CASE REPORT

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Risperidone Augmentation in Antidepressant-Resistant Somatic Symptom Disorder

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ABSTRACT

Chronic somatic symptoms are hallmarks of somatic symptom disorder (SSD), characterized by notable disruptions in the day to day lives of affected patients. Risperidone is an effective augmenting agent for treatment-resistant major depressive and obsessive-compulsive disorders. Although various antidepressants have been used for the pharmacotherapy of SSDs, no guidelines have been formulated for treatment-resistant or severe SSDs. To date, the efficacy of risperidone augmentation for the treatment of antidepressant-resistant SSD has not been reported. Here, we report the case of a 68-year-old female patient with SSD and comorbid persistent depressive disorder. Upon admission, laboratory tests revealed no abnormalities except for a high triglyceride level. Psychosocial functioning and depressive symptoms were evaluated using the Global Assessment of Functioning and Beck Depression Inventory II. The severe and persistent symptoms of the patient were remarkably alleviated following low-dose risperidone augmentation with mirtazapine combined with desvenlafaxine. Furthermore, notable therapeutic effect of risperidone augmentation was observed following a significant reduction in the subjective distress of the patient and functional recovery within a short period. Our report suggests that early augmentation with risperidone facilitates the analgesic effect of serotonergic/noradrenergic antidepressants and contributes significantly to the rapid amelioration of SSD severity.

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INTRODUCTION

Chronic somatic symptoms are hallmarks of somatic symptom disorder (SSD), leading to notable disruptions in the everyday lives of affected patients. SSD, as defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), supersedes the earlier DSM-IV-TR diagnoses of somatization disorder, undifferentiated somatoform disorder, and pain disorder. The DSM-5 key diagnostic features for SSD have shifted away from being characterized by medically unexplained symptoms to highlight the presence of immoderate thoughts, emotions, or behaviors that accompany somatic symptoms. Managing and treating SSD involves complex processes that usually require a gradual multidisciplinary approach.[1]

Findings from previous meta-analytic study indicate that antidepressants, including selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants, could be advantageous and efficacious in the pharmacological treatment of SSD.[2] Nevertheless, a considerable population affected by SSD did not achieve a treatment response, defined as over a 50% reduction in severity, after treatment with antidepressant monotherapy at sufficient doses and for sufficient duration.[3] For patients with SSD who do not respond to initial treatment, it may be necessary to either switch antidepressants, combine different antidepressants, or use augmentation strategies. Although the efficacy of aripiprazole as adjunctive therapy and quetiapine monotherapy for the treatment of somatic symptoms of major depression has been reported,[4,5] till date, no randomized controlled trials evaluating atypical antipsychotics as add-on therapy in the treatment-resistant SSD have been conducted.

Risperidone augments the effect of SSRI in the treatment of obsessive-compulsive disorder (OCD).[6] Since SSD has clinical features common to OCD, augmentation with risperidone may be effective for treatment-resistant SSD. Furthermore, paliperidone, the main metabolite of risperidone, has shown significant therapeutic effects as an add-on therapy to citalopram in patients with somatoform disorder.[3] However, to date, the effectiveness of risperidone augmentation in the treatment of antidepressant-resistant or severe SSD has not yet been reported. Herein, we describe a case in which a patient with SSD improved

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significantly after introducing low-dose risperidone to serotonergic/noradrenergic antidepressant therapy (including, mirtazapine and desvenlafaxine).

CASE PRESENTATION

A 68-year-old married woman, who complained of a severe burning sensation in her chest and back, dyspepsia, depressed mood, and insomnia, was admitted to our hospital. The patient's family had no history of psychiatric disorders. She had three sons. The second and third sons were living independently, but her first son, who had a language disorder, lived with her and her husband. After graduating from elementary school, she got married at the age of 24 years and worked as a farmer and housewife. She had an impatient personality and tended to pay attention to the smallest details; despite this, her husband tried to understand her. The patient had a good relationship with her family and was doing well in her daily life without any stressful events; however, she began to experience stress as her somatic symptoms gradually worsened around the age of 60 years. On examining her mental status, she showed excessive worry about the burning sensation, as well as the characteristic psychopathology of persistent depressive disorder (PDD), including chronic depressed mood, low self-esteem, and low energy. Because the somatic symptoms were too severe to be considered as accompanying symptoms of mood disorders and caused significant functional impairment in daily life, she was diagnosed with SSD and PDD. The patient had been treated with psychiatric medications, including mirtazapine (15–45 mg/day), alprazolam (0.5–1 mg/day), and clonazepam (0.5 mg/day), for dysthymia with SSD approximately 5 years prior to admission. She was also hospitalized in our psychiatric inpatient unit four times for approximately 1–2 weeks per admission. Besides psychiatric treatment, she had been administered medications including hydrochlorothiazide (12.5 mg/day), telmisartan (40 mg/day), atorvastatin (10 mg/day), esomeprazole (20 mg/day), and mosapride (10 mg/day) due to pre-existing medical issues (hypertension, gastroesophageal reflux disease, and hyperlipidemia). Before hospitalization, her psychiatric medications included mirtazapine (45 mg/day), alprazolam (1 mg/day), and clonazepam (0.5 mg/day). Somatic and depressive symptoms persisted without any changes regardless of 12 weeks of ongoing treatment. Upon admission, laboratory tests revealed no abnormalities except for a high triglyceride level (213 mg/dL). Psychosocial functioning and depressive symptoms were evaluated using the Global Assessment of Functioning (GAF) and Beck Depression Inventory II (BDI-II). On the first day, the GAF and BDI-II scores were 55 and 22, respectively. After 3 weeks, the patient was treated for SSD with comorbid PDD using desvenlafaxine (initially 50 mg/day, later increased to 100 mg/day), mirtazapine (45 mg/day), alprazolam (1 mg/day), and clonazepam (0.5 mg/day). In addition, we implemented supportive psychotherapeutic techniques such as praise, reassurance, ventilation, and encouragement of activities including exercise and interpersonal interactions at every interview. On the 21st day, she experienced a slight improvement in her depressive symptoms (BDI-II score, 17); her dyspepsia disappeared, but the severe burning sensation persisted. Twenty-one days after admission, risperidone was initiated at 0.5 mg/day, titrated up to 1.5 mg/day over 1 week, and the dosage of alprazolam was tapered to 0.5 mg/day without changing the dosage of other medications. There were no changes in her somatic symptoms from the first to the third day after risperidone administration. Four days after risperidone augmentation, the burning sensation was reduced by approximately half. After one week of risperidone supplementation, the patient reported that her burning sensation had improved by more than 80%. On the 28th day, benztropine (0.5 mg/day) was added because the patient complained of subjective discomfort in both lower extremities. On the 31st day after admission, the patient was discharged with GAF and BDI-II scores of 75 and 13, respectively. Two weeks after discharge, she visited our department and reported disappearance of her burning sensation. Over the course of these 3 months, the patient was taking medication without any adverse events and achieved complete recovery to the level of functioning prior to the illness. Four months after discharge, the burning sensation worsened again; therefore, the dose of risperidone was increased to 2 mg/day. Subsequently, the patient remained in remission for 2 months. Consent for the publication of all information was obtained from the patient.

MAIN POINTS

- Risperidone has shown efficacy as an augmentation agent in association with serotonergic antidepressants for treatment-resistant major depressive disorder as well as obsessive-compulsive disorder.
- Even though various classes of antidepressants have been used for treating somatic symptom disorder (SSD), no established treatment guidelines or algorithms for treatment-resistant or severe SSD exist.
- Our case highlights the effectiveness of low-dose risperidone augmentation in enhancing the analgesic effect of antidepressants, resulting in rapid amelioration of SSD severity.

DISCUSSION

To the best of our knowledge, this is the first case of low-dose risperidone addition to mirtazapine and desvenlafaxine in the treatment of SSD with PDD. Risperidone augmentation exhibited a notable therapeutic effect, as revealed by a significant reduction in the patient's subjective distress

and functional recovery within a short period. Previous research has indicated that the neurotransmission of serotonin (5-HT) and norepinephrine (NE) contributes to the analgesic effect on somatic symptoms via the inhibitory descending pain pathway. Abnormalities in the 5-HT and NE systems are regarded as the key biological causes of somatic symptoms.[7] Mirtazapine, known for its noradrenergic and specific serotonergic properties, is effective in alleviating both major depressive disorder (MDD) and pain symptoms.[8] Desvenlafaxine, serotonin, and norepinephrine reuptake inhibitors (SNRI) have demonstrated similar efficacy in the treatment of MDD and physical symptoms such as diabetic peripheral neuropathy.[9] In this case, there was no change in the severity of the burning sensation despite continued treatment with mirtazapine and desvenlafaxine for 3 weeks. Although various classes of antidepressants, such as tricyclic antidepressants, SSRI, and SNRI, are commonly used, there are no treatment guidelines or algorithms for the pharmacotherapy of treatment-resistant SSD.

Risperidone, an atypical antipsychotic, has potent antagonistic properties at dopamine D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1D}, α_1-, and α_2-adrenergic receptors and is an effective augmenting agent in SSRI-refractory MDD.[10] Risperidone can reverse SSRI-induced inhibition of NE activity by 5-HT_{2A} antagonism.[11] Moreover, antidepressant effect of venlafaxine combined with risperidone was facilitated by the supplementation of yohimbine, implying the critical role of α_2-adrenergic receptors.[12] 5-HT_{2A} and α_2-adrenergic receptor antagonism, which risperidone and mirtazapine share, can significantly enhance the 5-HT and NE transmission.[13] In our case, the addition of low dose of risperidone to mirtazapine with desvenlafaxine could help alleviate the burning sensation possibly through the synergistic interaction of 5-HT_{2A} and α_2-adrenergic receptors.

In a network meta-analysis on augmenting drugs to SSRI for treatment-resistant OCD, risperidone showed superior efficacy to placebo.[6] Because both SSD and OCD share clinical characteristics such as preoccupation and anxiety, augmentation using atypical antipsychotics could be effective for the treatment of SSRI-resistant SSD. The 6-week randomized trial demonstrated that patients with somatoform disorder benefited more from combination therapy with paliperidone than from citalopram monotherapy.[3] Successful addition of olanzapine or quetiapine to antidepressants has been reported in the treatment of SSD.[14,15] Furthermore, previous case series have shown the effectiveness of aripiprazole or blonanserin augmentation for SSRI in patients with SSD.[16,17] These findings imply that the dopaminergic, 5-HT, and NE systems may be involved in the therapeutic mechanism of SSD.

In previous augmentation cases, the dosage of aripiprazole was titrated to 6 or 18 mg/day, and that of blonanserin was raised to 8 or 12 mg/day.[16,17] On the other hand, in our case, the severe burning sensation improved rapidly without serious adverse events following adding 1.5 mg/day of risperidone to mirtazapine with desvenlafaxine. The present case indicates that adding a relatively low dose of risperidone to serotonergic/noradrenergic antidepressants could be safe and contribute to the rapid alleviation of severe somatic symptoms in patients with SSD.

This case report had several limitations. First, it cannot be ruled out that the observed analgesic effect may have been entirely due to mirtazapine and desvenlafaxine rather than low-dose risperidone augmentation because their therapeutic effects may have been delayed by approximately 4-6 weeks. Second, supportive psychotherapeutic interventions such as reassurance and ventilation, along with the co-administration of benzodiazepines, may have alleviated somatic symptoms. In the treatment of SSD, benzodiazepines may play a significant role as supportive therapy.[18] Third, we did not assess the patient's somatic symptoms using objective assessment scales. Lastly, we did not measure serum prolactin levels. Risperidone causes a more significant increase in prolactin levels than other atypical antipsychotic drugs owing to the incomplete crossing of the blood-brain barrier, and adjunctive aripiprazole therapy has been proven to be a safe and effective solution for risperidone-induced hyperprolactinemia.[19]

In summary, the adjunctive use of low-dose risperidone along with serotonergic/noradrenergic antidepressants was effective in treating severe SSD with PDD, suggesting a potential augmenting effect without serious adverse events. Future prospective studies with larger sample sizes are required to verify the clinical advantages of risperidone augmentation therapy in the treatment of antidepressant-resistant SSD.

Data Availability Statement: The data that support the findings of this study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author upon reasonable request.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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