29-year-old male with a 10-year history of schizophrenia is currently admitted to the inpatient psychiatric unit for his fourth relapse in two years. He is currently maintained on antipsychotic polypharmacy but still experiences persistent auditory hallucinations and paranoid delusions despite adherence. The team is considering transitioning to Clozapine monotherapy for treatment-resistant schizophrenia.

Search question: In adults with treatment-resistant schizophrenia (TRS), does clozapine monotherapy compared with antipsychotic polypharmacy improve positive symptom control and reduce relapse or rehospitalization rates?

Question type: What kind of question is this?

Prevalence
Screening
Diagnosis
Prognosis
Treatment
Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

If systematic reviews or meta-analyses are not available, randomized controlled trials (RCTs) would be the next most appropriate level of evidence, as they provide the most reliable way to directly compare clozapine monotherapy with antipsychotic polypharmacy while minimizing bias. However, in psychiatry, RCT data, especially in treatment-resistant schizophrenia, can sometimes be limited due to ethical and practical constraints. In those cases, prospective cohort studies may be helpful since they allow for direct observation of "real-world" outcomes over time, such as relapse and rehospitalization rates. Retrospective cohort studies can also contribute some useful information, especially when large datasets are available, but they are more prone to confounding variables and selection bias compared to prospective designs.

PICO search terms:

Population	Intervention	Comparison	Outcome
Treatment-resistant schizophrenia	Clozapine	Antipsychotic combination	Relapse rates
Refractory schizophrenia		Polypharmacy	Rehospitalization
Adult(s)		Combination therapy	Hospital readmission
Persistent psychosis		Dual antipsychotics	Positive symptom

Search tools and strategy used: Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters. Explain how you narrowed your choices to the few selected articles. For example, if your search returned 25 articles among the several databases used, what was the process used to determine which articles to use?

Database	Search Terms Used	Number of Results	Filters Applied
PubMed	("treatment resistant schizophrenia") AND ("clozapine") AND ("polypharmacy" OR "combination") AND	7	Last 10 years (2016-2026), English Language, Humans

	("readmission" OR "relapse")		
Google Scholar	Clozapine monotherapy versus antipsychotic polypharmacy for schizophrenia	304	2022-2026, Review articles only
Cochrane	Clozapine monotherapy versus antipsychotic polypharmacy for schizophrenia	4	None

For this PICO assignment, I searched three databases: PubMed, Cochrane Library, and Google Scholar. In PubMed, the initial search yielded around 30 articles, which I was able to narrow down to 7 after applying the filters listed above. The initial search in Google Scholar produced the largest number of articles (approximately 5,400), but after filtering to include only review articles published between 2022 and 2026, I was able to reduce this to around 300 articles. The Cochrane Library returned the smallest initial search, even before applying filters, which is expected since it mainly focuses on high-quality systematic reviews and meta-analyses. I then reviewed the titles and abstracts of the articles from each database and selected one highly relevant article from each to include in my analysis.

1. Efficacy and safety of clozapine in psychotic disorders—a systematic quantitative meta-review

Citation: Wagner E, Siafis S, Fernando P, Falkai P, Honer WG, Röh A, Siskind D, Leucht S, Hasan A. Efficacy and safety of clozapine in psychotic disorders-a systematic quantitative meta-review. Transl Psychiatry. 2021 Sep 22;11(1):487. doi: 10.1038/s41398-021-01613-2. PMID: 34552059; PMCID: PMC8458455.

Article type: Systemic quantitative meta-review

Abstract

A recent increase in the literature regarding the evidence base for clozapine has made it increasingly difficult for clinicians to judge “best evidence” for clozapine use. As such, we aimed at elucidating the state-of-the-art for clozapine with regard to efficacy, effectiveness, tolerability, and management of clozapine and clozapine-related adverse events in neuropsychiatric disorders. We conducted a systematic PRISMA-conforming quantitative meta-review of available meta-analytic evidence regarding clozapine use. Primary outcome effect sizes were extracted and transformed into relative risk ratios (RR) and standardized mean differences (SMD). The methodological quality of meta-analyses was assessed using the *AMSTAR-2* checklist. Of the 112 meta-analyses included in our review, 61 (54.5%) had an overall high methodological quality according to *AMSTAR-2*. Clozapine appears to have superior effects on positive, negative, and overall symptoms and relapse rates in schizophrenia (treatment-resistant and non-treatment-resistant subpopulations) compared to first-generation antipsychotics (FGAs) and to pooled FGAs/second-generation antipsychotics (SGAs) in treatment-resistant schizophrenia (TRS). Despite an unfavorable metabolic and hematological adverse-event profile compared to other antipsychotics, hospitalization, mortality and all-cause discontinuation (ACD) rates of clozapine surprisingly show a pattern of superiority. Our meta-review outlines the superior overall efficacy of clozapine compared to FGAs and most other SGAs in schizophrenia and suggests beneficial efficacy outcomes in bipolar disorder and Parkinson’s disease psychosis (PDP). More clinical studies and subsequent meta-analyses are needed beyond the application of clozapine in schizophrenia-spectrum disorders and future studies should be directed into multidimensional clozapine side-effect management to foster evidence and to inform future guidelines.

Key points:
- Clozapine is significantly superior to placebo and superior to FGAs and SGAs with regard to overall and positive symptom in TRS on a single-substance level
- Clozapine is associated with significantly lower hospitalization rates than other SGAs
- Clozapine may not be superior to other antipsychotics for overall symptom reduction in long-term RCTs exceeding 26 weeks
- Clozapine shows a pattern of superiority for all-cause discontinuation rates compared to most other antipsychotics, including SGAs like risperidone and quetiapine

I chose this article because it provides a comprehensive review of clozapine’s efficacy and safety across psychotic disorders, including treatment-resistant schizophrenia. Although it does not directly compare clozapine monotherapy to antipsychotic polypharmacy, it demonstrates the overall “power” of clozapine in improving positive symptoms such as hallucinations and delusions, reducing hospitalization, and lowering all-cause discontinuation rates. A low all-cause discontinuation rate indicates that patients are more likely to remain on treatment, reflecting that clozapine is generally well-tolerated. Another important point that the article emphasized is that delaying clozapine monotherapy in favor of ineffective antipsychotic treatment is associated with poorer mental health and functional outcomes.

2. Randomized controlled trial of clozapine in resistant schizophrenia and schizoaffective disorder

Citation: Peraire M, Arnau-Peiró F, Villar-García M, Benito A, Echeverria I, Haro G. Randomised controlled trial of clozapine in resistant schizophrenia and schizoaffective disorder. J Psychopharmacol. 2025 Nov;39(11):1284-1298.

Article type: Randomized controlled trial

Abstract

Background:

Clozapine (CLZ) stands out for its unique receptor profile, making it more effective than other antipsychotics, especially in treatment-resistant schizophrenia (TRS). There is growing evidence supporting its use in schizoaffective disorder (SZD), although diagnostic challenges and drug characteristics have complicated the implementation of specific clinical trials.

Aim:

Compare efficacy and tolerability of CLZ in real-world patients with TRS and SZD.

Methods:

Prospective, pragmatic, three-month, evaluator-blinded clinical trial with two randomised controlled arms (TRS groups) and a third fixed arm (SZD group). The clinical response was assessed by monthly visits during which the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), Montgomery–Asberg Depression Rating Scale (MADRS), Calgary Depression Scale for Schizophrenia (CDSS), Clinical Global Impression (CGI) and Udvalg für Kliniske Undersogelser were administered. One hundred twenty-seven participants (74.8% men, 25.2% women; 84 TRS, 42 SZD; mean age of 38.53) completed the follow-up.

Results:

Patients treated with CLZ showed a greater reduction in all the PANSS subscales, MADRS and CDSS. In cases of SZD, there was a significant decrease in positive (F: 3.72, $p < 0.05$) and negative (F: 6.58, $p < 0.01$) symptoms, the overall score of PANSS (F: 5.64, $p < 0.01$) and YMRS (F: 12.01, $p < 0.01$). Patients using CLZ had a better subjective perception of their treatment (χ^2: 17.29, $p < 0.01$). CLZ prescription was the only predictor of better outcomes across all the scales and improved substance use (dual disorders).

Conclusions:

CLZ was effective in reducing psychotic and affective symptoms in patients with dual psychosis, with better outcomes in SZD compared with TRS.

Key points:

- CLZ significantly reduces positive, negative, and total psychopathology scores on the Positive and Negative Syndrome Scale (PANSS)
- Both TRS-clozapine group and the TRS-control (polypharmacy) group showed improvement over time, but the clozapine group had lower (better) final symptom scores
- The efficacy of clozapine was not accompanied by an increase in serious side effects in this study
- Polypharmacy control group required more treatment for side effects by the end of the three-month follow-up compared to those on clozapine

I chose this article because it clearly demonstrates how effective clozapine monotherapy can be for patients with treatment-resistant schizophrenia. It shows that clozapine not only helps reduce positive and negative symptoms but also allows patients to rely less on other antipsychotics or sedatives, making treatment simpler. What stood out most is that patients on clozapine experienced fewer side effects and were more likely to stay on their medication compared with those taking multiple antipsychotics, which highlights both its effectiveness and tolerability in a real-world setting.

3. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis

Citation: Galling B, Roldán A, Hagi K, Rietschel L, Walyzada F, Zheng W, Cao XL, Xiang YT, Zink M, Kane JM, Nielsen J, Leucht S, Correll CU. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World Psychiatry. 2017 Feb;16(1):77-89. doi: 10.1002/wps.20387. PMID: 28127934; PMCID: PMC5269492.

Article type: Systemic review and meta-analysis

Antipsychotic polypharmacy in schizophrenia is much debated, since it is common and costly with unclear evidence for its efficacy and safety. We conducted a systematic literature search and a random effects meta-analysis of randomized trials comparing augmentation with a second antipsychotic vs. continued antipsychotic monotherapy in schizophrenia. Co-primary outcomes were total symptom reduction and study-defined response. Antipsychotic augmentation was superior to monotherapy regarding total symptom reduction (16 studies, N=694, standardized mean difference, SMD=–0.53, 95% CI: −0.87 to −0.19, p=0.002). However, superiority was only apparent in open-label and low-quality trials (both p<0.001), but not in double-blind and high-quality ones (p=0.120 and 0.226, respectively). Study-defined response was similar between antipsychotic augmentation and monotherapy (14 studies, N=938, risk ratio = 1.19, 95% CI: 0.99 to 1.42, p=0.061), being clearly non-significant in double-blind and high-quality studies (both p=0.990). Findings were replicated in clozapine and non-clozapine augmentation studies. No differences emerged regarding all-cause/specific-cause discontinuation, global clinical impression, as well as positive, general and depressive symptoms. Negative symptoms improved more with augmentation treatment (18 studies, N=931, SMD=–0.38, 95% CI: −0.63 to −0.13, p<0.003), but only in studies augmenting with aripiprazole (8 studies, N=532, SMD=–0.41, 95% CI: −0.79 to −0.03, p=0.036). Few adverse effect differences emerged: D2 antagonist augmentation was associated with less insomnia (p=0.028), but more prolactin elevation (p=0.015), while aripiprazole augmentation was associated with reduced prolactin levels (p<0.001) and body weight (p=0.030). These data suggest that the common practice of antipsychotic augmentation in schizophrenia lacks double-blind/high-quality evidence for efficacy, except for negative symptom reduction with aripiprazole augmentation.

Key points:

- No evidence that adding a second antipsychotic improved treatment response rates compared to monotherapy
- Polypharmacy increases the potential for drug-drug interactions, higher costs, decreased treatment adherence due to complex regimens, and specific side effects like prolactin elevation
- Patients with higher baseline symptom severity experienced less improvement when switched to a polypharmacy regimen

This article points out the downsides of using multiple antipsychotics in schizophrenia. It shows that adding a second antipsychotic doesn't actually improve treatment response compared to sticking with one. On top of that, polypharmacy can increase the risk of drug interactions, make treatment more expensive, and make it harder for patients to stick to their regimen. Side effects, like elevated prolactin levels, are also more common. Interestingly, patients who start out with more severe symptoms often see less benefit from adding another antipsychotic, which reinforces the idea that monotherapy, especially with clozapine for treatment-resistant cases, tends to be the safer and more effective approach.

What is the clinical "bottom line" derived from these articles in answer to your question?

In my current psychiatric unit, there's a difference of opinion between my two attendings when a patient isn't responding to treatment. One prefers adding a second antipsychotic while the other favors switching to clozapine monotherapy. While clozapine comes with the risk of agranulocytosis, seizures, and myocarditis, it is actually one of the most effective options for treatment-resistant schizophrenia. Evidence shows that clozapine not only improves positive and negative symptoms more reliably than polypharmacy but also reduces hospitalization rates, lowers all-cause treatment discontinuation, and is generally better tolerated, making it a preferred strategy for patients who have not responded to other antipsychotic regimens. Additionally, the use of polypharmacy is associated with increased side effects, higher costs, greater risk of drug-drug interactions, and lower adherence, without clear evidence of superior symptom control compared to clozapine monotherapy. To put it in an analogy, using multiple antipsychotics for treatment-resistant schizophrenia is like slapping patches on a big leak. It might feel like you're fixing things, but the problem keeps coming back, and the mess can cause new issues. Clozapine, on the other hand, is like calling in a skilled repair team. It takes more effort and careful monitoring, but it tackles the root of the problem and keeps things stable for the long term. All in all, clozapine monotherapy is preferred for treatment-resistant schizophrenia because it directly addresses the underlying illness, provides more reliable symptom control, reduces hospitalizations, and is better tolerated, whereas polypharmacy often adds complexity and risk without proven additional benefit.