Trends
in Psychiatry and Psychotherapy

JOURNAL ARTICLE PRE-PROOF
(as accepted)

Review Article

Haloperidol versus Second-generation Antipsychotics on the cognitive performance of individuals with schizophrenia and related disorders: pairwise meta-analysis of randomized controlled trials

Daniel Prates Baldez, Tais Boeira Biazus, Francisco Diego Rabelo-da-Ponte, Guilherme Pedro Nogaro, Dayane Santos Martins, João Pedro Soledade Signori, Vanessa Gnielka, Ives Cavalcante Passos, Letícia Sanguinetti Czepielewski, Maurício Kunz

http://doi.org/10.47626/2237-6089-2023-0664

Original submitted Date: 06-May-2023

Accepted Date: 21-Jun-2023

Haloperidol versus Second-generation Antipsychotics on the cognitive performance of individuals with schizophrenia and related disorders: pairwise meta-analysis of randomized controlled trials

Daniel Prates Baldez[a,b], Tais Boeira Biazus[b], Francisco Diego Rabelo-da-Ponte[d], Guilherme Pedro Nogaro[a], Dayane Santos Martins[a,c], João Pedro Soledade Signori[a], Vanessa Gnielka[a], Ives Cavalcante Passos[a,b], Letícia Sanguinetti Czepielewski [a,c], Maurício Kunz [a,b]

[a] Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos, 2350, Prédio Anexo, 90035-903 - Porto Alegre, Brazil

[b] Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2400, 90035-003 - Porto Alegre, Brazil

[c] Programa de Pós-Graduação em Psicologia, Instituto de Psicologia, Universidade Federal do Rio Grande do Sul, Brazil. Rua Ramiro Barcelos, 2600, 90035-003 - Porto Alegre, Brazil

[d] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom.

***Corresponding author:** Daniel Prates Baldez

Hospital de Clínicas de Porto Alegre/CPE, Laboratory of Molecular Psychiatry, Rua Ramiro Barcelos, 2350, Prédio Anexo, 90035-003 - Porto Alegre, Brazil; tel: +55-51- 33598845, fax: +55-51-33598846, e-mail: danielpratesbdz@gmail.com

This study was previously presented at a scientific event, as a poster entitled "Haloperidol versus second-generation antipsychotics on cognitive performance of individuals with schizophrenia and related disorders: paired meta-analysis of randomized controlled trials". Event name: III Gaucho Pharmacology Symposium. Institution: Federal University of Rio Grande do Sul. Date: November 10, 2022

ABSTRACT

Introduction. Despite previous literature, the superiority of Second-generation Antipsychotics (SGAs) relative to First-generation Antipsychotics– especially haloperidol – on cognitive management in schizophrenia is still controversial. Thus, we aimed to compare the effects of haloperidol versus SGAs on the cognitive performance of individuals with schizophrenia or related disorders**. Methods.** We conducted an updated systematic review and nine pairwise meta-analyses of double-blinded randomized controlled trials published up to October 30th, 2022, using Medline, Web of Science, and Embase. **Results**. Twenty-eight trials were included, enrolling 1,932 individuals. Compared to SGAs, haloperidol performed worse on cognitive composite (MD -0.13; 95% CI: -0.33 to -0.03; MD = mean difference, CI = confidence interval), processing speed (MD -0.17; 95% CI: -0.28 to -0.07), attention (MD -0.14; 95% CI: -0.26 to -0.02), motor performance (MD -0.17; 95% CI: -0.31 to -0.03), memory and verbal learning (MD -0.21; 95% CI: -0.35 to -0.08), and executive function (MD -0.27; 95% CI: -0.43 to -0.11). In contrast, there were no significant differences between SGAs and haloperidol on working memory (MD 0.10; 95% CI: -0.08 to 0.27), visual learning (MD 0.08; 95% CI: -0.05 to 0.21), social cognition (MD 0.29; 95% CI: -0.30 to 0.88), and visuoconstruction (MD 0.17; 95% CI: -0.04 to 0.39). **Conclusion**. Haloperidol had poorer performance in global cognition and in some cognitive domains, but with small effect sizes. Therefore, it was not possible to conclude that haloperidol is certainly worse than SGAs in the long-term cognitive management of schizophrenia.

Keywords: cognition, schizophrenia, haloperidol, antipsychotics, meta-analysis.

1. **Introduction**

Impairments in cognitive functions are considered a central feature and an important predictor of functionality in schizophrenia[1,2]. Individuals with schizophrenia are likely to perform poorer in several cognitive domains, including global cognitive scores[3–5]. The main challenge is establishing pharmacological treatments that effectively improve or reduce cognitive deficits in psychotic disorders. In the last decades, numerous studies have shown that Second-Generation Antipsychotics (SGAs) enhance cognitive performance in patients with psychosis, with better results when compared to First-Generation Antipsychotics (FGAs)[6–11]. Previous meta-analyses have confirmed the superiority of SGAs, but with a modest-to-moderate effect size[12–14].

Despite several evidence suggesting SGAs as a better option for long-term treatment in schizophrenia, especially considering their relative superiority to cognitive symptoms, the inferiority of FGAs is still controversial. A meta-analysis published by Mishara and Goldberg (2004) showed that the continued use of FGAs provided significant gains in multiple cognitive domains[15]. Moreover, more extensive clinical trials have also questioned the cognitive superiority of SGAs. The European First Episode Schizophrenia Trial study (EUFEST) analyzed 498 patients with schizophreniform disorder or first-episode schizophrenia and identified a moderate cognitive improvement in the cognitive tests for both SGAs and FGAs, finding no difference in the magnitude of improvement between haloperidol and SGAs[16]. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a double-blind randomized controlled trial (RCT) with neuropsychological testing of 817 individuals with schizophrenia, showed a similar effect of perphenazine, a FGAs, compared to olanzapine, risperidone, quetiapine, and ziprasidone[17]. Therefore, it is unclear the inferiority or non-inferiority of FGAs in cognitive management on psychosis.

Comparing the cognitive effects between FGAs and SGAs is of paramount importance, since both classes were widely used, but with different prevalence around the world. Several low- and middle-income countries keep using FGAs as one of the first options as maintenance treatment in psychotic disorders. The latest World Mental Health Report showed that some SGAs, such as risperidone and clozapine, were only included in less than 35% of national essential medicines lists in low-income countries[18]. In Brazil, for instance, haloperidol is the main antipsychotic considered essential medicines for public pharmaceutical assistance in the Brazilian Unified Health System (SUS), a national system that ensures access to medicines and health services for the entire population, especially for people with less financial resources[19]. In contrast, SGAs (clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) are considered specialized medications for pharmaceutical assistance, with more restricted access in the Brazilian public health system [19].

We previously conducted a systematic review and network meta-analyses to compare the individual effect of fourteen antipsychotics on the cognitive performance of individuals with schizophrenia and psychotic disorders[20]. In this study, we showed that haloperidol has the poorest outcomes in the treatment of cognitive symptoms, but with small effect sizes when compared to SGAs. Thus, considering these unfavorable – and inconclusive – findings, and the widespread use of haloperidol, we designed an updated, complementary analysis to directly compare the cognitive effects of haloperidol and other antipsychotics in the treatment of schizophrenia. The current study extends our previous analyses by assessing whether haloperidol remains with poorer cognitive outcomes even when compared to all other SGAs pooled together. This strategy aims to assess whether haloperidol should be considered a second-line treatment for the cognitive symptoms of schizophrenia.

2. **Methods**

As mentioned above, the present study is a secondary and update analysis of the systematic review and network meta-analyses previously published by our team[20]. The present study was already described in the original protocol (PROSPERO, number CRD42019142330)

2.1. **Systematic Review**

2.1.1. Search strategies

We conducted the systematic review using three databases: Medline (PubMed), Web of Science, and Embase. We first included all studies published up to November 30th, 2018, and we updated data on October 30th, 2022. The search included the following general terms: schizophrenia, psychosis, mood disorder, bipolar disorder, antipsychotic, cognition, memory, attention, working memory, executive function, neuropsychology, and randomized controlled trial. These terms were expanded by the synonym search, and the specific antipsychotic names were also included. We also analyzed all the bibliographic references of the selected studies and all systematic reviews previously published. We followed the Cochrane Handbook for Systematic Reviews of Interventions[21] and the PRISMA guidelines for systematic reviews and meta-analyses[22]. We point out that the original search strategy included different psychotic diagnoses to enable comparative analyses between schizophrenia and other disorders. However, in the current analysis, we only included studies related to schizophrenia, excluding studies with patients with bipolar disorder or psychotic depression. The PRISMA Checklist and the complete search strategies are available in Supplementary Materials 1 and 2.

2.1. Inclusion Criteria

We included only randomized double-blind controlled trials (RCTs). All studies analyzed individuals between the ages of 18 and 65 diagnosed with schizophrenia or related disorders (schizoaffective disorder and schizophreniform disorder) according to DSM-III, DSM-IV, or DSM-IV-TR criteria. We included trials with a follow-up greater than or equal to four weeks that compared haloperidol with one or more other antipsychotics – all administered orally. We included studies that measured cognitive performance using neuropsychological tests that considered at least one of the following criteria: (1) the test is completely described in the main compendium of neuropsychology[23,24], (2) the test is validated in the main cognitive assessment batteries in schizophrenia[25–28], and (3) the test presents a detailed description of its procedures in an article published in a high impact journal.

2.1.3. Exclusion Criteria

We excluded unblinded trials, co-intervention or adjunct therapy studies, studies with cognitive assessments performed by questionnaires or psychometric scales, trials with participants with neuropsychiatric comorbidities (attention-deficit/hyperactivity disorder, intellectual developmental disorder, and dementia), trials that included individuals with substance-use disorder, and studies that solely examined injectable antipsychotics. We also excluded studies that compared only SGAs versus SGAs, only FGAs versus FGAs, and trials that compared a unique antipsychotic with placebo.

2.1.4. Studies' selection

The screening phase (title and abstracts reading) and eligibility phase (full article reading) were executed independently by two authors (DPB and TBB), and the inconsistencies were analyzed by a third author (FDRP). Data extraction was also carried out by two independent researchers (DPB and GPN). The selections of the cognitive tests were conducted

by three trained neuropsychologists (FDRP, DSM, and LSC). The cognitive tests were allocated on cognitive domains by two investigators (FDRP and DSM), also independently, according to the major neuropsychology compendiums [23,24], the main cognitive assessment batteries in schizophrenia [25–28], and the test definition present in its validation articles (Supplementary Material 3). A third investigator (LSC) analyzed the divergences. We completed the original systematic review in November 2018, but the final analyses were conducted in October 2022 after the update.

2.2. Meta-analyses

Pairwise meta-analyses were carried out to compare the effect of haloperidol and all other antipsychotic agents on cognition. Antipsychotics were primarily classified into FGAs and SGAs[29], but we have included drugs from both types. We considered the following cognitive domains: attention, executive function, memory and verbal learning, motor performance, processing speed, social cognition, visual learning, visuoconstruction, and working memory. A cognitive composite score was estimated as described below. The selection of the cognitive domains was based on scientific literature [23–28].

We performed one meta-analysis for each cognitive domain through the results of cognitive tests (means and standard deviations) applied in the selected studies. We contacted the study's author in the absence of any published data, and we performed imputation data when the dispersion measures were not available (e.g., standard deviation). The imputation data considered the dispersion measures presented in other included studies (Supplementary Material 4). Studies that evaluated the same sample were grouped as a "single study" to avoid duplication in the statistical analysis. Besides, when different neuropsychological tests referring to a single cognitive domain were applied to the same sample, we considered only the cognitive

test with the largest sample size. More details are also presented in the Supplementary Material 4.

In meta-analyses with continuous outcomes, there are different ways of choosing which variable (measure) of a study (trial) will be used for the meta-analysis. We considered the difference (subtraction) between the mean obtained at the study's endpoint and the mean obtained at the study's baseline (Δ or change from baseline) as the measure to be meta-analyzed. We estimated one Δ for each cognitive test applied in each study's arm. The Δ was converted into z-scores (standardized Δ) to allow the results of different tests (with different metrics and units of measure) to be later combined into a single result from a cognitive domain. The standard deviation of Δ was estimated with a correlation index of 0.5 [30].

After measuring the standardized Δ, we calculated the cognitive domain score through the weighted arithmetic average of the standardized Δs, weighted for the number of patients (n) submitted to each test. This weighting was used because we consider that respective tests equally evaluate the cognitive domain. The association between neuropsychological tests and cognitive domains is described in Supplementary Material 3.

We estimated a composite cognitive score for studies that have not previously calculated this measure. The composite score was estimated through the simple arithmetic average of the domains included in the study, giving the same weight to all domains. The composite score was only estimated in studies that evaluated at least the following domains: attention, executive function, memory and verbal learning, processing speed, and working memory. More details are presented in the Supplementary Material 5.

Our meta-analyses were performed in the software R (version 4.2.1), using the package "meta". We used the inverse variance method and the random effect model to calculate the effect sizes, with a confidence interval of 95% (CI 95%). The summary measures were

estimated by mean difference (MD). We did not use the standardized mean difference (SMD) because the results of cognitive tests were previously standardized in z-scores (standardized Δ). The homogeneity was assessed by the Q and I^2 tests and the similarity was analyzed based on clinical characteristics of the included studies (Supplementary Material 6). We did not estimate publication bias because none of the direct comparisons included ten or more trials[31]. The results were presented in forest plots.

The risk of bias and the quality of evidence were assessed by the Cochrane Risk of Bias 1.0 tool[30] (Supplementary Material 7). That tool was applied by two independent authors and the disagreements were solved through discussion. The analysis was completed in October 2022.

3. **Results**

The study selection process is shown in Figure 1, the list of included studies is presented in Table 1, and the complete extraction table is presented in Supplementary Material 6. Briefly, we included 13,037 records in the first search and selected 28 studies for the meta-analysis, comprising 21 independent randomized double-blind controlled trials with 1,932 individuals. In update review, we extracted 2,364 more records; from these, only 2 articles were included to full-text reading, but none were selected for analysis – we did not find RCTs published from 2020 onwards that met our inclusion criteria. As to the selected studies, 67.29% were multicentered, 64.29% presented a follow-up under six months, 92.30% received industry sponsorship, and 89.29% allowed the sporadic use of anticholinergic during the study. Besides, 41.66% included inpatients exclusively, 29.17% included outpatients exclusively, and 29.17% included in and outpatients. We only found RCTs comparing haloperidol versus SGAs. There were no direct comparisons between haloperidol and FGAs.

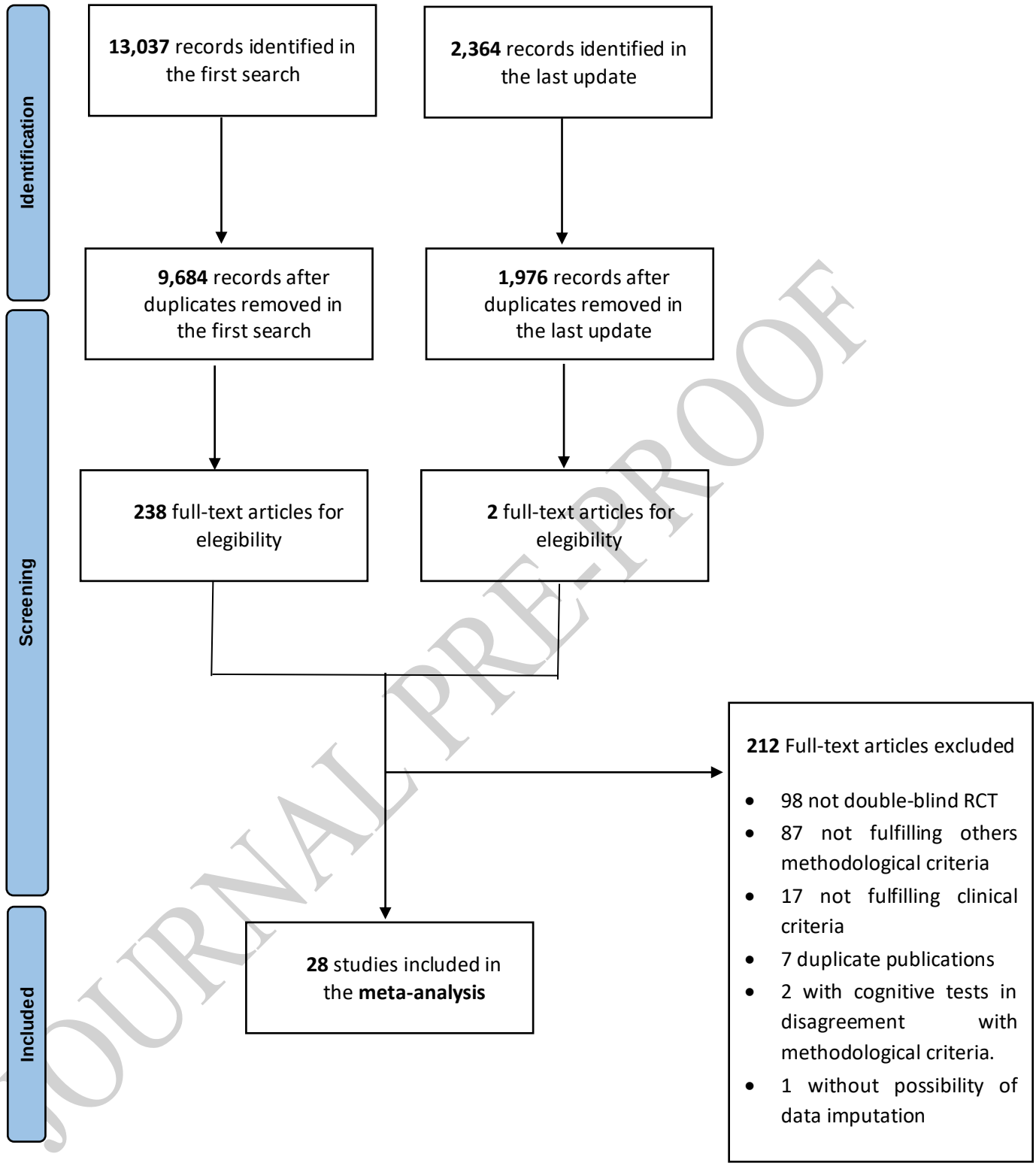


Figure 1. Study selection process.

Table 1. Simplified extraction table

First author, year	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	Drugs			Follow-up
ABDOLAHIAN, 2008 [32]								■			Risperidone (n = 35)	Haloperidol (n = 30)		24w
BILDER, 2002[6]	■	■	■	■	■	■	■	■		■	Clozapine (n = 24)	Haloperidol (n = 25)	Olanzapine (n = 26)	14w
											Risperidone (n = 26)			
BOULAY, 2007[33]	■	■	■				■				Olanzapine (n = 14)	Haloperidol (n = 11)		8w
BUCHANAN, 1994 [34]				■		■		■			Clozapine (n = 19)	Haloperidol (n = 19)		10w
GALLHOFER, 2007 [35]	■							■			Sertindole (n = 17)	Haloperidol (n = 17)		12w
GREEN, 2002 [36]		■	■	■	■		■	■			Risperidone (n = 32)	Haloperidol (n = 30)		2y
HARVEY, 2005 [37]	■	■			■	■		■			Risperidone (n = 169)	Haloperidol (n = 169)		12w
KEEFE, 2004[11] †	■	■	■		■	■	■	■		■	Olanzapine (n = 89)	Haloperidol (n = 78)		12w
KEEFE, 2006b[38] †	■	■	■		■	■	■	■		■	Olanzapine (n = 18)	Haloperidol (n = 8)		104w
KEEFE, 2006a [10]	■	■	■				■	■		■	Olanzapine (n = 159)	Haloperidol (n = 97)	Risperidone (n = 158)	52w
GREEN, 1997 [36]╬	■		■		■		■	■	■		Risperidone (n = 30)	Haloperidol (n = 29)		8w
KEE, 1998 [39]╬	■		■		■		■	■	■		Risperidone (n = 9)	Haloperidol (n = 9)		8w
KERN, 1998 [40]╬	■		■		■		■	■	■		Risperidone (n = 27)	Haloperidol (n = 29)		8w
KERN, 1999 [41]╬	■	■	■		■		■	■	■		Risperidone (n = 32)	Haloperidol (n = 32)		8w
MCGURK, 1997 [42]╬	■		■		■		■	■	■		Risperidone (n = 28)	Haloperidol (n = 28)		4w
MCGURK, 2004 [43]╬	■	■	■		■		■	■	■		Risperidone (n = 26)	Haloperidol (n = 27)		4w
KRAKOWSKI, 2008 [44]	■		■	■		■		■		■	Clozapine (n = 33)	Haloperidol (n = 33)	Olanzapine (n = 34)	12w
LEE, 2007 [45]								■			Risperidone (n = 10)	Haloperidol (n = 10)		8w
LINDENMAYER, 2007 [46]	■		■		■		■	■		■	Olanzapine (n = 16)	Haloperidol (n = 19)		12w
LIU, 2000 [47]		■									Risperidone (n = 19)	Haloperidol (n = 19)		12w
PURDON, 2000 [48]	■	■	■	■	■	■		■		■	Olanzapine (n = 21)	Haloperidol (n = 23)	Risperidone (n = 21)	54w
PURDON, 2001 [49]	■	■	■	■	■	■		■		■	Quetiapine (n = 13)	Haloperidol (n = 12)		24w
RÉMILLARD, 2005 [50] §	■	■			■			■			Risperidone (n = 15)	Haloperidol (n = 16)		12m
RÉMILLARD, 2008 [51] §	■	■			■			■			Risperidone (n = 14)	Haloperidol (n = 14)		12m
ROSENHECK, 2003 [52]			■		■						Olanzapine (n = 159)	Haloperidol (n = 150)		12m
SERGI, 2007 [53]	■	■	■		■		■	■	■	■	Risperidone (n = 40)	Haloperidol (n = 20)	Olanzapine (n = 40)	8w
SMITH, 2001 [54]								■			Olanzapine (n = 16)	Haloperidol (n = 13)		8w
VELLIGAN, 2002 [55]	■	■			■			■		■	Quetiapine300 (n = 17)	Haloperidol (n=15)	Quetiapine600 (n = 26)	24w

This table shows the complete list of included studies. The ten meta-analyses are represented in columns M1 to M10, according to the legend below. The studies included in a meta-analysis

are highlighted in the respective column. The studies that analyze the same sample are paired with the same symbol in superscript (†,‡,§). All studies were cited in the references section.

As to the complete sample, 81.19% had a diagnosis of schizophrenia (11.83% had schizoaffective disorder, and 6.98% had schizophreniform disorder), 82.14% had previous psychotic episodes, 85.71% had previous history of antipsychotic use, and 67.86% were considered non-refractory to treatment. Moreover, the mean duration of illness was 12.92 years (SD 6.97 years), and the mean age at onset of illness was 24.08 years (SD 7.39 years). Regarding the symptoms' severity, the sample had an average score of 81.78 (SD 13.98) on Positive and Negative Syndrome Scale (PANSS). We point out that the means described above were estimated considering only the studies that present the respective data. Studies without available data were excluded from the calculation of the percentages and means.

The main findings are presented below. The forest plots are presented in Figures 2, 3, and 4.

Figure 2a. Processing Speed

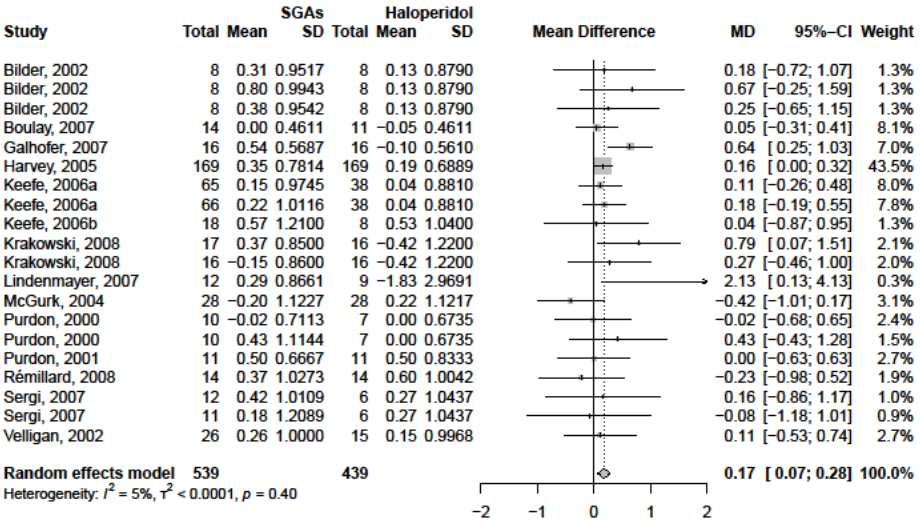


Figure 2b. Attention

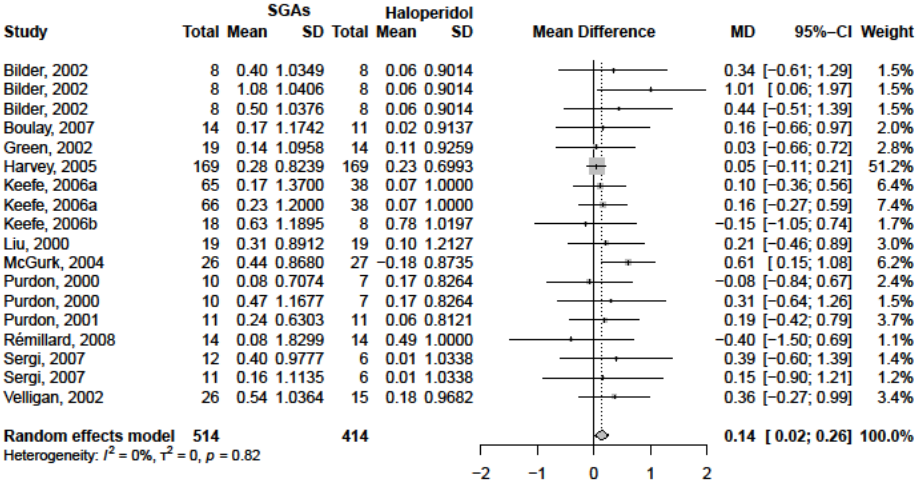


Figure 2c. Motor Performance

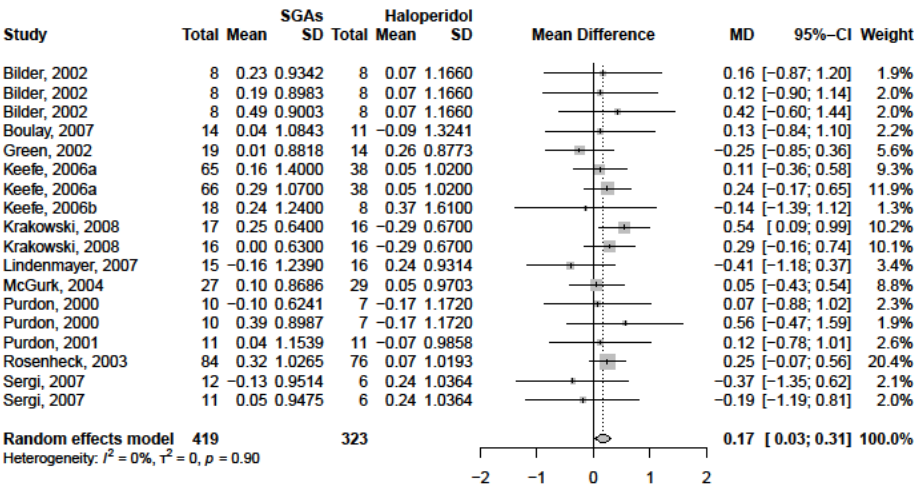


Figure 3a. Visuoconstruction

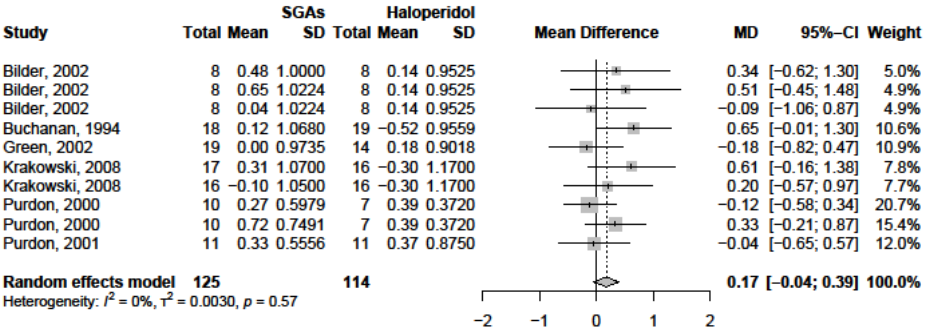


Figure 3b. Memory and Verbal Learning

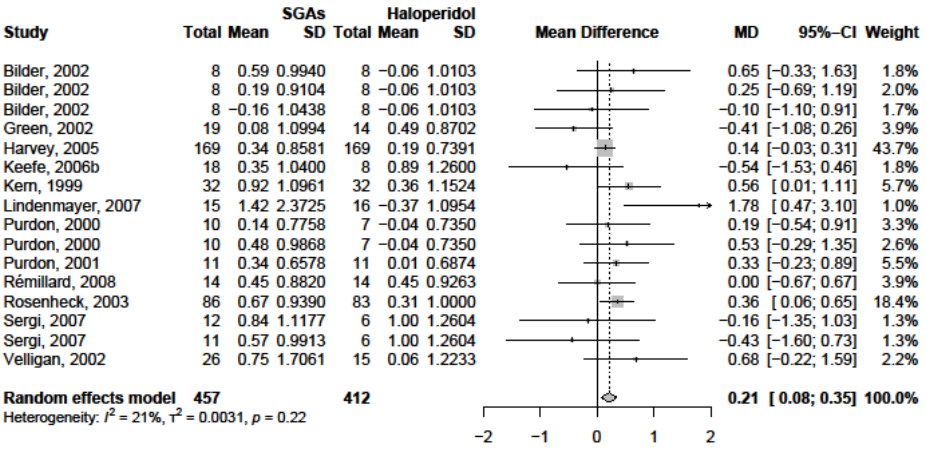


Figure 3c. Visual Learning

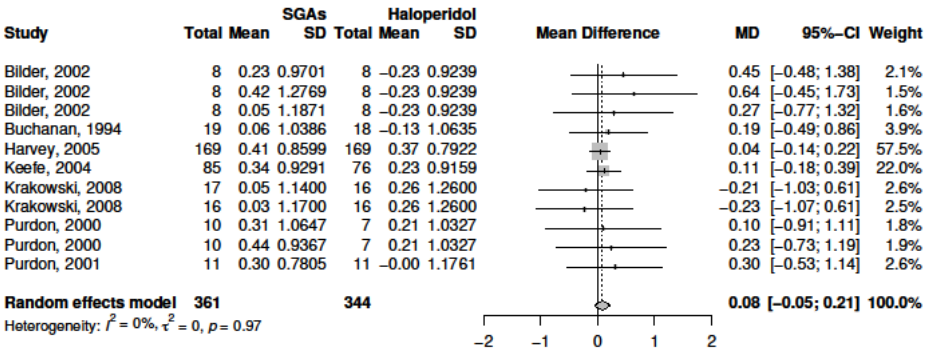


Figure 4a. Working Memory

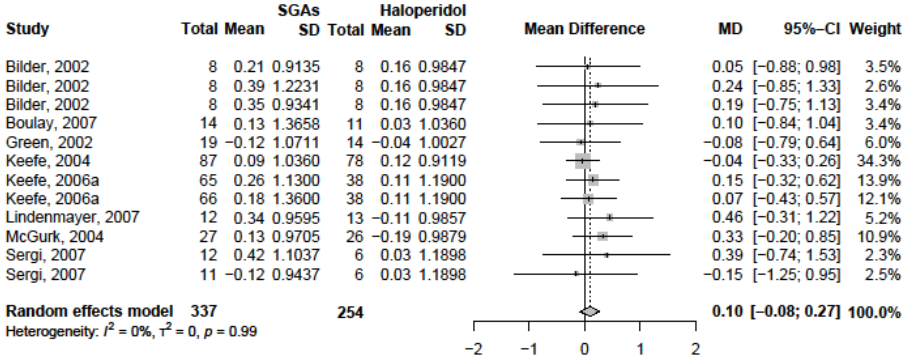


Figure 4b. Executive Function

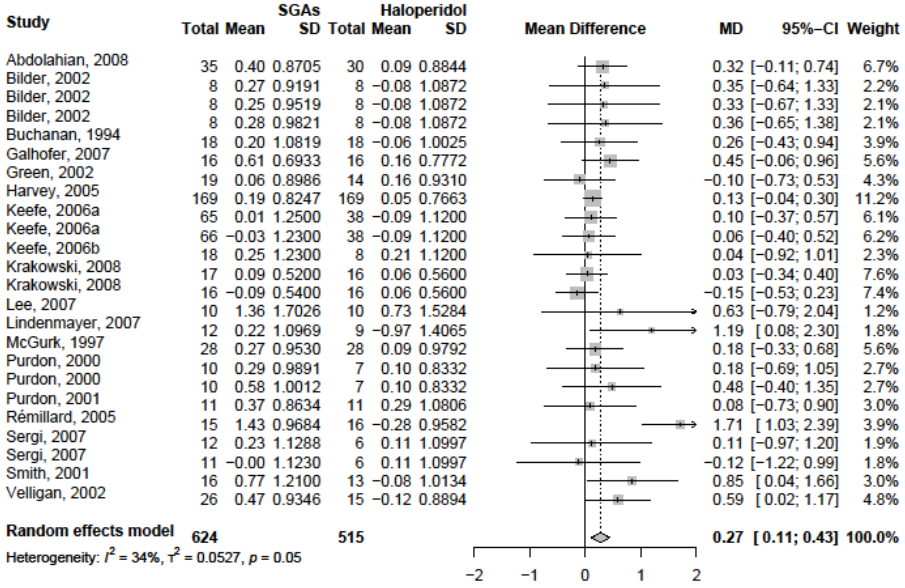
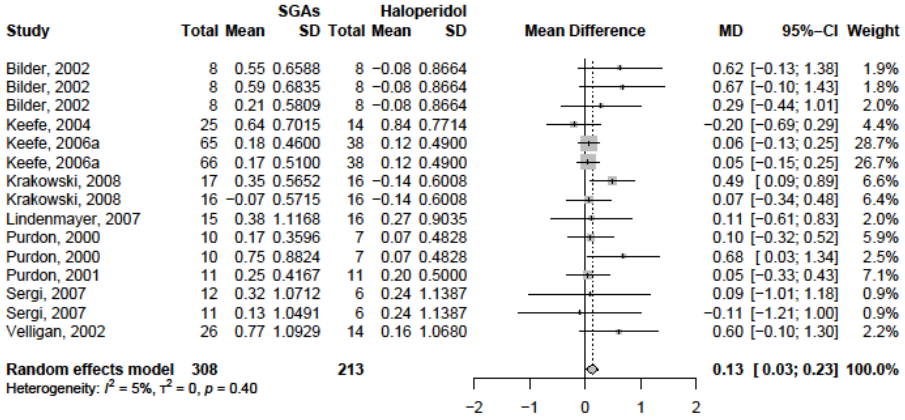


Figure 4c. Cognitive Composite Score



Figures 2, 3 and 4. Forest plots for cognitive domains and cognitive composite score.

Processing Speed: 14 trials were included, with 978 individuals. The mean age was 37.44 years (SD 8.75 years) and 74.00% males. The analysis included 6 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, risperidone, and sertindole. SGAs performed better than haloperidol (MD 0.17; 95% CI: 0.07 to 0.28). The sample showed low and non-significant heterogeneity (I^2=5%; p = 0.40). The results are shown in Figure 2a.

Each figure is a forest plot comparing atypical antipsychotics versus haloperidol in a respective cognitive domain, namely: processing speed (Figure 2a), attention (Figure 2b), motor performance (Figure 2c), visuoconstruction (Figure 3a), memory and verbal learning (Figure 3b), visual learning (Figure 3c), working memory (Figure 4a), executive function (Figure 4b), and cognitive composite score (Figure 4c).

In forest plots, each row represents an included clinical trial (for trials with only two arms). When the trial has three or more arms (studies that tested three or more drugs separately), each row represents a possible comparison between the study's drugs, making the same trial occupy more than one row.

For trials with three or more arms, all possible pairwise comparisons (between the drugs of each arm) must be performed in the meta-analysis. However, in our analysis, we considered only comparisons that included haloperidol and atypical agent. For instance, if a clinical trial included haloperidol, olanzapine and quetiapine, we only considered haloperidol versus olanzapine and haloperidol versus quetiapine comparisons, excluding olanzapine versus quetiapine.

For trials with three or more arms, the sample size (n) of each drug in a pairwise comparison is estimated by the ratio (division) between the total number of individuals who used the drug and the number of comparisons involving the respective drug. Hypothetically, in a trial with four arms (A, B, C, D), six comparisons are performed (A-B, A-C, A-D, B-C, B-D, C-D). If 90

subjects received drug A, the sample size (n) of drug A in each comparison (A-B, A-C and A-D) is 30 (90/30).

Legends: *Total* = number of participants, *Mean* = continuous variable considered in the metanalysis estimate, *SD* = Standard Deviation, *MD* = difference between means (or mean difference), *95%-CI*: 95% Confidence Interval, *Weight* = study' weight in the metanalysis.

Legends: M1 = processing speed domain, M2 = attention domain, M3 = motor performance domain, M4 = visuoconstruction domain, M5 = memory and verbal learning domain, M6 = visual learning domain, M7 = working memory domain, M8 = executive function domain, M9 = social cognition domain, M10 = cognitive composite score, n = number of individuals included in the study's arm, m = months, y = years, w = weeks.

Attention: 13 trials were included, with 928 individuals. The mean age was 38.26 years (SD 8.86 years) and 72.39% males. The analysis included 5 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, and risperidone. SGAs performed better than haloperidol (MD 0.14; 95% CI: 0.02 to 0.26). The sample showed non-significant heterogeneity (I^2=0%; p = 0.82). The results are shown in Figure 2b.

Motor performance: 12 trials were included, with 742 individuals. The mean age was 38.31 years (SD 8.66 years) and 80.97% males. The analysis included 5 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, and risperidone. SGAs performed better than haloperidol

(MD 0.17; 95% CI: 0.03 to 0.31). The sample did not show significant heterogeneity (I^2=0%; p = 0.90). The results are shown in Figure 2c.

Visuoconstruction: 6 trials were included, with 239 individuals. The mean age was 35.91 years (SD 8.68 years) and 80.78% males. The analysis included 5 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, and risperidone. There was no statistically significant difference between the SGAs and haloperidol (MD 0.17; 95% CI: -0.04 to 0.39). The sample did not show significant heterogeneity (I^2=0%; p = 0.57). The results are shown in Figure 3a.

Memory and verbal learning: 12 trials were included, with 869 individuals. The mean age was 38.64 years (SD 8.57 years) and 80.42% males. The analysis included 5 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, and risperidone. SGAs performed better than haloperidol (MD 0.21; 95% CI: 0.08 to 0.35). The sample showed low and non-significant heterogeneity (I^2=21%; p = 0.22). The results are shown in Figure 3b.

Visual learning: 7 trials were included, with 705 individuals. The mean age was 32.38 years (SD 8.03 years) and 75.16% males. The analysis included 5 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, and risperidone. There was no statistically significant difference between SGAs and haloperidol (MD 0.08; 95% CI: -0.05 to 0.21). The sample did not show significant heterogeneity (I^2=0%; p = 0.97). The results are shown in Figure 3c.

Working memory: 8 trials were included, with 591 individuals. The mean age was 39.47 years (SD 8.63 years) and 77.69% males. The analysis included 4 antipsychotics: clozapine,

haloperidol, olanzapine, and risperidone. There was no statistically significant difference between SGAs and haloperidol (MD 0.10; 95% CI: -0.08 to 0.27). The sample did not show significant heterogeneity (I^2=0%; p = 0.99). The results are shown in Figure 4a.

Executive functions: 18 trials were included, with 1139 individuals. The mean age was 37.17 years (SD 8.29 years) and 75.91% males. The analysis included 6 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, risperidone, and sertindole. SGAs performed better than haloperidol (MD 0.27; 95% CI: 0.11 to 0.43). The sample showed moderate heterogeneity but was not statistically significant (I^2=34%; p = 0.05). The results are shown in Figure 4b.

Social cognition: we found only 2 clinical trials that met our inclusion criteria. The complete sample (53 subjects) included only 3 drugs (haloperidol, olanzapine, and risperidone). Therefore, we decided not to perform the meta-analysis for social cognition.

Cognitive composite score: 9 trials were included, with 521 individuals. The mean age was 37.01 years (SD 8.56 years) and 75.76% males. The analysis included 5 antipsychotics: clozapine, haloperidol, olanzapine, quetiapine, and risperidone. SGAs performed better than haloperidol (MD 0.13; 95% CI: 0.03 to 0.23). The sample showed low and non-significant heterogeneity (I^2=5%; p = 0.40). The results are shown in Figure 4c.

4. **Discussion**

This study presents the largest meta-analyses comparing the effect of haloperidol and SGAs on the cognitive performance of individuals with schizophrenia. Our results demonstrated poorer performance of haloperidol on cognitive composite score and in the following domains: processing speed, attention, motor performance, memory and verbal learning, and executive function. However, these comparisons had small effect sizes, and there were no statistically significant differences between haloperidol and SGAs on working memory, visual learning, and visuoconstruction.

Previous meta-analyses of clinical studies demonstrated better results to SGAs on cognitive management of schizophrenia and related disorders. Keefe et al. (1999) revealed that SGAs are superior to FGAs to improve cognitive functions in individuals with schizophrenia, especially on verbal fluency, digit-symbol substitution, motor functions, and executive functions[14]. Woodward et al. (2005) also suggested that SGAs are better at improving overall cognitive function, especially processing speed and visual and verbal learning[12]. Guilera et al. (2009) ratified the SGAs' superiority on the global cognitive index, processing speed, psychomotricity, and language[56]. Désaméricq et al. (2014) showed poorer performance of haloperidol on global score (compared to quetiapine, olanzapine, and risperidone), memory (compared to ziprasidone and olanzapine), attention and processing speed (compared to quetiapine, ziprasidone, olanzapine, and amisulpride), and executive function (compared to quetiapine and olanzapine)[13]. Other previous reviews also corroborate these findings. Grada and Dinan (2007) suggested that SGAs had more efficacy in ameliorating inhibition, sustained attention, and set-shifting, all components of executive function[57]. Meltzer et al. (1996) demonstrated that clozapine - a prototype of SGAs - is especially superior to FGAs in some types of cognition, especially verbal fluency[58]. Lee and Park (2006) associated SGAs with better performance in memory and attention[59].

In contrast, two major RCTs questioned the advantages of SGAs in cognitive performance in schizophrenia. The EUFEST trial also found no differences among haloperidol (FGA) and amisulpride, olanzapine, quetiapine, and ziprasidone on a composite cognitive score[16]. Despite its large sample size, the EUFEST study had two limitations to be considered: (1) this was an open-label trial, which may have influenced the outcomes, and (2) the cognitive outcomes were assessed by a short cognitive battery, with only five neuropsychological tests, which may not have been able to estimate a global cognition evaluation adequately. The second study was the CATIE trial, that reported no differences in effectiveness between perphenazine (FGA) and olanzapine, quetiapine, risperidone, and ziprasidone (SGAs) on a cognitive composite score, processing speed, reasoning, working memory, verbal memory, and vigilance[17].

Although our study had shown some unfavorable results for haloperidol, our meta-analysis did not find a worse performance of haloperidol on working memory, visual learning, and visuoconstruction. Previously, Woodward et al. (2005) and Guilera et al. (2009) also did not identify the superiority of SGAs on working memory, visual learning, and visuospatial processing[12,56], while Désaméricq et al. (2014) did not test these respective domains[13]. However, our findings are not theoretically grounded in preclinical studies, which tend to demonstrate poor haloperidol results in working memory tasks[60–63]. Regarding social cognition, it was not possible to perform a meta-analysis because we found only two double-blind RCTs testing antipsychotics' effects in this domain. A previous study analyzed 15 articles and did not find any conclusive results on the possibility that antipsychotics could specifically facilitate social recovery[64]. About visuoconstruction, we did not find previous systematic reviews to comparatively evaluate our results.

Our findings should be interpreted considering our limitations and methodological choices. First, in our study, haloperidol showed unfavorable results with small effect sizes. This

raises a question about the clinical relevance of our findings, as small statistically significant differences may not be clinically significant. Second, the present study is not theoretically a post-hoc analysis, as it was described *a priori* as a secondary objective of the systematic review in the original protocol. However, we emphasize that all outcomes from secondary objectives have less methodological robustness.

Thirdly, we did not find enough data to assess the dose-dependent effect of haloperidol on cognition (in comparison with SGAs). In previous studies comparing SGAs versus FGAs, there is a recurrent concern that the superiority of the SGAs is justified by the higher doses of the FGAs commonly used in these trials[65]. However, a previous meta-analysis has already shown that the negative effects of high-dose haloperidol do not explain the cognitive improvements observed with SGAs[66]. Unfortunately, our review failed to detect the doses' influence because most of the included trials (19/28 studies) allowed a wide range of haloperidol doses in their samples. Therefore, these trials could not be classified as low-dose (<12 mg/day) or high-dose (≥12 mg/day), which did not enable subgroup analyses. Furthermore, more than half of these trials (15/28) did not present their average antipsychotic daily dose (mg per day), which also did not allow the conduction of secondary analyses.

Fourth, our meta-analyses included studies with a minimum follow-up of 4 weeks, which may be considered short by some authors, but appropriate for others. The minimum follow-up period required for clinical trials to adequately assess the cognitive effects of antipsychotics in schizophrenia is unclear. While Harvey and Keefe (2001) indicate that a four-week follow-up is sufficient to demonstrate the cognitive effect of antipsychotics and to exclude the effects of previously used medications[65], the MATRICS group suggested longer follow-ups[67]. Despite the divergences present in the literature, our study is in accordance with the above assumptions.

Fifth, our meta-analyses included individuals at different stages of schizophrenia, indiscriminately, with no specific analysis for each stage of the disease. Thus, our results did not consider the disease's severity as a moderating factor in the effect of antipsychotics on cognition. We could not avoid this limitation because most selected clinical trials gathered patients indistinctly, combining individuals in early stages of the disease and chronic patients. Sixth, we cannot exclude anticholinergics' influence in our results because most studies did not describe how these drugs were used. This is a relevant limitation, as anticholinergics are associated with cognitive impairment, and the concomitant use of these drugs is more associated with FGAs [68].

Seventh, we did not consider injectable drugs, such as depot preparations, in our analysis due to pharmacokinetic and pharmacodynamic differences between oral and injectable routes of administration[29]. In the future, we plan to perform additional analyses focusing exclusively on injectable medications. Eighth, our results may have been significantly influenced by industry bias, as most studies we analyzed were sponsored by pharmaceutical companies. It is important to emphasize that industry bias can exert a powerful influence on the research process [69]. **Finally,** due to the small number of randomized controlled trials designed to assess cognition as a primary outcome in schizophrenia, the results of our meta-analyses are based on secondary outcomes, which reduces the statistical power of our findings.

Our meta-analyses respected statistical and methodological homogeneity assumptions. All meta-analyses obtained results without statistically significant heterogeneity (Q test with p-value < 0.05), and our screening was able to select trials with methodological and clinical similarities: we only included double-blind randomized controlled trials, with subjects with a clear diagnosis of schizophrenia, and with no other neuropsychiatric comorbidities, including substance use disorder.

In conclusion, our meta-analyses showed a tendency for haloperidol to present less expressive benefits in the long-term cognitive management in schizophrenia when compared to SGAs. However, it was not possible to conclude that haloperidol is certainly worse than SGAs, because our findings showed small effect sizes, which may not be clinically relevant. Despite our methodological limitations, our results reiterate previous evidence that suggests a possible superiority of SGAs on processing speed, attention, motor performance, memory and verbal learning, executive function, and composite cognition.

Conflicts of interest declaration: Maurício Kunz reports personal fees from Daiichi Sankyo and Janssen-Cilag. The other authors declare no conflict of interest.

Acknowledgments: this study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - Finance Code 001.

References

1 Harvey PD, Parrella M, White L, Mohs RC, Davis KL. Convergence of cognitive and functional decline in poor outcome schizophrenia. Schizophr Res. 1999;35:77–84.

2 Sheffield JM, Karcher NR, Barch DM. Cognitive Deficits in Psychotic Disorders: A Lifespan Perspective. Neuropsychol Rev. 2018;28:509–33.

3 Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr Dis Treat. 2006;2:531–6.

4 Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. Neuropsychology. 1998;12:426–45.

5 Czepielewski LS, Alliende LM, Castañeda CP, Castro M, Guinjoan SM, Massuda R, et al. Effects of socioeconomic status in cognition of people with schizophrenia: Results from a Latin American collaboration network with 1175 subjects. Psychol Med. 2022;52:2177–88.

6 Bilder RM, Goldman RS, Volavka J, Czobor P, Hoptman M, Sheitman B, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry. 2002;159:1018–28.

7 Harvey PD, Green MF, McGurk SR, Meltzer HY. Changes in cognitive functioning with risperidone and olanzapine treatment: A large-scale, double-blind, randomized study. Psychopharmacology (Berl). 2003;169:404–11.

8 Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M. Improvement in social competence with short-term atypical antipsychotic treatment: A randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am J Psychiatry. 2006;163:1918–25.

9 Harvey PD, Siu CO, Hsu J, Cucchiaro J, Maruff P, Loebel A, et al. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: A short-term placebo- and active-controlled study followed by a 6-month double-blind extension. Eur Neuropsychopharmacol. 2013;23:1373–82.

10 Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, et al. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. Biol Psychiatry. 2006;59:97–105.

11 Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry. 2004;161:985–95.

12 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;8:457–72.

13 Désaméricq G, Schurhoff F, Meary A, Szöke A, Macquin-Mavier I, Bachoud-Levi AC, et al. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. Eur J Clin Pharmacol. 2014;70:127–34.

14 Keefe RSE, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: A review and meta-analysis. Schizophr Bull. 1999;25:201–22.

15 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. Biol Psychiatry. 2004;55:1013–22.

16 Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: A randomized, open-label clinical trial (EUFEST). Am J Psychiatry. 2009;166:675–82.

17 Keefe RSE, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007;64:633–47.

18 World Health Organization. (2022). World mental health report: transforming mental health for all. World Health Organization. https://apps.who.int/iris/handle/10665/356119.

19 Relação Nacional de Medicamentos Essenciais Rename 2022 [recurso eletrônico] / Ministério da Saúde, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde,

Departamento de Assistência Farmacêutica e Insumos Estratégicos. – Brasília: Ministério da Saúde, 2022.

20 Baldez DP, Biazus TB, Rabelo-da-Ponte FD, Nogaro GP, Martins DS, Kunz M, et al. The Effect of Antipsychotics on the Cognitive Performance of Individuals with Psychotic Disorders: Network Meta-Analyses of Randomized Controlled Trials. Neurosci Biobehav Rev. 2021;126:265–75.

21 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. 2011.

22 Moher D, Liberati A, Tetzlaff J, Altma D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6:e1000097.

23 Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment (5th ed.). Oxford University Press. 2012.

24 Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary. (3rd ed.). Oxford University Press. 2006.

25 Keefe RSE, Mohs RC, Bilder RM, Harvey PD, Green MF, Meltzer HY, et al. Neurocognitive assessment in the clinical antipsychotic trials of intervention effectiveness (CATIE) project schizophrenia trial: Development, methodology, and rationale. Schizophr Bull. 2003;29:45–55.

26 Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68:283–97.

27 Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. Am J Psychiatry. 2008;165:203–13.

28 Pietrzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ. A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. J Clin Exp Neuropsychol. 2009;31:848–59.

29 Stahl SM. Stahl's essential psychopharmacology : Neuroscientific basis and practical applications. Cambridge: Cambridge University Press. 2008.

30 Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011.

31 Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ (Online). 2011;343:1–8.

32 Abdolahian E, Mohareri F, Bordbar MRF. Haloperidol versus risperidone: A comparison of beneficial effect on cognitive function of patients with chronic schizophrenia. Iran J Psychiatry Behav Sci. 2008;2:14–20.

33 Boulay LJ, Labelle A, Bourget D, Robertson S, Habib R, Tessier P, et al. Dissociating medication effects from learning and practice effects in a neurocognitive study of schizophrenia: Olanzapine versus haloperidol. Cogn Neuropsychiatry. 2007;12:322–38.

34 Buchanan RW, Holstein C, Breier A. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biol Psychiatry. 1994;36:717–25.

35 Gallhofer B, Jaanson P, Mittoux A, Tanghøj P, Lis S, Krieger S. Course of recovery of cognitive impairment in patients with schizophrenia: A randomised double-blind study comparing sertindole and haloperidol. Pharmacopsychiatry. 2007;40:275–86.

36 Green MF, Marder SR, Glynn SM, McGurk SR, Wirshing WC, Wirshing DA, et al. The neurocognitive effects of low-dose haloperidol: A two-year comparison with risperidone. Biol Psychiatry. 2002;51:972–8.

37 Harvey PD, Rabinowitz J, Eerdekens M, Davidson M. Treatment of cognitive impairment in early psychosis: A comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry. 2005;162:1888–95.

38 Keefe RSE, Young CA, Rock SL, Purdon SE, Gold JM, Breier A. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res. 2006;81:1–15.

39 Kee KS, Kern RS, Marshall BD, Green MF. Risperidone versus haloperidol for perception of emotion in treatment- resistant schizophrenia: Preliminary findings. Schizophr Res. 1998;31:159–65.

40 Kern RS, Green MF, Marshall BD, Wirshing WC, Wirshing D, McGurk S, et al. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. Biol Psychiatry. 1998;44:726–32.

41 Kern RS, Green MF, Marshall BD, Wirshing WC, Wirshing D, McGurk SR, et al. Risperidone versus haloperidol on secondary memory: Can newer medications aid learning? Schizophr Bull. 1999;25:223–32.

42 McGurk SR, Green MF, Wirshing WC, Ames D, Marshall B, Marder SR, et al. The effects of risperidone vs haloperidol on cognitive functioning in treatment-resistant schizophrenia: the Trail Making Test. CNS Spectr. 1997;2:60–4.

43 McGurk SR, Green MF, Wirshing WC, Wirshing DA, Marder SR, Mintz J, et al. Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia. Schizophr Res. 2004;68:225–33.

44 Krakowski MI, Czobor P, Nolan KA. Atypical antipsychotics, neurocognitive deficits, and aggression in schizophrenic patients. J Clin Psychopharmacol. 2008;28:485–93.

45 Lee S-M, Chou YH, Li M-H, Wan F-J, Yen M-H. Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1101–7.

46 Lindenmayer J-P, Khan A, Iskander A, Abad MT, Parker B. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. Journal of Clinical Psychiatry. 2007;68:368–79.

47 Liu SK, Chen WJ, Chang CJ, Lin HN. Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: A trial of risperidone versus haloperidol. Neuropsychopharmacology. 2000;22:311–9.

48 Purdon SE, Jones BDW, Stip E, Labelle A, Addington D, David SR, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. Arch Gen Psychiatry. 2000;57:249–58.

49 Purdon SE, Malla A, Labelle A, Lit W. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. Journal of Psychiatry and Neuroscience. 2001;26:137–49.

50 Rémillard S, Pourcher E, Cohen H. The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: A 1-year follow up study. Schizophr Res. 2005;80:99–106.

51 Rémillard S, Pourcher E, Cohen H. Long-term effects of risperidone versus haloperidol on verbal memory, attention, and symptomatology in schizophrenia. Journal of the International Neuropsychological Society. 2008;14:110–8.

52 Rosenheck R, Perlick D, Bingham S, Liu-Mares W, Collins J, Warren S, et al. Effectiveness and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia. J Am Med Assoc. 2003;290:2693–702.

53 Sergi MJ, Green MF, Widmark C, Reist C, Erhart S, Braff DL, et al. Social Cognition and Neurocognition: Effects of Risperidone, Olanzapine, and Haloperidol. Am J Psychiatry. 2007;164:1585–92.

54 Smith RC, Infante M, Singh A, Khandat A. The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. International Journal of Neuropsychopharmacology. 2001;4:239–50.

55 Velligan DI, Newcomer J, Pultz J, Csernansky J, Hoff AL, Mahurin R, et al. Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res. 2002;53:239–48.

56 Guilera G, Pino O, Gómez-Benito J, Rojo JE. Antipsychotic effects on cognition in schizophrenia: A meta-analysis of randomised controlled trials. Eur J Psychiat. 2009;23:77–89.

57 Grada CO, Dinan T. Executive function in schizophrenia: what impact do antipsychotics have? Hum Psychopharmacol. 2007;22:397–406.

58 Meltzer HY, Thompson PA, Lee MA, Ranjan R. Neuropsychologic Deficits in Schizophrenia: Relation to Social Function and Effect of Antipsychotic Drug Treatment. Neuropsychopharmacology. 1996;14:28S-32S.

59 Lee J, Park S. Effects of Antipsychotic Drugs on Memory and Attention in Schizophrenia. Psychiatry Investig. 2006;3:55–65.

60 Rosengarten H, Quartermain D. The effect of chronic treatment with typical and atypical antipsychotics on working memory and jaw movements in three-and eighteen-month-old rats. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26:1047–54.

61 Castner SA, Williams G V., Goldman-Rakic PS. Reversal of Antipsychotic-Induced Working Memory Deficits by Short-Term Dopamine D1 Receptor Stimulation. Science (1979). 2000;287:2020–2.

62 Gemperle AY, McAllister KH, Olpe HR. Differential effects of iloperidone, clozapine, and haloperidol on working memory of rats in the delayed non-matching-to-position paradigm. Psychopharmacology (Berl). 2003;169:354–64.

63 Beatty WW, Rush JR. Spatial Working Memory in Rats: Effects of Monoaminergic Antagonists. Pharmacol Biochem Behav. 1983;18:7–12.

64 Kucharska-Pietura K, Mortimer A. Can antipsychotics improve social cognition in patients with schizophrenia? CNS Drugs. 2013;27:335–43.

65 Harvey PD, Keefe RSE. Studies of Cognitive Change in Patients With Schizophrenia Following Novel Antipsychotic Treatment. Am J Psychiatry. 2001:176–84.

66 Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: Dose effects and comparison to practice effects. Schizophr Res. 2007;89:211–24.

67 Buchanan RW, Davis M, Goff D, Green MF, Keefe RSE, Leon AC, et al. A Summary of the FDA-NIMH-MATRICS Workshop on Clinical Trial Design for Neurocognitive Drugs for Schizophrenia. Schizophr Bull. 2005;31:5–19.

68 Risacher SL, McDonald BC, Tallman EF, West JD, Farlow MR, Unverzagt FW, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. JAMA Neurol. 2016;73:721–32.

69 Fabbri A, Lai A, Grundy Q, Bero LA. The influence of industry sponsorship on the research agenda: A scoping review. Am J Public Health. 2018;108:e9–16.

Suplementary material

Contents

I. Supplementary material nº 1 – PRISMA Checklist

The PRISMA Checklist[1] can be found at http://prisma-statement.org/

Supplementary Table 1. PRISMA Checklist

Section and Topic	Item #	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5,6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl. II
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6,7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6,7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7,8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7,8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8, Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7,8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9

Section and Topic	Item #	Checklist item	Reported on page
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1, Suppl. IX
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 Suppl. VIII
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl. VII
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	10,11,12
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	10,11,12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	10,11,12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10,11,12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	10,11,12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Suppl. VII
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10,11,12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13
	23b	Discuss any limitations of the evidence included in the review.	14,15
	23c	Discuss any limitations of the review processes used.	14,15
	23d	Discuss implications of the results for practice, policy, and future research.	14,15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17

Section and Topic	Item #	Checklist item	Reported on page
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl. I-IX

II. Supplementary material nº 2 - Search Strategies

This paper is a complementary analysis of a systematic review previously published by our team [2]. For a complete understanding, we chose to replicate the entire article selection process as supplementary material.

The search was performed using three databases: MEDLINE (PubMed), Web of Science, and EMBASE. We included all studies published up to the initial search date (November 30th, 2018). Two additional strategies were adopted: backward reference searching (analysis of the bibliographic references of the selected studies) and the evaluation of systematic reviews previously published. An updated search was made on November 30th, 2019.

The search terms were initially defined by the researchers and the largest number of synonyms was included. The synonymous terms were identified using the "Mesh Terms" (MEDLINE) and "Emtree" (EMBASE) tools. The general terms are described in the table below, according to the acronym PICOS.

Supplementary table 2. Generic search terms

PICOS*	Search terms[1]
***P**opulation*	schizophrenia psychosis mood disorder bipolar disorder
***I**ntervention*	antipsychotic[2]
***O**utcome*	cognition neuropsychology memory attention working memory executive function
Study design	randomized controlled trial

*PICOS = population, intervention, comparators, outcomes, study design.

[1] These terms were expanded by the synonym search strategy.

[2] Each antipsychotic was named individually in the search strategy

The strategies used in each database are described below. The general terms and their synonyms were grouped by the Boolean operator "OR" and the different general terms were grouped by the Boolean operator "AND".

II.I. Search terms and strategy used in MEDLINE

(antipsychotic[Mesh] OR antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole[Mesh] OR aripiprazole OR amisulpride[Mesh] OR amisulpride OR benperidol[Mesh] OR benperidol OR asenapine[Mesh] OR asenapine OR blonanserin[Mesh] OR blonanserin OR brexpiprazole[Mesh] OR brexiprazole OR chlorpromazine[Mesh] OR chlorpromazine OR clozapine[Mesh] OR clozapine OR cariprazine[Mesh] OR cariprazine OR clopenthixol[Mesh] OR clopenthixol OR denzapine[Mesh] OR denzapine OR fluanxol[Mesh] OR fluanxol OR fluphenazine[Mesh] OR fluphenazine OR flupenthixol[Mesh] OR flupenthixol OR haldol OR haloperidol[Mesh] OR haloperidol OR iloperidone[Mesh] OR iloperidone OR levomepromazine[Mesh] OR levomepromazine OR lurasidone[Mesh] OR lurasidone OR olanzapine[Mesh] OR olanzapine OR pimozide[Mesh] OR pimozide OR pimavanserin[Mesh] OR pimavanserin OR paliperidone[Mesh] OR paliperidone OR pericyazine[Mesh] OR pericyazine OR perphenazine[Mesh] OR perphenazine OR pipotiazine[Mesh] OR pipotiazine OR prochlorperazine[Mesh] OR prochlorperazine OR promazine[Mesh] OR promazine OR quetiapine[Mesh] OR quetiapine OR risperidone[Mesh] OR risperidone OR sulpiride[Mesh] OR sulpiride OR sultopride[Mesh] OR sultopride OR leuprolide[Mesh] OR leuprolide OR trifluoperazine[Mesh] OR trifluoperazine OR thiothixene[Mesh] OR thiothexe OR zuclopenthixol[Mesh] OR zuclopenthixol OR ziprasidone[Mesh] OR ziprasidone OR zotepine[Mesh] OR zotepine) AND (cognition[Mesh] OR cognition OR neuropsychology[Mesh] OR neuropsychology OR "executive function"[Mesh] OR "executive function" OR "executive functions" OR "inhibitory control" OR "cognitive flexibility" OR "self control" OR "self monitoring" OR "self regulation" OR attention[Mesh] OR attention OR memory[Mesh] OR memory OR "episodic memory" OR "semantic memory" OR "prosodic memory" OR "working memory"[Mesh] OR working memory) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND (Schizophrenia OR Schizophrenia[Mesh] OR Schizophrenias OR "Schizophrenic Disorders" OR "Disorder, Schizophrenic" OR "Disorders, Schizophrenic" OR "Schizophrenic Disorder" OR "Dementia Praecox" OR "Disorder, Paranoid" OR "Disorders, Paranoid" OR "Paranoid Disorder" OR "Psychoses, Paranoid" OR "Paranoid Psychoses" OR "Paranoia" OR "Paranoid Schizophrenias" OR "Schizophrenias, Paranoid" OR "Paranoid Schizophrenia" OR "Delusional Disorder" OR "Delusional Disorders" OR "Disorder, Delusional" OR "Disorders, Delusional" OR Psychosis[Mesh] OR "Disorder, Psychotic" OR "Disorders, Psychotic" OR "Psychotic Disorder" OR "Psychosis" OR "Psychoses" OR "Schizoaffective Disorder" OR "Disorder, Schizoaffective" OR "Disorders, Schizoaffective" OR "Schizoaffective Disorders" OR "Schizophreniform Disorders" OR "Disorder, Schizophreniform" OR

"Disorders, Schizophreniform" OR "Schizophreniform Disorder" OR "Psychosis, Brief Reactive" OR "Brief Reactive Psychoses" OR "Brief Reactive Psychosis" OR "Psychoses, Brief Reactive" OR "Reactive Psychoses, Brief" OR "Reactive Psychosis, Brief" OR "Mood Disorder" OR "Mood Disorders" OR "Mood Disorders"[Mesh] OR "Disorder, Mood" OR "Disorders, Mood" OR "Affective Disorders" OR "Affective Disorders"[Mesh] OR "Affective Disorder" OR "Disorder, Affective" OR "Disorders, Affective" OR "Psychoses, Affective" OR "Affective Psychoses" OR "Psychotic Affective Disorders" OR "Affective Disorder, Psychotic" OR "Disorder, Psychotic Affective" OR "Disorders, Psychotic Affective" OR "Psychotic Affective Disorder" OR "Psychotic Mood Disorders" OR "Mood Disorder, Psychotic" OR "Psychotic Mood Disorder" OR "Mood Disorders, Psychotic" OR "Depression, Reactive, Psychotic" OR "bipolar disorder" OR "bipolar disorder"[Mesh] OR "Disorder, Bipolar" OR "Psychosis, Manic-Depressive" OR "Psychosis, Manic Depressive" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR "Affective Psychosis, Bipolar" OR "Bipolar Affective Psychosis" OR "Psychoses, Bipolar Affective" OR "Psychosis, Bipolar Affective" OR "Psychoses, Manic-Depressive" OR "Manic-Depressive Psychoses" OR "mania" OR "manias" OR "Psychoses, Manic Depressive" OR "Manic State" OR "Manic States" OR "State, Manic" OR "States, Manic" OR "Depression, Bipolar" OR "Bipolar Depression" OR "Manic Disorder" OR "Disorder, Manic" OR "Manic Disorders")

II.II. Search terms and strategy used in EMBASE

(antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole OR amisulpride OR asenapine OR benperidol OR blonanserin OR brexpiprazole OR chlorpromazine OR clozapine OR cariprazine OR clopenthixol OR denzapine OR fenotiazina OR fluanxol OR flupentixol OR fluphenazine OR flupenthixol OR haldol OR haloperidol OR iloperidone OR levomepromazine OR lurasidone OR mosapramine OR olanzapine OR pimavanserin OR paliperidone OR pericyazine OR perospirone OR perphenazine OR pimozide OR pipotiazine OR prochlorperazine OR promazine OR quetiapine OR remoxipride OR risperidone OR sertindole OR sulpiride OR sultopride OR leuprolide OR trifluoperazine OR thiothixene OR thioridazine OR zuclopenthixol OR ziprasidone OR zotepine) AND ('cognition' OR 'neuropsychology' OR 'executive function' OR 'executive functions' OR 'inhibitory control' OR 'cognitive flexibility' OR 'self control' OR 'self monitoring' OR 'self regulation' OR 'attention' OR 'memory' OR 'working memory' OR 'episodic memory' OR 'semantic memory' OR 'prosodic memory') AND ('randomized controlled trial" OR 'controlled clinical trial' OR randomized OR placebo OR 'drug therapy' OR randomly OR trial OR groups) AND (schizophrenia OR schizophrenias OR 'schizophrenic disorders' OR 'disorder, schizophrenic' OR 'disorders, schizophrenic' OR 'schizophrenic disorder' OR 'dementia praecox' OR 'disorder, paranoid' OR 'disorders, paranoid' OR 'paranoid disorder' OR 'psychoses, paranoid' OR 'paranoid psychoses' OR 'paranoia' OR 'paranoias' OR 'paranoid schizophrenias' OR 'schizophrenias, paranoid' OR 'paranoid schizophrenia' OR 'delusional disorder' OR 'delusional disorders' OR 'disorder, delusional' OR 'disorders, delusional' OR 'disorder, psychotic' OR

'disorders, psychotic' OR 'psychotic disorder' OR 'psychosis' OR 'psychoses' OR 'schizoaffective disorder' OR 'disorder, schizoaffective' OR 'disorders, schizoaffective' OR 'schizoaffective disorders' OR 'schizophreniform disorders' OR 'disorder, schizophreniform' OR 'disorders, schizophreniform' OR 'schizophreniform disorder' OR 'psychosis, brief reactive' OR 'brief reactive psychoses' OR 'brief reactive psychosis' OR 'psychoses, brief reactive' OR 'reactive psychoses, brief' OR 'reactive psychosis, brief' OR 'mood disorder' OR 'mood disorders' OR 'disorder, mood' OR 'disorders, mood' OR 'affective disorders' OR 'affective disorder' OR 'disorder, affective' OR 'disorders, affective' OR 'psychoses, affective' OR 'affective psychoses' OR 'psychotic affective disorders' OR 'affective disorder, psychotic' OR 'disorder, psychotic affective' OR 'disorders, psychotic affective' OR 'psychotic affective disorder' OR 'psychotic mood disorders' OR 'mood disorder, psychotic' OR 'psychotic mood disorder' OR 'mood disorders, psychotic' OR 'depression, reactive, psychotic' OR 'bipolar disorder' OR 'disorder, bipolar' OR 'psychosis, manic-depressive' OR 'psychosis, manic depressive' OR 'manic-depressive psychosis' OR 'manic depressive psychosis' OR 'affective psychosis, bipolar' OR 'bipolar affective psychosis' OR 'psychoses, bipolar affective' OR 'psychosis, bipolar affective' OR 'psychoses, manic-depressive' OR 'manic-depressive psychoses' OR 'mania' OR 'manias' OR 'psychoses, manic depressive' OR 'manic state' OR 'manic states' OR 'state, manic' OR 'states, manic' OR 'depression, bipolar' OR 'bipolar depression' OR 'manic disorder' OR 'disorder, manic' OR 'manic disorders') AND ([article]/lim OR [article in press]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)[1]

II.III. Search terms and strategy used in Web of Science

(antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole OR amisulpride OR asenapine OR benperidol OR blonanserin OR brexpiprazole OR chlorpromazine OR clozapine OR cariprazine OR clopenthixol OR denzapine OR fenotiazina OR fluanxol OR flupentixol OR fluphenazine OR flupenthixol OR haldol OR haloperidol OR iloperidone OR levomepromazine OR lurasidone OR mosapramine OR olanzapine OR pimavanserin OR paliperidone OR pericyazine OR perospirone OR perphenazine OR pimozide OR pipotiazine OR prochlorperazine OR promazine OR quetiapine OR remoxipride OR risperidone OR sertindole OR sulpiride OR sultopride OR leuprolide OR trifluoperazine OR thiothixene OR thioridazine OR zuclopenthixol OR ziprasidone OR zotepine) AND TÓPICO: (cognition OR neuropsychology OR "executive function" OR "executive functions" OR "inhibitory control" OR "cognitive flexibility" OR "self control" OR "self monitoring" OR "self regulation" OR attention OR memory OR "working memory" OR "episodic memory" OR "semantic memory" OR "prosodic memory") AND TÓPICO: (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial) AND TÓPICO: (Schizophrenia OR Schizophrenias OR “Schizophrenic Disorders” OR “Disorder, Schizophrenic” OR “Disorders, Schizophrenic” OR “Schizophrenic Disorder” OR “Dementia Praecox” OR “Disorder, Paranoid” OR “Disorders, Paranoid” OR “Paranoid Disorder” OR “Psychoses, Paranoid” OR “Paranoid Psychoses” OR “Paranoia” OR “Paranoias” OR “Paranoid Schizophrenias” OR “Schizophrenias,

Paranoid" OR "Paranoid Schizophrenia" OR "Delusional Disorder" OR "Delusional Disorders" OR "Disorder, Delusional" OR "Disorders, Delusional" OR "Disorder, Psychotic" OR "Disorders, Psychotic" OR "Psychotic Disorder" OR "Psychosis" OR "Psychoses" OR "Schizoaffective Disorder" OR "Disorder, Schizoaffective" OR "Disorders, Schizoaffective" OR "Schizoaffective Disorders" OR "Schizophreniform Disorders" OR "Disorder, Schizophreniform" OR "Disorders, Schizophreniform" OR "Schizophreniform Disorder" OR "Psychosis, Brief Reactive" OR "Brief Reactive Psychoses" OR "Brief Reactive Psychosis" OR "Psychoses, Brief Reactive" OR "Reactive Psychoses, Brief" OR "Reactive Psychosis, Brief" OR "Mood Disorder" OR "Mood Disorders" OR "Disorder, Mood" OR "Disorders, Mood" OR "Affective Disorders" OR "Affective Disorder" OR "Disorder, Affective" OR "Disorders, Affective" OR "Psychoses, Affective" OR "Affective Psychoses" OR "Psychotic Affective Disorders" OR "Affective Disorder, Psychotic" OR "Disorder, Psychotic Affective" OR "Disorders, Psychotic Affective" OR "Psychotic Affective Disorder" OR "Psychotic Mood Disorders" OR "Mood Disorder, Psychotic" OR "Psychotic Mood Disorder" OR "Mood Disorders, Psychotic" OR "Depression, Reactive, Psychotic" OR "bipolar disorder" OR "Disorder, Bipolar" OR "Psychosis, Manic-Depressive" OR "Psychosis, Manic Depressive" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR "Affective Psychosis, Bipolar" OR "Bipolar Affective Psychosis" OR "Psychoses, Bipolar Affective" OR "Psychosis, Bipolar Affective" OR "Psychoses, Manic-Depressive" OR "Manic-Depressive Psychoses" OR "mania" OR "manias" OR "Psychoses, Manic Depressive" OR "Manic State" OR "Manic States" OR "State, Manic" OR "States, Manic" OR "Depression, Bipolar" OR "Bipolar Depression" OR "Manic Disorder" OR "Disorder, Manic" OR "Manic Disorders")

III. Supplementary material nº 3 –Allocation of neuropsychological tests in cognitive domains

This paper is an up-date and complementary analysis of a systematic review and meta-analyses previously published by our team [2]. For a complete understanding, we chose to replicate the allocation of neuropsychological test as supplementary material.

The neuropsychological tests were allocated in the cognitive domains by two independent investigators, according to three aspects:

- The test definition present in main neuropsychology compendiums[3,4],
- the test definition present in the main cognitive evaluation batteries in schizophrenia [5678]
- The test definition present in its validation article[9].

Neuropsychological tests were allocated to one or more cognitive domains, depending on the researchers' decision. We considered that all tests equally evaluated a respective domain, except:

1. The animal naming test and the letter fluency test were grouped as a single score (verbal fluency), using the simple arithmetic average. This strategy was performed to verbal fluency did not have a greater weight in the calculation on executive function.

2. The tests that assessed the verbal memory domain were first categorized into three subgroups: short-term verbal memory, long-term verbal memory, and verbal learning. After estimating the result of each subgroup (z-scores), we estimated the simple arithmetic mean of these results to obtain the *memory and verbal learning* score. We carried out this strategy to the three subgroups had the same weight in the final estimate.

Supplementary table 4. The allocation of neuropsychological tests in cognitive domains

Neuropsychological tests (and measures)	Cognitive domain
Continuous Performance Test – Identical Pairs - d-prime	Attention
Continuous Performance Test - degraded-stimulus	Attention
D2 Cancellation test/ D2 Test of Attention – errors	Attention
Digit span - Forward (recall the digits in the correct order) - percentages	Attention

Digit span distractibility task	Attention
Identification Test - Cogstate[8]	Attention
Rapid Visual Information Processing – total hits, total errors - CANTAB[9]	Attention
Span of Apprehension – error score	Attention
Stroop Color-Word Test - correct responses, hit rate, number of errors, false alarms	Attention
Wechsler Memory Scale – Revised - Visual Memory Span - forward	Attention
Design Fluency Test	Executive function
Groton Maze Learning Test - Cogstate[8]	Executive function
Maze tests	Executive function
Ruff Figural Fluency Test	Executive function
Self-ordered pointing tasks/ Subjective ordered pointing tasks – errors	Executive function
Stroop Test – interference	Executive function
Stockings of Cambridge – problems solved on first choice and mean choices to correct - CANTAB[9]	Executive function
Trail Making Test – Part B – time to completion	Executive function
Tower of London – correct responses and execution time	Executive function
Verbal fluency – Category Fluency (animal naming) – correct responses	Executive function
Verbal fluency – Letter fluency (COWAT) – correct responses	Executive function
Wisconsin Card Sorting Test - perseverative errors, total errors, number of categories completed	Executive function
Continuous Performance Test – Identical Pairs – reaction time	Processing speed
Detection Test – Cogstate[5]	Processing speed
Digit Symbol/ Symbol Coding – correct responses	Processing speed
Reaction time – correct responses - CANTAB[9] and similar tests	Processing speed
Stroop Color-Word Test – reaction time, speed of naming, colors stripes	Processing speed
Trail Making Test – Part A – time to completion	Processing speed

Continuous Paired Associate Learning Tasks – Cogstate [8]	Working memory
Digit sequencing test – correct responses	Working memory
Digit span – Backward – percentages	Working memory
Letter–Number Sequencing Test/ Letter–number span test – number of correct trials	Working memory
One-Back Memory Task and Two-Back Memory Task – Cogstate [8]	Working memory
Peterson Consonantes Trigram Test	Working memory
Spatial reference memory test – delayed 5 seconds and delayed 15 seconds – errors	Working memory
Spatial working memory test – CANTAB[9]	Working memory
Spatial Working Memory Test – 5 sec and 15sec	Working memory
Visuospatial working memory	Working memory
Wechsler Memory Scale – III – Spatial Span Test –backward	Working memory
Wechsler Memory Scale – Revised – Visual memory span – backward	Working memory
Finger Tapping Test – number of taps	Motor performance
Grooved Pegboard – number of pegs successfully inserted	Motor performance
Motor Screening Test – mean errors – CANTAB[9]	Motor performance
Pin Test – total number	Motor performance
Rey-Osterrieth Complex figure test – copy	Motor performance
Rey-Taylor complex figure test- copy	Motor performance
Rey-Taylor complex figure test	Motor performance
Token motor task – number of tokens correctly placed	Motor performance
Logical memories task – number of recalled cues	Long-term verbal memory
Paragraph recall – delayed recall total	Long-term verbal memory

Rey Auditory Verbal Learning Test (RAVLT), Hopkins Verbal Learning Test-Revised (HVLT), California Verbal Learning Test (CVLT) – long-delay recall (CVLT), delayed recall – trial 7/ A7 (RAVLT)	Long-term verbal memory
Verbal recognition memory – delayed recall – correct responses - CANTAB[9]	Long-term verbal memory
Wechsler Memory Scale – Revised – Logical Memory – delayed – correct responses	Long-term verbal memory
Auditory Comprehension Test – story recall	Short-term verbal memory
Rey Auditory Verbal Learning Test (RAVLT), Hopkins Verbal Learning Test-Revised (HVLT), California Verbal Learning Test (CVLT) – trial 1/ list A	Short-term verbal memory
Verbal recognition memory – immediate recall – correct responses - CANTAB[9]	Short-term verbal memory
Wechsler Memory Scale – Revised – Logical Memory – immediate – correct responses	Short-term verbal memory
International Shopping List Task – Cogstate[8]	Verbal learning
Rey Auditory Verbal Learning Test (RAVLT), Hopkins Verbal Learning Test-Revised (HVLT), California Verbal Learning Test (CVLT) – Total number of words recalled correctly over three learning trials (HVLT), over trials 1 – 5 (RAVLT), and learning trial 1-5 (CVLT)	Verbal learning
Rey and Crawford Auditory Verbal Learning Tests	Verbal learning
Serial digital learning/ Digit Sequence Learning/ Benton Serial Learning Test	Verbal learning
Hooper visual Organization Test	Visuoconstruction
Wechsler Adult Intelligence Scale – Revised (WAIS-R) – Block Design – Total number of points, age-corrected	Visuoconstruction
Wechsler Adult Intelligence Scale – III (WAIS-III) – Object assembly	Visuoconstruction
Wechsler Adult Intelligence Scale – III (WAIS-III) Picture Completion	Visuoconstruction
Brief Visuospatial Memory Test-Revised (BVMT) – Total recall score over three learning trials	Visual learning
Design list learning/ Rey Design Learning Test/ Serial Design Learning Test	Visual learning
Paired Associates Learning – total errors - CANTAB[9]	Visual learning
Pattern Recognition Memory – immediate and delayed (correct responses and percentages) - CANTAB[9]	Visual learning

Rey-Osterrieth Complex figure test – total recall and immediate recall	Visual learning
Rey-Taylor complex figure test – immediate recall	Visual learning
Visual Learning Test – CogSate[8]	Visual learning
Wechsler Memory Scale – Revised – Visual pairs – total number of correct word associations	Visual learning
Wechsler Memory Scale – Revised – immediate recall	Visual learning
Wechsler Memory Scale – Revised – delayed recall	Visual learning
Wechsler Memory Scale – Revised – Figural memory – correct responses	Visual learning
Face Emotion Discrimination Test (FEDT) – correct responses	Social cognition
Facial Emotion Identification Test - correct responses	Social cognition
Half-Profile of Nonverbal Sensitivity - correct responses	Social cognition
Interpersonal Perception Task – correct responses	Social cognition
Maryland Assessment of Social Competence	Social cognition
Penn Emotional Acuity Test – correct responses	Social cognition
Social Cue Recognition Test - sensitivity	Social cognition
Social Emotional Cognition Test – Cogstate [8]	Social cognition
Social Skills Performance Assessment - total	Social cognition
Voice Emotion Identification Test – correct responses	Social cognition

IV. Supplementary material nº 4 - Imputation of missing data

This paper is a complementary analysis of a systematic review previously published by our team [2]. For a complete understanding, we chose to replicate the imputation data as supplementary material.

Some studies included in our meta-analyses did not describe the measures of dispersion (standard deviation, standard error, or confidence interval). In these cases, these measures were imputed from other included studies. The imputation was performed "between results of the same cognitive test, in the same unit of measurement". When a study presented the results of a cognitive test without the measures of dispersion, these values were imputed from another study that applied the same test (in the same measure).

Considerations:

- The imputation was not performed in the absence of another study that applied the same test and in the same unit of measurement.
- When several studies applied the same cognitive test, we chose the largest measure of dispersion as the measure to be used for imputation. This is the most conservative strategy for imputation data.
- In our study, we performed imputations in six included studies. They are described in the analysis table. The analysis table can be requested from the corresponding author.

Some studies presented their results only graphically. We used the *Web Plot Digitizer* [10] to extract the graphic data (mean and measures of dispersion). The *Web Plot Digitizer* is a website available from: https://apps.automeris.io/wpd/. All the results were checked manually by two independent researchers.

V. Supplementary material nº 5 - Calculation and standardization of cognitive test scores, cognitive domain scores, and cognitive composite cognitive

This paper is a complementary analysis of a systematic review previously published by our team [2]. For a complete understanding, we chose to replicate the calculation of cognitive scores as supplementary material.

We considered the result of a cognitive test as the difference between the mean obtained at study's endpoint and the mean obtained at study's baseline (Δ or *mean difference* or *change from baseline*).

$$\Delta = \bar{x}_{\text{endpoint}} - \bar{x}_{\text{baseline}}$$

Δ = mean difference (change from baseline)

$\bar{x}_{\text{endpoint}}$ = mean at endpoint

$\bar{x}_{\text{endpoint}}$ = mean at baseline

In the studies that did not present a *mean difference* (Δ), we estimated the standard deviation of Δ according to the following equation, using a correlation index of 0.5.

$$SD\Delta = \sqrt{(sd_{baseline})^2 + \left(sd_{endpoint}\right)^2 - 2\ corr\ x\ sd_{baseline} x\ sd_{endpoint}}$$

SD_{Δ} = standard deviation of *Δ*

$sd_{baseline}$= standard deviation at baseline

$sd_{endpoint}$ = standard deviation at endpoint

corr = correlation index

The result of a cognitive test (*mean difference*) were standardized by their standard deviation at baseline. Thus, we obtained the test results in z-scores.

$$\Delta \text{ standardized } = \frac{\Delta}{\text{sd baseline}}$$

Δ standardized = standardized mean differences

Δ = mean differences

$sd_{baseline}$ = standard deviation at baseline.

Likewise, the standard deviation of Δ was standardized by the standard deviation at baseline.

$$\text{SD } \Delta \text{ standardized } = \frac{\text{SD } \Delta}{\text{sd baseline}}$$

SDΔ standardized = standardized standard deviation

SDΔ = standard deviation of Δ

$sd_{baseline}$ = standard deviation in baseline

The cognitive domain score was estimated through the weighted arithmetic average of the standard scores from its respective cognitive tests, weighted for the sample size (*n*) of each test. This condition did not cause any harm to the analysis for considering that all tests equally evaluate the cognitive domain.

$$\bar{x}_n = \frac{\bar{x}_1 . n_1 + \bar{x}_2 . n_2 + \cdots + \bar{x}_n . n_n}{n_t}$$

$\bar{x}_n$ = domain score

x_1 = standardized average of test 1

n = number of patients tested in test 1

n_t = total number of patients assessed in the domain

The composite score was calculated through the simple arithmetic average of the domains present in the study. The simple arithmetic average allowed that all cognitive domains had the same weigh in the global cognitive estimative.

$$\bar{x}_n = \frac{\bar{x}_1 . + \bar{x}_2 + \bar{x}_3 + \ \ldots \ + \bar{x}_{11}}{n_t}$$

$\bar{x}_n$ = composite cognitive score

x_1 = standardized average of domain 1

n = number of patients tested assessed in the composite score.

n_t = total number of patients

Considerations:

1. We estimated a cognitive composite score only from studies that evaluated, at least, the following domains: executive function, memory, verbal learning, work memory, processing speed, and attention. We judged inappropriate the estimate of a composite cognitive score in the absence of these domains.

2. To estimate the standard deviation of the composite score, we considered the same sample size (*n*) for all domains, with the smallest *n* among the domains.

3. Some studies have presented the cognitive test results in more than one unit of measurement. In such cases, we performed the weighted average between them. For instance, if a study evaluated the Wisconsin Card Sorting Test through the measures of persevering errors and completed categories, we performed the weighted average of these outcomes. Afterwards, this estimate was included in the calculation of the executive function score.

4. An increase in the scores of a cognitive test could represent an improvement or a worsening. To gather the different tests into a single score (cognitive domain), it was necessary a standardization. Thus, to estimate a final test score, we maintained or changed its signs according to the meaning of this finding. If the result symbolized an improvement, we did not change the sign; if the final score symbolized a worsening, the sign was reversed. For instance, in the measurement of perseverative errors in the Wisconsin Card Sorting Test, an increase of this value represents a worsening. So, if the result found is -0.2 (the number of errors decreased by 0.2 z-scores), the negative sign is transformed to positive (because the reduction of errors designates improvement). The same rule dictated the elaboration of the global cognitive score.

VI. Supplementary material nº 6 – Characteristics of included studies

The supplementary table nº 5 is available at file "Supp_6_Extraction_table5_paper2" (click here to download). This table contains the main characteristics of the included studies.

VII. Supplementary material nº 7 - Cochrane Risk of Bias

We assessed the risk of bias from included clinical trials using the Cochrane Risk of Bias 1.0 tool[11]. The Cochrane Handbook for Systematic Reviews of Interventions can be found at https://training.cochrane.org/handbook/current. For more details, we provide the supplementary table nº 6.

Supplementary table 6. The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment Assessments should be made for each	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.

main outcome (or class of outcomes).		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, an what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Supplementary table 7. - Risk of bias table of included studies

	Sequence generation	Allocation concealment	Blinding participants and prescribers	Blinding assessor	Incomplete outcome data	Selective reporting
Abdolahian, 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bilder, 2002	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Boulay, 2007	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Buchanan, 1994	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
Galhofer, 2007	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Green, 1997	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear
Green, 2002	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Harvey, 2005	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Kee, 1998	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Keefe, 2004	Unclear	Unclear	Unclear	Unclear	High risk	High risk
Keefe, 2006a	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Keefe, 2006b	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Kern, 1998	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Kern, 1999	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Krakowski, 2008	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear
Lee, 2007	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Lindenmayer, 2007	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Liu, 2000	Low risk	Unclear	Unclear	Unclear	High risk	Unclear
McGurk, 1997	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
McGurk, 2004	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Purdon, 2000	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Purdon, 2001	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Rémillard, 2005	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Rémillard, 2008	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Rosenheck, 2003	Low risk	Unclear	Low risk	Unclear	Low risk	High risk
Sergi, 2007	Low risk	Low risk	Unclear	Unclear	High risk	Unclear
Smith, 2001	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Velligan, 2002	Unclear	Unclear	Unclear	Unclear	High risk	Unclear

VIII. Supplementary material nº 8 - List of included studies in the systematic review and meta-analyses

1. Abdolahian E, Mohareri F, Bordbar MRF: Haloperidol versus risperidone: A comparison of beneficial effect on cognitive function of patients with chronic schizophrenia. Iran J Psychiatry Behav Sci 2008; 2:14–20

2. Bilder RM, Goldman RS, Volavka J, et al.: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002; 159:1018–1028

3. Boulay LJ, Labelle A, Bourget D, et al.: Dissociating medication effects from learning and practice effects in a neurocognitive study of schizophrenia: Olanzapine versus haloperidol. Cogn Neuropsychiatry 2007; 12:322–338

4. Buchanan RW, Holstein C, Breier A: The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biol Psychiatry 1994; 36:717–725

5. Gallhofer B, Jaanson P, Mittoux A, et al.: Course of recovery of cognitive impairment in patients with schizophrenia: A randomised double-blind study comparing sertindole and haloperidol. Pharmacopsychiatry 2007; 40:275–286

6. Green MF, Marshall BD, Wirshing WC, et al.: Does risperidone improve verbal working memory in treatment-resistant schizophrenia? Am J Psychiatry 1997; 154:799–804

7. Green MF, Marder SR, Glynn SM, et al.: The neurocognitive effects of low-dose haloperidol: A two-year comparison with risperidone. Biol Psychiatry 2002; 51:972–978

8. Harvey PD, Rabinowitz J, Eerdekens M, et al.: Treatment of cognitive impairment in early psychosis: A comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry 2005; 162:1888–1895

9. Kee KS, Kern RS, Marshall BD, et al.: Risperidone versus haloperidol for perception of emotion in treatment- resistant schizophrenia: Preliminary findings. Schizophr Res 1998; 31:159–165

10. Keefe RSE, Seidman LJ, Christensen BK, et al.: Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004; 161:985–995

11. Keefe RSE, Young CA, Rock SL, et al.: One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res 2006; 81:1–15

12. Keefe RSE, Seidman LJ, Christensen BK, et al.: Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. Biol Psychiatry 2006; 59:97–105

13. Kern RS, Green MF, Marshall BD, et al.: Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. Biol Psychiatry 1998; 44:726–732

14. Kern RS, Green MF, Marshall BDJ, et al.: Risperidone versus haloperidol on secondary memory: Can newer medications aid learning? Schizophr Bull 1999; 25:223–232

15. Krakowski MI, Czobor P, Nolan KA: Atypical antipsychotics, neurocognitive deficits, and aggression in schizophrenic patients. J Clin Psychopharmacol 2008; 28:485–493

16. Lee S-M, Chou Y-H, Li M-H, et al.: Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. Prog Neuro-Psychopharmacology Biol Psychiatry 2007; 31:1101–1107

17. Lindenmayer J-P, Khan A, Iskander A, et al.: A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. J Clin Psychiatry 2007; 68:368–379

18. Liu SK, Chen WJ, Chang CJ, et al.: Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: A trial of risperidone versus haloperidol. Neuropsychopharmacology 2000; 22:311–319

19. McGurk SR, Green MF, Wirshing WC, et al.: The effects of risperidone vs haloperidol on cognitive functioning in treatment-resistant schizophrenia: the Trail Making Test. CNS Spectr 1997; 2:60–64

20. McGurk SR, Green MF, Wirshing WC, et al.: Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia. Schizophr Res 2004; 68:225–233

21. Purdon SE, Jones BDW, Stip E, et al.: Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. Arch Gen Psychiatry 2000; 57:249–258

22. Purdon SE, Malla A, Labelle A, et al.: Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci 2001; 26:137–149

23. Rémillard S, Pourcher E, Cohen H: The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: A 1-year follow up study. Schizophr Res 2005; 80:99–106

24. Rémillard S, Pourcher E, Cohen H: Long-term effects of risperidone versus haloperidol on verbal memory, attention, and symptomatology in schizophrenia. J Int Neuropsychol Soc 2008; 14:110–118

25. Rosenheck R, Perlick D, Bingham S, et al.: Effectiveness and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia. J Am Med Assoc 2003; 290:2693–2702

26. Sergi MJ, Green MF, Widmark C, et al.: Social Cognition and Neurocognition: Effects of Risperidone, Olanzapine, and Haloperidol. Am J Psychiatry 2007; 164:1585–1592

27. Smith RC, Infante M, Singh A, et al.: The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. Int J Neuropsychopharmacol 2001; 4:239–250

28. Velligan DI, Newcomer J, Pultz J, et al.: Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res 2002; 53:239–248

IX. Supplementary material nº 9 – List of studies excluded in the final phase of the systematic review.

IX. I. Studies excluded due to lack of data and impossibility of imputation

1. Jean Addington P, Donald Addington M: Neurocognitive Functioning in Schizophrenia: A Trial of Risperidone Versus Haloperidol. Can J Psychiatry 1997; 42:983

IX.II. Studies excluded for applying only neuropsychological tests in disagreement with our methodological criteria

1. Strauss WH, Klieser E, Luethcke H: Dyscognitive syndromes in neuroleptic therapy. Pharmacopsychiatry 1988; 21:298–299
2. Saletu B, Kiifferle B, Grünberger J, et al.: Quantitative EEG, SPEM, and Psychometrie Studies in Schizophrenics before and during Differential Neuroleptic Therapy. Pharmacopsychiatry 1986; 19:434–437

X - Supplementary material references

1 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. British Medical Journal. 2021:n21.

2 Baldez DP, Biazus TB, Rabelo-da-Ponte FD, Nogaro GP, Martins DS, Kunz M, et al. The effect of antipsychotics on the cognitive performance of individuals with psychotic disorders : Network meta-analyses of randomized controlled trials. Neuroscience and Biobehavioral Reviews. 2021;126:265–75.

3 Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary. (3rd ed.). Oxford University Press. 2006.

4 Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment (5th ed.). Oxford University Press. 2012.

5 Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68:283–97.

6 Keefe RSE, Mohs RC, Bilder RM, Harvey PD, Green MF, Meltzer HY, et al. Neurocognitive assessment in the clinical antipsychotic trials of intervention effectiveness (CATIE) project schizophrenia trial: Development, methodology, and rationale. Schizophr Bull. 2003;29:45–55.

7 Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. Am J Psychiatry. 2008;165:203–13.

8 Pietrzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ. A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. J Clin Exp Neuropsychol. 2009;31:848–59.

9 Ernst Nielsen R, Odur F, Østergaard T, Munk-Jørgensen P, Nielsen J. Comparison of the effects of Sertindole and Olanzapine on Cognition (SEROLA): A double-blind randomized 12-week study of patients diagnosed with schizophrenia. Therapeutic Advances in Psychopharmacology. 2014;4:4–14.

10 Rohatgi A. WebPlotDigitizer. 2020. Available at https://automeris.io/WebPlotDigitize.

11 Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011.