Aripiprazole in Addition to Clozapine in Partially Responsive Patients with Schizophrenia: A Critical Review of Case Series

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Abstract

The present review was conducted to ascertain whether the combination of clozapine and aripiprazole may have a clinical role in patients partially responsive to clozapine monotherapy. We conducted a systematic review of randomized clinical trials, open-label prospective studies, retrospective studies and case reports. The MEDLINE search yielded ten studies: three were open-label studies, one was a retrospective study and six were case reports. The three open-label studies included a total number of forty-eight patients with schizophrenia and schizoaffective disorders. Patients were relatively young with a long history of psychiatric illness. In two of these three studies aripiprazole (15 to 30 mg/day) was effective in reducing residual positive and negative symptoms that were not controlled by monotherapy with clozapine at medium-high dose regimens. A retrospective study, which included twenty-four young patients with schizophrenia and a long history of psychiatric illness, found improvements in terms of psychopathology, social functioning, metabolic abnormalities and weight problems. Finally, six case reports included a total number of eighteen patients with schizophrenia and schizoaffective disorders. Aripiprazole dosage ranged between 5 to 90 mg/day, and patient outcome was assessed after a period varying from three to forty-eight weeks. The combined treatment was reported to exert a beneficial effect in all patients, with a decrease of the side effects associated with clozapine treatment. The clinical experience on the use of aripiprazole in combination with clozapine, described in this review, should be considered as background information useful to design randomized studies and to interpret their findings, but cannot represent an evidence base to inform clinical practice.

Key Words: Aripiprazole, Clozapine, Schizophrenia

Introduction

Approximately one-fifth to one-third of patients with schizophrenia derive little or no benefit from treatment with conventional or novel antipsychotics (1). In these treatment-refractory patients, e.g., individuals who had not responded to, or had intolerable side effects from, conventional and atypical agents, clozapine has been shown to be the treatment of choice (2, 3), with low motor side effects and a beneficial effect in terms of mortality, largely explained by a considerable reduction in the rate of suicide (4-6). Nevertheless, approximately one-third of treatment-refractory patients have persistent positive and negative symptoms despite clozapine monotherapy of adequate dosage and duration (2, 3). In these patients partially responsive to clozapine, augmentation with a second antipsychotic is one of the most frequent therapeutic options employed in clinical practice, although the evidence supporting its efficacy is limited and contradictory (7-10).

In recent years the availability of newer antipsychotic

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Table 1 **Characteristics of Published Reports Assessing the Benefit and Safety of Aripiprazole as an Adjunctive Agent in Schizophrenic or Schizoaffective Patients Partially Responsive to Clozapine**

Author, Year	Trial Duration (weeks)	Sample Size	Diagnosis	Age Range or Mean Age (years)	Sex	Years of Illness (range or mean)	More than Six Months of Clozapine Monotherapy	Clozapine Dose (mg/day; range or mean)	Reason for Adding Aripiprazole
Prospective, open-label studies									
Henderson et al., 2006 (14)	6	10	Schizophrenia and schizoaffective disorder	38.7 m	MF	Long history	Yes	455 m	Residual positive and negative psychotic symptoms and side effects (weight gain, metabolic abnormalities)
Mitsonis et al., 2006 (15)	16	27	Schizophrenia	41.9 m	MF	18.3 m	Yes	478.3 m	Residual positive or negative psychotic symptoms
Ziegenbein et al., 2006 (16)	12	11	Schizophrenia	35.6 m	MF	13.7 m	Yes	736.4 m	Persistent psychotic symptoms
Retrospective study									
Karunakaran et al., 2006 (17)	33.8	24	Schizophrenia	39.0 m	MF	12.5 m	Yes	393.7 m	Residual positive or negative symptoms and side effects
Case reports									
Abu-Tair et al., 2006 (18)	3	5	Schizophrenia	19-54	M	12 m	NS	570 m	3 patients had not responded adequately to clozapine monotherapy and 2 patients had side effects
Ashton et al., 2006 (19)	36-48	2	Schizophrenia	22, 25	MF	NS	NS	400-800	Residual positive and negative psychotic symptoms and side effects (weight gain, salivation, sedation)
Clarke et al., 2006 (20)	4	3	Schizophrenia and schizoaffective disorder	32-61	M	Long history	Yes	300-700	Persistent negative symptoms
Pini et al., 2006 (21)	4-40	3	Schizophrenia and schizoaffective disorder	31-36	MF	1-21	NS	75-175	Residual positive and negative psychotic symptoms and side effects (weight gain, metabolic abnormalities)
Rocha & Hara, 2006 (22)	4-48	3	Schizophrenia and schizoaffective disorder	28-44	M	10-22	NS	200-400	Residual positive or negative psychotic symptoms and side effects (weight gain, metabolic abnormalities, sedation, salivation, obsessive-compulsive symptoms, chronic constipation, nocturnal enuresis)
Ziegenbein et al., 2005 (23)	16	2	Schizophrenia	36, 44	M	NS	NS	675-850	Residual positive or negative psychotic symptoms and side effects (weight gain, sedation, hypersalivation)

M=males; F=females; NS=not stated; m=mean

agents has increased the therapeutic options available in the management of clozapine partial responders and, among these newer agents, anecdotal reports have hypothesized a promising role for aripiprazole (11, 12). Aripiprazole has a unique pharmacological profile that includes partial agonism at D2 receptors, antagonism at 5HT2 receptors, and partial agonism at 5HT1A receptors (13). Theoretically, the combination of clozapine and aripiprazole may lead to greater D2 receptor antagonism and, additionally, may combine D2 and D4 antagonism (7).

In order to understand whether the combination of clozapine and aripiprazole may have a clinical role in patients partially responsive to clozapine monotherapy, we systematically reviewed published reports describing the outcome of this treatment strategy.

Methods

Search Strategy and Inclusion Criteria

A MEDLINE search for all studies published from January 1990 to June 2007 assessing the benefits and safety of aripiprazole as an adjunctive agent in schizophrenic or schizoaffective patients partially responsive to clozapine was conducted using the key words: "clozapine," "aripiprazole," "resistant," "refractory," "schizophrenia," "augmentation" and "adjunctive." We included any type of study design, including randomized clinical trials, open-label prospective studies, retrospective studies and case reports. Patients who received clozapine in addition to aripiprazole were excluded from this review. Papers missed by the electronic search were hand searched. No attempt was made to obtain data through direct contact with the pharmaceutical industry.

Ongoing randomized clinical trials assessing the efficacy and safety of aripiprazole as an adjunctive agent in clozapine-resistant schizophrenic or schizoaffective patients, or in patients partially responsive to clozapine, were also identified by searching ClinicalTrials.gov (http://clinicaltrials.gov/), a web-based repository of updated information about clinical research in human volunteers. Additionally, we searched the Current Controlled Trials (CCT) web site (http://www.controlled-trials.com/), a web-based repository set up in October 1998 in response to a growing demand for more openness concerning clinical trials.

Data Extraction

Included reports were critically reviewed and examined against the following set of parameters: clinical and demographic characteristics of patients, study type, duration of the trial, sample size, dosage and duration of clozapine monotherapy, clozapine dosage during the combined treatment, reasons for adding aripiprazole, aripiprazole dosage, clinical outcome, side effects during the combined treatment and outcome of clozapine monotherapy side effects. All reports were reviewed by two authors (SM and CB) and any disagreement was discussed with a third member of the team (AC).

Data Presentation

A descriptive summary was used to summarize study findings in conjunction with a tabular approach to recording the results.

Results

Characteristics of Published Studies

Ten studies were included in the present analysis. Of these, three were open-label studies (14-16), one was a retrospective study (17) and six were case reports (18-23) (see Table 1). Additionally, we identified four ongoing randomized clinical trials: three double-blind trials comparing clozapine plus aripiprazole versus clozapine plus placebo, and one trial comparing clozapine plus aripiprazole versus clozapine plus haloperidol. The expected total enrollment for each of the four ongoing randomized clinical trials ranges from 61 to 216 patients (see Table 2).

The main characteristics of the included studies, presented in Table 1, revealed that the three open-label studies included a total number of forty-eight patients with schizophrenia and schizoaffective disorders. Patients were relatively young with a long history of psychiatric illness. In these three studies, aripiprazole was added to address residual positive and negative symptoms that were not controlled by monotherapy with clozapine at medium-high dose regimens (see Table 1). In the study carried out by Henderson and colleagues, aripiprazole was additionally added to decrease the burden of side effects associated with clozapine treatment.

The retrospective study carried out by Karunakaran and colleagues included twenty-four relatively young patients with schizophrenia and a long history of psychiatric illness. Despite clozapine monotherapy, patients had persistent positive and negative symptoms, as well as side effects associated with treatment.

Table 1 shows that the six case reports included a total number of eighteen patients (sixteen were males) with schizophrenia (paranoid, hebephrenic and undifferentiated) and schizoaffective disorders. Patients' ages ranged from 19 to 61 years, and a long history of psychiatric illness was reported in most cases. The length of clozapine monotherapy indicated at least six months of treatment in the majority of cases, with dosages ranging from 75 to 850 mg/day. In these case reports, aripiprazole was added to tackle residual positive and negative symptoms and to minimize the side effects associated with clozapine treatment. In Clarke's case report, aripiprazole was added to reduce negative symptoms only.

Outcome of Patients Receiving Clozapine Combined with Aripiprazole

Prospective, Open-Label Studies

In the study carried out by Henderson and colleagues, a mean dose of 18 mg/day of aripiprazole was added, while the dose of clozapine remained stable (see Table 3). After six weeks, this combined treatment did not produce beneficial effects in terms of positive and negative symptoms, but was associated with improvements in terms of metabolic abnormalities and patient weight. By contrast, in the study by Mitsonis and colleagues, the addition of a fixed dose of 15 mg/day of aripiprazole produced the following outcomes: 34.7% of the sample presented between a 20 to 30% improvement in the Positive and Negative Syndrome Scale (PANSS) negative score; 26.1% showed an improvement between 30 to 40%; and, 17.4% showed an improvement over 40%. Similarly, in the study by Ziegenbein and colleagues, the addition of a mean dose of 26.4 mg/day of aripiprazole produced a mean reduction of 23.4% in the Brief Psychiatric Rating Scale (BPRS) total score over the three months. This reduction was explained by improvements in positive but not negative symptoms. This combined treatment was associated with decreased sedation, hypersalivation and weight problems (see Table 3). New side effects, including nausea, vomiting, insomnia, headache and agitation developed during this study.

Retrospective Study

A positive outcome was reported in the retrospective study carried out by Karunakaran and colleagues (see Table 3). Patients improved in terms of psychopathology, social functioning, metabolic abnormalities and weight problems, although five patients reported weight gain. In addition, one patient developed severe dyskinesia, and another patient developed atypical neuroleptic malignant syndrome. In these two cases, the observed side effects stopped when aripiprazole was discontinued.

Case Reports

In the six case reports aripiprazole dosage ranged from 5 to 90 mg/day, and patient outcome was assessed after a period varying from three to forty-eight weeks. Objective outcome measures were employed in one case report only (see Table 3), while in the remaining five case reports implicit clinical criteria were employed. The combined treatment was reported to exert a beneficial effect in all patients, and only one patient reported side effects (nausea at the beginning of treatment) (see Table 3). Six patients in four case reports reduced clozapine dosage, and some of these reported amelioration of clozapine side effects.

Discussion

We reviewed data of ninety patients partially responsive to clozapine included in six case reports, three open-label studies, and one retrospective study. Young adults with a long history of psychotic symptoms were more often included and, on the whole, male schizophrenic patients prevailed in the population analyzed. Overall, the combination of aripiprazole to clozapine was well tolerated and resulted in improvements on positive and, especially, negative symptoms; in addition, social functioning, sedation, metabolic

Table 2 Characteristics of Four Ongoing Randomized Clinical Trials Assessing the Beneficial Effect of Aripiprazole as an Adjunctive Agent in Schizophrenic or Schizoaffective Patients Partially Responsive to Clozapine

Clinical Trials.gov Identifier	Treatment Arms	Trial Duration (weeks)	Planned Sample Size	Diagnosis	Reason for Adding Aripiprazole	Primary Outcome
NCT00345033	Clozapine + aripiprazole versus clozapine + placebo	12	70	Schizophrenia and schizoaffective disorder	Side effects associated with clozapine treatment	Fasting lipids, including triglycerides and total cholesterol; weight; Body Mass Index (BMI); insulin resistance and glucose metabolism
NCT00300846	Clozapine + aripiprazole versus clozapine + placebo	16	200	Schizophrenia	Weight gain	Weight
NCT00328367	Clozapine + aripiprazole versus clozapine + placebo	48	61	Schizophrenia	Residual psychotic symptoms and side effects	Brief Psychiatric Rating Scale
NCT00395915	Clozapine + aripiprazole versus clozapine + haloperidol	48	216	Schizophrenia	Residual positive symptoms	Treatment discontinuation

Table 3 Main Results of Published Reports Assessing the Benefit and Safety of Aripiprazole as an Adjunctive Agent in Schizophrenic or Schizoaffective Patients Partially Responsive to Clozapine

Author, Year	Aripiprazole Dosage (mg/day)	Clozapine Dosage at the End of the Study	Positive Symptoms	Negative Symptoms	Side Effects During Combination Treatment	Outcome of Clozapine Side Effects				
						Sedation	Hypersalivation	Metabolic Abnormalities	Weight	Obsessive Symptoms
Prospective, open-label studies										
Henderson et al., 2006 (14)	18 m	Stable	Not improved (PANSS positive)	Not improved (PANSS negative)	Anxiety (3 pts)			✔	✔	
Mitsonis et al., 2006 (15)	15	Stable	Not improved (PANSS positive)	Improved (PANSS negative)	No					
Ziegenbein et al., 2006 (16)	26.4 m	Decreased (8 of 11)	Improved (BPRS positive symptoms)	Not improved (BPRS negative symptoms)	Nausea, vomiting, insomnia, headache, agitation, weight gain	✔	✔		✔	
Retrospective study										
Karunakaran et al., 2006 (17)	19.8 m	Decreased	Improved (clinical judgment)	Improved (clinical judgment)	Weight gain (5 pts), dyskinesia (1 pt), NMS (1 pt)			✔	✔	
Case reports										
Abu-Tair et al., 2006 (18)	20 (2 pts) 30 (3 pts)	Decreased (1 of 5)	Improved (PANSS positive)	Improved (PANSS negative)	NS					
Ashton et al., 2006 (19)	15 (1 pt) 90 (1 pt)	Decreased (2 of 2)	Improved (clinical judgment)	Improved (clinical judgment)	No	✔	✔		✔	
Clarke et al., 2006 (20)	30	Stable	Not present at baseline	Improved (clinical judgment)	No					
Pini et al., 2006 (21)	5 (2 pts) 15 (1 pt)	Stable	Improved (clinical judgment)	Improved (clinical judgment)	No				✔	
Rocha & Hara, 2006 (22)	15	Decreased (2 of 3)	Improved (clinical judgment)	Improved (clinical judgment)	Nausea (1 pt)	✔	✔	✔	✔	✔
Ziegenbein et al., 2005 (23)	15	Decreased (2 of 2)	Improved (clinical judgment)	Not present at baseline	NS	✔	✔		✔	

PANSS=Positive and Negative Symptoms Scale; BPRS=Brief Psychiatric Rating Scale; NMS=Neuroleptic Malignant Syndrome; m=mean; pts=patients; NS=Not Stated; ✔=improved

abnormalities and weight problems also benefited from the combined treatment. In some cases, these benefits were explained by the possibility of decreasing the dosage of clozapine.

The mechanism underlying the clozapine-aripiprazole synergic effect is still unknown. This combination strategy may lead to greater D2 receptor antagonism in mesolimbic pathways, and may combine D2 and D4 antagonism, although the role of D4 receptors in antipsychotic efficacy is unclear (24). In contrast to some of the other atypical antipsychotic agents, treatment with aripiprazole appears to be associated with minimal weight gain and minimal negative impact on metabolic parameters, a key aspect given that these adverse effects might occur during clozapine treatment.

The conclusions reached by the present analysis are limited by the fact that included studies were uncontrolled case series or retrospective chart reviews that enrolled patients on the basis of implicit criteria, employed improvement criteria based on personal impression, did not measure serum clozapine levels, and failed to follow patients in the long term. The lack of random allocation might have exaggerated the perceived benefit of aripiprazole added to clozapine through a mechanism of selection and publication bias, i.e., patients particularly suitable to be treated with aripiprazole in addition to clozapine might have been selected by the treating physicians, and case series of patients with a favorable outcome might more often have been published. Very likely, randomized evidence assessing the benefit of aripiprazole will be available in the next few years and, hopefully, will guide physicians in reaching a decision about optimal care in this difficult-to-treat patient population.

Under real world circumstances the need to provide effective therapeutic interventions to patients who do not have an optimal response to clozapine has been cited as the most common reason for simultaneously prescribing two or more antipsychotic drugs in combination treatment strategies (25). In Europe and the United States treatment guidelines recognize that the concurrent prescription of a second antipsychotic in addition to clozapine is a common sense strategy in these partially responsive patients (26-29). However, there is no evidence base to support one specific antipsychotic in combination with clozapine. The clinical experience on the use of aripiprazole in combination with clozapine, described in this review, should be considered as background information useful to design randomized studies and to interpret their findings, but cannot represent an evidence base to inform clinical practice.

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