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Clozapine augmentation with cariprazine for negative symptoms: a case series and literature review

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***Abstract*:** Only about 50% of patients with treatment-resistant schizophrenia respond to clozapine, and many more patients continue to experience ongoing and prominent negative symptoms. These negative symptoms, for which there are limited pharmacological options, may represent the greatest barrier to functional recovery. Cariprazine is a novel antipsychotic drug that is a partial agonist at dopamine D_2 and D_3 receptors with preferential binding to the D_3 receptor, antagonism of $5HT_{2B}$ receptors, and partial agonism at $5HT_{1A}$ receptors. Cariprazine is currently licenced for the treatment of schizophrenia in Europe and the United States and has also been approved for bipolar disorder in the United States. There is a limited body of evidence to suggest clinical effectiveness as an augmentation strategy for negative symptoms in those treated with clozapine. In this case series, we present five cases of successful treatment of negative symptoms by clozapine combined with cariprazine in treatment-resistant psychosis.

Keywords: augmentation, cariprazine, clozapine

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Introduction

Clozapine is a second-generation ('atypical') antipsychotic and dibenzodiazepine, with efficacy in treatment-resistant schizophrenia (TRS)–a failure to adequately respond to successive trials of two non-clozapine antipsychotics for 4–6 weeks.[1] Since the landmark study by Kane *et al.*,[2] clozapine has been regarded as the most effective antipsychotic for treating positive symptoms, preventing suicidal ideation and reducing the frequency and duration of hospital stays.[3–5] Despite this, up to 60% of patients treated with clozapine monotherapy will not respond or only partially respond to treatment.[6] Important factors that may influence response to clozapine treatment and the need for augmentation strategies include clozapine/norclozapine plasma levels, pharmacogenetics or changes in smoking status.[7,8] Management of these patients has remained a persistent public health problem.[9–11]

A particularly challenging symptom domain is the alleviation of negative and cognitive symptoms in schizophrenia, associated with significant long-term morbidity, poor functional outcomes and high rates of disability, of which clozapine has shown limited efficacy against.[12,13] Because of this, considerable focus has been placed on augmentation strategies for partial responders to clozapine, although compelling evidence for a particular intervention is lacking.[14] A class of medication that has attracted interest of late is the partial dopamine agonists, such as cariprazine.

Cariprazine is a novel antipsychotic, licenced for the treatment of schizophrenia in adults in the United Kingdom since 2018. It is also approved for treating manic, mixed and depressive episodes in bipolar I in the United States. Cariprazine exerts partial agonism at D_2 and D_3 receptors, with high selectivity for the D_3 receptor. It also has partial agonist activity at serotonin 5-HT_{1A} receptors (Table 1).[15] Cariprazine is distinct from other antipsychotics in that it has a high preferential affinity for the D_3 receptor, which is thought to be important in modulating mood and cognition.[16]

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Table 1. Receptor binding affinities.[26].

Receptor	Cariprazine (nM Ki)	Clozapine (nM Ki)
D_3	0.085*	
D_{2L}	0.49*	
5-HT_{2B}	0.58	
D_{2S}	0.69*	
5-HT_{1A}	2.6*	120
5-HT_{2A}	18.8	5.4
H_1	23.2	1.1
5-HT_7	111.0	
HT_{2C}	134.0	9.4
α_1	155.0	1.6

*Partial agonist.

Furthermore, some authors consider cariprazine as a potential 'oral depot' because of its long half-life (~2 days); however, this is yet to be evaluated in the literature.[17] Active metabolites include desmethyl-cariprazine and didesmethyl-cariprazine, the latter of which has a much longer half-life than cariprazine.[18] Reported adverse drug effects include insomnia, akathisia, constipation, nausea and vomiting.[19] Efficacy has been demonstrated in several short-term randomised controlled trials (RCTs) and a double-blinded extension study.[20–25] In a RCT study of patients with predominantly negative symptoms, the effect of cariprazine on negative symptoms was superior to risperidone.[26] Further studies have also suggested good outcomes on cognitive functioning, the mechanisms of which remain unelucidated.[27] There has been limited exploration in the literature of how cariprazine fares as an augmentation strategy in TRS. Preliminary work has suggested its effectiveness and safety in a small cohort of such patients.[28]

In this article, we report on five successful cases of clozapine augmentation with cariprazine to alleviate negative symptoms in TRS. In all cases, TRS was defined according to TRIPP criteria.[29]

Case studies

Case 1

The patient is a Eastern European 34-year-old female with a diagnosis of paranoid schizophrenia. Her first contact with psychiatric services was in her late 20s, where she presented with paranoid persecutory beliefs, auditory hallucinations (command type – asking her to end her life) and negative symptoms (blunted affect, emotional/social withdrawal in absence of clear depressive episode), which were interfering with her social and academic functioning. Prior to this she was prescribed alprazolam for anxiety for approximately 3 years. There was no notable family history. However, regular cannabis use in her adolescents up to first presentation and occasional ecstasy use were reported. The patient had sequential trials with aripiprazole (up to 10 mg for 6 weeks), amisulpride (up to 400 mg for 8 weeks), quetiapine (up to 300 mg for 7 months), and olanzapine (up to 20 mg for 6 weeks) with treatment only achieving partial response.

Given the lack of response to treatment and the patient's frequent and severe decompensations, it was decided to admit her and begin treatment with clozapine 2 years later. Clozapine was titrated up to a dose of 300 mg at night, achieving a plasma concentration of 0.52 mg/L. Reported adverse effects included constipation, weight gain (+12 kg), hypersalivation and tachycardia, in which she received concomitant senna, metformin, pirenzepine and bisoprolol treatment. The patient demonstrated improvement in positive symptoms with clozapine treatment, but her negative symptoms persisted despite reported compliance. The patient was thereby initiated on lurasidone up to a dose of 74 mg daily to augment clozapine after 11 months of monotherapy. At this time, her positive and negative syndrome scale (PANSS)[30] score was 80 (positive scale = 20; negative scale = 23; and general psychopathology = 37). She also scored 50 on the Global Assessment of Functioning (GAF)[31] scale. Given the lack of clinical response to treatment, lurasidone was discontinued after 2 months. The dose of clozapine was subsequently increased to 350 mg to address residual symptoms, with a recorded PANSS score of 66 (positive scale = 15, negative scale = 20, general psychopathology = 31). Her GAF score increased to 65. After a few months, the patient requested for a dose reduction of clozapine due to persistent sedation and weight gain. Her clozapine blood level at the time was 0.65 mg/L. The dose was therefore reduced to 275 mg daily.

In August 2019, the patient's clozapine was augmented with cariprazine at a starting dose of 1.5

mg daily to alleviate residual negative symptoms. The patient's baseline scale for the assessment of negative symptoms (SANS)[32] score was 50. The dose of cariprazine was eventually increased to 3 mg 5 months later due to self-reported intrusive thoughts. No adverse events were noted and her body weight remained unchanged. After 6 months of combined treatment, the patient displayed a fuller affect, an improvement in function and a reduction in residual positive symptoms. Her improved motivation enabled her to start a job as a dog walker and take up driving lessons. After 12 months of combination therapy her SANS score reduced to 22, equivalent to a 56% reduction. (According to Van Erp *et al.*,[33] this broadly equates to a PANSS negative scale score of 15.)

Case 2

The patient is a 60-year-old white British female with a diagnosis of paranoid schizophrenia and depression. Her first contact with psychiatric services was during early adulthood, where she presented with psychotic symptoms and prominent negative symptoms (self-neglect, confusion, apathy and ambivalence). After multiple admissions and unsuccessful trials of various antipsychotics including risperidone (up to 8 mg for 1 year), fluphenazine (37.5 mg every 2 weeks), chlorpromazine (up to 200 mg for 2 years), haloperidol (up to 15 mg for 3 years) the patient was stabilised on clozapine 325 mg in the late 90s. She was a heavy smoking and dependent on alcohol. Despite a reduction in positive symptoms, she continued to experience depressive and negative symptoms. To alleviate this, the patient was prescribed citalopram for 4 years.

The patient's last admission was 10 years after following a 2-week deterioration in mental state reported by her daughter with typical signs of relapse: self-neglect, poor oral intake and isolative behaviour. There had been a recent reduction in clozapine to 275 mg daily due to a high plasma level of 0.83 mg/L after the patient stopped smoking. During this admission, she presented with cognitive and negative symptoms of psychosis including distractibility, thought block, confusion, apathy and ambivalence. The patient's antidepressant was switched to venlafaxine up to 75 mg and sodium valproate was initiated as she showed minimal response on citalopram. She was eventually discharged on clozapine 275 mg, venlafaxine MR 225 mg and sodium valproate MR 800 mg daily. She was followed up by the home treatment team, where her clozapine dose was reduced further to 250 mg daily due to clozapine plasma level of 0.77 mg/L.

To address prominent negative symptoms, cariprazine 1.5 mg was added as an augmentation strategy. Her SANS score was 63. No adverse events were noted. The patient's weight reduced from 90 to 84 kg by October 2019. After 6 months of combined treatment, the patient showed further improvements and showed better engagement with medical staff. At this time, her SANS score was 37, equivalent to a 41% reduction.

Case 3

The patient is a 23-year-old Asian British male with a diagnosis of paranoid schizophrenia. His first contact with psychiatric services during early adulthood, where he presented with paranoid delusions, social isolation and irritability. He was arrested and detained under section 2 of the Mental Health Act (the legal framework for the assessment and treatment of a mental health disorders in the United Kingdom) after allegedly damaging property at his family home and reported aggression and inappropriate sexual remarks towards family members. There was no notable family history and previous criminal convictions. However, regular cannabis use from adolescent up to first presentation were reported. The patient had sequential trials with aripiprazole (up to 20 mg for 1 month), aripiprazole once monthly (400 mg for 2 months) olanzapine (up to 20 mg for 7 weeks), risperidone (up to 6 mg for 2 months), paliperidone palmitate (100 mg for 4 months) and haloperidol decanoate (100 mg every 4 weeks for 8 months) with treatment only achieving partial response.

Given the lack of response to treatment and the patient's frequent and severe decompensations, clozapine treatment was initiated. Clozapine was titrated up to a dose of 325 mg at night, achieving a plasma concentration of 0.74 mg/L. Reported adverse effects included tachycardia and hypersalivation, in which he received concomitant bisoprolol and hyoscine hydrobromide treatment. The patient demonstrated improvement in positive symptoms with clozapine treatment, but his negative symptoms persisted.

To address prominent negative symptoms, cariprazine 1.5 mg was added as an augmentation strategy 3 months after clozapine initiation. His

SANS score was 60. No adverse events were noted. The patient's weight remained unchanged. After 12 months of combined treatment, the patient displayed an improvement in function and showed better engagement with family. At this time, his SANS score was 15 equivalent to a 75% reduction.

Case 4

This was a 51-year-old white British male with a diagnosis of schizoaffective disorder, depressive type. His first contact with psychiatric services was in his late 20s, where he presented with persecutory delusions and suicidal thoughts. There were notes of family history of schizophrenia in first degree relatives. Overdose attempts were reported in his early 20s. Furthermore, 15 years later, the patient was diagnosed with an eating disorder by his community team due to a persistent liquid only diet and regularly inducing vomiting with secondary paralytic ileus, acute renal failure and severe oesophagitis. However, it was unclear whether this was neurotic or psychotic in nature. After multiple admissions and unsuccessful trials of various antipsychotics, including amisulpride (for 4 months), quetiapine and olanzapine (for 9 weeks), the patient was stabilised on clozapine 600 mg. His clozapine blood level at the time was 0.46 mg/L. Despite a reduction in positive symptoms, there remained a predominance of negative symptoms and suicidal ideation.

After a year, the patient was initiated on mirtazapine 15 mg daily after he attempted suicide. This was eventually increased to 45 mg daily in addition to cognitive behavioural therapy after a relapse triggered by cuts in his welfare benefits.

To address prominent negative symptoms, cariprazine 1.5 mg daily was added 10 years later. His SANS score was[32] 88. No adverse events were noted and the patient's weight remained unchanged. After 6 months of combined treatment, the patient displayed a fuller affect and showed better engagement with medical staff. The patients residual positive symptoms (command hallucinations) persisted. At this time, his SANS score was 24, equivalent to a 73% reduction. His clozapine blood level at the time was 0.49 mg/L.

Case 5

The patient is a 28-year-old white British male with a diagnosis of paranoid schizophrenia with a background of polysubstance misuse (cannabis, cocaine and mephedrone) since his early teens. His first contact with psychiatric services was during early adulthood, where he presented with somatic and paranoid delusions. He was arrested and detained under section 2 of the Mental Health Act after reported aggression towards family members. The patient had sequential trials with several antipsychotic medications, including amisulpride (for 1 month), risperidone and olanzapine (up to 20 mg for 3 months), with these treatments only resulting in partial response. He was eventually discharged on quetiapine and appeared to achieve stability, securing his own tenancy where he lived with his girlfriend and stepson. However, shortly after discharge he became non-compliant to treatment, leading to unsuccessful trials of aripiprazole and pipothiazine palmitate (100 mg monthly for 3 years).

In the following year he was admitted to a rehabilitation unit after increased auditory hallucinations, anxiety and suicidal ideation linked to polysubstance misuse. During this admission, he was initiated on clozapine treatment (up to 400 mg daily), with a marked improvement in psychotic symptoms, self-care and communication with caregivers and service users. However, the closure of the rehabilitation unit and reallocation to another unit caused the patient to become increasingly withdrawn and eventually refuse clozapine treatment. This led to an increase in positive and negative symptoms, self-neglect and verbal alterations necessitating several admissions to a psychiatric intensive care unit (PICU). Over the next 5 years, the patient was treated with haloperidol decanoate (up to 100 mg monthly for 1 year) and zuclopenthixol decanoate (600 mg weekly), with minimal response. Clozapine treatment was thereby restarted 5 years later, however, sub-therapeutic plasma levels suggested partial compliance. Despite this, improvement in positive symptoms were reported. The patient's clozapine was augmented with amisulpride (200 mg twice a day for 2 months) in an attempt to alleviate persistent negative symptoms.

The patient was then admitted to the National Psychosis Unit (NPU), a tertiary referral facility specialising in the treatment of refractory psychotic disorders, with the aim of establishing therapeutic clozapine plasma levels and augmentation with other medication to improve residual symptoms. At the time of presentation, the patient's

psychotropic medication included clozapine 700 mg daily and amisulpride 200 mg daily. His clozapine plasma level was therapeutic on admission (0.58 mg/L). His ratings on the positive and negative syndrome scale-6 (PANSS-6)[34] were as follows: positive scale = 12/21 and negative scale = 18/21. Vortioxetine treatment 10 mg daily was prescribed to treat persistent negative symptoms. However, the patient showed a minimal response. Given the lack of clinical response to amisulpride treatment, this was switched to cariprazine 1.5 mg daily. The patients baseline SANS[32] score was 88. Cariprazine's dose was reduced to alternative days because of possible exacerbation of positive symptoms which resolved with dose reduction. No adverse events were noted and his weight remain unchanged. After 6 months of clozapine and cariprazine treatment, the patient displayed a moderate improvement in negative symptoms with better engagement with caregivers. His clinical improvement enabled discharge from the tertiary care setting. After 6 months of combination therapy his SANS score reduced to 62 equivalent to a 56% reduction.

Outcomes on SANS are given in Figure 1

Discussion

Our findings

Clozapine is regarded as the treatment of choice in treatment-resistant schizophrenia, although approximately 40%–70% of patients will show an inadequate response to this treatment.[6] This represents a large proportion of patients who will likely continue to experience poor clinical outcomes of an already debilitating condition. To address this issue, a heightened interest has developed over the years in the augmentation of clozapine to try to improve symptom management, particularly of negative symptoms.

This report presents five cases of successful augmentation of clozapine with cariprazine for treatment-resistant negative symptoms. In all five cases, there was a reduction in negative symptoms after at least 6 months of treatment. Limitations inherent in a case series, including its retrospective nature and selection bias, are applicable in this study. Nonetheless, despite it being challenging to rate a patient's subjective experience, the use of validated assessments for negative symptoms (SANs) by the same medical team in all our cases strengthens our findings.[35] Our case series is somewhat limited by the small number of patients studied; however, to our knowledge, this is the largest naturalistic study to date on clozapine augmentation with cariprazine for residual negative symptoms. Furthermore, the lack of objective measures for treatment adherence limits our findings. This is particularly relevant as it has recently been suggested that withdrawal-associated symptoms can occur even between doses of clozapine.[36,37] Therefore, it is plausible beyond other possibilities, that cariprazine augmentation may have alleviated such symptoms. Nevertheless, empirical research in this area is required.

Comparison to other studies

Interestingly, a growing body of literature has demonstrated clinical effectiveness of clozapine in combination with partial D_2 agonists, particularly aripiprazole in both oral and injectable form.[38–45] As can be seen in Table 2, clozapine augmentation with cariprazine for negative symptoms has not been widely studied, with evidence limited to case reports and case series.[28,46] Nevertheless, the current evidence provides ground for cautious optimism. Consistent with our study, a recent case series by Berardis *et al.* demonstrated the effectiveness of cariprazine in combination with clozapine for the treatment of residual negative symptoms.[28] In their study, the authors described two patients who's PANSS score notably reduced along with a reduction in body weight after combination therapy. From a pharmacological perspective, Werner and Coveñas postulated that this improvement in symptoms were related to agonism of D_3 receptors.[19] Cariprazine's partial agonist effect at the 5-HT_{1A} receptor has been suggested to have a contributory antidepressant effect. Similar to our findings, there were no additional adverse effects observed with combination therapy in existing studies. In addition, there were no reported increase in body weight following combination therapy. Consistent with observations by Berardis *et al.*, one of our patients reported a reduction in weight after combined treatment.[28] While cariprazine's effect on metabolic parameters are believed to be minimal or benign, it is difficult to be certain whether the improvement in negative symptoms in this individual was secondary to weight loss or vice versa.[47,48]

Clinical implications and future studies

How do the current findings impact clinical practice? Negative and cognitive symptoms represent

Table 2. Summary of studies reporting clozapine augmentation with cariprazine.

Study	n	Clozapine dose (mg)	Maximum cariprazine dose (mg)	Duration (weeks)	Reason for prescribing cariprazine	Previous augmentation strategies	Outcome	Reported adverse effects
De Berardis *et al.*[28]	2	400	3	12	Partial response with clozapine monotherapy	Amisulpride 800 mg	Reduction in PANSS after 3 months Total score: 113–74 Positive: 22–18 Negative: 33–27 General: 58–44	N
		350	3	12	Partial response with clozapine monotherapy	None	Reduction in PANSS after 3 months Total score: 121–57 Positive: 27–9 Negative: 34–12 General: 70–29	N
Aubel[46]	1	100	3	6	Persistent negative symptoms	Amisulpride 300mg	Remission of psychotic symptoms Significant improvement in psychomotor drive and mood Discontinuation of clozapine	N

PANSS, The Positive and Negative Syndrome Scale.

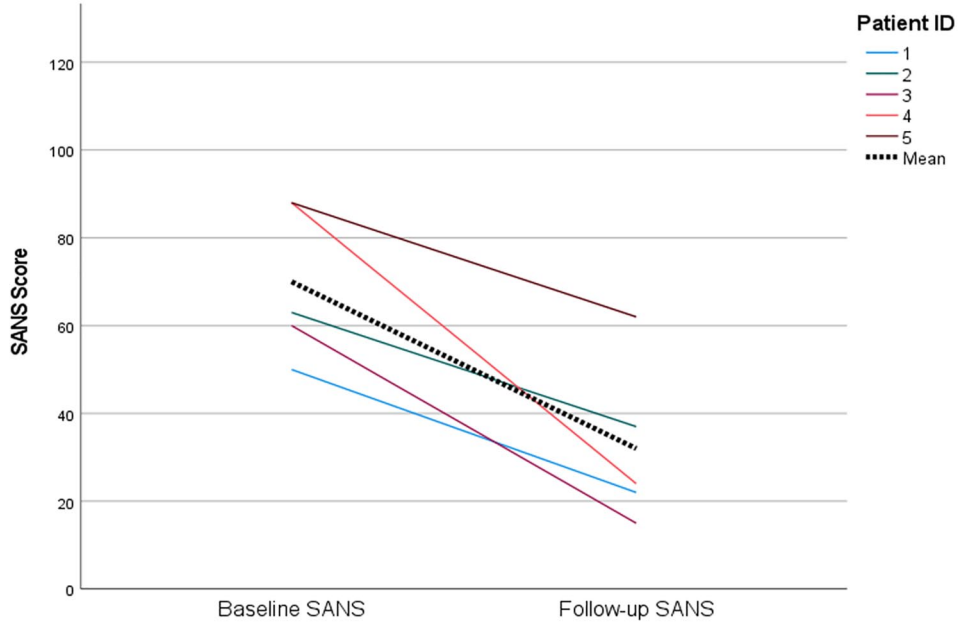

Figure 1. SANS scores.

some of the most debilitating aspects of schizophrenia, often resulting in long-term morbidity, significant functional impairments and reduced quality of life for patients and their carers.[15] These symptoms can broadly be divided into primary, secondary and persistent negative symptoms.[49] This is particularly relevant to patients with treatment-resistant schizophrenia, where clozapine monotherapy has only demonstrated marginal symptom relief.[50] While authors have rightly identified the inappropriate use of antipsychotic polypharmacy, this strategy may be warranted in some clinical situations, especially when patient safety is not compromised.[38] Our data add to a growing body of evidence suggesting a role for cariprazine in augmenting clozapine for residual negative

symptoms. As demonstrated by De Berardis *et al.*, the addition of cariprazine to clozapine may provide scope for dose reduction of the latter to improve tolerability.[51] Furthermore, in four cases, including existing case reports in the literature (Table 2), cariprazine was effective where other augmentation antipsychotics failed, including often preferred amisulpride. This may suggest that cariprazine is at least as equally effective as amisulpride, which has established evidence for augmentation purposes in clozapine-resistant patients.[52,53] However, methodologically rigorous studies, utilising large samples and well-controlled prospective designs is indicated to establish this. Also, the optimal dose of cariprazine as an adjunct to clozapine is unknown.

Conclusion

This case series suggests the safe and effective use of cariprazine as an augmentation strategy in TRS, particularly for the alleviation of negative symptoms. However, future work, utilising larger samples and well-controlled prospective designs are required to establish this effect.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: David Taylor is the Editor-in-Chief of Therapeutic Advances in Psychopharmacology. Therefore, the peer review process was managed by alternative members of the Board and the submitting Editor was not involved in the decision-making process.

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Ethics statement and patient consent

Written informed consent was obtained from the patients for the publication of their medical data. As this is a Case Series rather than clinical research, an approval by ethical committee was not required.

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