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Systematic Review

Aripiprazole Long Acting and Clozapine: Between Efficacy and Tolerability

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Abstract: Background: Patients affected by schizophrenia often experience a poor quality of life. Antipsychotics currently used reduce treatment compliance because of their side effects and their high non-responder rate. Antipsychotic polytherapy, also with Long-acting injectables (LAI) formulation, may increase the efficacy in refractory and non-compliant patients. This systematic review examines the coadministration of clozapine and aripiprazole LAI, studying its efficacy, tolerability and side-effects. Methods: The research was conducted on 6 August 2025, using PubMed, Scopus and Web of Science. The query search tool used was "*aripiprazole AND clozapine AND (Long acting OR injectable OR LAI OR combination)*". Only original papers written in English were considered; animal research, in vitro experiments, also studies not specifying the formulation of aripiprazole were excluded. Results: Our research produced 1637 records. Removing repeated, not written in English and off topic articles, six papers were selected for qualitative synthesis. Conclusions: Available evidence on the combined use of clozapine and long-acting injectable aripiprazole is limited and largely derived from small observational studies. The reviewed reports describe recurring clinical observations suggesting that this strategy may be applicable in selected patients with treatment-resistant schizophrenia, particularly in the presence of poor adherence or clozapine-related tolerability concerns. Reported outcomes include symptom stabilization, improved adherence, and possible benefits on residual symptoms and clozapine-related adverse effects. Nonetheless, the low certainty of the evidence prevents firm conclusions regarding efficacy and safety, highlighting the need for further prospective controlled studies.

Keywords: aripiprazole; clozapine; LAI; co-administration; compliance

1. Introduction

Schizophrenia is a chronic disease distinguished by a set of positive symptoms (thought disorders and hallucinations), negative symptoms (apathy; alienation and poverty of emotional externalization, thought and speech) and a various degree of cognitive decline regarding attention, memory and enforceability [1]. These symptoms, characterized by periods of remission interrupted by relapses, lower the quality of life of patients affected by schizophrenia. This is related to a higher risk of drugs abuse, violent behaviour and suicidal tendencies compared to the general population [2]. Current treatments aim to prevent relapses and control symptoms, allowing patients to keep interpersonal relationships and conduct a relatively normal life without the burden of serious side effects. Among these treatments, antipsychotics reflect these requests, but their side-effects and their high rate of non-responders lead to poor adherence and rehospitalizations [3]. Poor treatment compliance, despite the general

efficacy of antipsychotics for reducing symptoms, has a 40–60% prevalence in patients affected by schizophrenia. This is cause for concern because it is one of the major risk factors for psychotic relapses and its severe consequences [4].

1.1. Clozapine

Clozapine is the main atypical antipsychotic drug belonging to the Second-Generation Antipsychotics (SGAs). One of the major problems of treating patients with SGAs is the manifestation of extrapyramidal side effects (EPS) [5] together with the side effects of long-term medication with atypical antipsychotics. Despite this, the Food and Drug Administration (FDA) approved the use of clozapine as an antipsychotic because its efficacy prevails over its side effects in the treatment of patients [6].

1.2. Side Effects

Serotoninergic (5-HT1A, 5-HT2A, 5-HT2C), adrenergic (α1, α2), histaminergic H1 and muscarinic M1 are other receptors with an affinity for clozapine, and they are strictly linked to the most common side effect of this drug (orthostatic hypotension, sexual dysfunction, constipation, sedation, urinary retention, tachycardia and blurred vision). Seizures, weight gain, transient eosinophilia, leukocytosis, nausea, sialorrhea, benign hyperthermia and dizziness are, with the others above, common (1/100) side effects of clozapine treatment. High dosage of clozapine (>600 mg/day) is also more associated with seizures than medium (300–600 mg/day) or low (<300 mg/day) dosages [7].

Clozapine-induced weight gain is connected to its effects on 5-HT2A, 5-HT2C, H1 and α-receptors. This adverse event may lead to metabolic syndrome and a higher risk of developing type 2 diabetes mellitus and cardiovascular diseases (dyslipidemia, hypertension) [8]. Weight gain and its consequences also appear to be dose-related, since dosage reduction showed some benefits in randomized controlled trials thanks to antipsychotic polytherapy (addiction of aripiprazole) [9].

Antagonism on cholinergic (M1, M3) and serotoninergic (5HT-3, 5HT-7) receptors in the bowel could cause the deceleration of colonic transit time in patients under clozapine treatment, even at low dosages. This may cause constipation, which is one of the main causes of treatment interruption (frequency 15–60%). In severe cases, obstinate and untreated constipation can evolve to paralytic ileus and intestinal obstruction with potentially fatal consequences [10].

Uncommon side effects (1/1000) of clozapine are agranulocytosis, diabetes mellitus, metabolic syndrome, delirium, liver enzyme abnormalities, interstitial nephritis, stuttering, thrombocytopenia, dysphonia, neuroleptic malignant syndrome [7].

Clozapine-induced neutropenia is diagnosed when absolute neutrophil count (ANC) is inferior to 1500/mm^3; this occurs in about 3% of patients and it is potentially lethal, since 0.8–2% of them develop agranulocytosis (ANC < 500/mm^3) consequently, for unknown reasons. Transient neutropenia and ANC weekly fluctuations, although quite common during treatment, are rarely a cause of demission [11]. Due to these facts, the FDA established a national registry (Risk Evaluation and Mitigation Strategy) with obligatory ANC blood monitoring: weekly in the first 24 weeks; every 2 weeks in the next 24 weeks and, next, every 4 weeks until interruption of clozapine treatment [12]. Myocarditis and pericarditis, dilatated cardiomyopathy, heat stroke, hepatic failure, colitis, pancreatitis, pneumonia, respiratory failure, vasculitis, skin rash, ocular pigmentation, priapism, parotid gland swelling, rhabdomyolysis and QT prolongation are some of the rare (1/10,000) side effects [7].

QT prolongation occurs when QT interval, determined by electrocardiography, is >500 milliseconds or when QTc rises by >60 milliseconds from clozapine-free baseline, increasing the risk of torsade de pointes (TdP) and sudden cardiac death (SCD) [13]. Medium and high dosage of clozapine seem to be more likely to be associated with the alteration of the heart rhythm [14]. It was observed that some bothersome clozapine side effects (sedation, weight gain, constipation, sialorrhea, etc.) are a frequent reason for therapy discontinuation. Since this drug is the only one recommended for treatment-resistant schizophrenia (registered therapeutic failure with two other antipsychotics), which occurs in about 30% of cases [2], interruption of the treatment is not advisable.

1.3. Safety Discussion

Clozapine is associated with a well-characterized profile of rare but potentially life-threatening cardiovascular adverse events, including QTc prolongation, dilated cardiomyopathy, myocarditis, and pericarditis, which are largely considered intrinsic to clozapine exposure and occur most frequently during early treatment and titration phases. QTc prolongation is usually mild but may rarely progress to torsades de pointes; therefore, ECG

monitoring is recommended at treatment initiation, during polypharmacy, and in elderly patients, with dose reduction advised in case of significant QTc changes.

Clozapine-induced myocarditis, cardiomyopathy, and pericarditis represent uncommon yet clinically critical complications, with presentations ranging from subclinical laboratory abnormalities to fulminant and potentially fatal conditions. As summarized by De Berardis et al., a structured monitoring approach, including serial assessment of troponin, high-sensitivity C-reactive protein (hs-CRP), echocardiography, BNP, and routine vital signs, is essential, particularly during the first 28 days of treatment. Patients should be actively monitored for nonspecific systemic symptoms (e.g., fever, chest pain, flu-like symptoms, dyspnea, gastrointestinal complaints, or malaise). Defined laboratory thresholds (e.g., troponin ≥ 2× ULN or hs-CRP > 100 mg/L) warrant immediate clozapine discontinuation and cardiology referral.

Several factors may increase the risk of clozapine-related cardiac complications, including rapid dose titration, metabolic burden, concomitant use of valproate, SSRIs, illicit substances, and selected interacting medications. In this context, polypharmacy may act as a risk amplifier rather than an independent causal factor. Importantly, case reports, including one involving clozapine-related pericarditis in a patient receiving aripiprazole LAI, suggest that serious adverse events observed during combination therapy are more plausibly attributable to clozapine itself rather than to the LAI formulation [8].

In the absence of combination-specific safety guidelines for clozapine plus aripiprazole LAI, extending established clozapine monitoring protocols (e.g., the Ronaldson framework), with heightened clinical vigilance, appears to be a prudent approach when this strategy is considered in exceptional cases. From a real-world safety governance perspective, both NICE and the Maudsley Prescribing Guidelines emphasize that therapeutic drug monitoring of clozapine should precede any augmentation strategy, including LAI combinations, to exclude pseudo-resistance due to subtherapeutic exposure, non-adherence, or pharmacokinetic variability. In this sense, TDM (therapeutic drug monitoring) functions as a key risk-mitigation measure, supporting rational treatment sequencing and minimizing avoidable polypharmacy and cumulative adverse effects [15,16].

1.4. Aripiprazole

Aripiprazole is an SGA, however, due to its peculiar pharmacological profile, some authors define it as a "third generation" neuroleptic [17]. This quinolinone derivative is a partial agonist of D2, D3, D4, 5-HT1A and 5-HT2C receptors and an antagonist of 5-HT2A, H1 and α1 receptors. It behaves like a D-receptor agonist when dopamine levels are low and as an antagonist in the opposite situation; it has the same effect on two serotoninergic receptors. These activities seem to stabilize dopamine and serotonin pathways, but the full mechanism needs to be unveiled [18].

The antagonism of 5-HT2A receptors may improve negative symptoms and cognition; the partial agonism of 5-HT1A neuro-receptors probably acts on anxiety and depressive symptoms. Aripiprazole has an inferior affinity for H1 receptors compared to clozapine and other atypical antipsychotics, this can explain a lower incidence of weight gain, metabolic changes (glucose and cholesterol levels) and sedation during treatment [4]. Partial agonism on D2 receptors may be crucial to soften D2-linked side effects like hyperprolactinemia [19]. Prolactin secretion depends on various stimuli, with hypothalamic dopamine acting as the main inhibiting substance. Most antipsychotics tend to cause D2-blockade on lactotroph pituitary cells; this can result in asymptomatic hyperprolactinemia or in a bothersome set of symptoms including infertility, galactorrhea, hypogonadism, sexual disfunction, decreased libido and secondary bone loss [20,21].

According to several reviews, meta-analyses and individual studies on schizophrenia, aripiprazole does not seem to have a clinically relevant effect on QT prolongation [13]. It can also be ranked as one of the best neuroleptics in limiting weight gain and metabolic changes [22] and as the least linked to symptomatic hyperprolactinemia [20]. It has similar efficacy and a better safety profile than typical and atypical antipsychotics [22], which may help to improve treatment compliance [23]. Many research findings of the last few years have highlighted aripiprazole, thanks to its multimodal effect, as a potential medication for the treatment of different types of substance dependence [24] and in the treatment of behavioral disorders, including in adolescent patients [25].

1.5. Aripiprazole LAI

Long acting injectables (LAI) are used with the purpose to maintain stable blood levels during the drug administrations; this has a high role in ameliorate patient adherence. Also, periodical injections guarantee a stricter monitoring of patient response and adverse events [26]. LAIs are often used in combination with oral antipsychotics and psychotropics [27,28].

Aripiprazole LAI is the first-line injectable choice for patients undergoing oral aripiprazole therapy, since systemic exposure and effects appear to be similar enough prior dosage adjustment [4,29].

The side effects with higher incidence in aripiprazole LAI patients are weight gain (9%), akathisia (8%), insomnia (6%) and injection-site related pain (5%). Even if neutropenia has been reported in the clinical program with aripiprazole LAI (with a typical onset around day 16 after the first injection), in literature there is poor clinical evidence of these side effects related to this long-acting formulation [30].

Treatment with aripiprazole LAI is particularly favorable when negative symptoms persist or prevail (apathy; alienation and poverty of emotional externalization, thought and speech), even if caused by another antipsychotic. Several studies record a general improvement of positive and negative symptoms, a decreased rate of irritability and a better social/working life in treatment with Aripiprazole Once-Monthly (AOM) with inferior rates of sexual dysfunction, hyperprolactinemia, metabolic effects and extrapyramidal symptoms compared to those of several neuroleptics like clozapine, haloperidol, risperidone and paliperidone. All these factors contribute to strengthen treatment compliance with aripiprazole LAI [29].

1.6. Antipsychotic Polytherapy

Antipsychotic polytherapy may be considered as a valid candidate to increase the efficacy and the tolerability of the treatment, especially in resistant schizophrenia [31,32]; a second molecule could be added to counteract a specific symptom or to mitigate/prevent a peculiar adverse event caused by the first drug [33].

Combination strategies involving clozapine and aripiprazole have neurobiological basis foundations, since aripiprazole shows partial agonism to D2 neuro-receptors [34,35]. Also, thanks to the modulatory activity of clozapine receptors, it is possible to tone down positive and negative symptoms and to reduce clozapine-related adverse events, like hyperprolactinemia and sexual dysfunction [20]. Furthermore, partial agonism of aripiprazole on 5-HT2C and 5-HT1A receptors seems to counterbalance clozapine high affinity for 5-HT2C neuroreceptors and its adverse effects on metabolism (such as weight gain and dyslipidemia). The reasons behind the weight loss during aripiprazole and clozapine combined therapy are still unknown but possibly linked to the serotonin-orexin-histamine system [36]. These metabolic benefits occur even if the dosage of clozapine is not decreased [21].

According to the current literature, the risk of manifesting new, unforeseeable or enhanced side effects with a polytherapy approach appears to be very low (decreased psychotic polytherapy appears to be the best solution for clozapine-resistant schizophrenia patients, since it is not possible to remove clozapine administration [21].

The elimination of clozapine occurs via hepatic metabolism mainly through two cytochrome P450 isoenzymes, CYP1A2 and CYP3A4 [37]; aripiprazole is metabolized by CYP2D6 and CYP3A4 and is not expected to interfere with pharmacokinetic of other drugs processed by CYP enzymes in a clinically relevant way [4].

2. Eligibility Criteria

2.1. Population

Patients diagnosed with Schizophrenia, particularly those characterized by treatment resistance, poor clinical response, or low treatment adherence. The rationale for focusing on this population stems from the clinical challenge of managing refractory symptoms and the high relapse rates (40–60%) associated with traditional oral therapies.

2.2. Intervention or Exposure

Pharmacological combination of clozapine and aripiprazole in Long-Acting Injectable (LAI) formulation. The use of the LAI formulation is specifically targeted to ensure pharmacological stability and improve compliance.

2.3. Comparison

No direct comparator was analyzed, as the included evidence consists primarily of non-comparative case material. The evaluation focuses on clinical outcomes observed in individual cases.

2.4. Outcomes

The primary outcomes included clinical efficacy (improvement in positive and negative symptoms), tolerability (reduction in clozapine-related side effects), and treatment persistence (reduction in discontinuation rates).

Inclusion and Exclusion

The inclusion was restricted to original articles published in English to ensure the reliability of the primary data. Reviews, editorials, and book chapters were excluded to avoid data redundancy and focus on original evidence. Animal and in vitro studies were excluded as the focus is strictly on clinical translation and patient quality of life. Studies not explicitly mentioning the LAI formulation of aripiprazole were excluded. This is a critical distinction, as the rationale of this review is to investigate the synergistic benefit of a long-acting delivery system in improving patient outcomes compared to daily oral intake.

3. Methods

The selection, eligibility, and data extraction phases were conducted independently by three authors (LP, LDS, and MX). To ensure accuracy and minimize bias, all extracted data and selection outcomes underwent a formal cross-check by AM and AMo. Any discrepancies or doubtful cases were resolved through discussion and reached via consensus with the senior authors (AMo and MP), ensuring a rigorous validation process for all included information. The selection and eligibility phases were carried out independently by LP, LDS and MX with a final cross-check by AM and AMo. All discordant cases were evaluated by MP.

The research was carried out using PubMed, Scopus and Web of Science as search engines to collect the studies regarding the coadministration of clozapine and aripiprazole LAI or/and those concerning the side effects of these two molecules. The research was conducted on 6 August 2025, using "aripiprazole AND clozapine AND (long acting OR injectable OR LAI OR combination)" as a query search tool. The inclusion criteria considered were: not repeated articles in the three databases; the originality of the articles (e.g., review, metanalysis, commentary, letter to the editor with no available data, book chapter) and articles written in English. This research produced a total of 1637 results. (PubMed = 284; Scopus = 1115; WoS = 238). After removing duplicate articles (n = 397), 1240 were screened. Of these, 398 were considered not relevant based on title and abstract, 29 were not written in English, and 467 were non-original articles. Of the remaining 346 full-text articles, 337 did not meet the inclusion criteria and 3 were not available. Ultimately, 6 articles were included (Figure 1).

Risk of Bias

The methodological quality of the included studies was assessed using Joanna Briggs Institute (JBI) [38] critical appraisal checklists specifically designed for case reports (n = 5) and analytical cross-sectional studies (n = 1). All items across both checklists, including the CARE criteria for the clinical reporting of case reports and the JBI standards for cross-sectional evidence, indicated high completion rates and adequate reporting (detailed descriptions of the items for both the CARE checklists are provided in the Supplementary Material). Specifically, the evaluation covered key domains such as patient demographic characteristics, clinical history, diagnostic assessment, and the validity of outcome measurements. These findings indicate high reporting quality and clinical descriptiveness. However, internal validity and causality remain limited by design, as case-based evidence lacks control groups and is naturally subject to inherent risks of confounding or selection bias. Therefore, these results should be interpreted with caution.

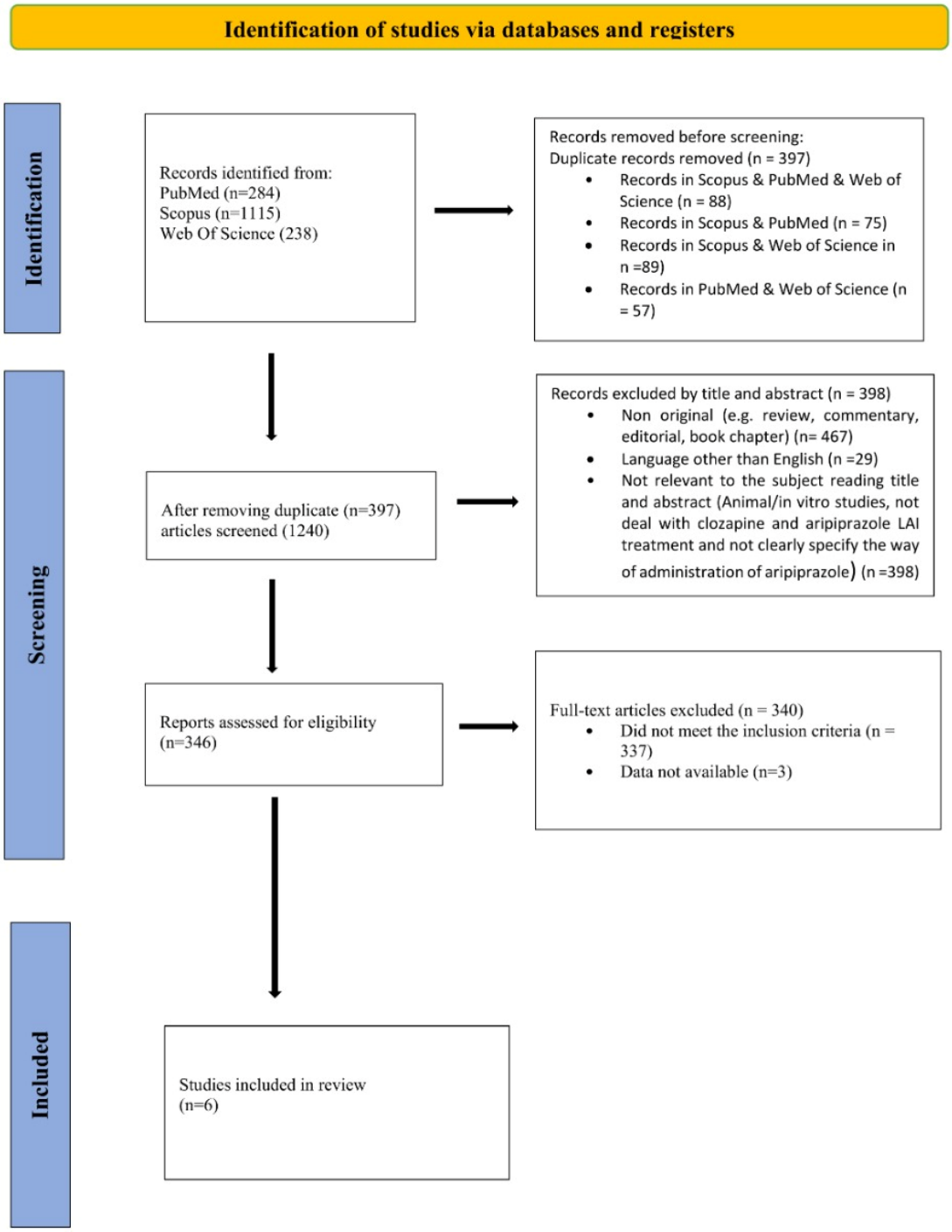

Figure 1. Preferred reporting items for systematic review.

4. Results

We retrieved a total of 6 articles which include 5 case reports and 1 cross-sectional study.

Sepede et al. [39] reported one case of treatment-resistant paranoid schizophrenia with documented non-response to multiple prior antipsychotic trials (oral haloperidol, risperidone, aripiprazole; LAI paliperidone and LAI risperidone). Baseline characteristics: severe psychopathology (PANSS = 80; BPRS = 70), poor functioning, BMI = 21.9. Clozapine treatment: 300 mg/day; plasma levels not reported; partial symptomatic response with sedation and myoclonus; dose reduction to 150 mg/day associated with loss of efficacy. Augmentation strategy: aripiprazole LAI, initiated and titrated to 400 mg IM every 28 days within 2 months. Clinical outcomes: sustained symptom improvement at >12-month follow-up, with PANSS reduction ≈ 50% and BPRS reduction ≈ 78.6%; CGI indicated clinical improvement. Safety and tolerability: no clinically relevant adverse events or treatment discontinuations reported during combination therapy. Follow-up: >12 months; BMI remained stable [40] (Table 1).

Table 1. Legend: PANSS: Positive and Negative Schizophrenic Symptoms; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; LAI: long acting injectable; ari: aripiprazole; clo: clozapine.

Author (Year)	Patients (N)	Diagnosis	Clozapine Dosage (MG/DIE)	Clozapine Plasma Levels (µg/L)	Aripiprazole Dosage (MG/Month)	Other Treatment	Benefit	Collateral Effects	Final Treatment
Sepede et al. (2016)	1	Paranoid schizophrenia	300 → 150	-	200 → 400	-	Symptoms significantly improved; PANSS 100 → 50%; BPRS 100 → 78,6%; CGI: 2; More active lifestyle.	-	Clozapine 150 mg/day; LAI aripiprazole 400 mg/month
De Berardis et al. (2018)	1	Schizoaffective disorder	100 → 0	-	400	valproate 500 mg; lorazepam 1 mg; quetiapine 50 mg/day; indomethacin 50 mg	Pericarditis vanished after clozapine discontinuation.	Clozapine-related pericarditis; elevation in body temperature (37 °C); mild shortness of breath.	lorazepam 1 mg; quetiapine 50 mg/day; valproate 500 mg; LAI aripiprazole 400 mg OM
Nilsson et al. (2017)	9 LAI ari; 36 clo + ari; 174 clo	Schizophrenia; Schizoaffective disorder; Bipolar disorder	≈300	-	≈280 clorpromazine; equivalent mg/day	-	Correlation between clozapine dose and Hearth rate	Tachycardia prevalence study: Clo monotherapy Group = 34%; Clo + ari group = 32%, LAI group = 16%	-
Balcioglu et al. (2020)	1	Schizophrenia	500	545 µg/L	400	-	Reduction in total PANSS score: 105–77	None	Clozapine 500 mg/day; LAI aripiprazole 400 mg/28 days
Harrison et al. (2021)	1	Paranoid schizophrenia	50	57-121 µg/L	400	-	Improve in mental state; Discharge	-	Clozapine 50 mg/day; LAI aripiprazole 400 mg/month
Orsolini et al. (2022)	1	Clozapine-resistent schizophrenia + cannabinoid use disorder	-	-	-	-	-	-	-

De Berardis et al. reported a single case of schizoaffective disorder in a young female patient with poor response and extrapyramidal adverse effects (parkinsonism) during previous treatment with haloperidol, risperidone, and valproate. Baseline context: persistent psychotic and affective symptoms; clozapine plasma levels not reported. LAI treatment: aripiprazole LAI 400 mg IM every 28 days, combined with valproate (500 mg twice a day) and lorazepam (1 mg/day), resulting in mild symptomatic improvement and resolution of parkinsonism. Clozapine augmentation: initiated at 100 mg/day after 6 days of titration. Adverse events: biochemical evidence of inflammatory response (CRP, troponin, CPK elevation) and echocardiographic findings consistent with clozapine-related pericarditis, with minimal clinical symptoms. Clozapine was discontinued and indomethacin introduced, leading to full resolution of laboratory and echocardiographic abnormalities within one week. Follow-up regimen: aripiprazole LAI 400 mg IM every 28 days quetiapine 50 mg/day, valproate 500 mg/day, lorazepam 1 mg/day. Outcome: clinical improvement and no further adverse effects reported [39] (PANSS/BPRS/CGI data not available).

Nilsson et al. conducted an observational study in 261 patients with schizophrenia evaluating heart rate (HR) changes associated with clozapine and LAI antipsychotic treatments. LAI exposure: perphenazine, zuclopenthixol, haloperidol, flupentixol, paliperidone, risperidone, fluphenazine, olanzapine, and aripiprazole. Clozapine subgroup: 174 patients, of whom 36 received concomitant oral aripiprazole. Outcomes: increased HR was observed in approximately 33% of patients treated with clozapine, independent of LAI exposure. A positive correlation was identified between clozapine dose (≥300 mg/day vs. <300 mg/day) and HR increase. However, current literature suggests that a direct causal relationship does not exist. Due to limited direct evidence regarding the Clozapine plus Aripiprazole combination, these findings should be interpreted cautiously. Safety outcome: HR changes were attributed primarily to clozapine rather than LAI treatment [41].

Balcioglu et al. described a case of a 22-year-old male with schizophrenia and persistent positive symptoms despite prior treatment with risperidone, olanzapine, and paliperidone. Baseline severity: PANSS total score 105. Clozapine treatment: oral clozapine titrated to achieve therapeutic plasma concentrations (545 μg/L) Augmentation strategy: aripiprazole LAI 400 mg IM every 28 days. Clinical outcomes: one week after the third LAI injection, a marked clinical improvement in positive symptoms and social functioning was observed, with PANSS total score reduction to 77. (35% decrease from the first admission; 25% decrease from the time aripiprazole was initiated). Adverse events: not reported. Safety outcome: the better safety profile of aripiprazole makes this strategy more sound, particularly for patients who are more vulnerable to extrapyramidal and metabolic adverse effects [42].

Harrison et al. reported a case series (n = 3), including one patient treated with clozapine and aripiprazole LAI. Patient characteristics: 40-year-old male with treatment-resistant paranoid schizophrenia, amphetamine use disorder, and poor adherence to oral antipsychotics. Clozapine treatment: 300 mg/day (serum levels 337–632 μg/L), discontinued due to adverse effects (weight gain, sedation, hypersalivation). LAI treatment: aripiprazole LAI 400 mg IM every 28 days without any relapses in short time observation, with short-term symptom stability but subsequent re-emergence of negative and disorganized symptoms. Re-augmentation: adjunctive clozapine 50 mg/day (serum levels 57–121 μg/L). Outcome: significant clinical improvement and functional recovery allowing progress toward discharge. (PANSS/BPRS/CGI data not available). Follow-up duration: observation period during the hospitalization, not better specified [43].

Orsolini et al. described a case of a 20-year-old male with clozapine-resistant schizophrenia and comorbid Cannabis Use Disorder experiencing relapse. Initial treatment: clozapine combined with brexpiprazole. Switch strategy: due to poor adherence, brexpiprazole was replaced with a two-injection start regimen of aripiprazole LAI. Clinical outcomes: after two months from the beginning of the clozapine-brexpiprazole combination treatment, a global psychopathological improvement was observed, with reductions of 43% in CGI score and 50% in BPRS total score. Improvements ≥30% were reported across multiple symptom domains, including positive, negative, affective, and hostility dimensions. Minor improvements were reported in the activation and anxiety. Adverse events: not available [44].

5. Discussion

This review provides preliminary, descriptive insights into a clinical practice occasionally reported in the literature, namely the coadministration of clozapine and aripiprazole LAI. Although clozapine labelling recommends monotherapy, the available evidence is limited to case reports and small case series, which describe heterogeneous clinical observations in selected patients and do not allow inferences regarding effectiveness, adherence benefits, or causality.

As shown in the case report of Sepede et al. [39], the patient appeared less sedated after being treated with the chosen drug, and started again to enjoy hobbies and activities, considered one of the best indicators of improvement in the quality of life. Furthermore, Nilsson MB et al. [41], in their comparative study, showed how

clozapine (and not LAIs) is more likely to give subjective or objective side effects, like increased heart rate. Even in case of serious side effects (such as clozapine-related pericarditis), as described in the report by De Berardis et al. [1], there is the possibility of re-establishing good health conditions with good medical management, that, in this case, consisted in the discontinuation of clozapine and treating patients with LAI monotherapy. The case report of Harrison et al. demonstrates the potential feasibility and efficacy of augmenting standard antipsychotic monotherapy with low-dose clozapine, he was no longer troubled by side effects. The case of Orsolini et al. [44] doesn't primarily focus on the co-administration of clozapine and aripiprazole long acting, but it brings up a critical issue in the treatment of treatment resistant patients affected by schizophrenia: poor adherence to psychopharmacology therapy. Although the patient showed a significant improvement on previous treatments (brexpiprazole and clozapine) his non-adherence propensity compromised the results.

All studies reported consistently favorable outcomes. The authors described an improvement in clinical outcomes through use of LAIs and other clozapine formulations to aid compliance.

Our interesting findings on these two medications used in combination are supported by the explanation of pharmacokinetics interactions between the two molecules examined. The mechanism of action of aripiprazole, classified as an atypical antipsychotic [45], differs from the other drugs of this group: it shows partial agonist activity at D2, D3, 5-HT1A, and 5-HT2C receptors. Aripiprazole shows a weak partial agonism also to other receptors (5-HT2A and 5-HT7) [46] beside the α1 antagonism [47]. Clozapine displays <60% occupancy of D2 receptors just like other SGAs [48] and high affinity to serotonin 5 HT2A receptors; high ratio of 5-HT2A inhibition to D2 inhibition explains the efficacy of atypical antipsychotics [49,50]. The specific pharmacokinetic mechanisms supporting the relationship between clozapine and aripiprazole remain uncertain. The additive effect and modulation of D2 and D3 systems [51,52] has to be considered, even if, according to Ziegenbein and coll. reflection, the efficacy of the combination of the two drugs is related to the synergistic action of their different receptors profile among the pharmacokinetic characteristics of these two molecules also because patients benefit from stable level of clozapine into serum after augmentation of aripiprazole [53]. In fact, Positron Emission Tomography (PET) studies of D2 blockage reveal that the poor antagonism of clozapine is enhanced by co-administration of aripiprazole and also show that only 70% of D2 is blocked, underlining how it is possible to benefit from treatment without many collateral effects [54,55]. This may increase patient's compliance to treatment preventing relapses and hospitalizations [53]. In addition to the findings of the present review, a study by Oloyede et al. combined a case series with a systematic review investigating clozapine augmentation with other long-acting injectable antipsychotics. This work provides complementary evidence supporting the feasibility of clozapine augmentation with other long-acting injectable antipsychotics. In their work, commonly reported clozapine-related adverse effects did not emerge during combined treatment with LAI antipsychotics, suggesting a generally well-tolerated therapeutic approach. Moreover, their preliminary findings indicate a potential clinical utility of LAIs in alleviating residual symptoms and possibly reducing hospitalization rates in patients optimized on clozapine treatment. Taken together, these observations reinforce the signals emerging from our review, supporting the potential applicability of clozapine–LAI combinations in selected, closely monitored patients. Further well-designed prospective investigations are required to confirm these findings and to better define the clinical role of this treatment strategy [56].

Furthermore, Vasiliu et al. [57] highlighted the possibility of adding Cariprazine or Brexpiprazole to an ongoing therapy with oral Clozapine in patients affected by URS (Ultra Resistant Schizophrenia). Vasiliu et al. concludes that existing data supporting the utility of Brexpiprazole augmentation in URS patients are scarce, with only 3 cases reported. As for Cariprazine, it might be a well-tolerated add-on option to lozapine in patients with URS. Favorable effects on general symptoms, negative and positive symptoms, and on the overall functionality were observed. Cariprazine also helps reduce BMI and counteracts weight gain. Adding Cariprazine may also allow Clozapine dose reduction. These findings are limited by the scarce long time monitoring. A longer duration of monitoring might have been useful to consolidate the reports on cariprazine's efficacy. Severe dystonia cases were reported during cariprazine treatment. Cariprazine and Brexpiprazole (even oral formulations) might offer a similar to Clozapine and Aripiprazole LAI augmentation. However, further controlled studies are warranted to confirm these observations.

Limitations

This systematic review provides a focused synthesis of the most recent evidence on the coadministration of clozapine and aripiprazole long-acting injectable. This work represents the inclusion of studies published within the last six years, reflecting current clinical practice and emerging interest in this pharmacological strategy. However, the findings must be interpreted with caution. The available evidence is limited by the small number of

included studies and by their predominantly descriptive nature, as most data derive from case reports and small case series, which are inherently vulnerable to publication and observer bias. Moreover, the lack of standardized psychopathological assessments and the absence of long-term prospective follow-up data preclude firm conclusions regarding efficacy, safety, and tolerability. Therefore, the current evidence should be considered low certainty and hypothesis-generating, primarily suggesting feasibility in selected and closely monitored patients rather than supporting definitive clinical recommendations. Lastly, the analysis of the grey literature is missing.

6. Conclusions

In this review, we tried to describe and give indications on a very important topic in psychiatry: the treatment of resistant schizophrenia and the improvement of the patient's compliance. This review synthesizes the currently available evidence on the co-administration of clozapine and long-acting injectable aripiprazole, an approach increasingly reported in complex clinical scenarios such as treatment-resistant schizophrenia and poor adherence to oral antipsychotic therapy. Across the included studies consistent clinical patterns emerge, suggesting that this combination may be feasible and potentially useful in selected patients with treatment-resistant schizophrenia, especially in the context of poor adherence or clozapine-related tolerability issues. This preliminary evidence also suggests a potential clinical utility of aripiprazole LAI in alleviating residual symptoms in patients optimized on clozapine treatment. Across the included reports, authors describe recurrent clinical themes, including: (I) stabilization or improvement of positive symptoms, (II) perceived improvements in treatment adherence with LAI formulations, and (III) the possibility of clozapine dose reduction or attenuation of clozapine-related adverse effects in selected cases. These findings derive predominantly from case reports and small case series and should therefore be considered hypothesis-generating. The current evidence base is insufficient to draw definitive conclusions regarding efficacy, safety, or tolerability, does not allow assessment of generalizability, and does not support routine clinical recommendations. Further well-designed prospective studies with standardized psychopathological assessments and long-term follow-up are required to better define the clinical role, effectiveness, and safety profile of this treatment approach.

Author Contributions

The selection and eligibility phases were carried out independently by L.P., L.D.S. and M.X. with a final cross-check by A.M. (Andrea Miuli) and A.M. (Alessio Mosca). All discordant cases were evaluated by M.P., A.M. (Andrea Miuli), A.M. (Alessio Mosca), L.P., L.D.S., M.X. and M.P. designed the study. L.D.S., M.X. and L.P. conducted the literature research and chose the papers to include in the quantitative synthesis. M.P. reviewed and valued the paper selected. A.M. (Andrea Miuli), A.M. (Alessio Mosca) and L.P. wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

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All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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