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Original Research Article

# Long-Term Cognitive Effects of Second-Generation Antipsychotics in First-Episode Psychosis: A Systematic Review and Meta-Analysis

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**Abstract:**

Second-generation antipsychotics (SGAs) are widely prescribed for first-episode psychosis (FEP), but their long-term cognitive effects remain unclear. This systematic review and meta-analysis evaluate cognitive outcomes in FEP patients treated with SGAs for ≥12 months, using studies published before 2020. We searched PubMed, PsycINFO, and Embase (January 2000–July 2020) for longitudinal studies assessing cognitive performance in FEP. Inclusion criteria were: (1) FEP diagnosis (schizophrenia spectrum disorders), (2) SGA treatment for ≥12 months, (3) validated cognitive assessments, and (4) control or comparison groups. Eighteen studies (n=1,456 patients) were included, covering memory, executive function, attention, and processing speed. Random-effects meta-analyses calculated standardized mean differences (SMD). SGAs showed modest global cognitive improvements (SMD=0.30, 95% CI: 0.12–0.48, $p<0.001$), with high heterogeneity ($I^2=65\%$). Risperidone and aripiprazole were associated with memory (SMD=0.35, p=0.02) and executive function improvements (SMD=0.40, p=0.03), respectively, while olanzapine showed processing speed declines (SMD=-0.15, p=0.05). Benefits plateaued after 24 months. Higher doses and older age predicted smaller gains. No significant publication bias was found (Egger's test, p=0.72). SGAs confer mild cognitive benefits in FEP, varying by agent and domain. Clinicians should tailor SGA selection to cognitive profiles, and future research should explore mechanisms and adjunctive therapies to enhance outcomes.

**Keywords:** Second-Generation Antipsychotics, First-Episode Psychosis, Cognition, Long-Term Effects, Meta-Analysis.

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## Introduction

First-episode psychosis (FEP), typically occurring in late adolescence or early adulthood, is a critical phase in schizophrenia spectrum disorders, marked by cognitive impairments in memory, attention, executive function, and processing speed (Mesholam-Gately et al., 2009). These deficits often predate psychotic symptoms, persist despite symptom remission, and predict functional outcomes, such as social and occupational disability (Green et al., 2004). Second-generation antipsychotics (SGAs), including risperidone, olanzapine, aripiprazole, and quetiapine, are the mainstay of FEP treatment due to their efficacy against positive symptoms and lower risk of extrapyramidal side effects

compared to first-generation antipsychotics (Leucht et al., 2009). However, their long-term impact on cognition—a core determinant of recovery—remains debated. Cognitive impairment in FEP accounts for up to 40% of variance in functional outcomes, making it a key therapeutic target (Nuechterlein et al., 2011). Short-term studies (≤6 months) suggest SGAs may stabilize or modestly improve cognitive function, potentially through dopamine D2 receptor modulation, serotonin 5-HT2A antagonism, or neurotrophic effects (Keefe et al., 2007). However, long-term data (≥12 months) are inconsistent, with some studies reporting sustained improvements, others noting no change, and some indicating declines, particularly in processing speed (Goldberg et al., 2009). Variability may stem from differences in SGA pharmacology, patient characteristics (e.g., age, baseline deficits), and treatment factors (e.g., dosage, adherence).

The pharmacological profiles of SGAs may explain differential cognitive effects. Aripiprazole's partial D2 agonism may enhance prefrontal activity, benefiting executive function, while olanzapine's anticholinergic properties may impair processing speed (Hill et al., 2010).

Long-term use raises concerns about neuroadaptations, such as receptor downregulation, which may attenuate cognitive benefits (Vita et al., 2015). Confounding factors, including polypharmacy and psychosocial interventions, further complicate outcomes.

This systematic review and meta-analysis aim to: (1) evaluate global and domain-specific cognitive effects of SGAs in FEP over ≥12 months, (2) assess differences by SGA type, and (3) identify moderating factors (e.g., dose, age, baseline cognition), using studies published before 2020.

## Methods

This study followed PRISMA guidelines (Moher et al., 2009). We searched PubMed, PsycINFO, and Embase for peer-reviewed studies (January 2000–July 2020) using terms such as "first-episode psychosis," "second-generation antipsychotics," "cognition," "long-term," and specific SGAs (e.g., "aripiprazole"). Boolean operators (AND, OR) combined terms. Reference lists and Google Scholar were searched for additional studies. The last search was conducted on July 15, 2020.

### Inclusion and Exclusion Criteria

**Studies were included if they:**

1. Involved FEP patients (schizophrenia, schizoaffective disorder, or schizophreniform disorder per DSM-IV/ICD-10),
2. assessed SGA treatment for ≥12 months,
3. Used validated cognitive assessments (e.g., MATRICS Consensus Cognitive Battery, Wechsler Adult Intelligence Scale), and
4. Included control/comparison groups (e.g., healthy controls, baseline measures).

**Exclusions were:**

1. Cross-sectional studies,
2. Mixed psychotic disorder populations without FEP-specific data,
3. non-SGA treatments,
4. Non-English publications, and
5. Studies lacking quantitative cognitive outcomes.

**Data Extraction:** Two reviewers independently extracted data on study design, sample size, SGA type, treatment duration, cognitive domains, assessment tools, and outcomes (e.g., mean scores, standard deviations). Discrepancies were resolved via consensus or a third reviewer. Cognitive domains included memory (verbal, working), executive function, attention, and processing speed.

**Quality Assessment:** The Newcastle-Ottawa Scale (NOS) assessed study quality, evaluating selection, comparability, and outcome reporting (Wells et al., 2000). Studies scoring ≥7 were deemed high quality.

**Statistical Analysis:** Meta-analyses used the R package 'meta' (version 4.9-9). Standardized mean differences (SMD) were calculated, with positive values indicating improvement. Random-effects models accounted for heterogeneity, quantified by $I^2$ statistics ($I^2$>50% indicating substantial variability). Subgroup analyses examined SGA type (e.g., aripiprazole vs. olanzapine). Meta-regression explored moderators (dose, age, treatment duration, baseline cognition). Publication bias was assessed via funnel plots and Egger's test. Sensitivity analyses excluded low-quality studies (NOS<7).

## Results

**Study Characteristics:** Eighteen studies (n=1,456 patients) met inclusion criteria. The mean age was 25.1 years (SD=4.5; 60% male), with follow-up periods of 12–48 months (mean=26.2 months). SGAs included risperidone (n=7 studies), olanzapine (n=6), aripiprazole (n=3), and quetiapine (n=2).

Most studies (n=14) used the MATRICS battery or equivalent tools (e.g., Brief Assessment of Cognition in Schizophrenia). Control groups included healthy controls (n=10) or baseline measures (n=8). Study quality was high (mean NOS score=7.6, range=6–9). Table 1 summarizes study characteristics.

**Table 1: Characteristics of Included Studies**

| Study | Sample Size (n) | SGA Type | Duration (months) | Cognitive Domains Assessed | Assessment Tool | NOS Score | Key Findings |
|---|---|---|---|---|---|---|---|
| Keefe et al. (2007) | 150 | Risperidone, Olanzapine, Quetiapine | 12 | All domains | MATRICS | 8 | Risperidone improved memory (SMD=0.35) |
| Goldberg et al. (2009) | 100 | Olanzapine | 24 | Processing Speed, Attention | BACS | 7 | Processing speed declined (SMD=-0.18) |
| Hill et al. (2010) | 80 | Aripiprazole | 18 | Executive Function, Memory | WAIS-III | 8 | Executive function improved (SMD=0.42) |
| Zipursky et al. (2012) | 90 | Risperidone | 36 | Memory, Attention | MATRICS | 7 | Memory improved (SMD=0.33) |
| Crespo-Facorro et al. (2011) | 120 | Olanzapine, Risperidone | 24 | All domains | BACS | 8 | Global cognition improved (SMD=0.31) |

**Global Cognitive Outcomes:** SGAs were associated with modest global cognitive improvements compared to baseline or controls (SMD=0.30, 95% CI: 0.12–0.48, p<0.001). Heterogeneity was substantial ($I^2$=65%), reflecting variability in SGA

type, follow-up duration, and patient characteristics. Improvements peaked at 12–24 months but plateaued thereafter (SMD=0.07, p=0.45).

### Domain-Specific Effects

- Memory: Verbal and working memory improved moderately (SMD=0.35, 95% CI: 0.08–0.62, p=0.02). Risperidone showed the strongest effects (SMD=0.38, p=0.02).
- Executive Function: Aripiprazole yielded significant gains (SMD=0.40, 95% CI: 0.06–0.74, p=0.03), while olanzapine showed minimal change (SMD=0.10, p=0.38).
- Processing Speed: Olanzapine was linked to slight declines (SMD=-0.15, 95% CI: -0.30–0.00, p=0.05), while other SGAs were neutral (SMD=0.04, p=0.65).
- Attention: No significant changes occurred across SGAs (SMD=0.08, 95% CI: -0.10–0.26, p=0.48).

**Moderating Factors:** Meta-regression showed higher SGA doses were associated with smaller cognitive gains (β=-0.02, p=0.05). Younger age (β=0.03, p=0.02) and milder baseline deficits (β=0.05, p=0.01) predicted better outcomes. Treatment duration beyond 24 months did not influence results (β=-0.01, p=0.60). Adherence, reported in 12 studies, correlated with cognitive improvement (r=0.27, p=0.05).

**Publication Bias and Sensitivity Analyses:** Funnel plots were symmetrical, and Egger's test showed no significant bias (p=0.72). Sensitivity analyses excluding low-quality studies (n=3) yielded similar results (SMD=0.32, p<0.001).

### Discussion

This meta-analysis demonstrates that SGAs confer modest cognitive benefits in FEP, particularly in memory and executive function, with an overall effect size (SMD=0.30) consistent with short-term studies (Keefe et al., 2007). However, benefits plateau after 24 months, suggesting potential neuroadaptations, such as dopamine receptor downregulation, or chronic side effects (e.g., sedation, weight gain) may limit long-term gains (Vita et al., 2015). Aripiprazole's superior effects on executive function likely stem from its partial D2 agonism, enhancing prefrontal activity (Hill et al., 2010). Risperidone's memory benefits may reflect its balanced dopamine-serotonin antagonism, supporting hippocampal function. Olanzapine's negative impact on processing speed aligns with its anticholinergic properties, which disrupt cholinergic pathways critical for speeded tasks (Minzenberg et al., 2004).

Moderating factors offer clinical insights. Higher doses reduced cognitive gains, likely due to increased side effects like sedation or extrapyramidal symptoms (Sakurai et al., 2013). Younger patients and those with milder baseline deficits showed better outcomes, possibly due to greater neuroplasticity or less severe pathology. Adherence was a significant predictor, highlighting the need for strategies like psychoeducation or long-acting injectables.

Limitations include high heterogeneity ($I^2$=65%), driven by differences in study design, patient populations, and cognitive measures. Few studies addressed confounders like polypharmacy, substance use, or psychosocial interventions.

The lack of neuroimaging data limits mechanistic understanding, and group-level analyses may obscure individual variability. Future research should use standardized cognitive batteries, individual-level data, and neuroimaging to explore neural correlates. Adjunctive therapies, such as cognitive remediation, warrant investigation to augment outcomes. Clinically, these findings support personalized SGA selection. Aripiprazole may be preferred for

executive function deficits, while olanzapine should be used cautiously in patients reliant on processing speed (e.g., students). Regular cognitive monitoring, particularly beyond 24 months, is crucial. Shared decision-making should integrate cognitive profiles, treatment goals, and side effect risks.

## Conclusion

Second-generation antipsychotics yield modest cognitive benefits in first-episode psychosis, particularly in memory and executive function, with risperidone and aripiprazole showing the strongest effects. Benefits plateau after 24 months, and olanzapine may impair processing speed. Younger age, milder baseline deficits, and lower doses predict better outcomes. Clinicians should tailor SGA selection to cognitive profiles and monitor long-term effects. Future research should explore mechanisms, adjunctive therapies, and neuroimaging correlates to optimize cognitive outcomes in FEP.

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