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Haloperidol–Aripiprazole Combination in Treatment-Resistant Schizophrenia: A Case Report After Clozapine Interruption

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Abstract | **Case Report**

Background: Treatment-resistant schizophrenia is most commonly managed with clozapine after failure of two adequate antipsychotic trials. However, clozapine discontinuation or unavailability may expose previously stabilized patients to relapse and creates major therapeutic challenges. Evidence supporting non-clozapine antipsychotic combinations remains limited, and the specific association of haloperidol and aripiprazole has been described only in sparse and conflicting reports. ***Case presentation:*** We report the case of a 34-year-old man diagnosed with schizophrenia in 2009 and later classified as having treatment-resistant schizophrenia after multiple unsuccessful antipsychotic trials. He achieved partial stabilization on clozapine 350 mg/day from 2019. In April 2023, clozapine was abruptly discontinued because of medication unavailability in Morocco. Despite treatment with olanzapine 20 mg/day, he developed worsening delusions, auditory hallucinations, negative symptoms, and insomnia, requiring hospitalization. Due to insufficient response and high metabolic risk, olanzapine was replaced by haloperidol 9 mg/day combined with aripiprazole 15 mg/day, later increased to 30 mg/day. Clinical improvement was observed during hospitalization, allowing discharge after one month. PANSS positive scores decreased from 18 to 10 and negative scores from 18 to 11 between April and May 2023, with subsequent patient stability. ***Conclusion:*** This case suggests that haloperidol–aripiprazole combination therapy may represent an individualized alternative when clozapine is unavailable, particularly in patients with high metabolic risk. However, the evidence remains insufficient to recommend this strategy routinely, and close clinical, neurological, metabolic, hormonal, and cardiac monitoring is required.

Keywords: Treatment-resistant schizophrenia; haloperidol; aripiprazole; antipsychotic polypharmacy; case report.

INTRODUCTION

Treatment-resistant schizophrenia remains a major therapeutic challenge and is generally defined by persistent symptoms despite adequate trials of at least two antipsychotic medications. Clozapine is considered the treatment of choice in this context and remains the only antipsychotic with established superiority for treatment-resistant schizophrenia. Current guidelines continue to recommend clozapine after failure of two adequate antipsychotic trials, while antipsychotic polypharmacy is generally reserved for selected situations and is not recommended as a routine substitute for clozapine [1,2].

However, in some clinical settings, clozapine may become temporarily or persistently unavailable. This situation is particularly problematic in patients who have achieved partial or complete remission under clozapine, as abrupt interruption may lead to symptom exacerbation, functional deterioration, rehospitalization, and increased caregiver burden. In Morocco, as in other resource-constrained contexts, access to clozapine may be inconsistent, forcing clinicians to consider individualized alternatives when continuation of clozapine is not possible.

The combination of haloperidol, a potent dopamine D2 receptor antagonist, and aripiprazole, a high-affinity partial D2 agonist, is pharmacologically complex. Available evidence remains limited and contradictory. Some reports suggest possible clinical benefit, whereas others describe worsening psychosis or cardiac safety concerns [5–8]. This report describes a patient with treatment-resistant schizophrenia who relapsed after abrupt clozapine interruption and subsequently improved under haloperidol–aripiprazole combination therapy.

Case Presentation

We report the case of a 34-year-old male patient diagnosed with schizophrenia in 2009. Over the course of his illness, several antipsychotic medications were prescribed at adequate doses and for periods of 6 or more weeks each, without satisfactory clinical response. The treatments tried included olanzapine, haloperidol, aripiprazole, and amisulpride. Based on persistent symptoms despite multiple antipsychotic trials, a diagnosis of treatment-resistant schizophrenia was retained, and clozapine was initiated in 2019.

The patient achieved partial clinical stabilization under clozapine 350 mg/day. Residual negative symptoms and intermittent auditory hallucinations persisted, but his overall condition remained stable and did not require hospitalization. Patient was fully adherent to his treatment during this period, and didn't report any side effects with the medication. In April 2023, clozapine became unavailable, leading to abrupt treatment interruption. The patient was subsequently prescribed olanzapine 20 mg/day. Despite this treatment, his clinical condition deteriorated, with worsening delusions, auditory hallucinations, negative symptoms, insomnia, and functional decline. Hospitalization was indicated, and patient was admitted to the clinical department of Ibn Nafis Psychiatric Hospital on April 10, 2023.

At admission, the therapeutic strategy was complicated by the patient's high metabolic risk. He was morbidly obese with a Body Mass Index (BMI) > 40, and his mother had diabetes mellitus. Given the lack of sufficient improvement under olanzapine and the concern for further metabolic deterioration, olanzapine was discontinued. Paraclinical investigations on admission included bloodwork (fasting glucose, HbA1c, lipid profile, ionogram, complete blood count, creatinin, transaminase) and an electrocardiogram (ECG). Patient's results were all within normal range.

A week after admission, decision to switch his antipsychotic treatment to a combination of haloperidol 9 mg/day and aripiprazole 15 mg/day was made.

At day 7 of combination therapy, the patient reported partial improvement in sleep and psychotic symptoms, although delusional ideation persisted. After two weeks, aripiprazole was increased to 30 mg/day while haloperidol was maintained at 9 mg/day. During the following weeks, improvement was observed in positive symptoms, negative symptoms, sleep quality, and overall cooperation with care. Patient was discharged on May 10, 2023, with regular outpatient follow-up.

The Positive and Negative Syndrome Scale was used to monitor clinical evolution. On April 14, 2023, the PANSS positive subscale score was 18 and the negative subscale score was 18. On May 11, 2023, shortly after discharge, the positive score had decreased to 10 and the negative score to 11. On June 26, 2023, the positive score was 7 and the negative score was 13. On September 4, 2023, the positive score was 10 and the negative score was 11. Overall, the patient remained clinically stable after discharge.

According to reports from the patient and his primary caregiver, his mother, social and relational functioning improved compared with his previous condition under clozapine. He also became more cooperative with treatment, partly because the new regimen did not require monthly hematological monitoring. Six months after discharge, he reported satisfaction with the treatment and showed greater social engagement than at previous stages of his illness.

Discussion

This case illustrates the clinical complexity of managing treatment-resistant schizophrenia when clozapine becomes unavailable. Clozapine remains the reference treatment after failure of two adequate antipsychotic trials, and its discontinuation may be associated with relapse or clinical destabilization [1,2]. In the present case, abrupt clozapine interruption was followed by worsening psychotic symptoms despite olanzapine 20 mg/day, eventually requiring hospitalization.

The use of combined haloperidol and aripiprazole in treatment-resistant schizophrenia remains insufficiently supported by current evidence. To date, no randomized controlled trials have specifically evaluated this combination as an augmentation strategy for persistent psychotic symptoms. Available data are limited to indirect evidence, case reports, and pharmacological analyses. The most robust findings derive from studies assessing adjunctive aripiprazole in patients treated with dopamine antagonists, including haloperidol, primarily for antipsychotic-induced hyperprolactinemia. These studies consistently demonstrate a significant reduction in prolactin levels but do not establish clear additional antipsychotic efficacy [3,4].

Clinical reports of the haloperidol–aripiprazole combination describe heterogeneous outcomes. One case report described symptomatic improvement without notable adverse effects, suggesting that this association may be beneficial in selected patients [5]. Conversely, other reports have described paradoxical worsening of psychosis following aripiprazole introduction in patients receiving dopamine antagonists [6,7].

From a pharmacodynamic perspective, these contradictory findings are biologically plausible. Aripiprazole is a high-affinity partial agonist at dopamine D2 receptors. When combined with a full antagonist such as haloperidol, it may competitively displace haloperidol from D2 receptors and produce a net

partial agonist effect [8,10]. In some patients, this may contribute to improvement, particularly by reducing prolactin elevation or limiting excessive dopamine blockade [3,4]. In others, especially those previously exposed to long-term potent D2 antagonism, this mechanism may theoretically increase dopaminergic signaling and worsen psychotic symptoms [6,7,9]. This concern may be particularly relevant in the context of dopamine supersensitivity [9].

In the present case, however, the combination was followed by clinical improvement, as shown by reductions in PANSS positive and negative subscale scores during hospitalization and maintenance of outpatient stability over four months. Several factors may explain the favorable response. First, haloperidol provided strong D2 antagonism, which may have contributed to the reduction of positive symptoms. Second, aripiprazole may have improved tolerability, motivation, negative symptoms, or prolactin-related effects, although prolactin levels were not available [3,4,8,10]. Third, avoiding continued olanzapine exposure was clinically relevant because of the patient's morbid obesity and family history of diabetes.

Nevertheless, this observation should be interpreted cautiously. The improvement cannot be attributed with certainty to the pharmacological combination alone. Hospitalization, improved adherence, structured care, sleep restoration, and environmental containment may also have contributed. Moreover, the follow-up period remains limited, and the absence of detailed metabolic, cardiac, prolactin, and extrapyramidal monitoring limits safety interpretation.

Recent reviews of antipsychotic polypharmacy emphasize that combination strategies may be considered in selected clinical situations but should not replace optimized monotherapy or clozapine when clozapine is available and tolerated [1,2]. In this context, the present case does not support routine use of haloperidol–aripiprazole combination therapy for treatment-resistant schizophrenia. Rather, it suggests that this association may be considered as an exceptional, individualized option when clozapine is unavailable and metabolic constraints limit the use of other alternatives.

Conclusion

This case describes clinical improvement following haloperidol–aripiprazole combination therapy in a patient with treatment-resistant schizophrenia who relapsed after abrupt clozapine interruption. Although the outcome was favorable, the available literature remains limited and contradictory. This combination should not be considered a standard alternative to clozapine. However, in selected cases where clozapine is unavailable, poorly tolerated, or temporarily inaccessible, haloperidol–aripiprazole combination therapy may represent a cautious individualized strategy, provided that close monitoring of psychotic symptoms, extrapyramidal symptoms, akathisia, prolactin levels, metabolic parameters, and EKG findings is ensured. Further studies are needed before this combination can be recommended in treatment-resistant schizophrenia.

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