Atomoxetine-Induced Vocal Tics in a Patient With Schizophrenia

To the Editor: Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter (NET) and has minimal affinity for other neurotransmitter transporters and neuronal receptors. As per currently available evidence, atomoxetine has demonstrated efficacy in improving attention-deficit hyperactivity disorder (ADHD) symptoms in children with comorbid tics and has also significantly improved comorbid tic symptoms.[1] Hence, it has been considered as an appropriate choice in patients with ADHD and comorbid tics, or with a history of possible medication-induced tics.

However, here have been a few reports of atomoxetine-induced tics[2–5] when used in children with ADHD.

Atomoxetine, through its mechanism of being an NET inhibitor, may selectively increase dopamine (DA) in the prefrontal cortex (PFC) while not increasing DA in subcortical areas. Accordingly, since persons with schizophrenia are thought to have a deficit of DA in the PFC, and excessive subcortical DA function, an NET inhibitor such as atomoxetine may increase DA-dependent, PFC-mediated neurocognitive functioning and reduce negative symptoms associated with this disorder without worsening the positive symptoms of schizophrenia.[6] Hence, there is a rationale and some preliminary evidence for its possible use in schizophrenia.

Case Report

A 17-year-old, single young man, temperamentally "slow to warm up," was initially noticed at age 15 to show decline in his academic performance and become socially withdrawn. Gradually, he was observed to have delusions of persecution and 2nd- and 3rd-person auditory hallucinations, in the absence of any previous medical or psychiatric history. The psychotic symptoms improved with olanzapine 10mg/day. This was reduced to 7.5 mg because of excessive sedation. The patient continued to report impairment in attention, concentration, and overall difficulty in studies, due to which academic decline continued. Because of persistent reports of difficulty in attention and concentration, a neuropsychological evaluation of his cognitive abilities was done. This showed inadequacy in motor speed, mental speed, visuo-spatial memory, working memory, verbal memory, set-shifting, and concept-formation. An impression of frontal and bitemporal involvement was made. The patient was started on atomoxetine 10 mg with the aim of reducing his cognitive impairment and enhancing subsequent overall functioning. One month after atomoxetine was started, he was noted to be producing ticking sounds from his throat. The frequency of these sounds, which were initially not noticed by the family, gradually began to increase over the next few months. These would occur numerous times throughout the day, but were absent during sleep. At consultation, a detailed physical examination revealed repeated ticking sounds from the throat, which patient would try to suppress by drinking water and swallowing repeatedly, but he was only partially successful. No other involuntary movements or coprolalia were observed. A complete hemogram and routine biochemical investigations, including blood sugars, renal, liver, and thyroid functions, were within normal limits. An impression of "vocal tics" was made. Since the onset of the vocal tics had begun after the start of atomoxetine therapy, a suspicion of atomoxetine-induced tics was noted, and a decision to stop atomoxetine was made. Within 5 days of stopping atomoxetine, the sounds from the throat subsided and stopped. The patient continues to remain symptom-free after more than 3 months of atomoxetine discontinuation. He has been advised to undergo cognitive remediation training to handle the cognitive deficits.

Discussion

The animal models of noradrenergic dysfunction have shown deficits in sustained attention and shifting attention, which are also known to exist in schizophrenia, and these deficits were shown to be reversed by drugs that improve noradrenergic transmission.[7] Atomoxetine has been known to increase the concentration of extracellular norepinephrine and dopamine threefold in the prefrontal cortex (PFC) by blocking the NET, where it has been shown that DA is predominately taken up nonselectively by NET. It does not increase extracellular dopamine or other monoamine concentrations in the subcortical areas.[6]

In adults with ADHD, there is some evidence that atomoxetine improves response inhibition[8] and executive functioning.[9] Because of the mechanism of selective increase of dopamine in the PFC and widespread increase of NE, it has been theorized that atomoxetine might also have a role in enhancement of cognitive functioning in patients with schizophrenia. There have been a few

studies with conflicting results on cognitive-function improvement with atomoxetine. In two double-blind, placebo-controlled studies, no improvement in overall cognition as compared with placebo was noted in schizophrenia patients,[10,11] but, in one study, the atomoxetine group showed significantly greater increase in working memory-related activation in the left dorsolateral prefrontal cortex.[11]

There have been a few reports of atomoxetine-induced tics[2–5] when used in children with ADHD. Many had a history of medication-induced tics; also, the possibility of comorbid Tourette's disorder in ADHD has to be considered. In this case, use of the adverse drug reaction probability scale by Naranjo et al.[12] (score of 6) indicated that the adverse effect was probably related to atomoxetine.

As per our knowledge, this is the first case report of atomoxetine-induced vocal tic in an adult having schizophrenia with no previous history of ADHD or movement disorder who was given atomoxetine as an agent for cognitive enhancement. This case highlights the possibility that atomoxetine, like other stimulants, probably poses an independent risk of inducing tics and hence may not be ideal in patients with tic disorders.

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