Buspirone as an Antidote to SSRI-Induced Bruxism in 4 Cases

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Background: One hypothesis to explain selective serotonin reuptake inhibitor (SSRI)-induced bruxism states that SSRIs increase extrapyramidal serotonin levels, thereby inhibiting dopaminergic pathways controlling movement. Previous reports have emphasized buspirone's postsynaptic dopaminergic effect as a partial antidote to the suppressed dopamine levels.

Case Reports: Four patients, recently started on treatment with the SSRI sertraline, presented with new-onset complaints attributable to SSRI-induced bruxism. All 4 responded to adjunctive buspirone, a serotonin-1A ($5\text{-}HT_{1A}$) receptor agonist, with relief of bruxism and associated symptoms.

Discussion: We expand the hypothesis put forth in previous reports by proposing that buspirone is not only acting postsynaptically in the extrapyramidal system, but also presynaptically on serotonergic neurons that influence masticatory modulation in the mesocortical tract. Our 4 cases support the concept of buspirone acting as a full agonist at the presynaptic $5\text{-}HT_{1A}$ somatodendritic receptors located on the cell bodies of raphe serotonergic neurons that project to the ventral tegmental area (VTA) of the midbrain. These serotonergic neurons modulate the firing of the mesocortical tract, which itself projects from the VTA to the prefrontal cortex and acts on masticatory muscle activity through inhibiting spontaneous movements such as bruxism. While the literature is confusing and contradictory on definitions of bruxism and etiologies of incompletely understood movement disorders, we believe SSRI-induced bruxism is best conceptualized as a form of akathisia.

(J Clin Psychiatry 1999;60:857–860)

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Three recent reports have linked selective serotonin reuptake inhibitors (SSRIs) and bruxism. Ellison and Stanziani[1] described 4 similar cases, 3 associated with fluoxetine and 1 with sertraline; all 4 involved nocturnal bruxism only. They reported that 3 of their 4 cases responded to buspirone, an effect they attributed to "buspirone's dopaminergic effect counteract[ing] SSRI-induced inhibition of extrapyramidal dopaminergic pathways."[1(p433)] The fourth patient's bruxism remitted simply by SSRI dose reduction. Likewise, Romanelli and colleagues[2] contributed the case of a woman, recently started on paroxetine treatment, who developed new-onset gritting, tooth pain, jaw tenderness, and dental findings consistent with bruxism. A nightly buspirone dose relieved her symptoms.[2]

Fitzgerald and Healy[3] offered 6 more cases that, unlike Ellison and Stanziani's[1] neat series and Romanelli's clean case,[2] illustrate the multiple confounds that bedevil efforts to make sense of the bruxism-SSRI phenomenon. Four of their 6 patients had had neuroleptic exposure, either currently or historically. All 4 of the neuroleptic patients had buspirone trials, only 1 of any benefit. Of the 2 patients taking SSRIs only, 1 had been given buspirone without effect. Five of the 6 cases had both diurnal and nocturnal bruxing symptoms, including both grinding and clenching, and only 1 described pure nocturnal bruxism. Fitzgerald and Healy's series,[3] as well as a richly detailed but inconclusive dental literature, reminds us that bruxism is a nonspecific term for numerous entities with multiple potential etiologies, most of which have a dopamine imbalance in common. Any consideration of idiopathic bruxism, however, must distinguish between cases of "peripheral" bruxism due to malocclusion and "central" bruxism resulting from neurotransmitter perturbations. These 2 broad entities would not be expected to respond similarly to pharmacologic maneuvers.

Central bruxism occurs in 2 polar opposite situations. Examples of hyperdopaminergic states are those induced by amphetamines and L-dopa, which elevate dopamine levels in the striatum and induce exaggeration of normal functioning manifested in the jaw muscles as tooth-grinding.[3,4] Relative hyperdopaminergic states also occur in the presence of cholinergic hypofunction.[5] The dopamine receptor hypersensitivity postulated to result from long-term neuroleptic exposure can also cause mastica-

tory muscle hyperactivity, characteristically manifested in the tooth-grinding of facial dyskinesias including tardive dyskinesia.[6,7] In these states, dopamine agonists and cholinergic antagonists aggravate symptoms, while dopamine depleters improve them.[5,8]

The clenching movements of dystonias, on the other hand, are hypothesized to result from hypodopaminergic states encountered in extrapyramidal system dysfunction.[2,3,9] Serotonin is believed to exert a modulatory influence on dopamine, the prime neurotransmitter in motor activity. Movement disorders very likely result when SSRI-enhanced serotonin (5-HT) levels reduce dopaminergic activity in either the mesocortical or nigrostriatal tracts.[10] Akathisia induced by both SSRIs and neuroleptics (through different mechanisms) is purported to be a "syndrome of dopamine deficiency."[9(p342)]

The proximity of the symptoms to SSRI treatment distinguishes the 4 cases reported here, rather than the nocturnal or diurnal nature of the bruxism (only 1 of the 4 cases was nocturnal). These are primarily "clean" cases; that is, the first 3 of our patients had no prior neuroleptic exposure, and the fourth had remote low-dose exposure only. We will make the case that Ellison and Stanziani's[1] explanation for buspirone's effectiveness—its mild postsynaptic dopaminergic activity—is a partial and incomplete explanation of how this compound works both presynaptically and postsynaptically to combat SSRI-induced hypodopaminergic function. We propose that a complete explanation lies in SSRI interference with mesocortical tract modulatory function.

CASE REPORTS

Case 1

Mr. A, a 35-year-old schoolteacher with a strong family history of depression and suicide, had presented with depressive and obsessional symptoms that remitted with sertraline, 100 mg/day. Along with the benefits, however, came new-onset bitemporal headaches within weeks of starting treatment that did not respond to aspirin and which he could not correlate with any particular stressors. He also noted an irritating symptom: "I'm clenching my masseter all the time." Bruxism, diurnal and possibly nocturnal, was diagnosed, and buspirone, 10 mg b.i.d., added. When Mr. A returned 1 month later, he reported that his jaws no longer clenched and that his headaches had dramatically reduced in both frequency and intensity.

Case 2

Ms. B, a 61-year-old housewife with no previous psychiatric history, was started on sertraline treatment, 100 mg daily, in the context of a recent cancer diagnosis. Sertraline dispelled her depressed mood, but induced intermittent anxiety that responded to alprazolam, 0.25 mg p.r.n. Her only remaining complaint was nocturnal bruxing that started in her first month on sertraline treatment. "I'm doing so much damage to my teeth from clenching during sleep," she reported. She had cracked 2 crowns and awoke each morning with sore jaws and teeth. Within a week of adding buspirone, 10 mg p.o. b.i.d., she reported a decrease in clenching. She also felt less anxious and no longer required p.r.n. alprazolam.

Case 3

Ms. C, a 38-year-old graduate student, had experienced many years of low mood, irritability, and poor sleep before starting sertraline, 150 mg daily, which raised her mood and reduced her irritability. She quickly became tolerant to temazepam, 30 mg, prescribed for sleep, and she also complained of "night-and-day jaw-clenching" that began in the first month of taking sertraline. After 3 weeks of adjunctive buspirone, 10 mg t.i.d., she reported that the clenching had completely remitted. Additional unanticipated benefits included reduced anxiety and better sleep. Of her sleep, she said, "it's still not great, but I need less of it."

Case 4

Ms. D, a 32-year-old mother of 3 young children, experienced a severe postpartum depression that responded to 100 mg/day of sertraline except for the unfortunate side effects of jaw tightness and an unremitting constriction-band headache that began within the first week of treatment and worsened as the sertraline dose was increased. The jaw tension and headache only gradually responded to adjunctive buspirone. The patient did not achieve full relief until her dose reached a total of 50 mg/day after a month of titrating it upward. After 2 months, she was able to taper the buspirone without recurrence of either bruxism or headaches.

DISCUSSION

Keeping in mind both that "most cerebral functions are the result of the converging actions of many different neurotransmitters"[11(p38)] and that simple explanations are hence likely to be simplistic, a convincing line of evidence nonetheless suggests a prominent role for serotonergic modulation of the dopaminergic neurons that directly control masticatory muscle motor activity. The neuroanatomy of masticatory modulation involves a 2-neuron chain. Serotonergic neurons with cell bodies in the midbrain raphe nucleus project to the ventral tegmental area (VTA) of the midbrain, where they synapse with the cell bodies of dopaminergic neurons that project to prefrontal cortex via the mesocortical tract.[12–14]

Within the mesocortical tract, dopamine serves to inhibit spontaneous movement.[15,16] As dopamine decreases in this tract, disinhibition increases, with movement released in the form of the characteristic repetitive muscle

contractions of bruxism.[16,17] While SSRIs alter dopamine levels in multiple central nervous system (CNS) tracts, the most sensitive and the first affected is the mesocortical dopamine tract, with the absence of dopaminergic autoreceptors possibly explaining its heightened sensitivity to serotonin's presynaptic antidopaminergic modulation.[9,18] We postulate that the mesocortical disinhibition takes the form of akathisia in general, with SSRI-induced bruxism as a specific form of akathisia.[9,16]

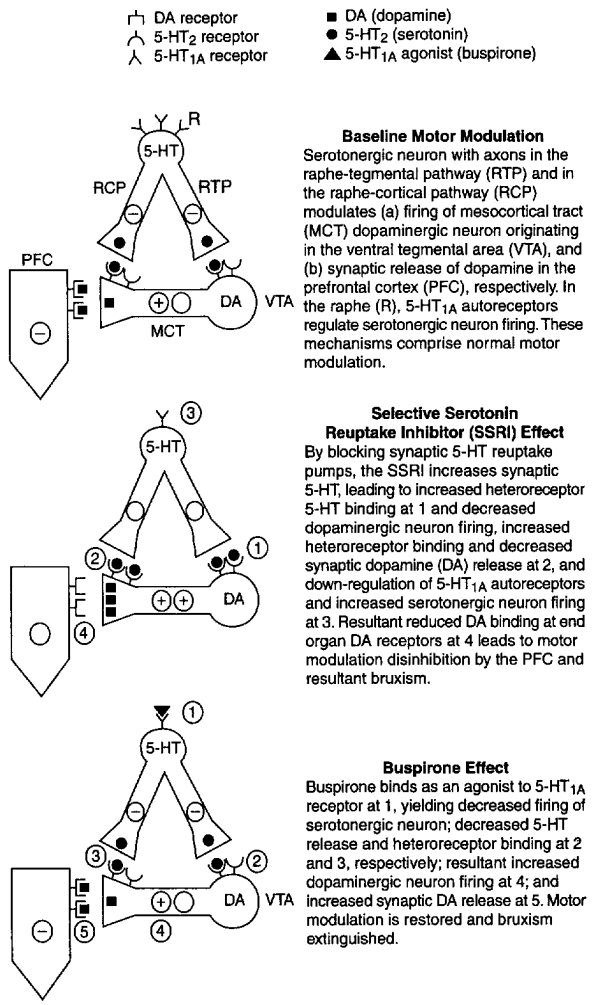
Complicating the neuroanatomical picture is the differential distribution of more than a dozen serotonin receptor subtypes, some of which activate and others of which inhibit neurons with which they are associated.[11] Agonists on both 5-HT_1 and 5-HT_3 receptors, including 5-HT_{1A} receptors, facilitate dopamine release, while agonists on 5-HT_2 receptors inhibit it.[14,19] Some of these serotonin receptors are autoreceptors; others are heteroreceptors. When receptors on a neuron bind the same transmitter that the neuron synthesizes, they are considered to be autoreceptors. When receptors bind a different neurotransmitter than that neuron synthesizes, they are designated heteroreceptors.[20]

We hypothesize that the disruption in SSRI-induced bruxism originates almost exclusively in the serotonergic neurons that project from the raphe to the VTA[12,21] and preferentially contain the 5-HT receptors that maintain "a tonic inhibitory influence on mesocortical dopamine function."[14(p729)] Presynaptically, the raphe neuron cell bodies have axons that synapse in the VTA with mesocortical tract dopamine neurons. These dopamine neurons contain both 5-HT_2 and 5-HT_{1A} heteroreceptors whose effects on the neuron oppose one another. When occupied by serotonin, the 5-HT_2 heteroreceptors at the dopamine cell body decrease the firing of the neuron, while at the same time, those at the synapse serve to down-regulate synaptic dopamine release.[9,13]

While a consequence of suppressed mesocortical tract dopamine levels is a disinhibition of movement, patients may complain of headaches or broken teeth without mentioning—or even noticing—the underlying causative SSRI-induced masseter hyperactivity.[8] Nonspecific headache is a common SSRI side effect. What distinguishes the headaches of Mr. A, however, were their new onset and specific location bitemporally at the masseter insertion. Ms. B at first reported only broken crowns, a new phenomenon for her, revealing sore jaws and nocturnal clenching only after additional questioning.

How, then, did buspirone relieve SSRI-induced extrapyramidal symptoms of dopamine insufficiency in these 4 cases? Buspirone acts primarily on 5-HT_{1A} receptors, found both presynaptically and postsynaptically,[22–24] and has different actions at postsynaptic and presynaptic sites. Postsynaptically, it acts as a partial agonist/antagonist, competing successfully with serotonin for 5-HT_{1A} binding sites.[25,26] Binding less effectively than serotonin and thus

Figure 1. Buspirone's Effect on Mesocortical Motor Modulation



having less intrinsic activity, buspirone causes reduced serotonergic activity compared with serotonin and hence enhanced dopaminergic activity. This is the explanation to which Ellison and Stanziani[1] attribute buspirone's efficacy against bruxism, an explanation that seems incomplete in that it does not include buspirone's robust presynaptic effect.

Presynaptically, buspirone binds as a full agonist to 5-HT_{1A} autoreceptors, yielding decreased firing of the raphe serotonergic neuron and resultant decreased serotonin inhibition of both mesocortical neuron firing and synaptic dopamine release.[22,26] Dopamine levels rise, and the mesocortical tract resumes its dopamine-mediated inhibition of spontaneous movements (Figure 1). An alternate strategy might be to switch from an SSRI to mirtazapine or nefazodone, both of which have 5-HT_2 antagonist activity. 5-HT_2 blockade would theoretically result in less inhibition of the VTA dopaminergic neurons and hence

less interference with mesocortical tract dopamine release. Goldstein and colleagues[27] demonstrated this effect with ritanserin, altanserin, and other 5-HT_2 antagonists.

As dopamine levels decrease further in response to SSRIs, the less sensitive nigrostriatal tract may begin to malfunction. Direct effects such as dystonia or parkinsonism may result and can accompany indirect effects on motor function manifested as akathisia. Differential effects of dopamine reduction on both mesocortical and nigrostriatal tracts can account for case reports of patients with both akathisia and parkinsonism.[9]

In summary, these 4 cases indicate that SSRI-induced bruxism most likely represents a variant of akathisia. Clinically, this series highlights (1) the need to ask about symptoms related to masseter-clenching in patients newly started on SSRIs; (2) the value of careful psychopharmacologic detective work with headache or dental complaints that may result from new-onset, unrecognized bruxism; and (3) the potential efficacy of a buspirone trial in ameliorating these symptoms. Larger clinical trials are indicated to confirm the value of buspirone in relieving SSRI-induced bruxism.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), temazepam (Restoril and others).

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