Case Report

Trazodone-related oromandibular dyskinesia

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Abstract

This is a report of a series of three cases of trazodone-induced oral lingual dyskinesias. Each case demonstrated a distinct pattern of the development of this dyskinesia after trazodone exposure for several months. All cases showed abrupt cessation of the movement disorder when the drug was discontinued. Two of the three cases had no prior exposure to any dopamine-blocking agents. One of the three had a distant exposure to a dopamine antagonist. Trazodone has a mechanism of action that can account for both the development and treatment of dyskinetic movements. This article will discuss proposed mechanisms for trazodone's action with an emphasis on case reports of dystonic movements being more prevalent in the elderly.

Keywords: Dyskinesia, oromandibular, trazodone

Case Reports

1. This 69-year-old male was diagnosed with generalized anxiety disorder and longstanding sleep onset difficulties which were initially thought to be a function of anxiety. Starting some five years ago the patient began to complain of severe difficulty in both sleep onset and sleep maintenance. Intercurrent trials of eszopiclone and suvorexant were attempted and found to be ineffective. Approximately four years ago trazodone was initiated at 100mg, which the patient initially found helpful for sleep maintenance. After some eight months, the dose was lowered to 50mg. Concurrently, he was successfully treated with escitalopram 10mg (for approximately 15 years) for generalized anxiety. Although his Epworth score was only 3, polysomnography showed the patient to have severe obstructive sleep apnea with an apnea/hypopnea index of 32 and oxygen nadir of 81%.

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At the fourth year of trazodone exposure, the patient manifested a buccal dyskinesia noted as lip puckering at three-second intervals. The patient himself had no awareness of this movement, although it disturbed his family. He had no prior exposure to antipsychotics, metoclopramide, lithium, or antidepressants other than listed. Initially, an association was made between the dyskinesia and escitalopram. Based on this, the escitalopram was tapered and discontinued. This led to a significant relapse of anxiety, but no change in the buccal movements. Subsequently, trazodone was discontinued. The Abnormal Involuntary Movement Scale (AIMS)[1] rating was 6, dropping down to 2 post-discontinuation. A titration of trazodone showed a near remission of the buccal dyskinesia with occasional (one per minute) movements.

2. This is a 64-year-old female with a history of recurrent major depression and later alcohol and nicotine use disorders of approximately three years' duration. The patient was originally treated for ten years with paroxetine followed by a period of nonresponsiveness which necessitated a switch of therapies to bupropion XL for one year, desvenlafaxine for three months, citalopram for four years, and ultimately sertraline for eight years to present. Augmentation of sertraline occurred with low-dose aripiprazole of 2–5mg. No abnormal movements were detected during the phase of exposure to aripiprazole or for the year after discontinuation. Post all discontinuation of

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alcohol, the patient was placed on trazodone 50mg for sleep disruption. Two months later, a lingual dyskinesia emerged. The patient's AIMS rating went from 5 during exposure to trazodone to zero after trazodone cessation. It was felt that there was no association between prior dopamine antagonist exposure and the development of the movement disorder.

3. This 37-year-old married female originally presented with major depression and obsessive-compulsive disorder of mild intensity. The patient had an initial eight years of exposure to citalopram followed by three years of sertraline. Her course was complicated by the diagnosis of chronic fatigue syndrome around the age of 36. Due to problems with sleep fragmentation, trazodone was employed for sleep management at 50mg for 2 months. The patient herself noticed the emergence of the lingual dyskinesia manifested by tongue protrusion multiple times per minute, which she found quite distressing. She had no intercurrent exposure to dopamine agonists or antagonists. Her AIMS rating was 5 at this point, but after withdrawal from trazodone returned to her baseline of zero.

Discussion

Tardive symptoms are usually associated with chronic use of dopamine-blocking agents. Oromandibular dyskinesias (OMD) can be acquired, inherited, or idiopathic in nature.[2,3] They are noted to be related to increasing age as well as mass lesions in the CNS, arteriovenous malformations, toxins, or hemorrhagic injury. Oromandibular dyskinesias can be either acute or chronic, often dependent upon the length of exposure to an offending agent as well as the patient's age. These types of extrapyramidal movements have been seen with many serotonin reuptake inhibitor medications but at a very low prevalence rate.[4]

Tardive dyskinesia refers to late-onset abnormal involuntary movements that are purposeless in nature. These most often affect the tongue, mouth, face, and limbs. Most classically, the disorder is thought to be associated with antipsychotic exposure for at least three continuous months with prevalence rates as high as 30%.[5,6]

Trazodone is a triazolopyridine 5HT2A and 5HT2C receptor antagonist class of antidepressant. Its off-label uses have included treatment of insomnia, delirium, and dystonias. It was introduced in the United States in 1978 and is considered to be low in anticholinergic properties with limited effect on cardiac induction.[7] It is greater than 90% protein bound, extensively metabolized by the 3A4 hepatic enzymatic system and is 75% excreted through urine. Its metabolite m-chlorophenylpiperazine (MCPP) has a ½ life of 4–14 hours with no significant affinity for dopaminergic receptors. However, MCPP is known to be a serotonin agonist. There are several models suggesting that trazodone use could result in the development of oromandibular dyskinesias. A number of studies including one conducted in rat models suggest that trazodone can, in fact, block post-synaptic striatal dopamine receptors. This previously undiscussed aspect of the drug may account for its capacity to develop tardive dyskinesia.[8-10]

Another emerging theory is that it may trigger extrapyramidal systems through inhibitory action on T-type calcium channels in the subthalamic nucleus, an effect seen in first-generation antipsychotics.[11] It may also be the case that 5HT2A receptor polymorphisms determine susceptibility to dyskinesias/dystonias with this agent, an effect that may be more prominent in the older population.[12] Curiously, case reports have suggested that trazodone can be used successfully to treat both tardive dyskinesia and akathisia produced by antipsychotics.[13,14] In this case series, two of the three patients were in their 60's which raises the question of whether older individuals who are somewhat more prone to age-related dyskinesias are at greater risk for their development after treatment with trazodone.

Conclusion

Many antidepressants have been associated with the development of tardive syndromes, although attention is most commonly focused on exposure to first- and second-generation antipsychotics due to their known D2 blocking activity. In reality, tardive dyskinesia is undoubtedly more multifactorial in nature. Trazodone has been commonly thought of as a benign agent used in both younger and older individuals in multiple off-label applications, most prominently for sleep induction and maintenance. Several case reports over the years, however, suggest that, especially in the older population, more consideration should be given to the chronic use of trazodone due to its capacity to induce oromandibular dyskinesias.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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