Augmentation of milnacipran by risperidone in treatment for major depression

Kunihiko Tani¹, Nori Takei¹,²,³, Masayoshi Kawai¹, Katsuaki Suzuki¹, Yoshimoto Sekine¹, Takao Toyoda¹, Yoshio Minabe¹ and Norio Mori¹

¹ Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Japan
² Stanley Foundation Research Center in Japan
³ Department of Psychological Medicine, Institute of Psychiatry, London, UK

Abstract

Milnacipran, one of the serotonin noradrenaline reuptake inhibitors (SNRIs) to which venlafaxine and duloxetine belong, is a new antidepressant that has recently become available in many countries. Despite the advances in pharmacotherapy, almost one third of patients with depressive illness respond inadequately to monotherapy with such an antidepressant. We herein describe five patients with major depression who responded partially, but not fully, to milnacipran alone and remarkably improved with an adjunct of risperidone. In addition, milnacipran plus risperidone was found to be a useful augmentation for treatment-refractory depression in 3 of the 5 patients. The minimum dose of risperidone, 0.5 or 1 mg/d, was efficacious. The time of response after addition of risperidone was within 4 d. Our experience suggests that an augmentation therapy of milnacipran plus risperidone is useful for treating patients with depression who only partially respond to various types of antidepressants and for treatment-refractory depression.

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Introduction

Milnacipran, one of the serotonin noradrenaline reuptake inhibitors (SNRIs) to which venlafaxine and duloxetine belong, is a new antidepressant that has recently become available in many countries. It has antidepressant efficacy similar to imipramine and is significantly superior to the selective serotonin reuptake inhibitors (SSRIs) (Clerc, 2001). Additionally, milnacipran has fewer cholinergic side-effects than tricyclic antidepressants (TCAs) (Kasper et al., 1996). Despite these advances, 29–46% of depressive patients respond inadequately to an antidepressant (Fava and Davidson, 1996). However, recent studies showed that atypical antipsychotic augmentation of SSRIs or the monoamine oxidase inhibitor (MAOI) is a useful strategy in treating individuals with major depression (Ostroff and Nelson, 1999; Shelton et al., 2001; Stoll and Haura, 2000). We herein describe five patients with major depression who responded partially, but not fully, to milnacipran and remarkably improved with an adjunct of risperidone.

Representative cases

Case 1

Mr T., a 53-yr-old high-school teacher, experienced agitation, headache, and nausea at age 51 yr. He gradually became depressed and developed further symptoms such as general fatigue, poor concentration, and insomnia. He visited a psychiatric hospital and was diagnosed with major depression for which treatment was immediately initiated. He was, however, unresponsive to various types of antidepressants, including TCAs and SSRIs. Due to frequent absences from work, he was referred to our hospital at age 53 yr. On admission, the patient’s score on the HAMD was 41. We started the patient on 50 mg/d milnacipran, and gradually titrated up to 200 mg/d. He felt that his depressive mood decreased, but many other depressive symptoms did not improve. We then added a 1-mg nocturnal dose of risperidone to his regimen. The
following morning, the patient felt that he had slept better than usual, after a long period of suffering from insomnia. Four weeks after the addition of risperidone, the remaining depressive symptoms had fully resolved.

Case 2

Mr K., a 42-yr-old public servant, developed depressive mood, anxiety, insomnia, low energy, and loss of appetite. He visited a mental clinic and was diagnosed with major depression. He partially responded to 75 mg/d amitriptyline and stopped taking this medicine at discretion. Two weeks after discontinuation of the treatment, he became confused at work and was brought by a colleague to the emergency room of our hospital. On medical examination, he had no physical illness. Because his disturbances seemed due to an exacerbation of depression, he was admitted to a psychiatric ward and received infusions of clomipramine at 25 mg/d for 3 d. After the infusions, milnacipran was started at 50 mg/d, and the dose increased to 300 mg/d over 7 wk. The patient’s depressive mood, loss of appetite, and reduced energy improved, but he continued to suffer from insomnia and anxiety. A 1-mg nocturnal dose of risperidone was then added. He slept well during the night, and 3 wk later his insomnia and anxiety were much improved. At this point, the patient was discharged with full remission.

Case 3

Ms. N., a 65-yr-old widow, had managed her building company for 30 yr after the death of her husband. At age 64 yr, she received an additional large tax bill because she had forgotten to send in her income tax return. From that time, she developed symptoms of early morning waking, depressed mood, increased worrying about the future, and impaired daily functioning. At a clinic, no physical problems were discovered. She was treated with etizolam (one of the benzodiazepines) and sulpiride, but her symptoms did not improve. She was then admitted to our hospital. On admission her HAMD score was 38. We started milnacipran at 50 mg/d, gradually increasing the dose to 200 mg/d. She showed a slight improvement as reflected on the HAMD (a score of 23), but her depressive symptoms such as loss of energy, general fatigue, and anxiety persisted. A 0.5-mg nocturnal dose of risperidone was then added, and 3 d later her symptoms began to improve. Two months after admission, she was discharged with no noticeable depressive symptoms.

Case 4

Mr Y., a 46-yr-old man, had worked as a psychosocial worker, but he had to leave his job due to protrusion of an intervertebral disk at the age of 36 yr. He had an operation the following year, but his backache did not improve. After the operation, the patient was distressed by a depressive mood, anxiety, insomnia, poor concentration, and loss of energy. He was subsequently diagnosed with major depression at a mental clinic. He responded relatively well to an antidepressant (name unknown), and his lumbago improved. He resumed work at age 38 yr, but the depressive symptoms returned 2 yr later. Although various types of antidepressants were tried, the patient failed to improve. Because of a protracted and chronic course of depression, he was admitted to our hospital at age 46 yr (with a HAMD score of 33). Milnacipran was initiated at 225 mg/d. One week after admission, we added a 1-mg nocturnal dose of risperidone to his regimen. The day following the adjunct of risperidone, the sleep disturbance from which he had suffered for a long time showed improvement. Three months after admission, he had almost complete remission from his depression.

Case 5

Ms. K., a 57-yr-old woman, had lived with her mother since her divorce at age 50 yr. After she had an operation for parathyroid adenomas at age 56 yr, she experienced insomnia, lack of appetite, general fatigue, nausea, headache, and dizziness. The physical examinations conducted in several hospitals were totally normal. She was seen in our hospital and diagnosed with major depression (HAMD score of 19). Milnacipran at 45 mg/d was started, and the dose was gradually increased to 100 mg/d. She showed a slight improvement (HAMD score of 10) but, 2 months later, she became worse again. A 1-mg nocturnal dose of risperidone was then added to the regimen. Four days after the augmentation, she felt that her mood was improved. After another 3 wk, her depressive symptoms were fully resolved.

Discussion

The clinical characteristics of the five patients are summarized in Table 1. Treatment with milnacipran alone was found to be effective in ameliorating some, but not all, depressive symptoms. The remaining and persistent depressive symptoms, however, remarkably improved immediately after adjunctive use of a low dose of risperidone. In addition, milnacipran plus
Risperidone was found to be a useful augmentation for treatment-refractory depression. Three patients (patient nos. 1, 3 and 4) who, despite active treatment, had a protracted course of depression, responded strikingly well to such an augmentation therapy. To our knowledge, this is the first case-series report on a successful augmentation therapy of milnacipran, an SNRI, with risperidone for patients with major depression, notably with a treatment-resistant course.

The dose of milnacipran in each patient at the time when risperidone was added was between 100 and 300 mg/d. We found a minimum dose of risperidone to exert a sufficient effect (0.5 or 1 mg/d). This finding is consistent with previous findings concerning other types of risperidone augmentation therapy (Ostroff and Nelson, 1999; Stoll and Haura, 2000). In these previous reports, the dose of risperidone was 0.5 mg/d for 9 out of a total of 13 patients, 1.0 mg/d for 3 patients, and 1.5 mg/d for the remaining 1 patient. Although the dose range was almost the same, more cases (4 out of 5) in our series were given 1.0 mg. The response to the addition of risperidone was very prompt; in fact, the time to response in our cases was from 1 to 4 d (see Table 1). This rapid response is also in agreement with previous reports (Ostroff and Nelson, 1999; Shelton et al., 2001). Additionally, in 3 of the 5 patients, disturbance of sleep was the first symptom to show improvement. This observation is also in line with previous reports on risperidone augmentation of SSRIs, showing that the first, beneficial effect to be seen is on sleep disturbance, followed by improvement in other symptoms (Ostroff and Nelson, 1999). Furthermore, none of our patients showed side-effects. Milnacipran has fewer drug interactions than other antidepressants because its levels of plasma protein binding are very low (Puozzo and Leonard, 1996) and milnacipran is not metabolized by the cytochrome P450 system (Briley, 1998). Therefore, milnacipran may be safer than other antidepressants, when it is used in combination with other compounds.

Although the mechanism by which risperidone augmentation of milnacipran exerts an action on the improvement of depressive symptoms is unclear, there is an animal study that provides a useful clue to this mechanism. Zhang et al. (2000) studied the effect of some atypical antipsychotics, including risperidone, in combination with SSRIs on neurotransmitter release in the rat prefrontal cortex using microdialysis. They demonstrated that atypical antipsychotic drugs, when in combination with SSRIs, produced a robust increase in the extracellular levels of dopamine and noradrenaline, and that the effect of SSRIs on the extracellular levels of serotonin was also sustained. These neurotransmitter activities may play a role in the improvement of depressive symptoms.

Our experience suggests that an augmentation therapy of milnacipran, an SNRI, plus risperidone is a useful strategy for treating patients with depression who respond only partially to various types of antidepressants and especially those with treatment-resistant depression. However, randomized controlled trials of such an augmentation therapy are needed to verify our findings.

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Statement of Interest
None.

References

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**Table 1. Characteristics of patients with major depressive disorder treated with milnacipran and risperidone (ris.)**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)/Gender</th>
<th>Milnacipran therapy before an adjunct of risperidone</th>
<th>HAMD change</th>
<th>Time to response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yr)</td>
<td>Maximum dose</td>
<td>Duration</td>
<td>Ris. dose</td>
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<tr>
<td>1</td>
<td>53/M</td>
<td>200 mg</td>
<td>6 wk</td>
<td>1 mg</td>
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<td>42/M</td>
<td>300 mg</td>
<td>7 wk</td>
<td>1 mg</td>
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<tr>
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<td>200 mg</td>
<td>6 wk</td>
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<td>4</td>
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<td>225 mg</td>
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<td>5</td>
<td>57/F</td>
<td>100 mg</td>
<td>9 wk</td>
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