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Clozapine augmentation with long-acting antipsychotic injections: A case series and systematic review

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Abstract

Background: Up to 30% of patients with a diagnosis of treatment-resistant psychosis remain symptomatic despite an optimal trial with the gold standard treatment, clozapine. Emerging evidence suggests the clinical utility of long-acting injections (LAI) in such clinical scenarios. In this study, we aimed to describe clozapine augmentation with LAIs in an inner London hospital and explore the literature on the clinical effectiveness of this treatment modality.

Methods: Patients prescribed clozapine, who were commenced on a LAI between 2007 and 2023 by the United Kingdom's largest mental health trust, were identified from electronic patient records. First, routine clinical data were used to describe the use, effectiveness, and safety of this augmentation strategy. Second, we conducted a literature search up to 1st June 2023 to identify published studies describing clinical outcomes after clozapine augmentation with a LAI. Clinical outcomes were collated and presented in a table, including hospitalisation rates and quantitative clinical assessments using validated scales.

Results: Of the 1248 patients prescribed clozapine in SLaM, three patients (0.2%) received augmentation with the following LAIs: olanzapine embonate, paliperidone palmitate and pipotiazine palmitate. This treatment strategy was clinically effective and generally well tolerated in all three cases. Twelve published studies between 2010 and 2022 were included in the review. Eight distinct LAIs were reported (4 first and 4 second generation antipsychotics), with risperidone and paliperidone most widely studied. All the identified studies were observational including mirror-image studies, case series and case reports. Duration of follow up varied from 3 months to 3 years. There was evidence that the use of LAIs with clozapine can significantly reduce clinical symptoms, hospitalisation rates and bed days. No serious adverse effects were reported.

Conclusion: This preliminary evidence suggests clinical utility of LAIs in alleviating residual symptoms and subsequently reducing hospitalisation

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rates in patients optimised on clozapine treatment. The current study warrants further investigations including a randomised controlled study to establish the clinical efficacy, tolerability, and place in therapy of this treatment modality.

KEYWORDS
augmentation, clozapine, depot, long acting injectable

1 | INTRODUCTION

Up to one-third of patients diagnosed with schizophrenia derive little therapeutic benefit from conventional antipsychotic treatment, commonly described as treatment-resistant schizophrenia (TRS).[1] The second-generation ('atypical') antipsychotic, clozapine, is well established as the treatment of choice for TRS. Several lines of evidence, including meta-analytic and epidemiological studies, demonstrate clozapine as the most effective antipsychotic for treating positive symptoms, preventing suicidal ideation and reducing the frequency and duration of hospital stays.[2–4] However, up to 30% of patients with TRS are unresponsive to clozapine treatment despite dose optimisation.[5] Untreated TRS has remained a persistent public health problem, with healthcare costs approximately 3-11-fold higher for patients with TRS, with a significant loss in patient quality of life.[6–8]

A particularly challenging area in the management of TRS is adherence to clozapine treatment. Current evidence indicates that approximately one in four patients are non-adherent to treatment with clozapine.[9] The reasons for this are multifaceted but are driven by adverse effects such as hypersalivation and sedation and the requirement for frequent haematological monitoring.[9,10] The potential consequences of non or partial adherence include reduced responsiveness to recommencement of clozapine treatment.[11]

In cases where clozapine monotherapy does not provide symptom alleviation, national and international clinical guidelines for psychosis recommend the addition of an antipsychotic.[12] However, there is significant ambiguity amongst clinicians whether this includes the use of LAI or depot formulations. This ambiguity is enhanced by recommendations that suggest that concomitant use of depot antipsychotics is contra indicated, owing to a suggested increased risk of agranulocytosis.[13] In this study, we carry out a literature review on the use of combined LAI and clozapine to manage TRS and we report a small case series of clozapine augmentation with LAI to manage TRS within a large National Health Service (NHS) Trust.

Significant outcomes

- This study suggests the clinical utility of LAI in treating residual symptoms in patients established on clozapine.
- Our cases and literature review suggests clozapine augmentation with LAIs are safe and well tolerated.
- The current evidence suggests that there is no increased risk of clozapine-induced agranulocytosis with LAI augmentation.

Limitations

- The results of this study do not allow for interpretation of the effectiveness of LAI augmentation in preventing relapse in patients treated with clozapine.
- The current review is limited by the low quality of evidence in the literature.
- Future research is warranted to determine patient views on clozapine augmentation with a LAI.

2 | MATERIALS AND METHODS

2.1 | Study setting and sample identification

The cohort was derived from the South London and Maudsley (SLaM) NHS Foundation Trust Clozapine. SLaM is a National Health Service Foundation Trust, one of the largest mental health organisations in Europe, responsible for the psychiatric care of over 1.3 million residents in South London.

For this study, patients were identified using the monitoring database used in SLaM, Zaponex Treatment Access System (ZTAS) and pharmacy dispensing data. We identified clozapine prescription with at least one dose of a LAI or depot between 1 January 2007 and 31 January 2023. This study period was selected because

electronic records were fully implemented during 2006 in SLaM. For this study, both first-generation depots and second generation LAIs are referred to as 'LAI'. Case records were then examined manually by two of the authors (E.O and H.C) to ascertain whether clozapine treatment was indeed augmented with a LAI. Patient demographics and clinical data were obtained from electronic medical records.

2.2 | Literature review: Search strategy and data extraction

We performed a systematic literature search using Medline, Embase and PsycINFO upto 1 June 2023. We used the following combination of search terms: schizophrenia AND depot OR once-monthly OR 3-month* OR long-acting OR LAI* OR monohydrate OR lauroxil or palmitate OR pamoate OR microsphere* OR dodecanoate OR decanoate or enanthate OR oenanthate OR acetate OR consta OR maintena OR zypadhera OR xeplion OR sustenna OR trinza) OR aripiprazole OR olanzapine OR risperidone OR paliperidone OR risperdal OR 9-OH-risperidone OR 9-hydroxyrisperidone OR haloperidol OR fluphenazine OR flupentixol OR flupenthixol OR zuclopenthixol OR pipothiazine; antipsychotic* OR dopamine blocker* OR neuroleptic*) AND (injection OR injectable OR depot OR long acting; AND clozapine. The search yielded a total of 665 results (see Appendix 1). Eligibility required papers to be written in English and published in peer-reviewed journals reporting data on adult patients who were concomitantly prescribed clozapine and a depot or LAI. The literature search was conducted independently by two researchers (A.D and E.O) in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The researchers screened titles and abstracts; eliminated duplicates; read the full texts of the remaining papers; selected the papers that met the inclusion criteria; and extracted relevant data. They also manually searched the references of the selected studies for additional articles to include. Discrepancies or disagreement were resolved through discussion. A PRISMA flow diagram is shown in Figure 1. The full results of the search and treatment characteristics are presented in Table 1.

2.3 | Ethics

This study was approved by the trust's Drug and Therapeutics Committee, the locally designated approval committee for all noninterventional prescribing outcome evaluations, and the analysis used anonymised clinical data.

3 | RESULTS

3.1 | Sample

The data for the 97 patients that met these criteria were manually screened and study eligibility verified from case notes. After screening, three patients were identified (0.2% of total clozapine cohort). Ninety-four patients were excluded as the combination was only used during a switch from LAI to clozapine or vice versa. Due to the small sample size, a case series was selected.

3.2 | Case 1

The patient is a White British 29-year-old male with a diagnosis of F20.0 paranoid schizophrenia. Secondary diagnoses included F60.2 dissocial personality disorder and F19.1 Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances Harmful use. His first contact with psychiatric services was in his twenties, where he presented with paranoid persecutory beliefs and auditory hallucinations. His physical health conditions included hypertension. The maternal uncle was diagnosed with paranoid schizophrenia and the grandmother was diagnosed with schizoaffective disorder. Regular cannabis uses in his adolescents up to first presentation were reported.

Over a 7-year period the patient had various antipsychotic oral and depot trials including aripiprazole long-acting injection (up to 400 mg monthly), paliperidone palmitate (up to 150 mg monthly), olanzapine embonate (up to 300 mg fortnightly), flupenthixol decanoate depot (up to 80 mg fortnightly) with treatment only achieving partial response. Repeated inpatient admissions including psychiatric intensive care unit (PICU) were reported during this period.

Given the lack of response to treatment and the patient's frequent and severe decompensations, it was decided to begin treatment with clozapine. Clozapine was titrated up to a dose of 400 mg at night, achieving a plasma concentration of up to 0.40 mg/L. Reported adverse effects included constipation, weight gain (+17 kg), hypersalivation and tachycardia, in which he received concomitant senna, hyoscine hydrobromide and bisoprolol treatment. The patient demonstrated an improvement in mental state with clozapine treatment however his insight remained poor. A year later it was agreed with his community team to switch to olanzapine long-acting-injectable (LAI) during his discharge planning meeting as it was deemed highly likely he would disengage with services and refuse clozapine treatment. After switching to olanzapine LAI, his mental state deteriorated

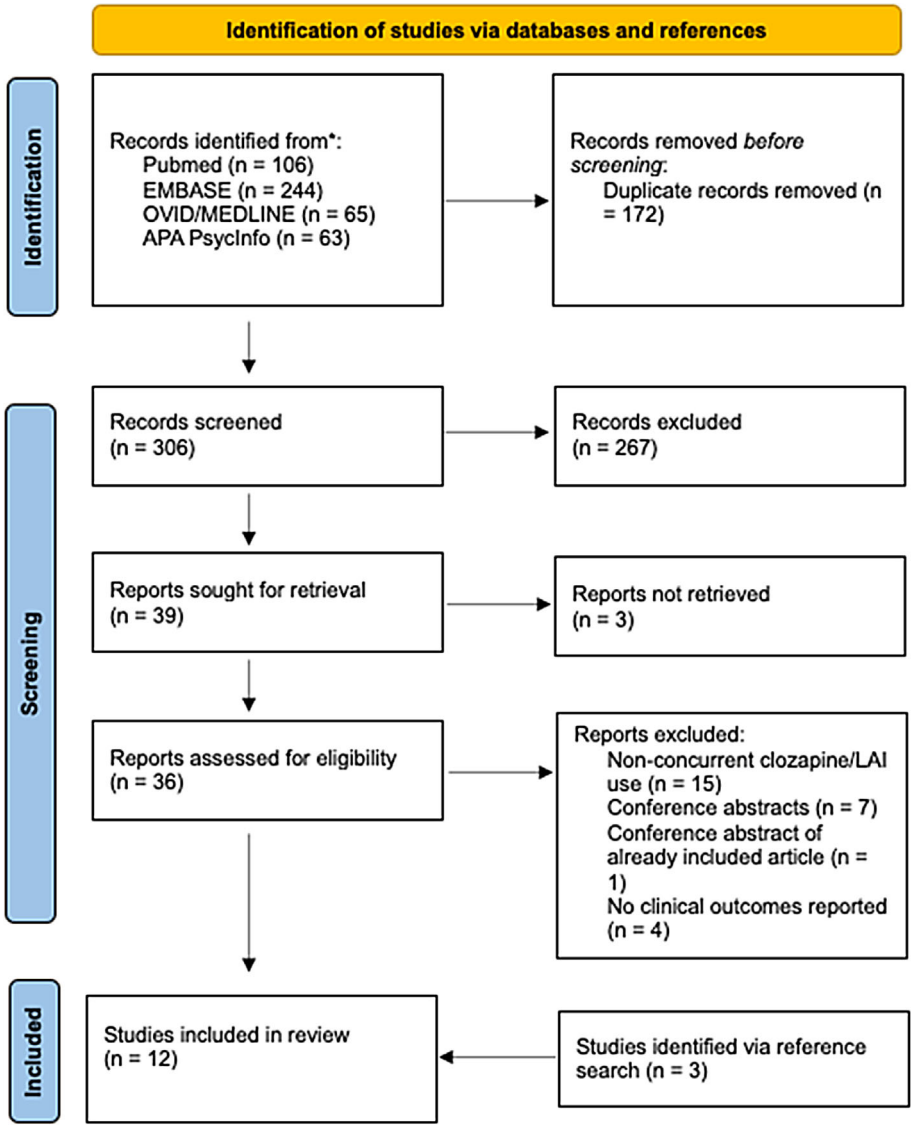

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

remarkably during cross-titration from clozapine over a 4-week period, causing a delay to his discharge.

To address the acute symptoms, the patient was re titrated on clozapine 300 mg daily in January 2022 prior to the next administration date for olanzapine LAI. Within a week of clozapine titration, the clinical team noted a significant improvement beyond the level that had previously been achieved on clozapine monotherapy. It was therefore agreed with the multidisciplinary team to keep the olanzapine depot in combination with clozapine treatment as a long-term management plan. As of January 2023, the patient remains mentally stable within supported accommodation and continues to receive olanzapine LAI and clozapine. A clozapine plasma concentration of 0.29 mg/L was recorded. Metabolic changes did occur within a year of augmentation of the clozapine with weight increasing by approximately 4.7 kg as well as a change in lipid profile (triglycerides from 4.2 to 4.5 mmol/L, cholesterol from 4.9 to 5.6 mmol/L, HDL from 0.9 to 0.7 mmol/L). The patient's HbA1c remained unchanged (32 mmol/mol).

3.3 | Case 2

The patient is a 40-year-old white British male with a diagnosis of F20.0 paranoid schizophrenia. His first contact with psychiatric services was during early adulthood, where he presented with psychotic symptoms (auditory hallucinations, bizarre and complex delusions). Poor self-care and physical aggression were also reported. The patient's mother was diagnosed with schizophrenia, living in supported accommodation. After multiple admissions and unsuccessful trials of various antipsychotics, the patient was initiated on clozapine 325 mg in 2014. Despite a reduction in positive symptoms, he continued to experience residual symptoms including complex delusions. Shortly following discharge to supported accommodation,

TABLE 1 Literature review summary.

Study	Country	*N*	Study design	Mean age *years* (SD)	Gender *n* (%)	Diagnosis *n* (%)	Mean duration of illness *years* (SD)	Follow-up duration	Augmenting antipsychotic
Balcioglu (2020)	Turkey	1	Case report	22	M: 1 (100)	SCZ 1 (100)	1	3 months	Aripiprazole
Bioque (2020)	Spain	50	Retrospective mirror-image	40.8 (11.8)	F: 13 (26) M: 37 (74)	SCZ: 33 (66) SZA: 13 (26) BD: 2 (4) O: 2 (4)	13.5 (9.7)	6 months	Paliperidone
Caliskan (2021)	Turkey	29	Retrospective mirror-image	40.9 (8.5)	M: 19 (66) F: 10 (35)	SCZ: 29 (100)	18.4 (6.6)	1 year	Risperidone (12) Paliperidone (9) Aripiprazole (4) Haloperidol (3) Zuclopenthixol (1)
Mutlu (2022)	Turkey	18	Case series	NR	M: 6 (33) F: 12 (66)	SCZ: NR SCA: NR	NR	1 year	Risperidone (5) Paliperidone (6) Zuclopenthixol (3) Flupenthixol (2) Haloperidol (1) Fluphenazine (1)
Grimminck (2020)	Canada	20	Retrospective mirror-image	NR	NR	SCZ: 20 (100)	NR	2 years	Risperidone (8) Paliperidone (6) Aripiprazole (1) Zuclopenthixol (3) Flupenthixol (1) Fluphenazine (1)
Harrison (2021)	Australia	3	Case series	NR	M: 3 (100)	SCZ: 3 (100)	NR	NR	Paliperidone (1) Risperidone (1) Aripiprazole (1)
Joo (2022)	South Korea	NR	Retrospective health insurance data review	NR	NR	NR	NR	NR	Paliperidone Aripiprazole Risperidone Haloperidol
Kim (2010)	South Korea	4	Case series	36.5 (8.29)	F: 2 (50) M: 2 (50)	SCZ: 4 (100)	14 (5.4)	3 years	Risperidone
Leung (2014)	Australia	24	Retrospective cohort	NR	NR	NR	NR	NR	Haloperidol (7) Fluphenazine (5) Paliperidone (3) Risperidone (9)

TABLE 1 (Continued)

Study	Country	*N*	Study design	Mean age *years* (SD)	Gender *n* (%)	Diagnosis *n* (%)	Mean duration of illness *years* (SD)	Follow-up duration	Augmenting antipsychotic
Mukherjee (2021)	Australia	28	Cross-sectional	47.8 (2.63)	F: 11 (40) M: 17 (60)	SCZ: 28 (100)	NR	NR	Zuclopenthixol (15) Risperidone (3) Paliperidone 4-Weekly (4) Paliperidone 12-Weekly (1) Olanzapine (1) Haloperidol 4-Weekly (1) Haloperidol 3-Weekly (1) Aripiprazole (1) Zuclopenthixol Oral and IM (1)
Sepede (2016)	Italy	1	Case report	21	M: 1 (100)	SCZ: 1(100)	3	1 year	Aripiprazole
Souaiby (2017)	France	17	Retrospective mirror-image	22.9 (4.4)	F: 6 (35) M: 11 (65)	SCZ: 13 (77) SZA 4(24)	19.4 (12)	3 years	Haloperidol (9) Risperidone (7) Pipotiazine (1)

	LAI added to clozapine (%)	Primary reason for LAI initiation *n* (%)	Mean LAI dose *mg* (SD)	Mean clozapine dose *mg* (SD)	Mean clozapine dose change after LAI initiation	Mean clozapine monotherapy duration before LAI initiation (SD)	LAI continuation rates (%)	Adverse drug reactions	Outcome
Balcioglu (2020)	100	Symptom improvement	400 monthly	500	NR	4 months	100	None	Reduction in total PANSS score: 105–77
Bioque (2020)	64	Symptom improvement 25 (50) Adherence 9 (18) Both 7 (14) Other 9 (18)	123 (34) monthly	263 (165)	330 ± 189–266 ± 164	NR	74	Reduction in UKU total score 10.76 ± 8.04–8.82 ± 6.63 ($p = 0.004$) No agranulocytosis	Reduction in BPRS total score 18.3 ± 7.71–7.84 ± 5.16 ($p < 0.001$) Reduction in number of admissions 0.86 ± 0.7–0.36 ± 0.63 ($p < 0.001$) Reduction in length of admission 39.08 ± 53.61–18.26 ± 41.23 ($p = 0.002$) Reduction in ED visits 1.26 ± 1.7–0.46 ± 0.97 ($p < 0.001$)

(Continues)

TABLE 1 (Continued)

	LAI added to clozapine (%)	Primary reason for LAI initiation *n* (%)	Mean LAI dose *mg* (SD)	Mean clozapine dose *mg* (SD)	Mean clozapine dose change after LAI initiation	Mean clozapine monotherapy duration before LAI initiation (SD)	LAI continuation rates (%)	Adverse drug reactions	Outcome
									Increase in PSP score 46.06 ± 118.7–60.86 ± 18.68, $p < 0.001$)
Caliskan (2021)	100	NR	42.70			(8.35)/14 days 111.11 (22.04)/28 days 400/28 days 300/28 days 200/14 days	447 (186)	462 ± 194–447 ± 186	NR[a]
NR	No							agranulocytosis	Reduction in number of admissions 1.66 ± 0.9–0.59 ± 0.73 ($p = 0.001$) Reduction in length of admission 73.52 ± 41.93–23.48 ± 35.98 ($p = 0.001$) Reduction in number of relapses 2.07 ± 0.84–0.69 ± −0.76 ($p = 0.001$)
Mutlu (2022)	50	Symptom improvement 6 (33) Adherence 9 (50) Both 3 (17)	42.5 (10)/14 days 1117 (24) monthly 200(0)/14 days 20 mg/28 days 150 mg/28 days 25 mg/28 days	415 (183)	NR	4.8 (5.6) years	100	Sedation (4) Weight gain (2) Hyperprolactinemia (2) Hypersalivation (5) Rigidity in legs (1) Transient cardiac Marker elevation (1) Myoclonic jerks (1) Sinus tachycardia (1) Bradykinesia (1)	Median reduction in number of admissions 2.5–0 Reduction in CGI 5–4 CGI-I 3 Increase in GAF 40–50

TABLE 1 (Continued)

	LAI added to clozapine (%)	Primary reason for LAI initiation *n* (%)	Mean LAI dose *mg* (SD)	Mean clozapine dose *mg* (SD)	Mean clozapine dose change after LAI initiation	Mean clozapine monotherapy duration before LAI initiation (SD)	LAI continuation rates (%)	Adverse drug reactions	Outcome
								Difficulty in speaking (1) Drowsiness (1) Epileptic seizure (1) Obsessions (1)	
Grimminck (2020)	100	NR	NR	NR	NR	NR	NR	NR	Reduction in ED visits 1.8 (95%CI = [0.58–3.02], $p = 0.024$) Reduction in number of admissions 0.85 (95%CI = [0.36–1.34], $p = 0.008$) No change in bed days
Harrison (2021)	0	Adherence Clozapine side effects	150 mg/monthly 100 mg/monthly 400 mg/28 days	200 50 50	NR	NR	100	None	Improvement in mental state Discharge
Joo (2022)	NR	NR	NR	NR	NR	NR	NR	NR	[c]Reduction in risk (HR) of admission Compared to no use (HR, 0.18; 95%CI, 0.13–0.27; $p < 0.001$) Compared to clozapine monotherapy (HR, 0.60; 95%CI, 0.41–0.88; $p < 0.001$)
Kim (2010)	100	Adherence 4 (100)	25/14 days 25/14 days 25/14 days 25/14 days	100 300 100 213	325 ± 150–175 ± 96	8.5 years (6)	100	No agranulocytosis No ECG changes Mean parameter changes: Blood glucose—3.5 Total cholesterol: 0.8	Reduction in number of admissions 0.8 ± 0.3 and 0.1 ± 0.1/year Reduction in length of admission 54.7 ± 33.1 and 4.2 ± 4.2 days/year

(Continues)

TABLE 1 (Continued)

	LAI added to clozapine (%)	Primary reason for LAI initiation *n* (%)	Mean LAI dose *mg* (SD)	Mean clozapine dose *mg* (SD)	Mean clozapine dose change after LAI initiation	Mean clozapine monotherapy duration before LAI initiation (SD)	LAI continuation rates (%)	Adverse drug reactions	Outcome
Leung (2014)	NR	NR	NR	NR	NR	NR	NR	NR	Discharge
Mukherjee (2021)	NR	NR	150–600[b] 25–50[b] 100–150[b] 175 405 300 100 400 200 + 20	461 (38)	NR	NR	NR	NR	Reduction in HoNOS item 10 score[a]
Sepede (2016)	100	Symptom improvement and adherence	400 monthly	150	300–150	2 months	100	None	Reduction in PANSS: 80–40 Reduction in BPRS scores: 70–15 Improvement in CGI score:2
Souaiby (2017)	77	NR	235/28 days 50/14 days 75/21 days	352 (86)	NR	NR	NR		Reduction in number of admissions 2.1 ± 1.0 and 0.8 ± 0.8/year p = 0.004) Reduction in length of admission 155.4 ± 89.7 and 26.6 ± 47.1 days/year

Abbreviations: BPRS, Brief Psychiatric Rating Scale; HoNOS, Health of the Nation Outcome Scale; HR, Hazard ratio; IM, Intramuscular; Mg, milligrams; NR, not recorded; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; UKU, Udvalg for Kliniske Undersogelser side effects scale.

[a]Inclusion criteria: at least 1 year on clozapine monotherapy.

[b]Denotes range.

[c]Reduction only seen with second-generation antipsychotics.

he relapsed in the context of non-adherence to clozapine and was admitted for re-titration. Similar events occurred in March 2016 due to clozapine non-adherence. During this period, his weight increased from 117 to 134 kg. The patient's baseline serum lipid profile revealed low-density lipoprotein (LDL) 1.6 mmol/L, HDL 0.6 mmol/L, and triglycerides 4.4 mmol/L. Metformin prescription was considered but ultimately not done due to unknown reasons. To address concerns regarding adherence, the clinical team decided to initiate paliperidone palmitate 150 mg monthly in 2016 to augment clozapine. After 2 weeks of augmentation, a substantial reduction of his psychotic as well as affective symptoms was reported, and within a month was discharged on a Community Treatment Order. The patient described himself as having clearer thoughts and feeling significantly calmer. The dose of clozapine was reduced to 300 mg at night, achieving a plasma concentration of up to 0.38 mg/L. His weight increased by a further 2 kg (136 kg). Since discharge the patient has remained clinically stable in the community. As of January 2023, the patient remains engaged with his community mental health team, with his last inpatient admission in 2016. Paliperidone palmitate 150 mg monthly was switched to the 3-monthly formulation in 2020. The notable metabolic changes after augmentation included an increase triglyceride to 6.1 mmol/L. The patient's HbA1c remained unchanged (32 mmol/mol).

3.4 | Case 3

The patient is an 85-year-old Black Caribbean male with a diagnosis of F25.0 schizoaffective disorder. His first contact with psychiatric services was during his late 30's, where he was initially diagnosed with paranoid schizophrenia. Notable family history included his brother and sister who were diagnosed with paranoid schizophrenia. Until the age of 60 years old, the patient was reported functional, working in civil service having attained a degree in Mathematics. Prior to his first inpatient admission 10 years later, the patient was living with his wife and two children.

During his first inpatient admission, the patient presented with affective symptoms of a manic type, poor self-care, hyper religious delusions and mild negative symptoms and was subsequently diagnosed with schizoaffective disorder. The patient was initiated on pipothiazine palmitate 150 mg 2-weekly to good effect and remained in the community for 2 years. He was subsequently re-admitted into hospital to reinitiate pipothiazine after becoming non-compliant. Despite re-initiation, the patient remained symptomatic.

The patient had sequential trials with fluphenazine decanoate (25 mg 6-weekly), pipothiazine palmitate (150 mg 2-weekly), risperidone (3 mg daily), paliperidone palmitate (75 mg monthly), aripiprazole (10 mg), zuclopenthixol decanoate (400 mg 2-weekly) and flupenthixol decanoate (20 mg 2-weekly) with treatment only achieving partial response. Depot or long-acting injections were often prioritised due to concerns around his adherence. Given the lack of response to treatment, clozapine treatment was initiated 10 years later. Despite a reported response, clozapine treatment was stopped within a year due to the patient's refusal to engage with blood tests. A course of ECT in combination with pipothiazine palmitate (150 mg 2-weekly) was trialled to poor effect.

Given the lack of response to treatment, clozapine treatment was added to his pipothiazine depot and monthly ECT prescription. Clozapine was titrated up to a dose of 325 mg at night, achieving a plasma concentration of 0.33 mg/L. The patient demonstrated improvement in positive and affective symptoms within a month. ECT was ceased and clozapine and pipothiazine continued. Three months later, he was discharged to a supported accommodation. Two years on, the patient remains compliant with his treatment and has not been re-admitted into hospital or required re-titration.

3.5 | Literature review

We retrieved a total of 12 relevant articles which included two case reports, three case series and seven retrospective observational studies, four of which followed a mirror-image design, representing a total of 195 patients (Table 1). Three studies were conducted in Turkey,[14,15] two in South Korea[16,17] two in Australia[18,19] and one in each of the following countries: Spain,[20] Canada,[21] Italy,[22] France[23] and the United States.[24]

Both first-generation and second-generation antipsychotics were reported as adjunctive treatment to clozapine, although second-generation appeared more frequently. First-generation antipsychotics included were haloperidol, flupenthixol, zuclopenthixol, pipotiazine and fluphenazine. Second generation antipsychotics included were paliperidone, risperidone and aripiprazole. Risperidone and risperidone were the most reported antipsychotics administered in combination with clozapine, in nine and eight out of 12 studies, respectively.

Duration of follow up varied from 3 months[14] to 3 years[21] and it was not reported in three study[16,19,24] and not applicable in one study.[18]

With regards to side effects, Bioque et al.[20] reported that the combination of clozapine with LAI resulted in fewer side effects and was well tolerated. Similarly, three of the studies[17,22,23] reported that the commonly seen clozapine side effects did not arise on a combination of clozapine plus LAI antipsychotics, indicating a well-tolerated combination.

All studies reported consistently favourable outcomes although to a varied extent and with different outcome measures. The most consistently studied outcome measure was the number of admissions during the duration of treatment.[1,17,20,21,23]

4 | DISCUSSION

4.1 | Study findings

Clozapine is the treatment of choice for TRS, although up to 60% of TRS patients exhibit an inadequate response to monotherapy.[5] In such scenarios, good clinical practice warrants an investigation of the differential causes for nonresponse, such as nonadherence, drug interactions, and adverse drug reactions.[12] However, despite efforts to address these factors and optimise clozapine treatment, many patients unfortunately do not demonstrate an adequate response, leaving a large proportion of patients with debilitating clinical features. In many cases, augmentation of clozapine with other psychotropic medication is recommended, however, non-adherence rates remain very high, and taking additional oral medication increases the rates of non-compliance.[25] To address this conundrum, researchers have recently developed an interest in the augmentation of clozapine with LAIs, to predominantly alleviate residual symptoms.[21,23,26] Our report presents three successful cases of clozapine augmentation with an LAI for TRS—namely, paliperidone, pipothiazine, and olanzapine. All three cases showed clinical improvement and tolerability with this strategy to alleviate residual symptoms. Furthermore, our preliminary literature review, supports the clinical effectiveness of clozapine augmentation with LAIs. The most cited reasons for LAI augmentation were symptom improvement and adherence concerns, suggesting effectiveness in at least these patient groups. This review corroborates a recent systematic review by Mutlu et al.[27] that examined clozapine augmentation with LAI antipsychotics and different formulations of clozapine such as intramuscular administration to improve compliance for clozapine users. The authors described an improvement in clinical outcomes through use of LAIs and other clozapine formulations to aid compliance. In contrast, our review specifically investigated LAI as a treatment modality for symptom improvement and treatment persistence.

4.2 | Literature review

There is a paucity of controlled, prospective data on clozapine augmentation with LAIs. Accumulating observational data indicates LAI clinical utility to augment clozapine treatment as demonstrated in Table 1. In 2022, Mutlu et al.[27] investigated clozapine augmentation with LAIs to address adherence concerns with clozapine monotherapy in a case series and systematic review. In their case series, the authors reported a significant reduction in hospitalisation rates (0.26 ± 0.34 vs. 0.11 ± 0.40; $z = -2.817$, $p = 0.005$) in 18 patients treated with clozapine and LAI. Consistent with our case series, nonadherence was the most common reason for augmentation (67%), closely followed by an insufficient response to clozapine monotherapy (50%). Notably, the authors demonstrated clinical improvement through median changes in Clinical Global Impression (CGI) (5 vs. 4), Clinical Global Impression—Improvement (CGI-I) (3), and Global Assessment of Functioning (GAF) (40 vs. 50) scores.[27] Such findings are further substantiated by mirror-image studies and case reports, which all record symptom improvement and reduced hospitalisation rates.[1,17,20,21,23] For example, a one-year mirror-image study ($n = 17$) by Souaiby et al.[23] reported a 62% and 82% reduction in hospitalisation rates (2.1 vs. 0.8) and bed days (155.4 vs. 26.6) respectively after clozapine augmentation with an LAI. Equally, Bioque et al.[20] conducted a 6-month mirror-image study involving 50 individuals diagnosed with schizophrenia or schizoaffective disorder ($n = 46$), delusional disorder ($n = 2$), and bipolar disorder ($n = 2$). The authors reported a mean reduction in hospitalisation rates (0.86 vs. 0.36), bed days (9.08 vs. 18.26 days), visits to emergency departments (1.26 vs. 0.46) and the Brief Psychiatric Rating Scale (BPRS) total score (18.32 vs. 7.84). The patients' mean Social and Occupational Functioning Assessment Scale total score significantly increased from 46.06 to 60.86. Consistently, a recent observational cohort study of 2250 patients reported that antipsychotic polypharmacy, including LAI formulations, were amongst the best treatment options for lowest risk of psychiatric ward readmission in treatment resistant.[28] Overall, these findings indicate the clinical utility of clozapine augmentation LAIs in improving clinical outcomes, particularly symptom improvement and related hospitalisation rates. From a service provider's viewpoint, the described reductions in hospital use are important as the predominant economic burden of untreated TRS is hospital use.[29]

4.3 | Tolerability and safety

A legitimate concern amongst clinicians and patients regarding clozapine augmentation with antipsychotics and LAI is the risk of compounding clozapine-induced side effects. From existing guidance, most treatment algorithms recommend that structurally different antipsychotics are

preferred for clozapine augmentation to avoid increased side effect burden.[12,30] Our limited case series suggests that augmentation was well tolerated, even with structurally similar antipsychotics, with no significant adverse effects reported. By comparison, existing studies have generally demonstrated safety and tolerability with first and second LAI augmentation. For example, Souaiby et al. found no change in body mass index, lipid profile and serum glucose levels.[23] Similarly, Bioque et al.[20] reported a reduction of a side effect scale and stability of plasma prolactin levels. Furthermore, Caliskan et al.[15] found no significant change in fasting serum glucose levels, lipid profile, and prolactin levels after initiating LAIs. Such findings may be related to the reduction in the mean clozapine dose reported in each study following augmentation. Still, more rigorous data on augmentation with oral antipsychotic formulations, including those with longer half-lives, suggests good safety and tolerability.[31,32] Therefore, by the same token, one might anticipate similar findings with LAIs.[30,32] Another important consideration from our case series is that partial response to clozapine was determined many months before augmentation with LAI. From a safety perspective, this may moderate the major concern of LAI augmentation increasing the risk of potentially fatal clozapine-induced adverse effects, given that the patient will be over the maximal period of risk which predominantly occurs in the first few months of treatment with clozapine.[33]

Unique to our case series, this study demonstrated the serendipitously successful augmentation of clozapine with olanzapine LAI. Of note, this is not in keeping with recommendations to augment with antipsychotic medication with a potential for increased propensity for adverse side effects, including metabolic syndrome. However, the existing literature suggests that such side effects are dose or, more precisely, receptor occupancy related.[34] On this basis, if the same receptors are implicated in clozapine or olanzapine-induced metabolic effects,[35] there may be little scope for increased risk due to receptor saturation with clozapine monotherapy even before augmentation. Furthermore, a substantial proportion of existing literature proposes successful clozapine augmentation with risperidone (or paliperidone) LAI, which only has a marginally lower metabolic risk compared to olanzapine.[36] Nevertheless, more definitive research, using large samples and well-controlled prospective designs, is warranted.

Increased use of LAI to augment clozapine treatment and its evaluation, particularly where adherence is compromised, has seemingly been hampered by clozapine manufacturer recommendations that contraindicate its use. This is based on suggestions of an increased risk of clozapine-induced agranulocytosis (CIA). However, if this were accurate, one would expect the same risk to be replicated with oral formulations. Instead, meta-analytic data show no increased risk of CIA.[32] Observational data with LAIs, through our case series and existing studies, also demonstrate no increased risk of CIA.[15,23] Beyond other possibilities, it is plausible that the absence of CIA cases were due to the addition of an LAI after the 'at-risk period' for CIA.[37] While a theoretical increased risk may exist in the early phase of initiation, best clinical practice dictates that clozapine augmentation should only be considered after an adequate trial with clozapine (i.e., ~6 months with confirmed adherence achieving a therapeutic plasma level),[12] at which point the risk of CIA would be extremely low. From a practical perspective, this consideration is especially important as it would be impossible to withdraw a LAI immediately in the event of a blood dyscrasias.

4.4 | Withdrawal symptoms and reduced response

Abrupt discontinuation of clozapine has been reported to cause withdrawal symptoms, broadly categorised as withdrawal-associated psychosis, cholinergic rebound, catatonia and serotonergic discontinuation symptoms.[38] Recent treatment algorithms predominately recommend reinitiating clozapine to alleviate such symptoms.[11] However, there is limited evidence to suggest a role for the structurally similar oral antipsychotic olanzapine in alleviating such symptoms.[39] Where clozapine is not effective, or compliance is a concern, there are benefits from consideration of the LAI formulations especially with regards to compliance. Indeed, a major clinical issue is that periods of noncompliance with clozapine, particularly when abrupt, may be implicated in reduced responsiveness to future trials of clozapine treatment.[11] While theoretical, it remains a possibility that augmentation with an LAI such as olanzapine could reduce the risk of reduced responsiveness to clozapine treatment by maintaining receptor blockade during discontinuation—however, future studies are necessary to investigate this possibility. Notably, untreated psychosis is associated with poorer prognosis and has been suggested to be biologically toxic to the brain.[40] This may further support the notion of augmentation with a less effective LAI in patients who are partially compliant with clozapine monotherapy as opposed to recurrent admissions and ever worsening level of functioning.

4.5 | Clinical implications and future studies

Untreated TRS and impaired adherence represents 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. While authors have appropriately highlighted the inappropriate use of antipsychotic polypharmacy, this strategy may be warranted in certain clinical situations, especially when patient safety is compromised by poor control of symptoms. In our study, only 0.2% of patient's treated with clozapine received LAI augmentation. To put this in context, we estimate that approximately 50% of patients treated with clozapine receive oral antipsychotic polypharmacy in our care setting.[41] This low proportion may suggest that augmentation with LAI may be stigmatised amongst clinicians.

Our cases and cases published elsewhere strongly suggest the combination of clozapine and an LAI gives greater symptom improvement than clozapine alone. Reductions in admissions may well be linked to this improved response and better functioning. The question as to whether the use of an LAI prevents relapse if clozapine is stopped (the 'belt and braces' concept) is not answered by data considered here. From a theoretical viewpoint such a property seems unlikely since it would suggest that clozapine was a non-essential part of the combination: a very unlikely proposition.

Existing observational studies reveal that perhaps polypharmacy is not as toxic as single medication higher dose alternatives[42] and adding LAIs to clozapine may provide scope for dose reduction of the latter to improve tolerability. From a practical perspective, administration of a LAI may be planned on scheduled visits for clozapine blood tests, thus avoiding the daily burden of pill taking and cover non-compliance. Clinicians should carefully, on a case-by-case basis, consider clozapine augmentation with an LAI where a partial response to monotherapy has been demonstrated and/or a risk of relapse due to partial or non-compliance with augmentation persists. For instance, if clinically stability has already been achieved by augmentation of clozapine with an oral antipsychotic but there are compliance concerns, switching to an LAI may be a viable option. Clinicians should notably be proactive in discontinuing LAI augmentation trials in cases of inadequate response, intolerability, or safety concerns.

Despite the study findings, several questions remain unanswered at present. For instance, it is unknown how patients view clozapine augmentation with a long-acting injection. Furthermore, the studies are limited, and better designed future studies are required to establish which patients benefit most from this treatment modality, how it affects long-term clinical outcomes and adverse effects, and which LAI should be preferred in clozapine augmentation. Finally, future studies are warranted to understand why some patients are more responsive to non-clozapine antipsychotics only when augmented with clozapine compared to monotherapy. One possibility is that clozapine reverses TRS such that people become responsive to non-clozapine antipsychotics again.

4.6 | Strengths and Limitations

To our knowledge, this is the first study to describe clozapine augmentation with a LAI in the UK. Our study corroborates existing data on the clinical effectiveness of clozapine augmentation with a LAI in addressing residual symptoms. The results of the present study need to be interpreted within the context of their limitations. First, limitations inherent in a case series, including its retrospective nature and potential recall bias, are applicable in this study. Second, the lack of validated assessment scales for assessing symptom changes in our case series limits our findings. Third, is the small number of patients represented in the literature review. While these limitations are arguably addressed by our literature review, considering the quality of the studies included, randomised controlled trials are warranted to assess its clinical and cost effectiveness. Of note, our literature review highlighted that some patients were treated with LAI and clozapine without a trial of clozapine monotherapy—it is likely that some of these patients may have achieved the same clinical outcomes with clozapine monotherapy.

5 | CONCLUSION

This preliminary evidence suggests clinical utility of LAIs in alleviating residual symptoms in patients optimised on clozapine treatment. The current study warrants further investigations to establish the clinical efficacy, tolerability, and place in therapy of this treatment modality.

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The authors declare no conflicts of interest.

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REFERENCES

1. Howes OD, McCutcheon R, Agid O, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017;174:216-229. doi:10.1176/appi.ajp.2016.16050503
2. Wimberley T, MacCabe JH, Laursen TM, et al. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. *Am J Psychiatry*. 2017;174:990-998.
3. Cho J, Hayes RD, Jewell A, et al. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. *Acta Psychiatr Scand*. 2019;139:237-247.
4. Siskind D, Reddel T, MacCabe JH, et al. The impact of clozapine initiation and cessation on psychiatric hospital admissions and bed days: a mirror image cohort study. *Psychopharmacology (Berl)*. 2019;236:1931-1935.
5. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can J Psychiatry*. 2017;62:772-777. doi:10.1177/0706743717718167
6. McGlashan TH. A selective review of recent north American long-term followup studies of schizophrenia. *Schizophr Bull*. 1988;14:515-542. doi:10.1093/schbul/14.4.515
7. Revicki DA, Luce BR, Weschler JM, et al. Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients. *Hosp Commun Psychiatry*. 1990;41:850-854. doi:10.1176/ps.41.8.850
8. Davies LM, Drummond MF. Economics and schizophrenia: the real cost. *Br J Psychiatry Suppl*. 1994;1994:18-21.
9. Legge SE, Hamshere M, Hayes RD, et al. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. *Schizophr Res*. 2016;174:113-119. doi:10.1016/j.schres.2016.05.002
10. Parkes S, Mantell B, Oloyede E, Blackman G. Patients' experiences of clozapine for treatment-resistant schizophrenia: a systematic review. *Schizophr Bull Open*. 2022;3. doi:10.1093/schizbullopen/sgac042
11. Blackman G, Oloyede E, Horowitz M, et al. Reducing the risk of withdrawal symptoms and relapse following clozapine discontinuation—is it feasible to develop evidence-based guidelines? *Schizophr Bull*. 2021;48:176-189. doi:10.1093/schbul/sbab103
12. Taylor DM, Barnes TRE, Young AH. *The Maudsley Prescribing Guidelines in Psychiatry*. John Wiley & Sons; 2018.
13. Mylan. Clozaril 25mg tablets. 2020. Accessed January 14, 2023 https://www.medicines.org.uk/emc/product/4411/smpc
14. Balcioglu YH, Gokcay H, Yesilkaya UH. One plus one sometimes equals more than two: long-acting injectable aripiprazole adjunction in clozapine-resistant schizophrenia. *Clin Neuropharmacol*. 2020;43:166-168. doi:10.1097/wnf.0000000000000404
15. Caliskan AM, Karaaslan M, Inanli I, et al. The effects of adding long-acting injectable antipsychotic drugs to clozapine on relapse and hospitalization in patients with treatment-resistant schizophrenia: a mirror-image retrospective study. *Int Clin Psychopharmacol*. 2020;36:30-33. doi:10.1097/YIC.0000000000000336
16. Joo SW, Kim H, Jo YT, et al. Comparative effectiveness of antipsychotic monotherapy and polypharmacy in schizophrenia patients with clozapine treatment: a nationwide, health insurance data-based study. *Eur Neuropsychopharmacol*. 2022;59(36–44):20220509. doi:10.1016/j.euroneuro.2022.03.010
17. Se Hyun K, Dong Chung J, Yong Min A, et al. The combined use of risperidone long-acting injection and clozapine in patients with schizophrenia non-adherent to clozapine: a case series. *J Psychopharmacol*. 2010;24(981–986):20091126. doi:10.1177/0269881109348174
18. Mukherjee H, Sazhin V. Predictors of functioning and clinical outcomes in inpatient with schizophrenia on clozapine augmented with antipsychotics. *Australas Psychiatry*. 2022;30(100–104):20210831. doi:10.1177/10398562211037339
19. Harrison Z, Haeney O, Brereton W. Augmentation of antipsychotic medications with low-dose clozapine in treatment-resistant schizophrenia-case reports and discussion. *Case Rep Psychiatry*. 2021;2021:20210619. doi:10.1155/2021/5525398
20. Bioque M, Parellada E, García-Rizo C, et al. Clozapine and paliperidone palmitate antipsychotic combination in treatment-resistant schizophrenia and other psychotic disorders: a retrospective 6-month mirror-image study. *Eur Psychiatry*. 2020;63(e71):20200716. doi:10.1192/j.eurpsy.2020.72
21. Grimminck R, Oluboka O, Sihota M, Rutherford DL, Yeung H. Combination of clozapine with long-acting injectable antipsychotics in treatment-resistant schizophrenia: preliminary evidence from health care utilization indices. *Prim Care Companion CNS Disord*. 2020;22:20200716. doi:10.4088/PCC.19m02560
22. Sepede G, Di Iorio G, Spano MC, et al. A case of resistant schizophrenia successfully treated with clozapine/long-acting injectable aripiprazole combination. *Clin Neuropharmacol*. 2016;39:322-324. doi:10.1097/wnf.0000000000000191
23. Souaiby L, Gauthier C, Rieu C, Krebs MO, Advenier-Iakovlev E, Gaillard R. Clozapine and long-acting injectable antipsychotic combination: a retrospective one-year mirror-image study. *Schizophr Res*. 2017;188:89-91. doi:10.1016/j.schres.2017.01.036
24. Leung JG, Chengappa KN, Ivanov E, et al. Antipsychotic agents used to augment clozapine during long-term inpatient hospitalizations. *Pharmacopsychiatry*. 2014;47(263–267):20141008. doi:10.1055/s-0034-1390469
25. Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry*. 2019;76:499-507. doi:10.1001/jamapsychiatry.2018.4320
26. Malla A, Tibbo P, Chue P, et al. Long-acting injectable antipsychotics: recommendations for clinicians. *Can J Psychiatry*. 2013;58:30-35.
27. Mutlu E, Karaçam Doğan M, Ertuğrul A, Anıl Yağcıoğlu AE. Combination with long-acting injectable antipsychotics and utilization of nonstandard formulations as compliance enhancing Methods for clozapine users: a systematic review and a case series. *J Clin Psychopharmacol*. 2022;42(298–307):20220203. doi:10.1097/jcp.0000000000001526
28. Luykx JJ, Stam N, Tanskanen A, et al. In the aftermath of clozapine discontinuation: comparative effectiveness and safety of antipsychotics in patients with schizophrenia who discontinue clozapine. *Br J Psychiatry*. 2020;217:498-505. doi:10.1192/bjp.2019.267
29. Kennedy JL, Altar CA, Taylor DL, et al. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol*. 2014;29:63-76. doi:10.1097/YIC.0b013e32836508e6

30. Wagner E, Löhrs L, Siskind D, et al. Clozapine augmentation strategies: a systematic meta-review of available evidence. Treatment options for clozapine resistance. *J Psychopharmacol*. 2019;33:423-435. doi:10.1177/0269881118822171
31. Oloyede E, Clark I, Mace S, Whiskey E, Taylor D. Clozapine augmentation with cariprazine for negative symptoms: a case series and literature review. *Therapeut Adv Psychopharmacol*. 2022;12:20451253211066642. doi:10.1177/20451253211066642
32. Siskind DJ, Lee M, Ravindran A, et al. Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. *Aust N Z J Psychiatry*. 2018;52:751-767. doi:10.1177/0004867418772351
33. Atkin K, Kendall F, Gould D, et al. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry*. 1996;169:483-488. doi:10.1192/bjp.169.4.483
34. Wu H, Siafis S, Hamza T, et al. Antipsychotic-induced weight gain: dose-response meta-analysis of randomized controlled trials. *Schizophr Bull*. 2022;48:643-654. doi:10.1093/schbul/sbac001
35. Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva V. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatr Dis Treat*. 2017;13(2231–2241):20170822. doi:10.2147/ndt.S113099
36. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7:64-77.
37. Oloyede E, Whiskey E, Casetta C, et al. Relaxation of the criteria for entry to the UK clozapine central non-Rechallenge database: a modelling study. *Lancet Psychiatry*. 2022;9:636-644. doi:10.1016/S2215-0366(22)00188-2
38. Blackman G, Oloyede E. Clozapine discontinuation withdrawal symptoms in schizophrenia. *Therapeut Adv Psychopharmacol*. 2021;11:20451253211032053. doi:10.1177/20451253211032053
39. Green A, Stephenson T, Whiskey E, Shergill SS. Closure beyond clozapine: successfully averting rebound symptoms in a patient with schizoaffective disorder and agranulocytosis. *BJPsych Open*. 2019;5(e43):20190522. doi:10.1192/bjo.2019.31
40. Lieberman JA, Fenton WS. Delayed detection of psychosis: causes, consequences, and effect on public health. *Am J Psychiatry*. 2000;157:1727-1730.
41. Kadra G, Stewart R, Shetty H, et al. Long-term antipsychotic polypharmacy prescribing in secondary mental health care and the risk of mortality. *Acta Psychiatr Scand*. 2018;138(123–132):20180529. doi:10.1111/acps.12906
42. Taipale H, Tanskanen A, Tiihonen J. Safety of antipsychotic polypharmacy versus monotherapy in a Nationwide cohort of 61,889 patients with schizophrenia. *Am J Psychiatry*. 2023;180:377-385. doi:10.1176/appi.ajp.20220446

SUPPORTING INFORMATION

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