TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Treatments for cognitive symptoms

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. 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 12 systematic reviews that met inclusion criteria[3-14].

- Moderate to high quality evidence suggests second-generation antipsychotics in general are associated with small improvements in processing speed, verbal fluency, learning, motor skills, long-term memory 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, or visuospatial processing.
- High quality evidence shows small benefits of first-generation antipsychotics over placebo for improving general cognitive functioning.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Treatments for cognitive symptoms

- 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 high quality evidence suggests sertindole may be superior to; clozapine, quetiapine, and first-generation antipsychotics for general cognitive ability; clozapine, quetiapine, and olanzapine for memory; clozapine, quetiapine, olanzapine and ziprasidone for executive functioning; and quetiapine for processing speed. Olanzapine may be superior to clozapine and first-generation antipsychotics for visuospatial skills and verbal fluency.
- Moderate quality evidence suggests small improvements in overall cognition, particularly memory, attention, processing speed, executive functioning with clozapine, olanzapine, and quetiapine (-pine antipsychotics) and with risperidone and ziprasidone (-done antipsychotics). Fluency was improved with -pine antipsychotics only. There were no significant improvements in visuospatial skills, language or motor functioning.
- 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.
- Moderate to high quality evidence suggests a small improvement in verbal learning with anti-dementia medications compared to placebo, with no significant improvements in overall cognition, memory, speed of processing, attention, problem solving, executive functioning, social cognition or visual learning. There were no differences in adverse events.
- Moderate quality evidence suggests no benefits of varenicline for cognition over placebo, and varenicline may cause more nausea.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Clissold M, Crowe SF

Comparing the effect of the subcategories of atypical antipsychotic medications on cognition in schizophrenia using a meta-analytic approach

Journal of clinical and experimental neuropsychology 2019; 41: 26-42

View review abstract online

Comparison 1	**Pre-post assessment of effectiveness of clozapine, olanzapine, or quetiapine (-pine antipsychotics).**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, some imprecision, direct) suggests small improvements in overall cognition, particularly memory, attention, processing speed, executive functioning and fluency with clozapine, olanzapine, and quetiapine (-pine antipsychotics). There were no significant improvements in visuospatial skills, language or motor functioning.**

Cognition

A significant, small improvement in overall cognition with clozapine, olanzapine, or quetiapine;

17 studies, N = 635, g = 0.254, 95%CI 0.204 to 0.303, $p < 0.0005$

Significant, small improvements were found for;

Nonverbal memory: 9 studies, N not reported, g = 0.342, 95%CI 0.197 to 0.488, $p < 0.0001$

Verbal memory: 11 studies, N not reported, g = 0.308, 95%CI 0.166 to 0.449, $p < 0.0001$

Attention/working memory: 15 studies, N not reported, g = 0.251, 95%CI 0.142 to 0.360, $p < 0.0001$

Processing speed: 11 studies, N not reported, g = 0.286, 95%CI 0.167 to 0.406, $p < 0.0001$

Executive functioning: 13 studies, N not reported, g = 0.224, 95%CI 0.103 to 0.344, $p < 0.0001$

Fluency: 12 studies, N not reported, g = 0.163, 95%CI 0.040 to 0.286, p = 0.009

Improvements were not significant for;

Visuospatial skills: 2 studies, N not reported, g = 0.419, 95%CI -0.120 to 0.958, p = 0.128

Language: 1 study, N not reported, g = 0.049, 95%CI -0.544 to 0.643, p = 0.871

Motor functioning: 3 studies, N not reported, g = 0.195, 95%CI -0.058 to 0.447, p = 0.131

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise apart from visuospatial skills and language.

Directness of results	Direct
Comparison 2	**Within-groups design of effectiveness of risperidone and ziprasidone (-done antipsychotics).**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, some imprecision, direct) suggests small improvements in overall cognition, particularly memory, attention, processing speed and executive functioning with risperidone and ziprasidone (-done antipsychotics). There were no significant improvements in visuospatial skills, fluency, language or motor functioning.**
Cognition	
A significant, small improvement in overall cognition with risperidone or ziprasidone; 12 studies, N = 516, *g* = 0.202, 95%CI 0.134 to 0.270, *p* < 0.0001 Verbal memory: 5 studies, N not reported, *g* = 0.397, 95%CI 0.187 to 0.608 *p* < 0.0001 Nonverbal memory: 4 studies, N not reported, *g* = 0.256, 95%CI 0.079 to 0.433 *p* < 0.0001 Attention/working memory: 8 studies, N not reported, *g* = 0.146, 95%CI 0.002 to 0.290, *p* = 0.046 Executive functioning: 7 studies, N not reported, *g* = 0.170, 95%CI 0.010 to 0.330, *p* = 0.037 Processing speed: 8 studies, N not reported, *g* = 0.168, 95%CI 0.018 to 0.318, *p* = 0.028 *Improvements were not significant for;* Visuospatial skills: 2 studies, N not reported, *g* = 0.212, 95%CI -0.274 to 0.698, *p* = 0.392 Fluency: 5 studies, N not reported, *g* = 0.191, 95%CI -0.039 to 0.420, *p* = 0.104 Language: 1 study, N not reported, *g* = 0.065, 95%CI -0.529 to 0.658, *p* = 0.831 Motor functioning: 2 studies, N not reported, *g* = 0.168, 95%CI -0.319 to 0.656, *p* = 0.498	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise apart from visuospatial skills, language and motor functioning.
Directness of results	Direct

Désaméricq G, Schurhoff F, Meary A, Szöke A, Macquin-Mavier I, Bachoud-Lévi AC, Maison P

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

European Journal of Clinical Pharmacology 2014; 70: 127-134 View review abstract online	
Comparison	**Effectiveness of individual antipsychotics.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, unable to assess precision, indirect) suggests quetiapine and olanzapine had the most positive effects on cognition, followed by risperidone, then ziprasidone, amisulpride, and haloperidol.**
General cognitive ability	
9 RCTs, N = 1,540 *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 = 0.09, 95%CI 0.00 to 0.18, $p < 0.05$ Risperidone: MD = 0.13, 95%CI 0.02 to 0.25, $p < 0.05$ Haloperidol: MD = 0.20, 95%CI 0.10 to 0.30, $p < 0.05$ *Greater improvement was found with olanzapine than;* Amisulpride: MD = 0.06, 95%CI 0.00 to 0.11, $p < 0.05$ Risperidone: MD = 0.10, 95%CI 0.02 to 0.18, $p < 0.05$ Haloperidol: MD = 0.17, 95%CI 0.10 to 0.24, $p < 0.05$ *Greater improvement was found with amisulpride than;* Haloperidol: MD = 0.11, 95%CI 0.03 to 0.19, $p < 0.05$	
Executive functioning	
Greater improvement was found with quetiapine than; Amisulpride: MD = 0.20, 95%CI 0.02 to 0.38, $p < 0.05$ *Greater improvement was found with* olanzapine *than;* Amisulpride: MD = 0.19, 95%CI 0.01 to 0.36, $p < 0.05$	
Consistency in results	Authors state that data are consistent.
Precision in results	Unable to assess (not standardised MD).
Directness of results	Direct and indirect comparisons combined.

Jin Y, Wang Q, Wang Y, Liu M, Su A, Geng Z, Lin Y, Li X

Alpha7 nAChR agonists for cognitive deficit and negative symptoms in schizophrenia: A meta-analysis of randomized double-blind controlled trials

Shanghai Archives of Psychiatry 2017; 29: 191-9

View review abstract online

Comparison	**Cholinergic enhancing drugs plus antipsychotic treatment vs. placebo plus antipsychotic treatment.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests no significant benefit of cholinergic medications for improving cognition.**

Cognition	
No significant differences between groups; 5 studies, N = 1,299, SMD = -0.10, 95%CI -0.46 to 0.25, p = 0.57, I^2 = 88%, p < 0.00001	
Risks	There were no significant differences in adverse events.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Kishi T, Ikuta T, Oya K, Matsunaga S, Matsuda Y, Iwata N

Anti-dementia drugs for psychopathology and cognitive impairment in schizophrenia: A systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2018; 21: 748-57

View review abstract online

Comparison	**Adjunctive anti-dementia drugs (donepezil, galantamine, rivastigmine or memantine) vs. adjunctive placebo.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, mostly consistent, precise, direct) suggests a small improvement in verbal learning with anti-dementia medications compared to placebo, with no significant improvements in overall cognition, memory, speed of processing, attention, problem solving, executive functioning, social cognition or visual learning. There were no differences in adverse events.**

Cognition
A significant, small improvement in verbal learning with anti-dementia medications; 14 RCTs, N = 487, SMD = -0.23, 95%CI -0.44 to -0.01, p = 0.04, I^2 = 57% *There were no significant improvements in;* Overall cognition: 6 RCTs, N = 532, SMD = -0.02, 95%CI -0.22 to 0.18, p = 0.83, I^2 = 37% Working memory: 15 RCTs, N = 501, SMD = 0.08, 95%CI -0.18 to 0.34, p = 0.53, I^2 = 65% Speed of processing: 12 RCTs, N = 417, SMD = 0.16, 95%CI -0.08 to 0.40, p = 0.19, I^2 = 33% Attention/vigilance: 9 RCTs, N = 330, SMD = -0.13, 95%CI -0.38 to 0.13, p = 0.34, I^2 = 28%

Reasoning/problem solving: 4 RCTs, N = 130, SMD = -0.10, 95%CI -0.45 to 0.24, p = 0.56, I^2 = 0% Executive functioning: 10 RCTs, N = 279, SMD = 0.02, 95%CI -0.27 to 0.31, p = 0.90, I^2 = 45% Social cognition: 2 RCTs, N = 64, SMD = 0.06, 95%CI -0.43 to 0.55, p = 0.82, I^2 = 0% Visual learning: 5 RCTs, N = 181, SMD = -0.03, 95%CI -0.26 to 0.21, p = 0.82, I^2 = 0%	
Risks	There were no differences in adverse events.
Consistency in results	Mostly consistent
Precision in results	Precise
Directness of results	Direct for anti-dementia class.

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

Comparison	**First generation antipsychotics vs. placebo or wash-out period (min 2 weeks).**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests small benefits of first-generation antipsychotics for improving general cognitive function.**
General cognitive ability	
A small, significant effect of improved general cognitive function with first-generation antipsychotics; 34 studies, N = 1,026, 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 and between-subject studies found a higher mean effect size in the between-subject studies. Meta-regression found no significant associations according to study quality, dose, symptom severity, year of publication, length of illness, age, or sex. A large effect size was reported for learning automaticity, a medium effect size was reported for perceptual processing, and small to medium effect sizes were reported for attention, language, and memory.	
Consistency in results	Consistent

Precision in results	Precise
Directness of results	Direct for antipsychotic class.

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

Comparison	**Second generation antipsychotics vs. other antipsychotics or placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) 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.**

General cognitive ability

37 RCTs, N = 3,526

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 Quetiapine: *d* = 0.36, 95%CI 0.01 to 0.72, *p* < 0.05	
Visuospatial skill	
Medium effects of greater improvement in visuospatial skill with olanzapine than; First generation antipsychotics combined: *d* = 0.41; 95%CI 0.04 to 0.78, *p* < 0.05 Clozapine: *d* = 0.44, 95%CI 0.05 to 0.83, *p* < 0.05	
Verbal fluency	
Small to medium effect of greater improvement in verbal fluency with olanzapine than; First generation antipsychotics combined: *d* = 0.26, 95%CI: 0.01 to 0.50, *p* < 0.05 Clozapine: *d* = 0.44, 95%CI 0.06 to 0.81, *p* < 0.05	
Consistency in results	Authors state that data are consistent.
Precision in results	Imprecise for general cognitive ability and executive functioning.
Directness of results	Direct

Tanzer T, Shah S, Benson C, De Monte V, Gore-Jones V, Rossell SL, Dark F, Kisely S, Siskind D, Drumonde Melo C

Varenicline for cognitive impairment in people with schizophrenia: Systematic review and meta-analysis

Psychopharmacology 2020; 237: 11-9

View review abstract online

Comparison	**Varenicline vs. placebo**
Summary of evidence	**Moderate quality evidence (small sample, some inconsistency, precise, direct) suggests no benefits of varenicline for cognition over placebo, and varenicline may cause more nausea.**
Cognition	
Varenicline was not superior to placebo for Overall cognition: 4 studies, N = 261, SMD = -0.022, 95%CI -0.154 to 0.110, p = 0.739, I^2 = 0% Attention: 4 studies, N = 264, SMD = -0.047, 95%CI -0.199 to 0.104, p = 0.540, I^2 = 0% Executive function: 3 studies, N = 198, SMD = -0.060, 95%CI -0.469 to 0.348, p = 0.772, I^2 = 65% Processing speed: 3 studies, N = 104, SMD = 0.038, 95%CI -0.232 to 0.308, p = 0.780, I^2 = 0% Sensitivity analyses for smoking status and study duration did not alter the results.	
Risks	Varenicline was associated with more nausea than placebo. There were no differences in headaches or insomnia.
Consistency in results	Consistent, apart from executive functioning.
Precision in results	Precise
Directness of results	Direct

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 View review abstract online	
Comparison	**Second generation vs. first generation antipsychotics for long term memory.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, unable to assess consistency, direct) suggests small benefits of second-generation antipsychotics over first-generation antipsychotics for improving long-term memory.**

Long-term memory

Small, significant effect suggests people on second-generation antipsychotics showed better long-term memory than people on first-generation antipsychotics;

17 studies, N = 939, g = 0.17, 95%CI 0.04 to 0.31, p = 0.01

This effect was retained when only randomised studies were included;

12 studies, N = 722, g = 0.159, 95%CI 0.01 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 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 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 to 0.49, $p < 0.05$

Clozapine vs. first-generation: 5 studies, N = 188, g = -0.064, 95%CI -0.35 to 0.23, $p > 0.1$

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

Quetiapine vs. first-generation: 3 studies, N = 111, g = 0.259, 95%CI -0.15 to 0.66, $p > 0.1$

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

Olanzapine vs. Clozapine: 2 studies, N = 80, g = 0.260, 95%CI -0.19 to 0.71, $p > 0.1$

Olanzapine vs. Risperidone: 7 studies, N = 618, g = 0.005, 95%CI -0.15 to 0.16, $p > 0.1$

Olanzapine and Risperidone vs. Clozapine: 5 studies, N = 174, g = 0.277, 95%CI -0.04 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 to 0.87, *p* < 0.05 Olanzapine and Risperidone vs. Clozapine: 5 studies, N = 174, *g* = 0.357, 95%CI 0.04 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.

Consistency in results	No measure of consistency is reported.
Precision in results	Precise.
Directness of results	Direct

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	**Adjunctive antidepressants vs. adjunctive placebo.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, direct) 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; Global memory: 9 RCTs, N = 432, *g* = 0.077, 95%CI −0.038 to 0.19, *p* = 0.19, I^2 = 46% Auditory verbal long-term memory: 4 RCTs, N = 110, *g* = 0.06, 95%CI −0.20 to 0.31, *p* = 0.66, I^2 = 41% Visuospatial long-term memory: 4 RCTs, N = 141, *g* = 0.07, 95%CI −0.45 to 0.59, *p* = 0.79, I^2 = 66% Long-term memory: 7 RCTs, N = 214, *g* = 0.11, 95%CI −0.18 to 0.40, *p* = 0.45, I^2 = 45% Auditory verbal working memory: 4 RCTs, N = 288, *g* = 0.11, 95%CI −0.12 to 0.34, *p* = 0.34, I^2 = 0% Visuospatial working memory: 4 RCTs, N = 123, *g* = 0.06, 95%CI −0.18 to 0.31, *p* = 0.61, I^2 = 7% Working memory: 8 RCTs, N = 412, *g* = 0.07, 95%CI −0.087 to 0.24, *p* = 0.37, I^2 = 0% Auditory verbal memory: 5 RCTs, N = 308, *g* = 0.08, 95%CI −0.081 to 0.25, *p* = 0.32, I^2 = 20% Visuospatial memory: 5 RCTs, N = 160, *g* = 0.06, 95%CI −0.16 to 0.29, *p* = 0.57, I^2 = 0%	
Attention	
No significant differences between groups; 5 RCTs, N = 321, *g* = 0.02, 95%CI −0.19 to 0.23, *p* = 0.84, I^2 = 0%	
Processing speed	
No significant differences between groups; 6 RCTs, N = 344, *g* = 0.09, 95%CI −0.031 to 0.21, *p* = 0.15, I^2 = 16%	
Visuospatial processing	
No significant differences between groups; 3 RCTs, N = 94, *g* = 0.14, 95%CI −0.73 to 1.00, *p* = 0.76, I^2 = 78%	
Verbal fluency	
No significant differences between groups; 5 RCTs, N = 327, *g* = 0.019, 95%CI −0.14 to 0.18, *p* = 0.81, I^2 = 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	**First generation vs. second generation antipsychotics for neuropsychological function.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, precise, consistent, direct) 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;

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: $p > 0.05$)

Processing Speed

A small, significant effect of improved processing speed with second generation antipsychotics;

15 studies, N = 451, g = 0.21, 95%CI 0.07 to 0.35, $p = 0.003$ (Q: $p > 0.05$)

Post-treatment, a small effect size suggests patients receiving clozapine, olanzapine or risperidone showed improved processing speed;

Clozapine: 16 studies, N = 326, g = 0.35, CI not reported, $p < 0.006$ (Q: $p > 0.05$)

Olanzapine: 12 studies, N = 648, *g* = 0.43, CI not reported, *p* < 0.006 (Q: *p* > 0.05)
Risperidone: 9 studies, N = 299, *g* = 0.30, CI not reported, *p* < 0.006 (Q: *p* > 0.05)
No improvements were reported for patients on quetiapine;
Quetiapine: 6 studies, N = 107, *g* = 0.35, CI not reported, *p* > 0.05 (Q: *p* > 0.05)
Verbal fluency
A small, significant effect of improved verbal fluency with second generation antipsychotics;
15 studies, N = 449, *g* = 0.16, 95%CI 0.02 to 0.30, *p* = 0.024 (Q: *p* > 0.05)
Post-treatment, medium effect sizes show improved performance in patients receiving olanzapine, clozapine or quetiapine;
Quetiapine: 6 studies, N = 107, *g* = 0.63, CI not reported, *p* < 0.006 (Q: *p* > 0.05)
Clozapine: 15 studies, N = 319, *g* = 0.44, CI not reported, *p* < 0.006 (Q: *p* > 0.05)
Olanzapine: 11 studies, N = 651, *g* = 0.25, CI not reported, *p* < 0.006 (Q: *p* > 0.05)
Patients receiving risperidone showed no significant improvement post medication;
Risperidone: 5 studies, N = 207, *g* = 0.06, CI not reported, *p* > 0.05 (Q: *p* > 0.05)
Learning
A small, significant effect of improved learning with second generation antipsychotics;
14 studies, N = 442, *g* = 0.24, 95%CI 0.10 to 0.38, *p* < 0.001 (Q: *p* > 0.05)
Post-treatment, a medium effect size shows patients receiving olanzapine, clozapine or risperidone had improved learning;
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 study, 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 (medium to large samples, precise, consistent, direct) 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 between groups in executive function, verbal fluency, motor skills, or processing speed.**
Global cognition	
Small, significant effect suggests improved global cognitive with low dose haloperidol, but not high dose haloperidol compared to second generation antipsychotics; All studies: 14 studies, N = 611, g = 0.18, 95%CI 0.08 to 0.28, $p < 0.05$ Low dose (< 10mg): 6 studies, N = 392, g = 0.20, 95%CI 0.07 to 0.33, $p < 0.05$ High dose: 6 studies, N = 173, g = 0.13, 95%CI -0.05 to 0.31, $p > 0.05$ 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; All studies: 11 studies, N = 538, g = 0.32, 95%CI 0.19 to 0.43, $p < 0.05$ Low dose: 6 studies, N = 371, g = 0.37, 95%CI 0.23 to 0.51, $p < 0.05$ High dose: 5 studies, N = 167, g = 0.20, 95%CI 0.00 to 0.40, $p < 0.05$ 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;	

All studies: 7 studies, N = 420, *g* = 0.27, 95%CI 0.14 to 0.40, *p* < 0.05 Low dose: 3 studies, N = 252, *g* = 0.22, 95%CI 0.05 to 0.39, *p* < 0.05 High dose: 3 studies, N = 141, *g* = 0.28, 95%CI 0.06 to 0.50, *p* < 0.05 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; All studies: 5 studies, N = 313, *g* = 0.20, 95%CI 0.05 to 0.35, *p* < 0.05 Low dose: 4 studies, N = 294, *g* = 0.22, 95%CI 0.06 to 0.38, *p* < 0.05 *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 the 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 data are 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** View review abstract online	
Comparison	**First generation vs. second generation antipsychotics for people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests olanzapine and risperidone may improve cognition more than haloperidol.** **There were fewer extrapyramidal side effects and akathisia with olanzapine and risperidone compared to haloperidol, although olanzapine and risperidone caused more weight gain. There was less use of benzodiazapines with olanzapine compared to haloperidol, and moderate quality evidence (imprecise) also suggests less use of anticholinergeric 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 = 1,932, *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 anticholinergeric 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 0.61, $p < 0.05$). Risperidone was better than sulpiride (1 RCT, N = 58, g -1.18, 95%CI -1.74 to -0.63, $p < 0.01$).
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 benzodiazapines, 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* = Hedges' g standardised mean difference, GAF = Global Assessment of Function scale, I^2 = 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, RR = relative risk, SANS = Scale for the Assessment of Negative Symptoms, SMD = standardised mean difference, TMT-A/B = Trail Making Test subsection A or B, vs. = versus, WCST = Wisconsin Card Sorting Task

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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[15].

† 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[15].

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[16]. 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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. 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.

‡ 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.

§ 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[17].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Mishara AL, Goldberg TE (2004): A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biological Psychiatry* 55: 1013-22.
4. Thornton AE, Van Snellenberg JX, Sepehry AA, Honer W (2006): The impact of atypical antipsychotic medications on long-term memory dysfunction in schizophrenia spectrum disorder: a quantitative review. *Journal of Psychopharmacology* 20: 335-46.
5. Woodward ND, Purdon SE, Meltzer HY, Zald DH (2005): A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *International Journal of Neuropsychopharmacology* 8: 457-72.
6. Woodward ND, Purdon SE, Meltzer HY, Zald DH (2007): A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects. *Schizophrenia Research* 89: 211-24.
7. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU (2013): 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* 16: 1205-18.
8. Desamericq G, Schurhoff F, Meary A, Szoke A, Macquin-Mavier I, Bachoud-Levi AC*, et al.* (2014): Long-term neurocognitive effects of antipsychotics in schizophrenia: A network meta-analysis. *European Journal of Clinical Pharmacology* 70: 127-34.
9. Nielsen RE, Levander S, Kjaersdam Telleus G, Jensen SOW, Ostergaard Christensen T, Leucht S (2015): Second-generation antipsychotic effect on cognition in patients with schizophrenia-a meta-analysis of randomized clinical trials. *Acta Psychiatrica Scandinavica* 131: 185-96.
10. Vernon JA, Grudnikoff E, Seidman AJ, Frazier TW, Vemulapalli MS, Pareek P*, et al.* (2014): Antidepressants for cognitive impairment in schizophrenia - A systematic review and meta-analysis. *Schizophrenia Research* 159: 385-94.
11. Clissold M, Crowe SF (2019): Comparing the effect of the subcategories of atypical antipsychotic medications on cognition in schizophrenia using a meta-analytic approach. *Journal of clinical and experimental neuropsychology* 41: 26-42.
12. Kishi T, Ikuta T, Oya K, Matsunaga S, Matsuda Y, Iwata N (2018): Anti-dementia drugs for psychopathology and cognitive impairment in schizophrenia: A systematic review and meta-analysis. *International Journal of Neuropsychopharmacology* 21: 748-57.
13. Jin Y, Wang Q, Wang Y, Liu M, Su A, Geng Z*, et al.* (2017): Alpha7 nAChR agonists for cognitive deficit and negative symptoms in schizophrenia: A meta-analysis of randomized double-blind controlled trials. *Shanghai Archives of Psychiatry* 29: 191-9.
14. Tanzer T, Shah S, Benson C, De Monte V, Gore-Jones V, Rossell SL*, et al.* (2020): Varenicline for cognitive impairment in people with schizophrenia: Systematic review and meta-analysis. *Psychopharmacology* 237: 11-9.
15. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
16. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
17. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*