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# EFFICACY OF ARIPIPRAZOLE IN ANTIDEPRESSANTS-INDUCED TARDIVE DYSTONIA AND TARDIVE DYSKINESIA: A CASE REPORT

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## INTRODUCTION

Tardive syndromes (TDS) are a group of movement disorders. Tardive dyskinesia is the best-known type of TDS. Another type of TDS is tardive dystonia. TDS cause body parts to move uncontrollably. Tardive dyskinesia and tardive dystonia are caused by dopamine receptor blocking agents, mostly antipsychotics but occasionally antidepressants (Jankovic 1995). However, tardive dystonia associated with antidepressants is rare and often under-recognized (Lee et al. 2013). There is one case that shows duloxetine-related tardive dystonia and tardive dyskinesia (Chen et al. 2010). The extrapyramidal symptoms (EPS) reported with tricyclic antidepressant (TCA) monotherapy appear to be unrelated to age but are often dose-related (Gill et al. 1997). Other risk factors include prior exposure to neuroleptics and/or lithium or estrogens. In some cases, the EPS resolve without any reduction of the TCA dose (Gill et al. 1997). It has been theorized that serotonin reuptake inhibition exerts an indirect dopamine blocking effect. Experiments on monkeys have demonstrated that SSRIs can induce dyskinetic movements (Korsgaard et al. 1985).

To our knowledge, there is no previous report on whether aripiprazole, a dopamine partial agonist, improves tardive dystonia and tardive dyskinesia simultaneously. Herein, we report on the case of a patient with major depressive disorder who was treated with aripiprazole for tardive dystonia and tardive dyskinesia, which were developed after long-term administration of amitriptyline, trazodone and short-term treatment with escitalopram.

## CASE REPORT

Mrs. Kim is 56-year-old Korean woman whose husband died of cancer 14 years ago. After her husband's death, she has suffered from a depressed mood, insomnia, anxiety, fatigue, poor appetite, and functional impairment. According to her family and herself, she does not have history of head trauma, seizure, medical disease and substance misuse. She has one son and three daughters. Her son has been treated for schizophrenia. There was no family history of neuropsychiatric disorders, except for her son.

She had been diagnosed with major depressive disorder at a local clinic by a psychiatrist 12 years ago. She had been treated with amitriptyline (10mg/day), trazodone (25mg/day), and flurazepam (15-30mg/day) from August 2002 to April 2013. She never received antipsychotic agent treatment. During this period, fluctuating depressive and anxious symptoms were seen without any apparent extrapyramidal symptoms.

On April 2013, she first complained of neck torticollis as cervical dystonia, but there was no hand tremor, limb rigidity, bradykinesia or other signs of parkinsonism. She went to another psychiatric clinic and began to receive Procyclidine (5mg/day) but it did not work, and her medical regimen was changed to Benztropine (1-2mg/day). She received amitriptyline (10mg/day), Benztropine (2mg/day), Lorazepam (2mg/day) medication for 1 month. However, distressing involuntary pulling and protruding of the neck movement, oral dyskinesia and excessive eye blinking began to occur, so she stopped all her medication and did not visit any clinics from May 2013 until January 2014. Repetitive, involuntary, purposeless movements subsided within several weeks after she stopped her medications. However, in January 2014, she suffered from a depressed mood, intractable insomnia, chest tightness, and anxiety. She began her treatment at a local clinic by a psychiatrist, and received Escitalopram (5mg/day), Benztropine (2mg/day), Trazodone (25mg/day), and Clonazepam (1.5mg/day) in May 2014. About 3 days after she started her medication, the same movements, including involuntary pulling and protruding of the neck, oral dyskinesia, and excessive eye blinking recurred. The symptoms worsened, despite adding anticholinergics and benzodiazepine to her regimen. The patient stopped taking all of her medication again. After going off her medication for several weeks, the patient did not see an improvement in her symptoms, and she visited our outpatient clinic on May 29, 2014. We decided to admit her. During her hospitalization, we presumed a diagnosis of tardive dystonia (her Simpson-Angus Rating Scale (SARS) score was 6) and tardive dyskinesia (her score on the Abnormal Involuntary Movement Scale

(AIMS) was 3), and a series of laboratory tests was performed. These tests included a complete blood count, liver, renal, and thyroid function tests, blood prolactin level, blood glucose level, copper, ceruloplasmin, antinuclear antibody test, hepatitis B surface antigen, hepatitis C antibody test, and a brain MRI. These examinations showed no specific findings.

We started her on Vitamin E (1000IU/day), Clonazepam (1.5mg/day), Benztropine (2mg/day), and, after contacting a neurologist to treat her idiopathic cervical dystonia (antecollis, lateral torticollis to the neck), we added Trihexyphenidyl (2mg/day), Levodopa/Carbidopa (50/200mg/day), baclofen (20mg/day). Her medications were maintained for two days, and a mild improvement in tardive dystonia was noted but her involuntary movements worsened. Also, she complained of severe anxiety, severe nausea, blurred vision, dry mouth, and wanted to stop these medications and leave the hospital. Consequently, we stopped the levodopa/carbidopa, tapered the benztropine from 2 mg to 1 mg, and reduced the Trihexyphenidyl from 2mg to 1mg, while adding aripiprazole (0.5mg/day). The patient left the hospital on June 7, 2014.

During outpatient setting treatment, the aripiprazole dosage was increased (1.5mg/day). Apparent improvements in her neck dystonia, involuntary movements, anxiety, and depression symptoms were noted 10 days later. However, mild oral dyskinesia (AIMS score of 1) and mild cervical dystonia (SARS score of 2) persisted during the following 6-week outpatient clinic follow-up.

## DISCUSSION

Mrs. Kim's symptoms meet the diagnostic criteria for tardive dyskinesia proposed by Schooler and Kane (Schooler 1982), tardive dystonia by Burke et al. (Burke 1982) and the ESRS for dystonia by Chouinard and Marolese (Chouinard 2005).

TDS affects voluntary muscles. In all forms of TDS, the movements usually affect normal functioning and can be embarrassing. TDS also can cause anxiety. This is a strong feeling of worry even when nothing is wrong. In spite of the 2013 American Academy of Neurology (AAN) guidelines on treating and managing tardive syndromes, presently there is no reliable, effective treatment available for TDS and the withdrawal of neuroleptics is often recommended (American Psychiatric Association 1992).

The pathophysiology of Tardive dyskinesia is not fully understood and a simple theory cannot account for all manifestations of the condition. The widely accepted model is the supersensitivity of the striatal postsynaptic dopamine receptors due to chronic neuroleptic treatment (Klawans & Rubovits 1972, Tarsy & Baldessarini 1973, Schatzberg & Nemeroff 1995).

In this theory, chronic neuroleptic treatment leads to denervation supersensitivity due to an up-regulation and increased number of dopamine receptors. As a result, there is an increased number of interactions between dopamine and dopamine receptors. Also, the pathophysiologic basis of tardive dystonia remains obscure. A possible role for serotoninergic and noradrenergic modulation of cholinergic pathways was suggested in tardive dystonia (Remington 1998).One of the more popular theories is that the repetitive stimulation of the D1 receptor by endogenous dopamine, resulting in the sensitization of the D1-mediated striatal output in the presence of D2 receptor blockade, is a fundamental mechanism mediating tardive dyskinesia and tardive dystonia (Trugman et al. 1994).

Aripiprazole is a dopamine D2 receptor partial agonist, with partial agonistic activity at the serotonin-1A (5-HT1A) receptors, and antagonistic activity at the 5-HT2A receptors (Burris et al. 2002). Due to its unique mechanism of action, aripiprazole has a dopamine stabilization effect and has been reported to normalize dopamine up-regulation (Inoue et al. 1997). Also, its action as a 5-HT1A partial agonist leads to the activation of the 5-HT1A autoreceptor, causing the increased release of dopamine (Eskow et al. 2007). These mechanisms may explain the improvement of symptoms of TD after aripiprazole treatment. Several case studies have suggested that aripiprazole can improve TD caused by typical and atypical antipsychotics (Kang & Kim 2011). However, cases of aripiprazole-induced TD have also been reported, but these reports have some limitations, such as the small number of cases, the failure to show a convincing temporal correlation of symptom onset with administration of the medication, and non-drug-related risk factors for TD-like TD symptoms on the placebo group (Kang & Kim 2011). Reports on the effectiveness of aripiprazole as a treatment for TDS are mixed. Although, the improvement of TD symptoms suggested that our patient's improvement of symptoms was mainly related to the use of aripiprazole, we could not rule out the effects of concomitant medications, such as lorazepam. But what is remarkable in this case is that tardive dystonia also could be treated with aripiprazole.

## CONCLUSION

We reported a patient with antidepressants-induced tardive dystonia and tardive dyskinesia treated with aripiprazole. To the best of our knowledge, this is the first report of simultaneous treatment for tardive dystonia and tardive dyskinesia with aripiprazole. In spite of several limitations, this case may show that unique pharmacological profile of aripiprazole can be an option in such situations.

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