Role of aripiprazole in treatment-resistant schizophrenia

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Abstract: About one third of patients with schizophrenia respond unsatisfactorily to antipsychotic treatment and are termed “treatment-resistant”. Clozapine is still the gold standard in these cases. However, 40%–70% of patients do not improve sufficiently on clozapine either. In the search for more efficacious strategies for treatment-resistant schizophrenia, drugs with different pharmacological profiles seem to raise new hopes, but are they valid? The aim of this review was to evaluate the evidence for aripiprazole as a potential strategy in monotherapy or combination therapy for patients with treatment-resistant schizophrenia. The evidence for aripiprazole monotherapy and for the combination of aripiprazole with psychotropics other than clozapine is scant, and no recommendation can be made on the basis of the currently available data. More effort has been made in describing combinations of aripiprazole and clozapine. Most of the open-label and case studies as well as case reports have shown positive effects of this combination on overall psychopathology and to some extent on negative symptoms. Several reports describe the possibility of dose reduction for clozapine in combination with aripiprazole, a strategy that might help so-called “treatment-intolerant” patients. The findings of four randomized controlled trials with respect to changes in psychopathology seem less conclusive. The most commonly found beneficial effects are better metabolic outcomes and indicators of the possibility of reducing the clozapine dose. However, other side effects, such as akathisia, are repeatedly reported. Further, none of the studies report longer-term outcomes. In the absence of alternatives, polypharmacy is a common strategy in clinical practice. Combining aripiprazole with clozapine in clozapine-resistant or clozapine-intolerant patients seems to be worthy of further investigation from the pharmacological and clinical points of view.

Keywords: aripiprazole, clozapine, antipsychotic, treatment-resistant schizophrenia

Treatment-resistant schizophrenia and its management challenges

Schizophrenia is a severe psychiatric disorder with one-year incidence rates of about 15/100,000 persons that affects about 26.3 million people worldwide,1 making schizophrenia and schizophrenia-related disorders frequently chronic illnesses. Schizophrenia is among the 20 leading causes of disability, and ranks even higher in low-income countries and in men.1 Since the serendipitous discovery of chlorpromazine in the 1950s, antipsychotic drugs have been effective treatments for psychotic symptoms and have reduced hospitalization rates.2 The majority of patients with schizophrenia respond adequately to treatment with antipsychotics.3 However, more than a third of patients do not respond to conventional first-choice treatments2 and are deemed to be “treatment-resistant”.

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There have been repeated debates on the definition of treatment resistance and treatment response, and trials have inconsistently used one or the other definition. A well-known definition of treatment resistance is the one based on the criteria put forward by Kane et al, ie, at least three prior antipsychotic treatments within the previous 5 years at chlorpromazine dosages ≥ 1000 mg/day for at least 6 weeks without sufficient reduction of positive symptoms or lack of a period of good functioning in the last 5 years; additional requirements are moderately severe symptoms as well as lack of improvement with haloperidol ≤ 60 mg/day for at least 6 weeks. In the available research trials, patients are usually deemed treatment-resistant when 1–3 trials of antipsychotic drugs, each lasting for more than 4–6 weeks at adequate doses, ie, chlorpromazine-equivalent doses of 400–1000 mg/day, have failed to reduce positive symptoms sufficiently. For clinical decision-making in real-life settings, several guidelines propose treatment resistance after 2–3 trials, including at least one atypical antipsychotic in adequate dosages for at least 4–6 or 6–8 weeks without satisfactory clinical improvement, thus taking into account a multidimensional approach of clinical symptoms, psycho-social functioning, and well-being. After that, treatment with clozapine should be considered.

Indeed clozapine, the first atypical antipsychotics introduced in the early 1970s, is still the gold standard for patients with schizophrenia whose symptoms do not sufficiently improve on antipsychotic treatment, and its superior efficacy in treatment resistance is well documented. However, about 40%–70% of patients with treatment-refractory schizophrenia do not respond fully, even to clozapine. Further, its general use, especially at effective dosages, can be limited by a series of relevant to the point of life-threatening side effects, such as sedation, salivary, metabolic disturbances, weight gain, emerging obsessive-compulsive symptoms, agranulocytosis, cardiomyopathy, and delirium or seizures, thereby introducing a further subgroup of seemingly treatment-resistant patients, ie, those who are treatment-intolerant. Other important factors that might be related to insufficient response are comorbid substance misuse, inadequate duration of treatment, and inadequate dosage. Also, with discontinuation rates for antipsychotic medications of 74% after 18 months in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study and up to 90% after one year in a later study, nonadherence or diminished treatment adherence, reflecting patient satisfaction, acceptability, quality of life, and insight, have to be taken into account as one further reason for insufficient responses.

Potential nonfatal side effects associated with clozapine such as hypersalivation, weight gain, and sedation may even foster lower adherence rates, as well as increased issues of (self-) stigmatization, low self-esteem, and relapse.

A recently published overview of systematic reviews evaluated the effectiveness and safety of different antipsychotics in treatment-resistant schizophrenia, and concluded that the main advantage of atypical antipsychotics lies in their more favorable safety profile, which might also increase adherence to treatment. In the same vein, combination therapy of antipsychotics might also be useful, to the point of superiority of antipsychotic polypharmacy suggested for specific patient groups. Indeed, a meta-analysis by Taylor et al conveyed evidence for a modest effect of augmenting clozapine with a second antipsychotic without significant losses in tolerability in the short term. However, important considerations, such as long-term effects and the choice of antipsychotics, are still uncertain, and clear evidence favoring one adjunctive strategy over another are still scarce.

In the search for other strategies to treat treatment-resistant schizophrenia, drugs with unique pharmacological profiles such as aripiprazole raise new hopes, but are they valid? The aim of this review was to evaluate aripiprazole, its advantages and pitfalls as a potential strategy in monotherapy or combination therapy for patients with treatment-resistant schizophrenia.

Rationale for aripiprazole in treatment-resistant schizophrenia

Pharmacology

Among the currently available antipsychotic drugs, aripiprazole shows a unique pharmacological profile. Via its partial agonism, it binds with high affinity to dopaminergic D₂ and D₃ receptors and serotonergic 5-HT₁A receptors, and acts as an antagonist at 5-HT₂A and 5-HT₂C receptors. Unlike other antipsychotic drugs, the affinity of aripiprazole for muscarinergic and histaminergic H₁ receptors is low. Strong dopamine D₂ blockade and activity at the serotonin receptors as well as at postsynaptic D₃ receptors might be responsible for its efficacy in reducing positive and somewhat negative symptoms, respectively.

Early clinical trials of aripiprazole in schizophrenic patients have shown antipsychotic efficacy comparable with that of risperidone or haloperidol. In a recent Cochrane review of 2595 patients included in nine randomized controlled trials (RCT) on the efficacy of aripiprazole versus placebo in schizophrenia and schizophrenia-like psychoses, a significant benefit of aripiprazole was found for short-term
Advantages of aripiprazole

A lower propensity for extrapyramidal side effects, sedation, weight gain, hyperprolactinemia, and other potential side effects can be deduced from the pharmacological profile of aripiprazole. Treatment of schizophrenia with aripiprazole has been shown to induce fewer side effects compared with treatment using first-generation antipsychotics as well as with olanzapine and risperidone with regard to metabolic, prolactin-related, and dystonic side effects or QTc prolongation. Conversely, switching treatment to aripiprazole could reduce weight gain under olanzapine or clozapine according to a recent meta-analysis including 784 patients. However, mean weight reduction was modest (−2.55 ± 1.5 kg). Other groups have found similar tendencies towards weight gain for aripiprazole and other antipsychotics, such as perphenazine in treatment-resistant patients and risperidone in patients termed “chronic” or suffering from their first schizophrenic episode. A critical review concludes that the potential advantages of aripiprazole with respect to weight changes are still conflicting and need confirmation in a larger sample.

In a clinical practice analysis, aripiprazole, quetiapine, and amisulpride did not carry an increased risk of diabetes mellitus. In a head-to-head meta-analysis of the metabolic side effects of second-generation antipsychotics in RCT, aripiprazole (like amisulpride) showed intermediate or low elevations in weight, cholesterol, and glucose levels in comparison with other second-generation antipsychotics. A meta-analysis comparing amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone found aripiprazole to be a second-generation antipsychotic with a statistically significant lower risk and lower mean change in QTc interval.

Further to these effects, adding aripiprazole, a partial dopamine agonist, to a strong dopamine agonistic antipsychotic such as haloperidol has been shown to reverse hyperprolactinemia and associated menstrual disturbances in a highly significant number of patients compared with placebo. The industry-sponsored STAR (Schizophrenia Trial of Aripiprazole) study revealed improvement in sexual dysfunction with aripiprazole, in addition to decreases in prolactin levels.

The relatively fewer metabolic side effects might be one of the reasons explaining the recent finding by Azekawa et al of a significantly longer time to discontinuation of treatment compared with olanzapine, risperidone, and olanzapine or clozapine according to a recent meta-analysis including 784 patients. However, mean weight reduction was modest (−2.55 ± 1.5 kg). Other groups have found similar tendencies towards weight gain for aripiprazole and other antipsychotics, such as perphenazine in treatment-resistant patients and risperidone in patients termed “chronic” or suffering from their first schizophrenic episode. A critical review concludes that the potential advantages of aripiprazole with respect to weight changes are still conflicting and need confirmation in a larger sample.

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emergent obsessive-compulsive symptoms during treatment with aripiprazole have also been reported in two cases.

Problems with aripiprazole
Notwithstanding the abovementioned safety benefits of aripiprazole, this antipsychotic may also pose new problems, in addition to those known from other antipsychotics. Adverse effects such as nausea, insomnia, and agitation have a higher occurrence rate with aripiprazole compared with typical antipsychotics and with placebo. Recently published adverse effects at a single case report level are rhombodyalysis and transient myopia.

Extrapyramidal symptoms and akathisia
In early industry-sponsored clinical trials, aripiprazole showed slightly more extrapyramidal symptoms and akathisia compared with placebo, but less than for haloperidol or risperidone. Later, there were several reports of general extrapyramidal symptoms, acute dystonic reactions, and tardive dyskinesia in patients on treatment with aripiprazole. On the other hand, in some cases, treatment with aripiprazole led to improvements in antipsychotic-induced tardive dyskinesia. A commonly reported side effect of treatment with aripiprazole is akathisia. A recent review of clinical trials assessing the occurrence of akathisia in patients with schizophrenia and schizoaffective disorders reported mild to moderate akathisia in 9% of aripiprazole-treated and 6% of placebo-treated patients, 12.5% of aripiprazole-treated versus 24% of haloperidol-treated patients, and 11% of aripiprazole-treated versus 6% of olanzapine-treated patients. However, discontinuation due to akathisia was low, with 0.3% for aripiprazole versus 0% for placebo, 0.9% for aripiprazole versus 2.3% for haloperidol, and 1.2% for aripiprazole versus 0.2% for olanzapine. This analysis did not reveal compromise in clinical response due to treatment-emergent akathisia. However, it should be noted that in everyday clinical practice it is not always easy to distinguish clearly whether agitation, worsening of psychotic symptoms, and akathisia are side effects of medication or inherent in the acute illness. A number of management strategies for akathisia occurring with second-generation antipsychotics have been reported, with different levels of evidence.

Exacerbation of psychosis and induction of manic episodes
Several clinical reports describe exacerbations of psychotic symptoms either on treatment with aripiprazole or during addition therapy with aripiprazole to different antipsychotic; the hypothesis being that dopamine agonism by aripiprazole during a hypodopaminergic state occurring with concomitantly prescribed antipsychotics may lead to exacerbation of positive psychotic symptoms. Another rarely reported but important adverse event is drug-induced mania. Until now, very few cases have been described, but the potential ability of aripiprazole to precipitate manic episodes is a noteworthy phenomenon that has been described in schizoaffective disorder, in schizophrenia, in obsessive-compulsive disorder, and generalized anxiety disorder. Although manic reactions seem to be marginal with respect to frequency of occurrence, they might have a biological plausibility and warrant clinical precautions.

Suicidality
To our knowledge, there are three published reports of increased suicidality after initiation of aripiprazole (one in “psychosis”, one in depression, and one article published in Dutch, with no English abstract available).
with high-dose aripiprazole (75 mg/day) without occurrence of adverse events. In summary, the evidence for aripiprazole monotherapy is currently based on one RCT with at least somewhat disputed data interpretation.

**Aripiprazole as an alternative to clozapine**

For the various reasons described above, many patients discontinue treatment with clozapine. There is a dearth of studies dealing with the dilemma of discontinuing and switching from clozapine in treatment-refractory schizophrenia. Two articles, including four cases, present precisely the results of switching from clozapine to aripiprazole, one due to lack of satisfactory response, the other three due to treatment intolerance because of neutropenia. The authors describe safe switches and clinically relevant effects with respect to symptom reduction and functioning. No broad conclusions can be drawn from these case series.

**Aripiprazole and clozapine**

Although combination of clozapine with another antipsychotic in patients having an unsatisfactory response is common in real-world settings, evidence-based strategies for combination therapy in clozapine-refractory schizophrenia are sparse. In recent years, efforts have been made to ascertain the evidence of such case report-based strategies. A few RCT have focused on the efficacy of combinations of clozapine with risperidone, haloperidol, amisulpride, sulpiride, and aripiprazole. Combining clozapine, a multireceptor drug with low affinity for the dopamine D2 receptor, and an antipsychotic with antidopaminergic properties follows a comprehensible neurobiological rationale regarding the pharmacodynamics of complementary receptor profiles. Pharmacokinetic interactions between clozapine and aripiprazole, such as effects on plasma levels, are not probable, given that aripiprazole and clozapine are metabolized by different cytochrome P450 (CYP) isoenzymes, ie, CYP3A4 and CYP2D6 for clozapine, and CYP1A2 and to a lesser extent CYP2D6 for clozapine.

Starting off with promising case reports and retrospective clinical observations, a small number of RCT were initiated to analyze the combination of clozapine and aripiprazole in treatment-resistant schizophrenia. Most of the open-label and case studies as well as case reports show positive effects of this combination on overall psychopathology and on negative symptoms. Several reports describe the possibility of dose reduction for clozapine in combination with aripiprazole, a strategy that might help so-called treatment-intolerant patients. Indeed, a review of 94 patients in 11 publications reports a clozapine dose reduction from 476.7 mg/day to 425 mg/day alongside an improvement in psychopathology, and a reduction in clozapine-related side effects with mean aripiprazole add-on therapy of 20.5 mg/day.

To our knowledge, four RCT of aripiprazole in clozapine-refractory patients with schizophrenia have been published (see Table 1), three of which were double-blind and placebo-controlled one comparing aripiprazole with haloperidol using blinded raters. These RCT together included a total of approximately 400 patients. The trial by Fleischhacker et al investigated metabolic parameters as primary outcome variables, but outcome data on psychopathology are also reported. The findings of these RCT with respect to changes in psychopathology seem less optimistic than those of the case reports and open-label trials. Two trials report no benefits from aripiprazole in combination with clozapine compared with placebo or with haloperidol. Improvements in negative symptoms were reported by Chang et al only after secondary analysis and by Muscatello et al only for alogia compared with the several promising non-RCT reports mentioned above.

However, it should be noted that most RCT have included patients on stable mean clozapine doses at the lower end of the efficacy range (310.7 ± 73.1 mg/day, 383 ± 158.2 mg/day, 404 ± 104.8 mg/day, 421 ± 142 mg/day), raising the question of whether patient symptoms were really refractory to treatment or if they were not treated at high enough doses because of intolerance. Furthermore, it is generally recommended to assess the efficacy of clozapine in treatment-resistant patients after a minimum of 3–6 months because delayed improvement is possible. However, RCT have used different inclusion criteria, thereby limiting comparability. For example, in the study by Muscatello et al, patients had to be on clozapine treatment for at least one year, but on a stable dose for a minimum of only one month. Fleischhacker et al included patients who had been on a stable clozapine dose for a minimum of 3 months, Chang et al reported on a minimum treatment of one year with at least 2 months at a stable clozapine dose ≥ 400 mg, and finally, Barbui et al included patients on stable clozapine doses for at least 6 months.

The strongest beneficial effects of adding aripiprazole to clozapine that runs through the findings of the RCT, case reports, and open-label studies combined are better metabolic outcomes and indicators of the possibility for reducing the clozapine dose. However, other side effects, such as akath-
Table 1 Randomized controlled trials in treatment-resistant schizophrenia using add-on aripiprazole to clozapine

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Control group</th>
<th>Diagnosis</th>
<th>Definition of treatment-resistance</th>
<th>Sample size</th>
<th>Duration</th>
<th>Mean clozapine dose</th>
<th>Mean aripiprazole dose</th>
<th>Significant changes in psychopathology</th>
<th>Significant other changes</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Chang et al&lt;sup&gt;106&lt;/sup&gt;</td>
<td>DB RCT</td>
<td>Placebo</td>
<td>Schizophrenia</td>
<td>BPRS ≥ 35 or &gt; 2 SANS global item scores of ≥ 3 and treatment with clozapine for at least one year with a stable dose of 400 mg/day or more for at least 8 weeks (unless intolerable)</td>
<td>62</td>
<td>8 weeks</td>
<td>290.6 ± 101.0 mg/day (PG) versus 304.3 ± 104.9 mg/day (TG)</td>
<td>17.0 ± 7.4 mg/day (PG) versus 15.5 ± 7.1 mg/day (TG)</td>
<td>Secondary analyses: greater improvement triglyceride levels lower</td>
<td>Ns differences</td>
<td></td>
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<tr>
<td>Fleischhacker et al&lt;sup&gt;106&lt;/sup&gt;</td>
<td>DB RCT</td>
<td>Placebo</td>
<td>Schizophrenia</td>
<td>Residual positive, negative or other symptoms and safety/tolerability problems and stable clozapine dose of 200–900 mg/day for at least 3 months</td>
<td>203</td>
<td>16 weeks + 12 weeks open-label extension phase</td>
<td>362.6 ± 158.7 mg/day (PG) versus 383.8 ± 158.2 mg/day (TG)</td>
<td>12.9 mg/day (PG) versus 11.1 mg/day (range 5–15 mg, TG)</td>
<td>PANSS, ns differences</td>
<td>TG: decrease in body weight, BMI, total and LDL-cholesterol</td>
<td></td>
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<tr>
<td>Barbui et al&lt;sup&gt;107&lt;/sup&gt;</td>
<td>RCT</td>
<td>Haloperidol (mean dose 2.8 ± 1.7 mg/day)</td>
<td>Schizophrenia</td>
<td>Persistent presence of positive symptoms, at least 6 months stable clozapine dose of ≥ 400 mg/day</td>
<td>106</td>
<td>12 weeks</td>
<td>452 ± 118 mg/day (TG) versus 483 ± 158 mg/day (CG)</td>
<td>11.8 ± 5.1 mg/day</td>
<td>BRPS, ns decrease in discontinuation rate</td>
<td>Ns difference in discontinuation rate</td>
<td>Greater decrease in LUNSERS in TG</td>
</tr>
<tr>
<td>Muscatello et al&lt;sup&gt;108&lt;/sup&gt;</td>
<td>DB RCT</td>
<td>Placebo</td>
<td>Schizophrenia</td>
<td>BPRS ≥ 25 and clozapine therapy for at least one year with doses of 200–450 mg/day and stable dosage for at least one month</td>
<td>31</td>
<td>24 weeks</td>
<td>341.2 ± 77.5 mg/day (PG) versus 310.7 ± 73.1 mg/day (TG)</td>
<td>10 mg/day until week 12, then 15 mg/day until week 24</td>
<td>TG: week 12, improvement of thought disorder, SAPS total score; week 24, improvement of bizarre behaviour; SAPS and BRPS total scores and alogia</td>
<td>Semantic fluency worsened from week 12–24</td>
<td>35.7% (n = 5) restlessness, 12.4% (n = 3) insomnia, 7.1% (n = 1) nausea in TG</td>
</tr>
</tbody>
</table>

Abbreviations: DB, double-blind; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; RCT, randomized controlled trial; AE, adverse events; SAE, severe adverse events; TG, treatment group; PG, placebo group; CG, control group; LUNSERS, Liverpool University Neuroleptic Side Effect Rating Scale; PANSS, Positive and Negative Syndrome Scale; BRPS, Brief Psychiatric Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; LDL, low-density lipoprotein; BMI, body mass index; PRL, prolactin; n.s, not significant.
Aripiprazole and other psychotropics
Other strategies have to be sought for patients who do not respond adequately to clozapine or its augmentation, or who are clozapine-intolerant. High-level evidence for specific augmentation strategies combining clozapine with other antipsychotics is still rather scant, and even moreso for combinations of antipsychotics other than clozapine. However, in the absence of alternatives, polypharmacy is a common strategy in clinical practice, and encouraged by meta-analytical data favoring antipsychotic combinations over monotherapy in some clinical situations, such as combinations including clozapine, a trial duration of more than ten weeks, and parallel initiation of antipsychotic combinations and combinations of first-generation and second-generation antipsychotics. 20

Combining aripiprazole with another antipsychotic seems to be worthy of further investigation from a pharmacological point of view, but relevant studies are almost nonexistent. A retrospective case series of combinations of aripiprazole with a wide range of other psychotropics in treatment-resistant patients, including six patients with schizophrenia, reported moderate to adequate improvement and good tolerability. Combinations included risperidone long-acting injection and haloperidol, clozapine, ziprasidone, quetiapine and olanzapine, and quetiapine and risperidone, all of which were augmented with aripiprazole. 114

In a multicenter RCT of 323 patients with schizophrenia or schizoaffective disorder with a chronic course, but not explicitly termed treatment-resistant, adjunctive administration of aripiprazole 2–15 mg/day with risperidone 4–8 mg/day or quetiapine 400–800 mg/day revealed no significant improvement in psychiatric symptoms assessed by PANSS, but was broadly well tolerated. 115 No further conclusions can be drawn regarding aripiprazole combined with other psychotropics for treatment-resistant schizophrenia from the available data.

Conclusion
From the pharmacological and clinical points of view, aripiprazole seems worthy of further investigation for clozapine-resistant and clozapine-intolerant patients. The evidence for aripiprazole monotherapy and for the combination of aripiprazole with psychotropics other than clozapine is scant, and no recommendations can be drawn from the currently available data. More effort has been made in describing combinations of aripiprazole and clozapine. While open-label and case studies show improvement in overall psychopathology and in negative symptoms, results of RCT are inconclusive regarding effects on psychopathology. Given the potential of most antipsychotics to induce deleterious metabolic effects, the repeated finding of a lesser metabolic impact of aripiprazole is noteworthy. This, as well as the potential effects concerning dosage reduction, might be of particular value in patients treated with clozapine. However, other side effects, such as agitation and akathisia, have been repeatedly reported, and others, such as exacerbation of psychosis, seem rare but severe. In summary, in this specific population unresponsive to previous treatment, a combination of clozapine with aripiprazole, as well as other augmentation strategies for clozapine, seem worthy of further exploration. However, given the lack of clearcut evidence for an advantage of antipsychotic polypharmacy in general, no confident recommendations can be made and careful clinical appraisal of the risk-benefit ratio of all options is warranted.

Disclosure
The authors report no conflicts of interest in this work.

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