

Stiff-person syndrome in a patient with comorbid bipolar and panic disorders: A case report and literature review

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Abstract

Stiff-person syndrome (SPS) is a neurologic disorder characterized by muscle stiffness, rigidity, and muscle spasms, and it can increase a patient's risk for falls. It is recognized as a rare disease with limited clinical guidelines to manage the condition and its symptoms. Currently, there is even less clinical guidance for the management of common comorbid conditions in these patients. This patient case report aims to evaluate the efficacy of various medications for symptom management in a patient with SPS and comorbid psychiatric disorders, specifically bipolar I and panic disorder. Throughout the patient's course of treatment, various medications were trialed, including fluoxetine, hydroxyzine, valproic acid, propranolol, and clonazepam. Ultimately, fluoxetine, hydroxyzine, and propranolol were discontinued due to adverse drug reactions and incomplete symptom resolution. The patient's bipolar I disorder was adequately managed with valproic acid. Once the clonazepam was changed from as-needed to scheduled dosing, the patient's panic disorder and anxiety-triggered spasms were well controlled. The efficacy of benzodiazepines, specifically high doses of diazepam, in alleviating muscle spasms and anxiety in SPS has been demonstrated in the literature. Case reports including patients with SPS that are prescribed selective serotonin reuptake inhibitors provide controversial evidence as some studies report exacerbation of SPS symptoms with prolonged use. As this case report and literature review suggest, patients with SPS and comorbid panic disorder and anxiety-triggered spasms may benefit from the use of benzodiazepines. The use of other medication classes for the treatment of other comorbid psychiatric disorders in a patient with SPS is lacking evidence.

Keywords: stiff-person syndrome, stiff-man syndrome, SPS, bipolar disorder, panic disorder, benzodiazepines, clonazepam, selective serotonin reuptake inhibitors, SSRIs, fluoxetine

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Background

Stiff-person syndrome (SPS), also known as stiff-man syndrome, was first reported in 1956.¹ It is an uncommon neurologic disorder characterized by muscle stiffness, rigidity, and muscle spasms, and it increases the patient's risk of falls. Stiff-person syndrome occurs in women 2 to 3 times more frequently than men, and the prevalence is approximately 1 in 1 million.^{2,3} Most patients with SPS present with autoantibodies against glutamic acid decarboxylase. This can lead to inhibition of glutamic acid decarboxylase and gamma-amino butyric acid (GABA)

synthesis. Gamma-amino butyric acid is the brain's primary inhibitory neurotransmitter, and a decrease in GABA may cause muscle hyperactivity.³

In addition to neurological abnormalities, patients with SPS are frequently diagnosed with psychiatric disorders, such as depression, anxiety, and phobias.⁴ In 1 study⁵ including 43 patients with SPS, 44% of patients reported agoraphobia and other situation-specific phobias. Currently, pharmacologic management of comorbid psychiatric disorders in patients with SPS is not well defined. The aim of this case report is to review both the treatment of SPS in a patient with comorbid psychiatric disorders and the management of psychiatric disorders in a patient with SPS. Specific psychiatric disorders that are reviewed in this case report are bipolar I and panic disorder.

Case Report

The patient was a 58-year-old white female with past medical history significant for SPS, panic disorder with agoraphobia, bipolar I disorder, posttraumatic stress disorder, type 1 diabetes, hypothyroidism, and chronic leukemia. Within the year preceding the initial visit, she had fallen 5 times. Social history for this patient included both emotional and physical abuse. She reported smoking 1 pack of cigarettes per day starting at age 13 but quit smoking in 2011. The patient denied excessive use of caffeine or alcohol and denied any illicit substance use. The time between visits was approximately 1 month.

She presented to an outpatient behavioral health clinic for an initial appointment (Table) with the following medication regimen: valproic acid 1000 mg extended-release at bedtime for bipolar I disorder, clonazepam 0.5 mg twice daily as needed for panic disorder, insulin lispro 5 units 3 times daily before meals and insulin glargine 18 units at bedtime for type 1 diabetes, and levothyroxine 100 mcg daily for hypothyroidism (Table). The patient's primary concern for this visit was her SPS, which she believed was being exacerbated by her uncontrolled panic disorder and vice versa. During this visit, she described stiffening episodes during which she could not move her legs because they felt "too heavy" and was stuck midstride. The patient presented with tremors, stiffness, and jerking movements throughout her appointment. She used a quad cane and could walk steadily.

During the initial appointment, fluoxetine 10 mg daily and hydroxyzine 25 mg as needed were added to her medication regimen. During the second visit, she presented with less anxiety. Because the fluoxetine seemed to be improving symptoms related to mood and anxiety, it was increased to 20 mg daily. When the patient presented to the clinic on the following visit, she reported improved

sleep quality and a reduction in tremors. At this time, the fluoxetine dose was increased to 40 mg daily.

After the fluoxetine dose was increased to 40 mg daily, the patient reported an improvement in her symptoms related to anxiety, but she had been feeling more stiff and tremulous when attempting to eat. Clonazepam 0.5 mg twice daily as needed was changed to scheduled dosing for panic disorder and anxiety-triggered spasms. Prior to this change, the patient was utilizing 10 to 12 tablets of clonazepam 0.5 mg each month. At the following appointment, the patient reported that clonazepam was beneficial for morning stiffness and reducing panic symptoms that occur at the onset of stiffness. It was also reported that the patient seemed brighter and calmer with the increase in her fluoxetine dose to 40 mg daily. During the sixth visit, the patient stated, "I am doing the best on these medications, and they are working for me." She confirmed medication compliance and denied side effects. At the seventh visit, she endorsed to noncompliance with fluoxetine due to "feeling like a zombie" and hydroxyzine due to "funny feeling." She was taking less than 10 capsules of hydroxyzine each month prior to discontinuing both the hydroxyzine and the fluoxetine on her own. Propranolol 10 mg twice daily was added for tremors and high blood pressure; however, she self-discontinued due to edema. The patient reports reduced frequency of panic attacks and less anxiety and stiffness, which she attributes to unspecified diet changes.

Discussion

Although evidence is limited, previous case reports and studies have demonstrated the safe and effective use of antidepressant and anxiolytic medications in treating patients with SPS and comorbid bipolar and panic disorders. The initial regimen included 3 different classes of medications, which were intended to alleviate symptoms related to bipolar I and panic disorder. Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line treatment for panic disorder by the American Psychiatric Association and have also demonstrated efficacy for bipolar depression.^{6,7} The anxiety and depression symptoms in a patient with SPS may be a result of reduced or impaired GABAergic inhibition; however, in the case of our patient, the symptoms exist comorbidly.⁸ Our patient also exhibited a level of agoraphobia in the presence of her motor symptoms, which may have increased her risk of falls.⁵ Phobias may be managed with the use of benzodiazepines and SSRIs.⁹ Due to the rarity of SPS with comorbid bipolar and panic disorders, few studies have been published to support the use of antidepressants, particularly SSRIs, for symptom management. The efficacy of benzodiazepines in the treatment of SPS has been demonstrated in literature

TABLE: Timeline of patient’s clinical course

Visit No. ^a	Visit Summaries
1	<ul style="list-style-type: none">• Intake appointment• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID as needed• Number of PRNs used per month: 12 tablets of clonazepam 0.5 mg• Reported psychiatric symptoms: uncontrolled panic disorder, unspecified symptoms• Reported SPS symptoms: stiffening, unable to move legs, getting stuck midstride• Medication adjustments made: added fluoxetine 10 mg daily and hydroxyzine 25 mg PRN
2	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID as needed, fluoxetine 10 mg daily, hydroxyzine 25 mg PRN• Number of PRNs used per month: 10 tablets of clonazepam 0.5 mg, fewer than 10 capsules of hydroxyzine 25 mg• Reported psychiatric symptoms: improved mood and decreased anxiety• Reported SPS symptoms: none documented• Medication adjustments made: increased fluoxetine to 20 mg daily
3	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID as needed, fluoxetine 20 mg daily, hydroxyzine 25 mg PRN• Number of PRNs used per month: 10 tablets of clonazepam 0.5 mg, fewer than 10 capsules of hydroxyzine 25 mg• Reported psychiatric symptoms: improved sleep quality• Reported SPS symptoms: decreased tremulousness• Medication adjustments made: fluoxetine increased to 40 mg daily
4	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID as needed, fluoxetine 40 mg daily, hydroxyzine 25 mg PRN• Number of PRNs used per month: 10 tablets of clonazepam 0.5 mg, fewer than 10 capsules of hydroxyzine 25 mg• Reported psychiatric symptoms: decreased anxiety• Reported SPS symptoms: increased stiffness and tremor while eating• Medication adjustments made: clonazepam 0.5 mg BID PRN changed to BID scheduled
5	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID, fluoxetine 40 mg daily, hydroxyzine 25 mg PRN• Number of PRNs used per month: fewer than 10 capsules of hydroxyzine 25 mg• Reported psychiatric symptoms: decreased panic symptoms, patient appeared brighter and more calm• Reported SPS symptoms: decreased stiffness• Medication adjustments made: no medication changes
6	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID, fluoxetine 40 mg daily, hydroxyzine 25 mg PRN• Number of PRNs used per month: fewer than 10 capsules of hydroxyzine 25 mg• Reported psychiatric symptoms: patient reports, “I am doing the best on these medications and they are working for me.”• Reported SPS symptoms: none documented• Medication adjustments made: no medication changes

TABLE: Timeline of patient’s clinical course (continued)

Visit No. ^a	Visit Summaries
7	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID, fluoxetine 40 mg daily, hydroxyzine 25 mg PRN• Number of PRNs used per month: fewer than 10 capsules of hydroxyzine 25 mg• Reported psychiatric symptoms: patient reports “feeling like a zombie” and hydroxyzine making her “feel funny”• Reported SPS symptoms: none documented• Medication adjustments made: discontinued fluoxetine 40 mg daily and hydroxyzine 25 mg as needed by patient, added propranolol 10 mg BID for tremors
8	<ul style="list-style-type: none">• Currently prescribed medications: valproic acid 1000 mg HS, insulin lispro 5 units TID before meals, insulin glargine 18 units HS, levothyroxine 100 mcg daily, clonazepam 0.5 mg BID, propranolol 10 mg BID• Number of PRNs used per month: none• Reported psychiatric symptoms: less anxiety due to dietary changes• Reported SPS symptoms: less stiffness due to dietary changes• Medications adjustments: discontinued propranolol 10 mg BID due to edema

BID = twice daily; HS = bedtime; PRN = as needed; SPS = stiff-person syndrome; TID = three times daily.

^aThe time between visits was approximately 1 month.

with results similar to the outcome of this case.² The National Institute of Neurological Disorders and Stroke has conducted research related to SPS and has shown that patients with SPS respond to high doses of diazepam.¹⁰ Benzodiazepines enhance the GABA-inhibitory effect at receptors, alleviating muscle spasms and anxiety; this class is considered the first therapeutic option for SPS. The National Institute of Neurological Disorders and Stroke does not include any data or information regarding the treatment of patients with SPS and comorbid psychiatric illness.

Initially, fluoxetine and hydroxyzine were efficacious in the management of the patient’s SPS symptoms, panic disorder, and depressive symptoms related to bipolar I disorder. The gradual titration of fluoxetine was intended to avoid an increase in anxiety symptoms, which can be caused by the activating property of serotonergic agents.¹¹ Although the patient was prescribed fluoxetine 40 mg, she reported using clonazepam as needed more frequently due to the lack of full symptom management, which led to clonazepam 0.5 mg becoming scheduled twice daily. This could have been due to the delayed onset of action of SSRIs as these medications can take 4 to 8 weeks to reach their full potential.¹¹ Both fluoxetine and hydroxyzine were eventually discontinued from our patient’s medication regimen due to side effects, such as sedation, and lack of full symptom resolution.

A previous case report, completed by Culav-Sumić et al,⁸ included a patient with SPS and depressive symptoms that was initially treated with paroxetine. Despite an adequate duration of treatment and dose, the patient’s anxiety and depression symptoms worsened and eventu-

ally remained resistant to medication trials, including the high-dose diazepam regimen. Another study completed by Benavides et al¹² compiled 4 case reports, which highlighted the exacerbation of SPS symptoms related to the starting dose of serotonin-norepinephrine reuptake inhibitors. These patients reported “worsening spasms” and “mental fogging” despite the addition of supplemental treatment with benzodiazepines and intrathecal baclofen. Currently, there are no recommendations for the use of SSRIs or serotonin-norepinephrine reuptake inhibitors in patients with SPS. Based on evidence from previous studies and our case report, use of these medication classes seems controversial, and more studies are needed to assess their use in patients with SPS.

Anticipatory anxiety is common in patients with SPS, and frightening situations may precipitate stiffness and spasms leading to falls, which has been reported in this patient case.¹² Early recognition of stressors is essential in developing a strategy to effectively manage and reduce the risk of falls. A prior case report¹³ of a 51-year-old female with progressing SPS and generalized anxiety disorder has supported the hypothesis that the use of benzodiazepines is effective by enhancing GABAergic inhibitory transmission. Although there are confounding factors, it is thought that the increased frequency of clonazepam use in this patient resulted in improvement of the patient’s symptoms with less frequency of stiffness and anxiety. Clonazepam 2.5 to 6 mg is the most commonly used dose for patients with SPS symptoms overall.³

Throughout the patient’s treatment at the outpatient behavioral health clinic, the patient was followed by the

clinical pharmacists. Because SPS is a relatively rare condition, the clinical pharmacists were essential in researching pharmacologic treatment options for patients with SPS and comorbid psychiatric illnesses. As discussed in this case report, there is not a clear guideline on how to manage both SPS and psychiatric illnesses concurrently. The clinical pharmacists were able to use their clinical judgment to help the treatment team determine what medication changes should be made.

Conclusion

Our patient with SPS and comorbid bipolar and panic disorder benefited most from benzodiazepine therapy. The treatment regimen with an SSRI failed to adequately maintain the patient's symptoms and led to a need for increased frequency of benzodiazepine use. This anti-anxiety class of medication has shown in this patient to alleviate psychiatric symptoms associated with SPS although more studies are needed to define optimal management for a patient with SPS with comorbid bipolar and panic disorder. It is important for providers to discuss patient goals and expectations prior to, during, and at discontinuation of medication management. The role of a clinical pharmacist is essential in monitoring and managing patient history and management.

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