Is Sleep Apnea the Missing Link in Escalating Tardive Dyskinesia?

Case Reports

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ABSTRACT

Tardive Dyskinesia (TD) is a potentially irreversible movement disorder that has been documented to occur from extended exposure to antipsychotic medications (1). Sleep Apnea is a condition of disordered breathing leading to repeated sleep interruptions. This potentially life-threatening condition has been associated with other comorbidities including cardiovascular disease, obesity, and diabetes (2). Current literature linking sleep apnea to an increased risk of developing tardive dyskinesia is lacking. This article will review three case studies that bring awareness to a potential link between sleep apnea and the development of TD in patients treated with antipsychotic medications. It will also discuss the importance of screening for and treating sleep apnea in behavioral health patients. Also The cases demonstrates a clear temporal association between untreated severe OSA and worsening of TD symptoms, with significant improvement achieved through OSA treatment. It strongly suggests that OSA can be a potent exacerbating factor for TD. Clinicians should maintain a high index of suspicion for OSA in TD patients, especially those reporting symptom fluctuation worse in the mornings or refractory to standard interventions. Systematic screening for and treatment of OSA should be incorporated into the comprehensive care plan for individuals with TD.

Key Words: Antipsychotic adverse reaction, pharmacogenomics, sleep apnea, tardive dyskinesia.

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BACKGROUND

Tardive Dyskinesia (TD) is a potentially irreversible disorder characterized by involuntary hyperkinetic movements. TD is typically caused by prolonged exposure to antipsychotic medications. The movements may impact muscles of the face, lips, tongue, cheeks, jaw, and extremities. Severity can range from mild causing no patient distress to severe and disabling[1,2]. Exact etiology of TD is not clearly understood; however, it is believed that after chronic dopamine blockade there is an upregulation of postsynaptic dopamine receptors as well as neuronal oxidative damage[3]. Potential variables that increase the risk of developing TD have been identified and include variations of medication metabolization (specifically CYP2D6 activity)[4], head injury, female gender, preexisting movement disorders, and advanced age[3]. While it has been previously thought that newer atypical antipsychotic agents were less likely to cause TD the potential is still present particularly when there are co-existing risk factors. While many of the risk factors associated with higher prevalence of developing TD are not modifiable, the selection of the antipsychotic used is. Medication metabolization is a variable that may be considered in lowering a patient's risk for developing TD if pharmacokinetic considerations are known prior to the selection of the antipsychotic. CYP2D6 is believed to play a role in the metabolization of approximately 25% of prescription medications along with almost every atypical antipsychotic agent[4]. When pharmacogenomic testing is utilized, clinicians are provided with CYP2D6 and other pharmacokinetic considerations. This aids in individualizing pharmacotherapy specific to their patient's genetic variation in metabolization of medications which could potentially reduce their risk of adverse reactions including TD.

Sleep apnea occurring in patients with psychiatric disorders is well established and multi-factorial. Various sources attempt to discuss the link between atypical antipsychotic use and sleep apnea with some suggesting there is a weight-independent association between the two[5]. It has been discussed that use of an atypical antipsychotic induces sleep apnea without notable change to a person's physical characteristics. There has been reports that (obstructive) sleep apnea may induce oxidative stress, systemic inflammation, and sympathetic activation[6]. In another study it was concluded that "the anterior to mid-insular cortex shows lower GABA and higher glutamate levels in OSA compared with health subjects[7]." It has been established that both GABA and glutamate play an important role in dopaminergic

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activity and that dopaminergic changes and oxidative stress are linked to development of TD[8]. Inhibition of D2 presynaptic receptors increases release of dopamine. The excess dopamine can lead to more free intracellular dopamine which can then cause neuronal damage from the oxygen radical formation leading to the development of TD[8]. "Glutamatergic projections to the midbrain play a major role in regulating activity of mesostriatal dopamine neurons. Direct pathways from the prefrontal cortex to the midbrain have an excitatory influence and enhance dopamine release, whereas indirect pathways involving GABAergic interneurons have the opposite effect[9]." Prescribers may not be able to identify if a patient first had TD or OSA, or if the antipsychotic exposure alone led to the development of TD. However, the previous discussion describing the cascade of intracellular events and neuronal damage supports considering OSA testing for patients taking antipsychotics.

CASE PRESENTATIONS

Case one is a 21-year-old Caucasian female. Diagnoses include autism spectrum disorder, nightmares, insomnia, sleep apnea, tardive dyskinesia, and bipolar 1 disorder. She was prescribed quetiapine 150mg/daily for several years, this agent was discontinued and replaced with cariprazine 1.5mg/daily in February 2021. Previous medications include buspirone, methylphenidate, and sertraline. Current medications are cariprazine 1.5mg daily, trazodone 150mg nightly, and prazosin 1mg nightly. Pharmacogenomic testing reveals that she is a cyp2d6 poor metabolizer which does not change dosing recommendations for use of cariprazine. Quetiapine has clinical considerations cautioning dose as serum level may be elevated in patients with poor cyp2d6 metabolization, thus lower dosing is recommended. Records indicate quetiapine dosing did not exceed 150mg daily. Involuntary movements of the mouth were first observed March of 2024 with abnormal involuntary movements scale (AIMS) score of 5. Valbenazine 40mg daily was initiated in March of 2024. In April 2024 AIMS score was reduced to 0, with no remaining abnormal movements observed or reported. Sleep apnea, both obstructive and central, was diagnosed June 2024 with an apnea-hypopnea index (AHI) of 31.

Case two is a 65-year-old Caucasian male. His diagnoses include major depression disorder, anxiety, hypertension, coronary artery disease, hyperlipidemia, sleep apnea, and tardive dyskinesia. He has previously taken cariprazine, quetiapine, brexiprazole, aripiprazole, levomilnacipran, bupropion, and trazodone. Current medications include deutrabenazine XR 24mg daily, dextromethorphan-bupropion 45-105mg twice daily, mirtazapine 30mg nightly, desvenlafaxine 50mg daily, atorvastatin 80mg daily, carvedilol 25mg daily, isosorbide mononitrate 30mg daily, melatonin 5mg nightly. Pharmacogenomic testing revealed cyp2d6 poor metabolization indicating FDA label identifying potential gene-drug interaction for the antipsychotic agents aripiprazole and brexiprazole. Involuntary movements of the face were first identified by family and friends of the patient in December 2023. Patient had an abnormal involuntary movements score (AIMS) of 11 January 2024. Deutrabenazine was initiated in January and his AIMS reduced to 8 by April 2024 and then further reduced to 0 by June of 2024 despite not using the prescribed continuous positive airway pressure (CPAP) device. Sleep apnea was diagnosed in January 2024, with AHI of 49.

Case three is a 52-year-old Caucasian male. His diagnoses include bipolar 2 disorder, history of traumatic brain injury, sleep apnea, hyperlipidemia, atrial fibrillation, hypertension, history of myocardial infarction, tardive dyskinesia, and monoclonal gammopathy of unknown significance. He has previously taken desvenlafaxine, brexiprazole, lamotrigine, quetiapine, aripiprazole, duloxetine, fluoxetine. Current medications include valbenazine 80mg daily, desvenlafaxine 25mg daily, lamotrigine 200mg twice daily, amantadine 100mg three times daily, gabapentin 100mg three times daily prn, famotidine 40mg daily, solriamfetol 150mg daily, lumateperone 42mg daily, levomefolate calcium 7.5mg daily, sotalol 80mg twice daily, atorvastatin 80mg nightly, nitrogylcerin 0.4mg prn, fluticasone propionate 50mcg/actuation 2 sprays each nostril daily, metoprolol tartrate 75mg daily, aspirin 81mg daily, lisinopril 10mg daily, melatonin 10mg nightly, Repatha SureClick 140mg/mL administer 1mL under the skin every 14 days. Pharmacogenomic testing shows cyp2d6 extensive (normal) metabolization, there are no identified pharmacokinetic gene considerations regarding previous or current antipsychotic medications. He was diagnosed with sleep apnea in 2019 with AHI of 27. Documentation shows tardive dyskinesia was diagnosed in 2020 by a neurologist with AIMS score of 23 documented in March of 2022. Valbenazine was initiated February 2021 at 40mg day, but there are documented lapses in compliance for various reasons. After valbenazine was increased to 80mg day AIMS score reduced over time with lowest documented AIMS score of 3 in May of 2024. Documentation supports that he did treat OSA from time of diagnosis using continuous positive airway pressure (CPAP) until he obtained INSPIRE in October of 2023.

DISCUSSION

Tardive Dyskinesia (TD) results from damage to the brain thought to be from oxidation of dopamine in dopaminergic neurons and oxygen radicals that damage other neurons[8]. The intermittent hypoxemia that occurs with sleep apnea causes neuroinflammation and neurotoxicity[10]. When combining antipsychotic medications that block presynaptic D2 receptors leading to neuronal damage with the injury that occurs from sleep apnea a patient may have increased risk of developing tardive dyskinesia. The case studies presented support this theory as they do not all share other known risk factors for the development of tardive dyskinesia. They differ in their diagnoses, antipsychotic agents used, age, gender, and

differing cytochrome P450 2D6 metabolization. These case studies support the significance in screening and identifying sleep apnea in patients taking antipsychotic medications. Sleep apnea may increase the risk of antipsychotic side effects including TD, but may also play a role in other outcomes for mental health patients. Patients with sleep apnea may suffer with more severe psychiatric symptoms including suicidality with research supporting sleep apnea may be an independent risk factor for the development of psychiatric conditions[11]. In conclusion, prescribers initiating and managing antipsychotic medications for their patients should be aware of the potential overlap and shared symptoms that occur in sleep apnea and psychiatric disorders with a goal to reduce adverse reactions, improve outcomes, and enhance quality of life for their patients.

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