Letters to the Editor

Adding Aripiprazole to Clozapine

To the Editor:

In a recent article in this journal by Mulè et al. (1), it is concluded that the addition of aripiprazole in schizophrenic patients who have responded only partially to clozapine treatment might be beneficial. To this we would like to add some further important clinical findings on adding aripiprazole to clozapine.

Some studies have suggested that aripiprazole might improve metabolic functions in schizophrenic patients (2). Henderson et al. (3), in fact, examined the effect of adding aripiprazole to clozapine-treated subjects on the metabolic functioning of their patients. They conclude that there was a significant decrease in weight, body mass index (BMI), and lipids. Weight decreased on average 2.7 kilos (range +0.9–5.9), BMI 1.0 kg/m^2 (range 0.1–2.1), total cholesterol 26.6 mg/dl (range 3–52), and triglycerides 98.1 mg/dl (range +38–353). Their exploratory study, however, was limited to six weeks.

When aripiprazole was marketed in the Netherlands, many patients requested a switch to this new drug. Furthermore, a number of psychiatrists who were treating patients on clozapine added aripiprazole. Therefore, we decided to treat patients who were having severe metabolic side effects from clozapine and who requested aripiprazole with this new combination. We expected at least a reduction in weight and lipids. We summarize our treatment experiences retrospectively. Our case series consists of eight men and three women. Their mean age was 39.5 years (standard deviation [SD] 5 years) with a range from 32 to 47 years. Schizophrenia was diagnosed 13.2 years before (SD 6.7 years) with a range of 4 to 26 years. All patients were stabilized on clozapine with a mean dosage of 500 mg (range 200–900 mg) for at least a year. During this year, no significant changes in psychotropic medication were necessary. Positive symptoms of schizophrenia were absent or mild. Negative symptoms were present, but not invalidating. In each case, the patients were considered sufficiently controlled. Routine control measures in our patients on clozapine consisted of blood pressure and body weight control, clozapine blood levels, leucocytes, glucose and lipids assessment. All patients received 15 mg of aripiprazole. Before and after twelve weeks of treatment with the addition of aripiprazole, the clinical condition of the patients was evaluated with our regular standard.

One of the patients relapsed during these twelve weeks. It appeared that this patient discontinued the clozapine treatment. She recovered after restarting clozapine. At twelve weeks, ten patients reported feeling more active, enjoying more of daily life, and stated experiencing more emotions. One patient felt no difference and, in consultation with him, it was decided to discontinue the aripiprazole. In more objective terms, we established the difference in mean arterial pressure (MAP), which was not significantly altered (MAP x1=92, SD=7.3; MAP x2=93.6, SD=5.9; paired T-test t=-1.05, p=.32). Weight decreased, but not significantly (x1=115.5, SD=20.2; x2=112.9, SD=19.3; t=1.5, p=.17). As expected BMI was congruent with this (x1=37.2, SD=7.1; x2=36.3, SD=6.1; t=1.5, p=.16). Fasting glucose (x1=7.5, SD=2.9; x2=7.3, SD=4.2; t=.28, p=.79) did not decrease. Neither total cholesterol levels (x1=5.9, SD=1.2; x2=5.7, SD=1.3; t=.5, p=.63) nor triglycerides (x1=2.7, SD=1.1; x2=2.6, SD=1.1; t=.5, p=.6) or HDL (x1=.8, SD=.2; x2=1.2, SD=.9; t=-1.4, p=.2) or LDL (x1=3.8, SD=1.1; x2=3.4, SD=1.4; t=1.2, p=.3) showed any significant differences.

Contrary to our expectations, and to the verbal reports of our patients, none of the objective measures showed any difference in the time span of twelve weeks. It also contradicts the findings of Henderson et al. (2006): while their subjects were comparable to our sample in duration of illness, their mean weight and BMI were considerably less than in our samples.

Our most important finding is that these morbidly obese patients reported a subjective improvement of well-being. Although our data does not support the findings of Henderson et al. (3), the results of Mulè et al. (1) and the subjective reports of our patients do merit, in our opinion, a double-blind, randomized clinical study with morbidly obese patients on clozapine by adding aripiprazole for a period of at least one year.

References

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Elevated Ammonia Levels on Depakote

To the Editor:

Drs. Mayerhoff, Schleifer and Nurenberg, in their article "Valproic Acid-Associated Neurological Syndrome in Chronic Mental Illness: A Case Report" featured in the January 2008 issue of this journal, describe a 48-year old woman who had some improvement in her aggressive outbursts on Depakote, but also developed confusion, disorientation and other dementia-like symptoms.

As patients with urea cycle disorder can develop elevated ammonia levels on Depakote, even after some duration on Depakote and at therapeutic levels such as 83.6 ug/ml in this patient, I wonder what the patient's serum ammonia level was? As other factors influence the urea cycle, the clinical picture can present as a fluctuating course. If she was already compromised by elevated ammonia, she would have less tolerance and an exaggerated reaction to diphenhydramine and Robitussin at therapeutic doses. Likewise, a recurrence of symptoms with re-exposure to Depakote would be expected in patients with a genetic metabolic disorder. I would wonder about her reaction to other medications affected by the urea cycle.

Since ammonia can be easily checked in patients taking valproate who develop confusion, this can sometimes be treated while continuing a beneficial medication, and would be a way to evaluate confused patients without unnecessarily depriving patients of the benefit of Depakote.

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Dr. Mayerhoff and Colleagues Reply

To the Editor:

The authors would like to thank Dr. Livingston for her thoughtful comments and for the reminder that urea cycle abnormalities and elevated ammonia may contribute to adverse drug effects following Depakote administration. This topic is of great interest and complexity. While the majority of patients who have increased ammonia levels when taking valproic acid are asymptomatic (1), those who are symptomatic tend to clear very rapidly when valproic acid is discontinued. Increased ammonia usually occurs early in the course of valproate treatment, especially with urea cycle disorders or decompensated liver disease (2). Neither of these conditions was prominent in our patient who had been treated throughout with valproic acid and demonstrated normal liver function tests since at least 2003. At that time, a spot ammonia level was found to be normal (53 uM). Further complicating the assessment of ammonia in relation to toxicity is that a significant number of patients with increased ammonia levels when taking valproic acid are asymptomatic (1).

Accordingly, while it would have been of interest to have a series of ammonia levels for our patient, it would not likely have provided information of immediate relevance to clinical management in this case. We do concur that clarification of the true predictive value of both normal and abnormal ammonia levels in patients showing potential toxicity to valproic acid would be of considerable use in the assessment of patients taking this agent.

References

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