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Case Report

Suppression of antipsychotic-induced tardive dyskinesia with aripiprazole in an elderly patient with bipolar I disorder

Wu W-Y, Chan H-Y, Tan HK-L, Suppression of antipsychotic-induced tardive dyskinesia with aripiprazole in an elderly patient with bipolar I disorder.

Introduction: Aripiprazole has a low risk for causing extrapyramidal syndrome and can remit neuroleptic-induced tardive dyskinesia (TD). Here, we presented a case in which TD was suppressed, but not cured, by long-term aripiprazole treatment.
Case: This 74-year-old male patient had bipolar I disorder and had developed TD many times after several antipsychotic treatments. The lowest chlorpromazine dose equivalent among the previous antipsychotic treatments was 25 mg/day of quetiapine. His TD always improved immediately after the dosage was shifted to aripiprazole. However, his insomnia or other psychiatric symptoms worsened the first three times when the treatment was shifted to aripiprazole, making the transition a failure. Before the fourth attempt of aripiprazole transition, the patient was in a euthymic state but again developed TD under olanzapine 10 mg/day treatment. During the fourth attempt of aripiprazole transition, his TD had remained in complete remission for more than 1 year after the dosage shifted to 10 mg/day of aripiprazole. He developed TD again when we tapered the aripiprazole dose to 5 mg/day, but his TD remitted when we restored his aripiprazole dose to 10 mg/day.
Conclusion: Aripiprazole could be an effective drug in elderly bipolar patients with antipsychotic-induced TD while the patients are in a euthymic state. However, aripiprazole may only suppress TD rather than cure it.

Wei-Yi Wu[1], Hung-Yu Chan[1,2,3], Happy Kuy-Lok Tan[1]

[1]Department of Psychiatry, Taoyuan Mental Hospital, Taoyuan, Taiwan; [2]Department of Psychiatry, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan; and [3]Department of Psychology, Chung Yuan Christian University, Chung-Li, Taiwan

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Hung-Yu Chan, Department of Psychiatry, Taoyuan Mental Hospital, 71, Long-show Street, 33058 Taoyuan city, Taiwan.
Tel: +886 3 3698553;
Fax: +886 3 3699498;
E-mail: jan30@seed.net.tw

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Introduction

Tardive dyskinesia (TD) is known as a serious and irreversible adverse effect of long-term antipsychotic treatment. TD generally occurs in vulnerable populations such as people with advanced age, mood disorders, a high total-drug exposure, pre-existing drug-induced Parkinsonism, TD history, diabetes mellitus, mental retardation, organic brain damage, alcoholism and smoking (1). The mechanism of TD is unclear, but dopamine D_2 receptor hypersensitivity is the most popular hypothesis. Atypical antipsychotics exhibit different mechanisms and a lower risk for TD compared with conventional antipsychotics. It has been shown that atypical antipsychotics may have a therapeutic effect on pre-existing TD (2). However, TD can be induced by atypical antipsychotics and the incidence might be correlated with D_2 receptor affinity (3). Aripiprazole is an atypical antipsychotic and acts as a partial agonist at the dopamine D_2 receptors. Previous studies have shown that aripiprazole has a low risk for inducing TD and can even alleviate atypical antipsychotic-induced TD in patients with schizophrenia or schizoaffective disorder (4,5). Nevertheless, some studies have reported that aripiprazole induces or worsens TD and the mechanism for this may be the relative hypo-dopaminergic state in the brain, in which a substantial proportion of the dopamine D_2 receptors are occupied by a dopamine-partial agonist (6,7). Therefore, the role of aripiprazole in TD is still controversial. Here, we present a case of an elderly Asian man with bipolar I disorder whose neuroleptic-induced TD was alleviated with an aripiprazole treatment while he was in a euthymic state. However, his TD was only suppressed rather than being cured by aripiprazole.

Case report

The 74-year-old male patient was diagnosed with bipolar I disorder and his initial presentations were lack of sleep, more talkative than usual, hyperactivity, buying sprees and having multiple plans at the age of 50. He had been admitted to the acute ward three times because of manic episodes. His second hospitalization was in December 2005 and the medications included valproic acid and clotiapine. Valproic acid 1000 mg/day was prescribed during the first hospitalization, whereas clotiapine 80 mg/day had been used for ~6 years. The patient developed abnormal involuntary movements of the tongue and lower jaw at that time, and then received an extensive laboratory workup and computerized tomography examination of the brain to determine the etiology of his movement disorder. The results of these examinations were unremarkable and he was diagnosed with neuroleptic-induced TD. The score on the Abnormal Involuntary Movement Scale (AIMS) was 10. Clotiapine was then discontinued, but his TD persisted. Eight months later, zotepine was used to treat the manic symptoms and the TD temporarily subsided. One year later, he developed TD again and the dosage of zotepine was switched to aripiprazole 10 mg/day. His rating on the Young Mania Rating Scale (YMRS) was 11 before and 15 after the use of aripiprazole. The TD of the patient improved within 1 week, but the dosage of aripiprazole was switched to quetiapine 1 month later because of persistent manic symptoms. Another month later, TD developed for the third time under quetiapine 100 mg/day treatment. Aripiprazole 10 mg/day was used again and TD improved rapidly. However, the dosage of aripiprazole was again switched to quetiapine 6 months later because of insomnia. To prevent TD, a low dose of quetiapine 25 mg/day was tried at this time. However, the patient developed a manic episode and the TD reappeared, leading to his third hospitalization in May 2009. After admission, his dosage was switched to aripiprazole to 10 mg/day with full remission of TD in 1 week. His score on the AIMS was 9 at the time of admission and declined 0 to 2 weeks later. The YMRS was 19 before and 15 after aripiprazole treatment. Because the manic symptoms did not substantially improve, the dosage of aripiprazole was switched to olanzapine to 10 mg/day 2 weeks later. Neither the manic symptoms nor TD were observed for 8 months. Nevertheless, the patient developed TD again and the dosage of olanzapine was changed to aripiprazole to 10 mg/day. The YMRS total score was zero before and after the use of aripiprazole. In the following year, neither manic symptoms nor TD were observed. We tried to taper aripiprazole to 5 mg/day after 1 year of remission, but TD occurred again with an AIMS score of five. We maintained the aripiprazole dosage at 5 mg/day for 1 year, but the severity of the TD did not change. We then increased the dosage of aripiprazole to 10 mg/day again and his TD fully remitted in 2 weeks. A year later, neither TD nor the manic symptoms recurred. Except for valproic acid (800 mg/day; serum level between 50 and 100 mg/l) as the only concomitant medication, no benzodiazepines, vitamins or anticholinergic agents were given to this patient in the past 7 years. This patient did not have any dental problems and did not wear dentures.

Discussion

Lithium and some atypical antipsychotics are indicated for maintenance therapy of bipolar I disorder. However, lithium has a narrow therapeutic index and an overdose could be fatal. Occasionally, lithium toxicity can occur at doses close to the therapeutic doses, particularly in elderly patients. Because of this, we did not use lithium to treat the manic episodes of our patient or for maintenance therapy. The manic symptoms of the patient relapsed when he was on valproic acid monotherapy. Therefore, an atypical antipsychotic became necessary to prevent a relapse of mood episodes in this patient.

Atypical antipsychotics have a low risk for TD and may have a therapeutic effect on pre-existing TD (2). The incidence of TD is particularly low with quetiapine and clozapine (8). Although quetiapine has a fast dissociation profile for the dopamine D_2 receptors, which might have benefits for TD, it is still a dopamine receptor antagonist and could induce TD in some vulnerable patients (1). Previous studies have demonstrated that the dose of quetiapine that induced TD was as low as 75 mg/day (9). However, the patient in this study developed his fourth TD only under 25 mg/day of quetiapine. His vulnerability to TD may be because of his mood disorder diagnosis, old age and multiple histories of TD.

Aripiprazole is a newer atypical antipsychotic that is indicated for manic and mixed episodes of bipolar disorder and for adjunctive therapy with lithium and valproic acid for bipolar I disorder. Aripiprazole is a partial agonist of D_2-receptors that has an antagonist profile in the hyperdopaminergic state and an agonist profile in the hypodopaminergic state, operating as a stabilizer for the dopaminergic function and normalizing D_2-receptor upregulation (10). These characteristics may explain why aripiprazole did not induce TD after long-term use in our patient.

The first onset of TD in our patient occurred when he took clotiapine. After we discontinued clotiapine, his TD persisted for 8 months. Although his TD subsided during zotepine treatment, it reappeared after

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1 year of zotepine treatment. Thus, we thought that his TD was only suppressed rather than being cured by zotepine. The leading hypothesis of TD development is that it is caused by the hypersensitivity of D_2 receptors. According to this hypothesis, we were concerned that TD of the patient would persist or exacerbate if we discontinued zotepine and did not use aripiprazole. We did not discontinue zotepine for a while and did not provide other antipsychotics to observe the changes in the severity of TD of the patient. We could not definitely conclude that zotepine discontinuation had no role in his TD improvement. However, the result of his previous antipsychotic discontinuation, together with the dopamine D_2 receptors hypersensitivity hypothesis, suggested that zotepine discontinuation was not the principal reason for his TD improvement. Moreover, some studies have reported that aripiprazole can ameliorate TD within 48 h (11). Under such circumstances, we assumed that aripiprazole played a role in his TD improvement when we changed his antipsychotic treatment from zotepine to aripiprazole.

Aripiprazole and quetiapine have different pharmacodynamic properties, which could contribute to their different response against TD in this case. Quetiapine is a partial antagonist of 5-HT_{1A} receptors, but aripiprazole is their agonist. Some findings have suggested that 5-HT_{1A} receptor agonists are promising therapeutic agents for reducing l-DOPA-induced dyskinesia and motor fluctuations (12). This hypothesis may explain the improved dyskinetic movements observed with aripiprazole treatment, and their aggravation with quetiapine. In addition, the stronger antagonistic profile of quetiapine in the H_1 and α_1 receptors, compared with those of aripiprazole, may also be another reason for the quetiapine-related TD in this case (13,14).

Whether atypical antipsychotics treat or just suppress TD remains controversial (15). Previous studies have shown contradictory results regarding the effects of aripiprazole for TD treatment. Some studies reported that aripiprazole alleviated TD, (4,5) but others reported that it worsened TD (6,7). We tapered the aripiprazole dosage from 10 to 5 mg/day when our patient had been free of TD for 1 year, but his TD recurred. We maintained the dosage for 1 year and his TD severity remained the same. The TD of the patient was again ameliorated when we restored his aripiprazole dose to 10 mg/day. This result suggests that aripiprazole only suppressed rather than curing TD. Suppression means that aripiprazole may only improve the TD symptoms temporarily, and thus the TD would reappear in the future. Previous reports of aripiprazole treatment for neuroleptic-induced TD did not try tapering or discontinuing the dose. Hence, it is unclear whether aripiprazole cured TD or not in these cases. More long-term studies on the effects of aripiprazole on TD are thus needed.

Our patient had insomnia or restlessness side effects when using aripiprazole during manic episodes. His acute manic symptoms could not be effectively controlled and even worsened from aripiprazole use, and therefore aripiprazole was discontinued. Several studies have shown that replacing other antipsychotics with aripiprazole may worsen psychiatric symptoms in patients with schizophrenia (16). However, no studies have reported that aripiprazole may worsen the mood symptoms in bipolar disorder. This case showed that aripiprazole may worsen the mood symptoms in a patient with bipolar disorder and the finding is similar to those of previous schizophrenia studies (17). Therefore, for some patients with bipolar disorder and TD, it would be possible to replace other antipsychotics with aripiprazole when they are in a euthymic state.

Our patient required an antipsychotic for maintenance therapy to prevent a relapse of his manic episodes. When he developed TD, we searched for an antipsychotic having a double benefit, including bipolar I disorder prophylaxis and TD improvement. The results of the Cochrane systematic review indicate that evidence of the effectiveness of benzodiazepines (including diazepam) (18), vitamin E (19) and other treatments (20) for neuroleptic-induced TD is still inconclusive. We also aimed to keep the medications of our patient as simple as possible to prevent drug–drug interactions. Benzodiazepines increase the risk of falling and sedation side effects in elderly patients. Therefore, we did not include benzodiazepines or vitamins for the TD treatment of our patient.

Conclusion

In the past, TD was considered an irreversible side effect following long-term antipsychotic treatment. In recent years, there have been many reports on the alleviation of neuroleptic-induced TD, using atypical antipsychotics. We found that aripiprazole may ameliorate neuroleptic-induced TD in patients with bipolar disorder and the appropriate time to use it may be when patients are in a euthymic state. However, aripiprazole may only suppress TD rather than cure it. More studies on the use of aripiprazole for TD management are needed to confirm the results of this report.

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Conflicts of Interest

All authors declared that they have no conflicts of interest in this work.

Supplementary materials

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