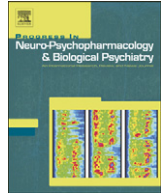




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# Progress in Neuro-Psychopharmacology & Biological Psychiatry

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## Letter to the Editor (Case report)

### Courses of aripiprazole-associated tardive dyskinesia: Report of two cases

#### 1. Introduction

Tardive dyskinesia (TD) is a syndrome of involuntary movements, consisting of abnormal, involuntary, irregular choreoathetoid movements of muscles over the head, limbs, and trunk. It usually develops in predisposed individuals during 6 months of antipsychotic drug treatment or longer. With the unique drug profile of partial dopamine D2 receptor agonist, partial 5-HT<sub>2A</sub> agonist, and 5-HT<sub>2A</sub> antagonist (Shapiro et al., 2003), aripiprazole is associated with unpredictable consequences in terms of TD. There have been case reports of emerging TD after use of aripiprazole (Evcimen et al., 2007; Maytal et al., 2006; Sajbel et al., 2005), while some reports demonstrate improvement of TD following aripiprazole therapy (Duggal, 2003; Grant and Baldessarini, 2005; Lykouras et al., 2007; Witschy and Winter, 2005). Here we present courses of aripiprazole-associated TD of two cases with different outcomes of dyskinesia.

#### 2. Case reports

Ms. A, a 41-year-old Taiwanese woman, suffered from schizophrenia with presentations of persecutory delusions, referential delusions and auditory hallucinations for 4 years. Her psychotic symptoms subsided gradually under treatment with amisulpiride 200 mg/day. She had good insight of her illness and good drug adherence, and was competent for a job at an information technology company. However, she was concerned over amenorrhea after treatment with amisulpiride. We thus started combination therapy with amisulpiride 200 mg/day and aripiprazole 10 mg/day after 14 months of amisulpiride monotherapy. She remained mentally stable and had regular menstrual cycles since then. However, parkinsonian symptoms including rabbit syndrome, mask face and hand tremor appeared after 11 months of combination therapy with amisulpiride and aripiprazole, and persisted for 4 months. Her parkinsonian symptoms improved after we discontinued amisulpiride and used aripiprazole 15 mg/day monotherapy. Unexpectedly, dyskinetic symptoms (involuntary chewing movement, tongue protrusion, athetosis of fingers) developed 3 months after amisulpiride was discontinued, with a score of 24 by the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). Although suffering from the dyskinetic symptoms, she was reluctant to change antipsychotics because she was satisfied with the improvement in cognitive function and positive psychotic symptoms. Some of her dyskinetic symptoms, such as perioral movements and athetosis of fingers, were much improved one month after taking vitamin E 400 I.U./day, although dyskinetic tongue protrusion persisted (AIMS: 14). Until now, her remaining dyskinetic symptoms has sustained for 21 months, although her psychotic symptoms are under control with continuous treatment with aripiprazole.

Ms. B, a 52-year-old Taiwanese woman has suffered from schizophrenia with initial presentations of loose lifestyles, social withdrawal and persecutory delusions since her early forties. She had had stable mental status under treatment with 50 to 200 mg/day of sulpiride for

6 years. However, she discontinued all the psychotropic medications, and then she was admitted to our psychiatric ward because of recurrence of psychotic symptoms. During hospitalization, sulpiride was replaced by aripiprazole, with an initial dose of 5 mg/day and up-titration to 10 mg/day in one week. Both her positive and negative psychotic symptoms improved. She was discharged with the same prescription and referred to the psychiatric daycare center for further mental rehabilitation. However, oral buccal dyskinesia, presenting as involuntary chewing and crunching movements, developed after 2-months of aripiprazole treatment. Diphenhydramine 150 mg/day were added, and her dyskinetic symptoms improved gradually and disappeared in 3 to 4 months.

#### 3. Discussion

The two cases presented above both had experience of prior antipsychotics and developed dyskinesia after 3 months of aripiprazole monotherapy. They were both females with relatively advanced age, but did not have histories of head injury or organic brain dysfunction. Ms. A met the Schooler–Kane research criteria for TD. However, there was no formal rating on dyskinetic symptoms for Ms. B. A diagnostic issue involves differentiation of TD from antipsychotics withdrawal dyskinesia. Withdrawal emergent dyskinesia typically occurs within a few days after dosage reduction or discontinuation, and then followed by rapid improvement over several weeks or rarely 2 to 3 months (Schultz et al., 1995). For these two cases, antipsychotics withdrawal dyskinesia was less likely since dyskinetic symptoms emerged after 3 months of aripiprazole monotherapy. Furthermore, for the case of Ms. A, the dyskinetic symptoms persisted for more than one year. The temporal relationships suggest that the development of TD for these two cases may be attributable to switching to aripiprazole from other antipsychotics. For the case of Ms. B, the dyskinetic symptoms improved and remitted. However, it's hard to determine whether the improvement was related to administration of diphenhydramine.

Some evidence revealed that lower risks for TD were associated with second-generation antipsychotics (Correll et al., 2004), including aripiprazole (Miller et al., 2007). The pathophysiology of TD is still controversial. The hypothesis of dopamine hypersensitivity, the most widely accepted theory, proposes that the nigrostriatal dopamine system develops increased sensitivity to dopamine as a consequence of chronic dopamine receptor blockade induced by antipsychotics (Klawans et al., 1985). The intrinsic activity of aripiprazole at the dopamine receptor would appear to be approximately 25% of that dopamine alone when the D2 receptors become saturated. Aripiprazole appears to exert its activity as a dopamine agonist for individuals in hypodopaminergic state, whilst acting as a dopaminergic antagonist when dopaminergic activity is increased (Shapiro et al., 2003). We hypothesized that, for some cases, the dopamine receptor may be up-regulated or hypersensitive after long term antipsychotic treatment, and that the property of dopamine D2 receptor partial agonism in aripiprazole may result in hypersensitivity of nigrostriatal

dopamine system, and thus lead to TD. After all, it is important to note that despite of the unique pharmacologic mechanism profile, we should still pay attention to the possibility of TD associated with aripiprazole. The unpredictable consequences in terms of TD after switching from other antipsychotics to aripiprazole warrant careful follow-up.

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