -1.54, 95%CI -2.12 to -0.97, p < 0.01), were associated with lower glucose change than sulpiride.

Olanzapine resulted in more total cholesterol change than molindone (1 RCT, N = 35, g 1.02, 95%CI 1.30 to 1.75, p < 0.01), sulpiride (1 RCT, N = 53, g 5.12, 95%CI 4.01 to 6.23, p < 0.01), and haloperidol (3 RCTs, N = 501, g 0.17, 95%CI 0.00 to 0.35, p = 0.05). Risperidone resulted in less total cholesterol change than sulpiride (1 RCT, N = 58, g -1.36, 95%CI -1.93 to -0.80, p < 0.01)

For triglyceride change, olanzapine (1 RCT, N = 53, g 3.32, 95%CI 2.49 to 4.15, p < 0.01) and clozapine (1 RCT, N = 59, g 5.02, 95%CI 3.98 to 6.05, p < 0.01) were worse than sulpiride, and amisulpride was worse than haloperidol (1 RCT, N = 207, g 0.34, 95%CI 0.06 to
Treatments – For Cognitive Symptoms

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Authors report inconsistency in results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise for symptoms and cognition</td>
</tr>
<tr>
<td></td>
<td>Precise for extrapyramidal side effects, akathisia and use of benzodiazepines, imprecise for other side effects</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Consistency in results
Authors report inconsistency in results

Precision in results
Precise for symptoms and cognition
Precise for extrapyramidal side effects, akathisia and use of benzodiazepines, imprecise for other side effects

Directness of results
Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = Confidence Interval, CIGT = Category Instance Generation Test, COWAT = Controlled Oral Word Association Test, CPT = Continuous Performance Task, d = Cohen’s d = standardised mean differences (see below for interpretation of effect size), g = Hedge’s g standardised mean difference, GAF = Global Assessment of Function scale, I² = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IQ = Intelligence Quotient, JTC = Jumping to Conclusions, N = number of participants, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), PANSS = Positive and Negative Symptoms Scale, Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, SANS = Scale for the Assessment of Negative Symptoms, RR = relative risk, TMT-A/B = Trail Making Test subsection A or B, vs. = versus, WCST = Wisconsin Card Sorting Task
**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 which 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.

† 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 which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect.

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\(^\text{15}\). InOR 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 unforeseen 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. Unstandardised (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.

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

§ 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\(^\text{16}\).

‖ 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.

This topic is yet to be reviewed by a content expert.
Treatments – For Cognitive Symptoms

References