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SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS MAY EXACERBATE STIFF-PERSON SYNDROME

OPEN

Stiff-person syndrome (SPS) is a neuroimmunologic disorder characterized by painful spasms and muscle rigidity attributed to impaired inhibitory γ -aminobutyric acid (GABA) descending pathways.¹ The immunopathogenesis remains unknown and the pathogenic significance of antibodies against glutamic acid decarboxylase (GAD) is controversial. Herein, we report 4 cases of anti-GAD65-positive patients with SPS (table e-1 at Neurology.org/nn) who had significant worsening of symptoms and disability with the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine (table e-2). While causation cannot be proven, these observations suggest the importance of investigating the relationship between SNRI use and SPS clinical exacerbations (figure, A).

Case reports. *Case 1.* A 51-year-old woman with remote stroke developed gradual onset ataxia and frequent falls and required a cane to ambulate within 4 months of symptom onset (figure, B). Her symptoms failed to improve despite therapy with benzodiazepines, gabapentin, and tizanidine. She was prescribed duloxetine 30 mg daily for pain. Over the next 4 weeks, she developed worsening spasms and gait dysfunction, and required a walker to ambulate. Five months after symptom onset, elevated anti-GAD65 antibodies were detected in serum (11,350 U/mL). EMG was consistent with the diagnosis of SPS. Duloxetine was discontinued and she was treated with IV immunoglobulin (IVIg), benzodiazepines, and tizanidine, with marked improvement in symptoms. She remains stable on IVIg at 14 months.

Case 2. A 38-year-old woman with anti-GAD65-positive SPS, stable for 35 months with remote IVIg use, developed worsening hip pain and was prescribed duloxetine 30 mg daily (figure, B). Within 2 weeks, she had significant worsening in musculoskeletal symptoms and complained of mental fogging. She was treated with benzodiazepines and duloxetine was discontinued. She gradually improved to her

baseline over the course of 4 weeks and remains stable at 9 months.

Case 3. A 49-year-old woman with anxiety disorder and anti-GAD65-positive stiff-limb syndrome required intrathecal baclofen pump for symptom management (figure, B). After IVIg therapy and a period of relative clinical stability, she developed worsening anxiety and was prescribed duloxetine 30 mg daily. Within 1 week of starting duloxetine, she developed painful spasms in her torso and legs, dysphagia, and respiratory distress. She was hospitalized and intubated for airway protection. Her examination was most notable for downbeating nystagmus and severe torso and leg rigidity. Duloxetine was discontinued, and she was treated with IVIg and clinically improved; however, she developed several medical complications and has had a fluctuating clinical course.

Case 4. A 30-year-old man with diabetes, hypothyroidism, depression, and anti-GAD65-positive SPS developed worsening mood and pain (figure, B). Within 8 months of symptoms onset, he was treated with steroids and prescribed duloxetine 30 mg daily. He experienced severe painful spasms that were refractory to IVIg treatment over 18 months. Duloxetine was gradually titrated to 90 mg daily and within 1 month of this increase, he developed continuous severe painful torso spasms requiring hospitalization. He underwent plasmapheresis for acute SPS exacerbation with modest improvement. After discharge from the hospital, he discontinued duloxetine and noted a remarkable improvement of musculoskeletal symptoms. His pain reliever and benzodiazepine use also decreased. He was treated with rituximab for maintenance immunotherapy and remains neurologically stable.

Discussion. These 4 cases support a role for noradrenergic circuits in the clinical exacerbation of SPS (figure, A). Previous studies found that rapidly injected clomipramine severely aggravated clinical symptoms in a patient with SPS.² Clonidine, which is an α_2 adrenergic receptor agonist, was shown to improve SPS symptoms.^{2,3} Taken together, these results may point to a critical function of noradrenergic signaling in the pathophysiology of SPS.³ These findings may also account for the observation that stress and anxiety often precipitate SPS attacks.

Supplemental data at
Neurology.org/nn

(A) Proposed model of serotonin and norepinephrine in SPS. (B) Clinical course of serotonin-norepinephrine reuptake inhibitor (SNRI) use in patients. Clinical exacerbations noted with blue arrow. 5-HT = 5-hydroxytryptamine; IVIg = IV immunoglobulin; NE = norepinephrine; PLEX = plasmapheresis; SLS = stiff-limb syndrome; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Many patients with SPS have comorbid neuropsychiatric disorders, including anxiety and depression.¹ The clinical observations presented here suggest caution should be taken when considering use of SNRIs in the management of comorbid neuropsychiatric disorders or musculoskeletal discomfort in patients with SPS. As we cannot exclude chance association, further study is required to identify the causal relationship between SNRI use and SPS clinical exacerbations.

These cases suggest the importance of investigating the relationship between SNRIs and SPS in a prospective case-control study. Early recognition and a careful review of medication use may help prevent disease exacerbations in SPS.

Notably, serum autoantibody testing was otherwise negative in all patients. Anti-GAD antibodies are associated with reduced GABA levels^{4,5} and appear to be associated with clinical symptoms of

SPS when passively transferred into animal models.⁶ However, the pathogenicity of anti-GAD antibodies remains controversial. Autoantibodies to multiple antigens have been described in patients with SPS spectrum disorders.⁷ Further investigation is required into the role of antibodies to various other antigens in SPS spectrum disorders.

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CORRECTION

Serotonin-norepinephrine reuptake inhibitors may exacerbate stiff-person syndrome

In the Clinical/Scientific Note "Serotonin-norepinephrine reuptake inhibitors may exacerbate stiff-person syndrome," by D.R. Benavides and S.D. Newsome,¹ there is an omission in the figure. In panel C, the x-axis label under Cases 1-3 should read "Time from SNRI (weeks)." The authors regret the error.

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1. Benavides DR, Newsome SD. Serotonin-norepinephrine reuptake inhibitors may exacerbate stiff-person syndrome. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e281. doi: 10.1212/NXI.0000000000000281.