Adjunctive aripiprazole decreased metabolic side effects of clozapine treatment

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Abstract

Clozapine is an atypical antipsychotic indicated for the treatment of refractory schizophrenia. Clozapine treatment is associated with the metabolic side effects. Weight gain, hyperlipidemia and hyperglycemia are the risk factors for onset of diabetes and cardiovascular disorders. We report a case vignette of a patient in whom the decrease in negative and general psychopathology after adjunctive aripiprazole appeared simultaneously with a reduction of clozapine-induced increase in weight and metabolic measures. Combined application of clozapine and aripiprazole is in accordance with a neurobiological rationale and appears to be a safe and well tolerated.

CASE REPORT

INTRODUCTION

Clozapine is a drug of choice in treatment-refractory patients with schizophrenia. Remington *et al.* [9] reviewed augmentation strategies in refractory schizophrenia, when clozapine is ineffective or only partially effective. These include combinations of antipsychotics. Clarke *et al.* [2] reported on three cases of successful clozapine augmentation with aripiprazole, that resulted in the reduction of negative symptoms. Pigott *et al.* [8] reported that the effect of aripiprazole on metabolic laboratory values does not differ from the effects of placebo. Clozapine treatment is associated with a range of adverse effects such as weight gain, hyperlipidemia, hyperglycemia and hypertension [5]. Because of safety concerns, it appears advisable to combine clozapine with an antipsychotic that does not induce treatment emergent weight gain or metabolic effects. Recently, the combination of clozapine and aripiprazole has become a matter of clinical interest [1, 7, 8, 10, 14, 19]. The dose of clozapine can be reduced gradually to 50% of the mainetance dose without many problems [2]

We report a case vignette of a patient in whom the decrease in negative and general psychopathology after adjunctive aripiprazole appeared simultaneously with a reduction of clozapine-induced increase in weight and metabolic measures.

CASE REPORT

A 25-year-old single male with no history of psychiatric disorders in the family. His development since childhood until late adolescence was unremarkable. He has been always physically healthy.

He worked as a farmer and the last two years is on disability payments because of mental illness. In 2003 he started to experience auditory hallucinations. He developed a delusion of control by aliens. He was also affected by thought broadcasting and thought insertion. He did not visit a psychiatrist in 2003. In 2004 he called police and asked for protection against delusional threats to the world and to himself. The police brought him to the hospital. He was evaluated and the diagnosis of schizophrenia according to ICD 10 criteria was established. In addition to bizarre paranoid delusions and auditory hallucinations his emotions were blunted and his motivation inappropriate. Initially he was treated for 4 months with olanzapine (20 mg a day). For a few weeks olanzapine was combined with haloperidol, however, any improvement has not been observed. Amisulpride (1200 mg a day) was given for next 2 months with no improvement. Because of a lack of response, clozapine was started in March 2005. The dose had been titrated up to 400 mg. In May 2005 the patient had a seizure and subsequently his clozapine dose was reduced to 300 mg. He was put on the adjunctive clonazepam and his EEG has been monitored regularly. The improvement was not observed earlier than 7 months since starting clozapine. The positive symptoms disappeared, but residual negative symptoms (blunted affect, social withdrawal and loss of motivation) persisted. Because of the patient's incomplete response and depressed mood, venlafaxine ER (300 mg a day) was added in November 2005. After 12 months on clozapine treatment, the patient gained weight and his serum levels of cholesterol and triglycerides increased.

Because of the persisting negative symptoms, aripiprazole was added to clozapine in March 2006. We expected that it will relieve the negative symptoms and allow for a lower clozapine dose. We also hoped that aripiprazole may have a beneficial effect on patient's metabolic status. Aripiprazole was started at the dose of 7.5 mg per day and increased to 10 mg within a month. In the course of the next two months, Venlafaxine was gradually discontinued (in April-May 2006) .

In May 2006 , Clozapine was reduced to a dose 200 mg per day and after 6 months (in September 2006) to 150 mg per day. After four months of combined treatment, the severity of negative symptoms measured by SANS decreased 40% and also negative symptoms and general psychopathology subscales of the PANSS were reduced 37 and 27% respectively. In addition, the patient lost 12 kg and his abdominal circumference shortened 7 cm. His serum cholesterol and triglyceride levels decreased already in May 2006, and after 4 months of combined treatment they were substantially lower. Cholestetrol serum level was within the normal range. In October 2007, Clozapine was reduced to a dose 100 mg per day. The reduction of weight and the improvement of negative symptoms continued, and the values of cholesterol and triglycerides (TAG) have remained low also 20 months after starting the patient on clozapine (Table 1).

We did not detect any undesirable treatment emergent symptoms after the addition of aripiprazole.

DISCUSSION

Karunakaran *et al*. [7] reported on a retrospective chart study in which patients after the addition of aripiprazole to clozapine had their clozapine doses reduced, their weight decreased in most cases, and their negative symptoms and social functions improved. Similarly, Rocha and Hara [14] described three cases of combined treatment associated with clinical improvement and reduction of weight. Recently, Henderson *et al*. [6] reported on the improvement of metabolic disturbances over 6 weeks in the course of an open study of aripiprazole adjunctive to clozapine. The authors observed a statistically significant decrease in the average weight, average fasting total serum cholesterol and triglycerides in 10 patients with stable clozapine plasma levels. In a retrospective chart study, Spurling at al. [16] observed a weight reduction and a significant drop in total cholesterol level in the group of patients switched from second-generation antipsychotics to aripiprazole. DeHert *et al*. [4] described a significant reduction in fasting glucose, insuline resistance index, and serum lipids levels as well as decrease in body weight, and waist circumference in a group of 31 patients with schizophrenia who were either started on or switched to aripiprazole. Our report describes a case of marked and lasting reductions in the number of metabolic indices (fasting cholesterol, triglycerides, obesity and waist circumference). It is also in agreement with report of the advantages of aripiprazole combined with clozapine in patients with residual symptoms of schizophrenia. In our opinion, it supports the need to investigate the potentially beneficent metabolic impact of the combined treatment in addition to its clinical effects. The lasting character of the weight reduction and lowering of serum cholesterol and TAG levels makes the explanation of these changes by mere reduction of the clozapine dose or by the withdrawal of venlafaxine unlikely.

Among the possible explanation of the aripiprazole's effect on metabolic parameters are the interactions of aripiprazole with serotonine and histamine receptors. Kroeze *et al*. [9] found the affinity to H_1 receptors to be the best predictor of the short-term weight increase in patients treated to H_1 blocking agents. Aripiprazole has low affinity with H_1 receptors. Aripiprazole is also a partial agonist on $5HT_{2c}$ receptors [15], the blockade of which by e.g. olanzapine or clozapine is associated with the increased food intake.

Quality of life and subjective well-being with antipsychotic treatment markedly increase in our patient. Quality of life and adherence to treatment can be neg-

Table 1. Changes in weight, serum lipid values and negative symptoms over 20 months of combined treatment with Aripiprazole and Clozapine.

	April 2005 (before CLOZ)	March 2006 (after 8 months on CLOZ)	May 2006 (after 2 months on ARI-CLOZ)	July 2006 (after 4 months on ARI-CLOZ)	November 2006 (after 8 months on ARI-CLOZ)	November 2007 (after 20 months on ARI-CLOZ)
Weight (kg)	70	107.8	100.4	95.7	86.7	87
BMI	22.86	35.2	34.6	33.2	30.1	30.1
Waist circumference (cm)	n.a.	115	108	108	92.5	94
Cholesterol (mmol/l)	4.28	6.98	5.09	4.54	4.92	4.48
Triglycerides (mmol/l)	2.13	8.47	3.06	1.97	2.63	2.32
SANS score	**n.a.**	**50**	**38**	**30**	**25**	**25**

ARI-CLOZ- combined treatment with Aripiprazole and Clozapine; CLOZ – clozapine treatment; BMI – Body Mass Index

atively affected by drug-induced side-effects including obesity [11, 17, 18]

The case report provides an additional argument for controlled studies aimed at answering the question whether combined treatment with aripiprazole and clozapine in treatment resistant patients may decrease the risks of metabolic syndrome in addition to improving persistent residual symptoms.

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