

CASE REPORT

Negative Symptoms in Schizophrenia Respond to Milnacipran Augmentation Therapy: A Case Report

Nobuhiko Hoaki, Takeshi Terao, Goto Shinjiro, and Kensuke Kodama

Department of Neuropsychiatry, Oita University Faculty of Medicine, Oita, Japan

Corresponding author: Takeshi Terao, Department of Neuropsychiatry, Oita University Faculty of Medicine, Idaigaoka 1-1, Hasamamachi, Yufu, Oita, 879-5593, Japan; E-mail: terao@med.oita-u.ac.jp

Abstract

We report a 37-year-old male patient with schizophrenia and negative symptoms including blunted affect, avolition, alogia and asociality. Unexpectedly, the addition of milnacipran, a serotonin and noradrenaline reuptake inhibitor and approved as an antidepressant, to his existing psychotropic regimen including aripiprazole selectively improved his negative symptoms. The present findings suggest that milnacipran addition to aripiprazole may be useful for treating negative symptoms in some schizophrenic patients. The present findings may warrant further controlled studies to substantiate the potential of role of milnacipran in treating the disabling negative symptoms of schizophrenia (German J Psychiatry 2009; 12: 32-34).

Keywords: schizophrenia, negative symptoms, milnacipran, aripiprazole

Received: 7.10.2008

Revised version: 8.1.2009

Published: 15.5.2009

Introduction

The negative symptoms of schizophrenia are often treatment-resistant and create a significant obstacle to global function. Although the benefits of second-generation antipsychotics including aripiprazole on negative symptoms appear to be modest, several studies have investigated the augmenting effects of antidepressants' on antipsychotic efficacy. Most recently a meta-analysis (Sepe et al., 2007) shows no significant difference between placebo and selective serotonin reuptake inhibitors (SSRIs) augmentation on antipsychotics in improving negative symptoms. However, a few reports (Gama et al., 2006; Nakanishi et al., 2004) have examined the augmenting effects of serotonin and noradrenaline reuptake inhibitors (SNRIs), and at least one report has shown milnacipran augmentation for anxiety or depression in schizophrenia, although not for negative symptoms per se. Another report (Doron et al.) has shown venlafaxine augmentation for depression in schizophrenic patients, but not for negative symptoms. To date, there has been no evidence to indicate the effects of SNRI augmentation on the negative symptoms of schizophrenia.

Here, we describe a schizophrenic patient whose negative symptoms responded remarkably well to milnacipran augmentation. To our knowledge, this is the first report which shows milnacipran augmentation of antipsychotics on negative symptoms of schizophrenia.

Case Report

In September 200X, a 37-year-old male schizophrenic patient was admitted to our university hospital. His negative symptoms included blunted affect, avolition, alogia, and asociality. Other symptoms were compulsive behaviors, dysmorphophobia and delusion of persecution. According to DSM-IV-TR, the symptoms of the patient met the criteria of schizophrenia, residual type, although he had mild depressive state which was rated as 10 points by Hamilton Rating Scale for Depression.

He received aripiprazole and it was increased to 24 mg per day, but his electrocardiogram began to prolong QT_c and it was again decreased to 21 mg per day. Other combined drugs were 1,000 mg per day of valproate, and 3 mg per day

of clonazepam which was added for augmenting aripiprazole. His negative symptoms, however, were refractory to this combination, whereas his positive symptoms such as delusion of persecution moderately improved.

In October 200X, 25mg per day of milnacipran was added to the ongoing psychotropics and gradually increased to 100 mg per day. Subsequently, he began to smile naturally, initiate conversations with other patients and participate in daily activities. These changes were remarkable.

Thereafter, he began to complain of frequent urination and, as milnacipran was suspected as a potential cause, milnacipran was decreased to 75 mg per day without change to the doses of the other psychotropics. At this point, his frequent urination actually worsened and his negative symptoms were clearly exacerbated. As such, it appeared that that frequent urination may have been a psychiatric symptom rather than a side effect of milnacipran. A few days after milnacipran was returned to 100 mg per day, there were no further complaints of frequent urination and his negative symptoms remarkably improved once again.

After discharge, he gradually adjusted himself to daily life through exercise such as jogging at home, and 4 months after discharge he was able to return to his former employment and continues his work for 5 months until now.

Discussion

According to DSM-IV-TR, the symptoms of the patient did not meet the criteria of schizoaffective disorder. An alternative diagnosis of the patient could be schizophrenia, residual type. Nonetheless, we cannot completely deny the possibility that his depressive symptoms probably derived from schizophrenia responded to milnacipran addition because he had mild depressive state which was rated as 10 points by Hamilton Rating Scale for Depression.

Chang et al. (2008) reported a randomized, double-blind, placebo-controlled study which evaluated the efficacy and safety of aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia. As a result, improvement was significantly greater with aripiprazole treatment than with placebo for negative symptoms. Although our patient did not receive clozapine, his negative symptoms did not respond to aripiprazole.

In view of the apparent dose-response relationship between milnacipran addition and this patient's negative symptoms (better at the dose of 100 mg per day vs. worse at the dose of 75 mg per day) it is possible to say, at least in this case, that milnacipran was effective in treating negative symptoms. It remains unclear, however, why frequent urination did not reoccur upon the return to the original dose of milnacipran 100 mg per day. If frequent urination was in fact a psychiatric symptom (e.g., the expression of a hypochondriacal tendency), the return to the original dose may have improved the symptom even though it did not respond to the first challenge of 100 mg per day. According to the information from drug company, dysuria was reported to happen in the

range of 1.9–11.6%. In this patient, however, it is unlikely that frequent urination was due to dysuria induced by milnacipran.

With regard to the mechanism of milnacipran augmentation, milnacipran has both serotonergic and noradrenergic reuptake inhibition. As previously mentioned, there are currently no reports to suggest that SSRIs augment the effect of antipsychotics' on the negative syndrome¹. It is important to note that a major difference between SSRIs and SNRIs such as milnacipran is that the latter has noradrenaline reuptake inhibition. Given that noradrenergic underactivity has been assumed to be associated with negative symptoms (Yamamoto et al., 2004), it is possible that milnacipran's noradrenergic action may have had an important role in reducing the negative symptoms. Siris et al. (1990) reported a double-blind maintenance treatment trial of adjunctive imipramine vs. placebo to fluphenazine decanoate and benzotropine. Fourteen schizophrenic or schizoaffective patients, who had had postpsychotic depression or negative symptoms unresponsive to adjunctive benzotropine but responsive to adjunctive imipramine were switched to imipramine addition or placebo addition in combination with fluphenazine decanoate and benzotropine. Consequently, all 6 patients tapered to placebo relapsed into their depression-like, negative symptom state, whereas only 2 of 8 patients maintained on imipramine had such relapse. Although their results cannot differentiate depressive symptoms and negative symptoms, imipramine also increase noradrenergic activity as well as serotonergic activity.

While the present case provides only anecdotal evidence and has many limitations, given of the intractable nature of negative symptoms, the present findings may warrant further controlled studies to substantiate the potential of role of milnacipran in treating the disabling negative symptoms of schizophrenia.

References

- Chang JS, Ahn YM, Park HJ, Lee KY, Kim SH, Kang UG, Kim YS. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*, 2008; 69:720-731.
- Doron M, Baruch S, Roni S, Yuval M. Venlafaxine for the treatment of depressive episode during the course of schizophrenia. *J Clin Psychopharmacol* 2004; 24: 653-655.
- Gama CS, Zanatto VC, Picon F, Lobato MI, Belmonte-de-Abreu PS. Efficacy of milnacipran in treating anxiety symptoms in schizophrenic patients receiving clozapine: a case series study. *Rev Bras Psiquiatr* 2006; 28: 339-42.
- Nakanishi S, Kunugi H, Takahashi T. Efficacy of milnacipran for depressive symptoms in schizophrenia spectrum disorder. *Psychiatry Clin Neurosci* 2004; 58: 226-227.
- Sepe AA, Potvin S, Elie R, Stip E. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative

- symptoms of schizophrenia: a meta-analysis. *J Clin Psychiatry* 2007; 68: 604-610.
- Siris SG, Mason SE, Bermanzohn PC, Alvir JM, McCorry TA. Adjunctive imipramine maintenance in post-psychotic depression/negative symptoms. *Psychopharmacol Bull* 1990; 26:91-94.
- Yamamoto K, Hornykiewicz O. Early Proposal for a noradrenaline hypothesis of schizophrenia. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2004; 28: 913-922.