

Research Article

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Can Cariprazine Substitute Clozapine in Treatment-Resistant Schizophrenia When Clozapine is Ineffective?

Devarssa Pratheepan^{1*} and Hamid Rahmanian²

¹Pharmacy student, SGUL, United Kingdom

²Consultant Psychiatrist, SGUL, United Kingdom

*Corresponding author

Devarssa Pratheepan, Pharmacy student, SGUL, United Kingdom.

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Introduction

Treatment-Resistant Schizophrenia (TRS) affects approximately one third of individuals with schizophrenia and is defined by persistent symptoms despite two adequate antipsychotic trials. Clozapine remains the only evidence-based treatment for TRS, yet 40 to 60% of patients fail to respond, and many discontinue due to metabolic, cardiovascular, or haematological toxicity.

Cariprazine, a dopamine D3-preferring partial agonist, has demonstrated efficacy for negative symptoms and cognitive related domains. Its long half-life and favourable metabolic profile making it suitable as a substitute when clozapine is ineffective or intolerable.

This systematic review evaluates whether cariprazine can replace clozapine in TRS.

Systematic Review Methodology

Search Domains / Databases

- Natural Institutes of Health
- Frontiers
- ResearchGate
- ScienceDirect

Search Terms

- “cariprazine AND clozapine-resistant schizophrenia”
- “cariprazine AND treatment-resistant schizophrenia”
- “cariprazine AND clozapine non-response”
- “cariprazine AND clozapine intolerance”
- “cariprazine monotherapy AND TRS”
- “cariprazine switch AND schizophrenia”
- “cariprazine AND clozapine discontinuation”
- “dopamine D3 partial agonist AND clozapine failure”
- “antipsychotic switch AND cariprazine”
- “cariprazine after clozapine”

Inclusion Criteria

- Human participants with TRS
- Documented clozapine: no response or intolerance
- Cariprazine used as a replacement for clozapine
- Extractable clinical outcomes
- Studies in English
- Any study design except animal or preclinical

Exclusion Criteria

- Cariprazine used as adjunct to clozapine
- No clozapine failure documented
- Wrong diagnosis
- Early psychosis or non-TRS populations
- Reviews without primary data
- Case reports < 5 patients unless directly reporting clozapine substitution

Screening Process

A structured screening process was undertaken to identify studies evaluating whether cariprazine can substitute clozapine in individuals with treatment-resistant schizophrenia (TRS). Searches were conducted across four domains: the National Institutes of Health, Frontiers, ResearchGate, and ScienceDirect. Search terms included Boolean combinations such as “cariprazine AND clozapine-resistant schizophrenia”, “cariprazine AND clozapine non-response”, and “cariprazine switch AND schizophrenia”.

A total of 13 records were identified. After removal of duplicates, titles and abstracts were screened against predefined inclusion and exclusion criteria. Studies were excluded if they did not involve TRS, did not document clozapine failure, or used cariprazine as an adjunct rather than a substitute. Full-text screening was performed for all potentially relevant articles. Three studies met all eligibility criteria and were included in the final synthesis [1-3].

Included Studies

Table 1: Characteristics of Included Studies Evaluating Cariprazine as a Substitute for Clozapine in Treatment-Resistant Schizophrenia.

TRS = treatment-resistant schizophrenia, SANS = Scale for the Assessment of Negative Symptoms.

Study	Design	Sample	Clozapine Failure Type	Cariprazine Regimen	Outcome
Montgomery et al., 2023[1]	Case Report	1	Not responsive and intolerant	1.5 to 3 mg / day monotherapy	Marked improvement in SANS, positive symptoms, functioning
Vasiliu, 2021 (Case 2)[2]	Case Series	1	Not responsive and relapse on clozapine	Up titrated to monotherapy	Symptom remission, functional recovery
Dombi et al., 2021[5]	Observational	TRS subgroup (n = 10 to 15)	Insufficient effectiveness of previous antipsychotics including clozapine	Flexible dosing	Significant improvement in negative symptoms and global functioning

Excluded Studies

Table 2: Studies Excluded After Full-Text Screening with Reasons for Exclusion. Adjunct= cariprazine used alongside clozapine rather than as a substitute.

Study	Reason for Exclusion
Siwek et al., 2024[4]	This study focused on adjunct therapy and clozapine was not discontinued.
Darriba, 2021[5]	This study also focuses on adjunct therapy. There is no switch to monotherapy.
Durgam et al., 2016[6]	This journal was not on treatment-resistant schizophrenia or clozapine failure.
Cariprazine (Vraylar): CADTH Reimbursement Recommendation: Indication: As monotherapy for: bipolar mania: acute management of manic or mixed episodes associated with bipolar I disorder in adults. (2022)[7]	This is not primary clinical date; it is a policy document.
Marder et al., 2019[8]	This journal is about acute schizophrenia not treatment-resistant schizophrenia. Also, clozapine failure is not mentioned.
Pappa, Arturas Kalniunas and Maret, 2023[9]	This study addresses early psychosis; it does not include treatment-resistant schizophrenia and clozapine failure.
Selvan et al., 2024[10]	This is a narrative review; it does not include primary TRS data.
Fagiolini et al., 2020[11]	This journal is from an expert panel which did not have extractable treatment-resistant cases.
Pappa et al., 2025[12]	Cariprazine used as adjunct to clozapine not as substitution.
Carmassi et al., 2024[13]	Treatment-resistant schizophrenia and clozapine was not documented.

Comparison of Findings
Symptom Improvement

Across all three studies, cariprazine monotherapy following clozapine discontinuation produced consistent improvements:

- Negative symptoms: Significant reductions in SANS and PANNS-N scores (e.g. 64.7% reduction in SANS in [1].
- Positive symptoms: Decreased hallucinations, delusions, and disorganisation
- Affective and cognitive domains: Improved motivation, emotional expression, and cognitive engagement

Functional Outcomes

All studies reported meaningful functional gains:

- Increased social interaction
- Improved daily functioning
- Return to employment or structured activity
- Enhanced communication and insight

These improvements were particularly notable in patients who had deteriorated on clozapine.

Tolerability and Safety

Cariprazine demonstrated a favourable tolerability profile:

- No metabolic deterioration
- No cardiovascular complications
- No haematological abnormalities
- Mild akathisia in some cases

This contrasts with clozapine-related:

- Weight gain
- Tachycardia
- Hypersalivation
- Metabolic syndrome

No study reported:

- Withdrawal psychosis
- Rebound symptoms
- Severe adverse events

Overall Comparative Interpretation

Across all three included studies:

- Cariprazine was better tolerated than clozapine
- Cariprazine improved negative symptoms more consistently

- Functional recovery was robust and sustained
- Safety profile was favourable, especially for patients with metabolic or cardiovascular issues on clozapine

This comparison supports the hypothesis that cariprazine may be a viable substitute for clozapine in selected TRS cases.

Discussion

This systematic review identified three studies where cariprazine was used as a substitute for clozapine after documented failure or intolerance. Across these studies, cariprazine monotherapy consistently improved clinical outcomes, particularly negative symptoms and functional recovery.

Why Might Cariprazine Work When Clozapine Fails?

- D3-preferring partial agonism may target motivational and cognitive circuits not adequately modulated by clozapine
- Favourable metabolic profile allows continuation in patients who cannot tolerate clozapine
- Long half-life supports adherence and reduces relapse risk

Clinical Implications

Cariprazine may be considered when:

- Clozapine is ineffective
- Clozapine causes intolerable side effects
- Blood monitoring is not feasible
- Negative symptoms predominate

However, it should not be considered equivalent to clozapine in evidence strength.

Limitations of This Review

This systematic review has several important limitations that must be acknowledged.

The available evidence base is extremely limited: only three studies met the inclusion, consisting of two single-patient case reports and one observational study with a small subgroup of patients who had documented clozapine failure. The absence of randomised controlled trials (RCTs) or large prospective cohorts significantly restricts the strength and generalisability of the conclusions.

The included studies demonstrated substantial heterogeneity in diagnostic criteria, definitions of treatment resistance, prior antipsychotic exposure, and outcome measures. This variability prevented quantitative synthesis and limits comparability across studies.

The reliance on case-based evidence introduces a high risk of publication bias. Positive outcomes are more likely to be reported, while unsuccessful or neutral switches from clozapine to cariprazine may remain unpublished.

The observational study did not exclusively recruit clozapine-resistant patients; only a subset met the criteria for clozapine failure [5]. Extracting data from this subgroup introduces risk of misclassification and reduces internal validity.

Follow-up durations varied widely and long-term outcomes remain unclear. Sustained remission, relapse rates, and functional trajectories after switching from clozapine to cariprazine are insufficiently studied.

Finally, the review included publications in English only, which may exclude relevant international evidence.

Collectively, these limitations highlight the need for more rigorous and systematic research before firm clinical recommendations can be made.

Conclusions

This systematic review identified three studies in which cariprazine was used as a substitute for clozapine following documented clozapine non-response or intolerance in individuals with treatment-resistant schizophrenia. Across all included studies, cariprazine monotherapy was associated with clinically meaningful improvements in negative symptoms, positive symptoms, and functional outcomes, with a favourable tolerability profile.

Although the evidence is limited to small-scale and uncontrolled designs, the consistency of improvement across cases suggests that cariprazine may represent a promising alternative for patients who cannot continue clozapine due to inefficacy or adverse effects. Its pharmacological profile, particularly D3-preferring partial agonism, provides a plausible mechanism rationale for its effectiveness in domains where clozapine may be insufficient.

However, given the scarcity and low quality of available evidence, cariprazine cannot currently be recommended as a standard replacement for clozapine in TRS. Instead, it may be considered on a case-by-case basis when clozapine is not viable.

Robust clinical trials are urgently needed to determine whether cariprazine can reliably serve as a third-line monotherapy in TRS.

Recommendations For Future Research

Based on the findings and limitations for this review, several key areas for future research are identified

Conduct Randomised Controlled Trials (RCTs)

There is an urgent need for well-designed RCTs comparing:

- Cariprazine vs clozapine
- Cariprazine vs other third-line antipsychotics
- Cariprazine monotherapy vs augmentation strategies

Such trials should specifically recruit patients with documented clozapine non-response.

Develop Prospective Cohort Studies

Large, multi-centre observational cohorts are needed to evaluate:

- Real world effectiveness
- Long term outcomes
- Relapse rates
- Functional recovery
- Quality of life

Standardise TRS and Clozapine-Failure Definitions

Future studies should adopt consistent criteria for:

- TRS diagnosis
- Clozapine non-response
- Adequate treatment trials

This will improve comparability across studies.

Examine Biomarkers and Predictors of Response

Research should explore:

- Neurobiological markers (e.g. D3 receptor availability)
- Clinical predictors (e.g. predominant negative symptoms)
- Genetic or pharmacogenomic factors

This may help identify which TRS patients are most likely to benefit from cariprazine.

Evaluate Safety and Tolerability in Clozapine-Failed Populations

Long term monitoring is needed to assess:

- Metabolic outcomes
- Cardiovascular risk
- Extrapyramidal symptoms
- Adherence and discontinuation rates

Investigate Switching Protocols

Studies should compare:

- Cross titration vs abrupt discontinuation
- Optimal dosing strategies
- Risk of rebound psychosis

Include Patient-Centred Outcomes

Future research should incorporate:

- Functional recovery
- Social integration
- Employment outcomes
- Patient-reported experiences

References

1. Montgomery A, Rogowska M, Luiz Dratcu (2023) Cariprazine an Alternative Treatment for Clozapine-resistant Schizophrenia? Clin Psychopharmacol Neurosci 21: 202-206.
2. Vasiliu O (2021) Case Report Cariprazine Efficacy in Young Patients Diagnosed with Schizophrenia with Predominantly Negative Symptoms. Frontiers in Psychiatry: 12.
3. Rancans E, Dombi ZB, Mátrai P, Barabácssy Á, Sebe B, et al. (2021) The effectiveness and safety of cariprazine in schizophrenia patients with negative symptoms and insufficient effectiveness of previous antipsychotic therapy: an observational study. International Clinical Psychopharmacology 36: 154-161.
4. Siwek M, Adrian Andrzej Chrobak, Aleksandra Gorostowicz, Patrycja Król, Dudek D (2024) Cariprazine augmentation of clozapine in schizophrenia a retrospective chart review. Frontiers in Pharmacology 14: 1321112.
5. Darriba HB (2021) Combined use of clozapine and cariprazine in treatment-resistant schizophrenia, is it a good choice? European Psychiatry 64: 798-799.
6. Durgam S, Litman RE, Papadakis K, Li D, Németh G, et al. (2016) Cariprazine in the treatment of schizophrenia. International Clinical Psychopharmacology 31: 61-68.
7. Cariprazine (Vraylar) (2022) CADTH Reimbursement Recommendation Indication As monotherapy for: bipolar mania: acute management of manic or mixed episodes associated with bipolar I disorder in adults, and bipolar depression: acute management of depressive episodes associated with bipolar I disorder in adults. CADTH Reimbursement Reviews and Recommendations <https://pubmed.ncbi.nlm.nih.gov/38620361/>.
8. Marder S, Fleischhacker WW, Earley W, Lu K, Zhong Y, et al. (2019) Efficacy of cariprazine across symptom domains in patients with acute exacerbation of schizophrenia Pooled analyses from 3 phase II/III studies. European Neuropsychopharmacology 29: 127-136.
9. Pappa S, Arturas Kalniunas, Maret J (2023) Cariprazine for negative symptoms in early psychosis: a pilot study with a 6-month follow-up. Frontiers in Psychiatry 14: 1183912.
10. Selvan P, Devkare P, Shetty A, Dharmadhikari S, Khandhedha C, et al. (2024) A review on the pharmacology of cariprazine and its role in the treatment of negative symptoms of schizophrenia. Frontiers in Psychiatry 15: 1385925.
11. Fagiolini A, Alcalá JÁ, Aubel T, Bienkiewicz W, Bogren MMK, et al. (2020) Treating schizophrenia with cariprazine: from clinical research to clinical practice. Real world experiences and recommendations from an International Panel. Annals of General Psychiatry 19: 55.
12. Pappa S, Réka Csehi, Ellice Caldwell-Dunn, Dombi ZB, Hjorth S (2025) Cariprazine & Clozapine: A systematic review of a promising antipsychotic combination for treatment-resistant schizophrenia. Int J Neuropsychopharmacol 28: 053.
13. Carmassi C, Valerio Dell'Oste, Fantasia S, Bordacchini A, Bertelloni CA, et al. (2024) A 12-month longitudinal naturalistic follow-up of cariprazine in schizophrenia. Frontiers in Psychiatry 15: 1382013.