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Comparing the Effects of Atypical Antipsychotic Polypharmacy on Metacognitive Function in Schizophrenia: Considering AI-assisted Interventions as a Future Direction—a Pilot Study

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Abstract: *Metacognitive impairments are central to schizophrenia and strongly linked to limited insight and poor functional outcomes. While atypical antipsychotics effectively reduce positive symptoms, their influence on metacognition remains unclear. This pilot study explores how different antipsychotic regimens may affect metacognitive belief patterns, while also considering artificial intelligence (AI) only as a future direction for augmenting cognitive interventions. Twelve participants (eight with schizophrenia, four healthy controls) were assessed using the Metacognitions Questionnaire-30 (MCQ-30). Patients were prescribed either clozapine with amisulpride or two-drug combinations selected from risperidone, aripiprazole, and quetiapine. Between-group comparisons were conducted using one-way ANOVA with post hoc tests. Effect sizes and post hoc power analyses were calculated. No significant differences emerged in cognitive confidence or cognitive self-consciousness. However, patients receiving dual-drug combinations from risperidone, aripiprazole, and quetiapine reported stronger positive beliefs about worry and greater perceptions of thought dangerousness. These trends suggest that certain multi-drug regimens may intensify maladaptive metacognitive beliefs. This study provides preliminary observations that antipsychotic polypharmacy may influence metacognitive functioning in schizophrenia. While AI was not applied here, future research could examine whether digital tools may one day support metacognitive awareness and regulation alongside pharmacological care.*

Keywords: *metacognition; schizophrenia; antipsychotics; A.I. perspective.*

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1. Introduction

Schizophrenia is a multifaceted psychiatric disorder marked by hallucinations, delusions, and cognitive disturbances, including metacognitive dysfunction—the ability to evaluate and reflect on one's own thought processes. Metacognition, first conceptualized as the ability to think about one's own thinking (Flavell, 1979), is a key domain affected in schizophrenia. Metacognitive dysfunction has been strongly associated with reduced insight, poorer real-world functioning, and increased treatment resistance (Lysaker et al., 2013; Vohs et al., 2014). Individuals with limited metacognitive skills often misinterpret internal experiences and face challenges in achieving self-agency and social reintegration (Voruganti et al., 1998).

Atypical antipsychotics remain central to the treatment of schizophrenia, particularly for alleviating positive symptoms. However, their influence on metacognitive functioning is less well understood. Some evidence suggests that certain agents may promote cognitive organization (Millan et al., 2014), while others caution that polypharmacy could contribute to cognitive dulling or reinforce rigid belief patterns (Lysaker et al., 2011). Given the increasing prevalence of antipsychotic combination therapy (Corell & Gallego, 2012), clarifying its potential effects on metacognition is clinically important.

Recent developments in digital psychiatry highlight the potential for artificial intelligence (AI) to support patients with severe mental illness. Applications such as automated language analysis and behavioural modelling have shown promise in monitoring cognition, predicting relapse, and supporting adaptive coping strategies (Insel, 2017; Bedi et al., 2015). While AI tools were not implemented in the present study, we consider them a potential future avenue for complementing pharmacological care by enhancing self-reflection and cognitive insight.

The present pilot study therefore aimed to explore differences in metacognitive beliefs among individuals with schizophrenia receiving distinct antipsychotic regimens compared with healthy controls. Using the Metacognitions Questionnaire-30 (MCQ-30) (Cartwright-Hatton & Wells, 1997), we examined domains such as positive beliefs about worry, cognitive confidence, and self-reflectiveness. Our objective was not to draw causal conclusions but to generate preliminary observations that may inform future studies, including those integrating digital approaches.

2. Ethical Note

All study procedures adhered to the Declaration of Helsinki. Approval was obtained from the Ethics Committee of the Institute of Psychiatry 'Socola' Iași, Romania (Decision No. 195/17.03.2023). Informed consent was obtained from all participants after they were fully briefed on the study's purpose, rights, and confidentiality measures. Capacity to provide informed consent was assessed clinically: each patient was required to demonstrate a basic understanding of study procedures and the voluntary nature of participation before enrolment.

3. Study Design

The study followed a cross-sectional, comparative design. Twelve individuals between the ages of 18 and 65 took part, including eight patients with schizophrenia (Table 1.) and four healthy controls. A DSM-5 diagnosis of schizophrenia was confirmed by a psychiatrist for all patients. To ensure clinical stability, patients were required to have been on a stable antipsychotic regimen for at least three months prior to assessment. Exclusion criteria included an acute psychotic episode, comorbid psychiatric disorders such as major depression or bipolar disorder,and substance misuse (including alcohol) within the preceding three months. Additional exclusions included a history of major neurological disorders or intellectual disability. Treatment adherence was verified through clinical evaluation and medical records. Healthy controls were recruited from the community, had no psychiatric or neurological diagnoses, and no history of antipsychotic medication use.

Table 1. Schizophrenia patients' demographic description

Age	Sex	Illness	Debut	Antipsychotic treatment
50	Masculin	SCZ	34	Clozapina+amisulpride
64	Masculin	SCZ	40	Risperidona+aripiprazol
48	Masculin	SCZ	30	Clozapina+amisulpride
72	Feminin	SCZ	51	Risperidona+aripiprazol
64	Feminin	SCZ	48	Quetiapina+risperidone
54	Feminin	SCZ	32	Clozapina+amisulpride
55	Feminin	SCZ	28	Clozapina+amisulpride
44	Masculin	SCZ	25	Quetiapina+risperidone

Patients were grouped according to their current medication regimen, which reflected ongoing clinical prescribing practices and was not randomized. One subgroup was receiving clozapine in combination with amisulpride, while the other subgroup was receiving two-drug combinations drawn from risperidone, aripiprazole, and quetiapine. Each patient had been maintained on the prescribed regimen for a minimum of three months before inclusion in the study.

4. Metacognitive screening

Metacognitive beliefs were assessed using the Metacognitions Questionnaire-30 (MCQ-30), a validated self-report measure developed by Wells and Cartwright-Hatton (2004). The instrument consists of 30 items scored on a four-point Likert scale ranging from 1 ("do not agree") to 4 ("agree very much"), and it evaluates five domains: positive beliefs about worry, negative beliefs regarding the dangerousness or uncontrollability of thoughts, cognitive confidence, the need to control thoughts, and cognitive self-consciousness.

The MCQ-30 is supported by strong psychometric evidence across both clinical and general populations (Spada, Mohiyeddini, & Wells, 2008). In schizophrenia research, it has been used to explore the connection between thought beliefs and symptoms such as paranoia and poor insight (Morrison & Wells, 2003; Lysaker et al., 2013).

5. Statistical analysis

Statistical analysis of numerical data resulting from the metacognitive screening of the participants was performed using GraphPad Prism software (version 10.0.0 for Windows, GraphPad Software, Boston, Massachusetts USA). The results were expressed as means ± SEM (standard error of the mean). One-way ANOVA followed by post hoc analysis (Tukey's HSD test) was conducted to test the differences between the groups.

Post-hoc power analyses were conducted in G*Power 3.1 for each of the metacognitive belief outcomes using the observed group means, standard deviations, and sample sizes (Control: n = 4; CLO+Ami: n = 4; Risp+Arip+Que: n = 4). One-way ANOVA (fixed effects, omnibus) was selected with $\alpha = 0.05$ (two-tailed). Effect sizes were expressed as Cohen's f for omnibus tests and Cohen's d for pairwise group comparisons (approximated via independent-samples t tests).

All five outcomes showed very large effect sizes and correspondingly high power despite the small sample sizes (Table 2). Cohen's f values ranged from 1.12 to 3.18, yielding an omnibus power of 0.99–1.00.

Table 2. Omnibus ANOVA effect sizes and statistical power

Outcome	f	Omnibus power (α=0.05)
Cognitive confidence	1.30	0.99+
Positive beliefs about worry	3.18	~1.00
Negative beliefs about danger	1.76	~1.00
Need to control thoughts	1.12	0.99
Cognitive self-consciousness	1.28	0.99

Power for pairwise group contrasts was more variable. Comparisons between Controls and Risp+Arip+Que consistently showed very large effect sizes (d = 1.18–6.88) and high power (0.67–1.00). By contrast, comparisons involving CLO+Ami showed lower power due to higher within-group variance. For example, Control vs CLO+Ami yielded medium–large effect sizes (d = 0.54–1.39) but low-to-moderate power (0.11–0.73), and CLO+Ami vs Risp+Arip+Que comparisons showed moderate to large effects (d = 0.72–1.96) but only modest power (0.19–0.68).

6. Results

For cognitive confidence (Figure 1A) and cognitive self-consciousness (Figure 1C), no significant group differences were observed. By contrast, positive beliefs about worry (Figure 1B) showed a significant overall effect in the one-way ANOVA ($F(2,9) = 15.10$, $p = 0.001$). Post hoc comparisons indicated that the risperidone + aripiprazole + quetiapine group scored higher than both controls ($p = 0.001$) and the clozapine + amisulpride group ($p = 0.028$).

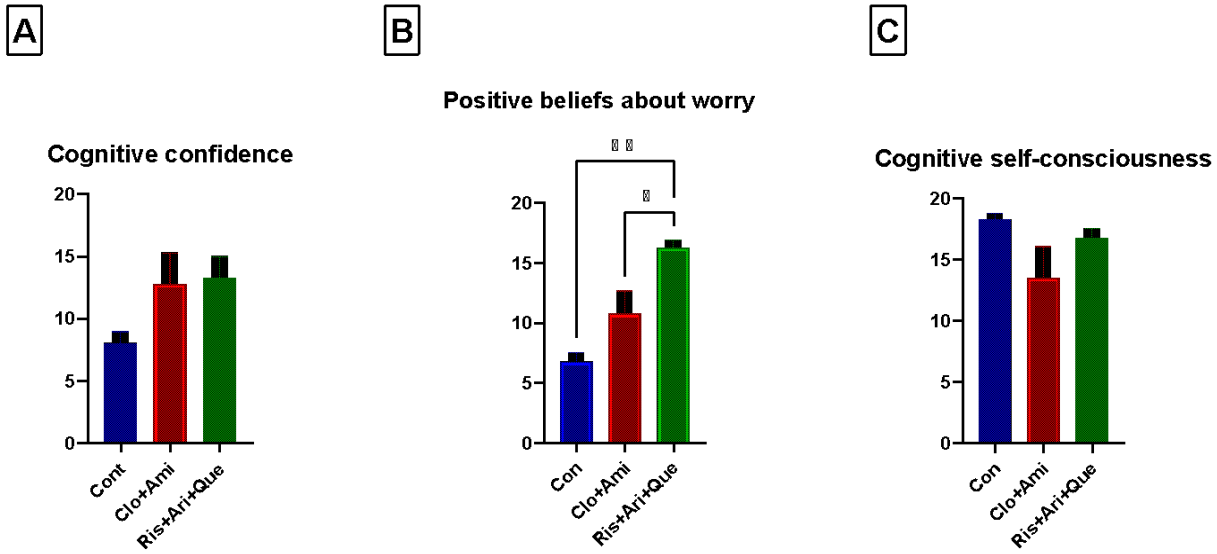

Figure 1. Graphical representation of the MCQ-30 scores for Cognitive confidence (A); Positive beliefs about worry (B); Cognitive self-consciousness (C); Data are represented as mean ± SEM in the case of Control (n=4), for Clo+Ami (n=4) and Risp+Ari+Que (n=4); "" indicate significant differences at the level of p<0.05 using one-way ANOVA followed by Tukey's multiple comparison test.*

For negative beliefs about danger (Figure 2A), the one-way ANOVA revealed a significant overall effect, $F(2,9) = 4.64$, $p = 0.041$. Post hoc analysis showed that the risperidone + aripiprazole + quetiapine group scored significantly higher than controls ($p = 0.037$). In contrast, no significant group differences were observed for the need to control thoughts (Figure 2B).

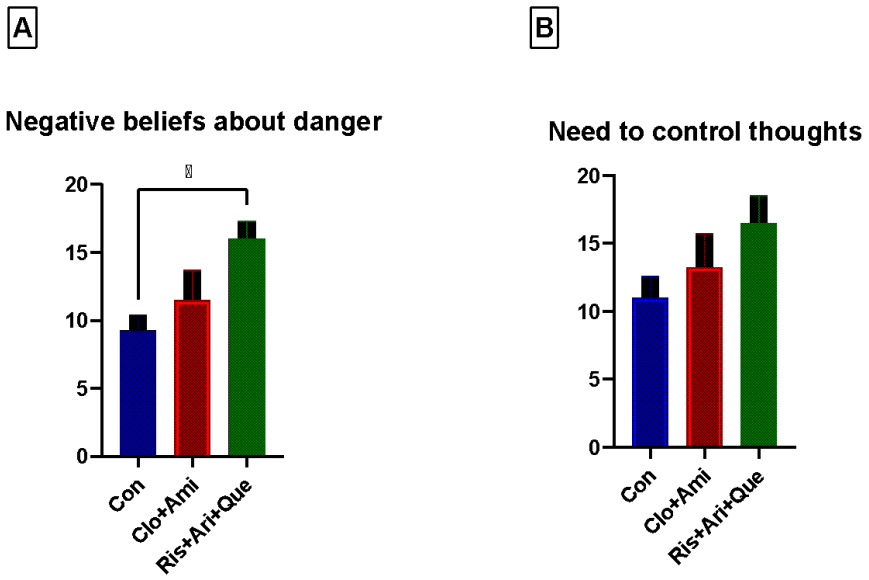

Figure 2. Graphical representation of the MCQ-30 scores for Negative beliefs about danger (A); Need to control thoughts (B); Data are represented as mean ± SEM in the case of Control (n=4), for Clo+Ami (n=4) and Risp+Arip+Que(n=4); "" indicate significant differences at the level of p<0.05 using one-way ANOVA followed by Tukey's multiple comparison test.*

7. Discussion

This pilot investigation provides preliminary insights into how different antipsychotic regimens may influence metacognitive beliefs in schizophrenia. Consistent with earlier work (Dimaggio & Lysaker, 2010; Moritz & Lysaker, 2018), the patterns observed here suggest possible differences in cognitive-affective profiles depending on medication combinations.

Although no statistically significant differences emerged in cognitive confidence, patients on triple-drug combinations showed higher endorsement of positive beliefs about worry. These findings may reflect cognitive-affective rigidity that warrants further exploration in larger studies. Similarly, the observed differences in negative beliefs about uncontrollability and thought danger, while tentative, align with existing literature on maladaptive metacognitive processes in psychosis (Morrison, Wells, & Nothard, 2002; Freeman & Garety, 2014).

Self-reflective awareness (cognitive self-consciousness) was highest among healthy participants, consistent with prior evidence that schizophrenia is frequently associated with reduced introspective ability (Lysaker, Buck, & Ringer, 2007). It is possible that certain antipsychotic regimens contribute to this limitation, for example, through extrapyramidal side effects or by influencing prefrontal dopaminergic functioning (Stahl, 2013; Keefe et al., 2007).

Further analysis suggested that patients in the triple-drug combination group involving risperidone, aripiprazole, and quetiapine tended to score higher on negative beliefs about the uncontrollability of thoughts, a pattern that is in line with previous reports on thought fusion and anxiety in psychosis (Freeman & Garety, 2014). Although these results did not reach statistical significance, a similar trend appeared in relation to the perceived need to suppress or control thoughts, which would be consistent with maladaptive coping styles described in schizophrenia (Morrison, Wells, & Nothard, 2002).

These results underscore the potential value of considering new avenues for cognitive support in schizophrenia. Although speculative at present, future advances in artificial intelligence (AI) may offer complementary strategies to pharmacological treatment. For example, natural language processing and behavioral modeling have shown promise in monitoring cognitive processes and predicting relapse in research contexts (Bedi et al., 2015; Corcoran et al., 2018). Extrapolating from such developments, one could envisage AI-informed tools that provide

feedback, encourage self-reflection, or assist with cognitive flexibility in patients receiving complex medication regimens.

Potential Role of AI in Supporting Metacognitive Rehabilitation

Although not applied in this study, recent advances in artificial intelligence (AI) suggest possible avenues for supporting metacognitive rehabilitation in schizophrenia. AI-driven systems have been increasingly explored in psychiatry for their capacity to monitor speech, cognition, and behavior in real time, allowing for early identification of cognitive disruptions and relapse risk (Bedi et al., 2015; Corcoran et al., 2018; Polari et al., 2021). Applied prospectively, such tools could offer individualized feedback and adaptive exercises to strengthen self-reflectiveness, cognitive flexibility, and insight—domains often compromised in schizophrenia (Lysaker et al., 2013; Moritz & Lysaker, 2018).

Moreover, digital platforms incorporating natural language processing and ecological momentary assessment have shown feasibility in detecting thought disorganization and monitoring cognitive-affective states (Insel, 2017; Fusar-Poli et al., 2019). In theory, these technologies might be adapted to deliver metacognitive prompts, guide patients through self-monitoring tasks, or integrate psychoeducational content tailored to ongoing needs. Such applications remain speculative at present but represent an innovative complement to pharmacological treatment that warrants systematic evaluation in future research.

In summary, this exploratory investigation suggests preliminary associations between antipsychotic polypharmacy and specific metacognitive beliefs in schizophrenia. Although tentative, these observations underscore the value of examining metacognition as a treatment-relevant dimension and point toward future possibilities for integrating pharmacological and digital strategies to support cognitive recovery.

8. Limitations and Future Directions

Several limitations of the current study warrant attention. First, the sample size was extremely small, which increases the risk of both Type I and Type II errors despite the large effect sizes observed. Second, treatment regimens were not randomised but reflected existing clinical prescriptions, introducing potential confounding factors such as illness duration, comorbidities, and prior treatment history. Third, although power analyses suggested high achieved power for omnibus tests, some pairwise contrasts were underpowered, particularly in the clozapine plus amisulpride group. Finally, the study relied solely on self-report measures, which may not fully capture the complexity of metacognitive processes.

Future research should address these limitations by recruiting larger and more diverse samples, controlling for illness-related and treatment-related confounders, and employing multimodal approaches that combine self-report with behavioural or neurocognitive measures. Incorporating digital tools, including AI-driven interventions, could provide an innovative means of enhancing insight and self-reflection, though such approaches require careful ethical consideration and validation in clinical contexts.

Speculatively, AI-informed approaches could be operationalized in several practical ways. For instance, smartphone applications and wearable devices may one day provide ecological momentary assessments to track fluctuations in thought patterns, speech, and affect in daily life (Insel, 2017; Polari et al., 2021). Natural language processing could be used to detect disorganized speech or perseverative thinking (Bedi et al., 2015; Corcoran et al., 2018), which might then trigger adaptive feedback or prompt patients to engage in structured metacognitive exercises. Digital agents could also deliver psychoeducational content or short cognitive training tasks in real time, supporting the identification of maladaptive beliefs and encouraging alternative interpretations. These possibilities remain speculative but illustrate how AI-based systems could, in the future, complement pharmacological interventions by offering scalable, individualized support beyond the clinic.

9. Conclusion

This pilot study adds to a growing body of literature examining the interaction between pharmacological treatment and cognitive functioning in schizophrenia. Findings suggest that complex drug regimens, particularly those involving risperidone, aripiprazole, and quetiapine, may influence beliefs about worry and thought control.

Although no digital methods were employed in this study, there is a theoretical rationale for exploring whether AI-informed approaches could one day complement medication by addressing metacognitive impairments. Such possibilities remain prospective and require careful investigation in future research.

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