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Tardive Dyskinesia: Treatment with Aripiprazole

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Tardive dyskinesia is characterized by choreiform movements, or rhythmic abnormal involuntary movements of the face, mouth, tongue, trunk, and limbs. It is frequently associated with the use of neuroleptic medications. The choreiform movements are irreversible in some patients, even after the drug is withdrawn. Although no reliable treatment for tardive dyskinesia exists, atypical antipsychotics are associated with a significantly lower incidence of tardive dyskinesia than typical antipsychotics. Moreover, recent reports suggest that atypical antipsychotics may have a beneficial effect on tardive dyskinesia remission. Until recently, evidence for the effectiveness of aripiprazole on tardive dyskinesia has been mixed. Aripiprazole has a unique mechanism of action and has various effects in tardive dyskinesia. The drug acts as a partial D_2 receptor agonist that can stabilize D_2 up-regulation, and as a partial 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist, and can increase the release of dopamine in the striatum.

KEY WORDS: Aripiprazole; Tardive dyskinesia.

INTRODUCTION

Tardive dyskinesia (TD) is characterized by persistent slow writhing and sudden involuntary movements. The oral lingual region is the area most commonly involved, but the condition can affect nearly every muscle system, from the limbs to the respiratory muscles.[1)]

The incidence of TD associated with atypical antipsychotics appears to be about one-fifth of that observed with first-generation "typical" antipsychotics.[2-4)] In a recent review of studies using comparable doses of antipsychotic drugs, the annualized incidence of TD was estimated to be 3.9% with atypical antipsychotics and 5.5% with conventional antipsychotics, showing an estimated 2- to 3-fold decline in the risk of TD with the administration of atypical antipsychotics.[5)]

TD is irreversible in some patients and persists even after medication is stopped;[6,7)] thus, it is important to prevent the development of TD.

The most important predictors of TD are older age, female gender, affective disorders, the presence of extrapyramidal side effects (EPS), diabetes mellitus, and certain parameters of neuroleptic exposure.[8)] Thus, it is critical that people who have these risk factors not be exposed to typical antipsychotics, which are associated with the development of TD symptoms.

Presently, no reliable, effective treatment is available for TD and the withdrawal of neuroleptics is often recommended.[9)] However, many patients cannot tolerate drug withdrawal and alternative atypical neuroleptics should be considered for this population.

Margolese *et al.*[10)] recommended the following treatment algorithm for cases that did not improve with conventional TD management: 1) discontinuation of anticholinergic therapy, 2) a switch to clozapine, 3) initiation of suppressive therapy using a conventional antipsychotic agent or tetrabenazine, and 4) addition of an experimental treatment, including donepezil, melatonin, branched-chain amino acids, vitamin E or vitamin B6, and drug reduction.

Thus, for patients who need antipsychotic medications, such as those with schizophrenia, bipolar illness, and many off-label conditions, atypical antipsychotic agents are the drugs of choice. Although atypical antipsychotics reduce the risk of extrapyramidal side effects and TD, they do not completely eliminate it, and the risk of developing TD remains a clinical concern.[3)]

Because atypical neuroleptics reduce the risk of TD, it may be reasonable to conclude that they are beneficial in

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Table 1. Cases of treatment of tardive dyskinesia with aripiprazole reported in the literature

Author	Year	Number of patients	Age (years)	Underlying disorder	Previous drug (dose, duration)	Type of dyskinesia	Dose/day (mg)	Treatment response
Duggal[12]	2003	1 F	41	Schizoaffective disorder	Haloperidol (not stated)	Choreoathetoid movement of the upper extremities and truncal dyskinesia	30 mg/day	Modest improvement
Grant *et al.*[13]	2005	1 F	54	Major depression, persecutory delusion	Haloperidol (7.5 mg/day, 6 months)	Dyskinetic oral movements	10 mg/day	Disappeared and re-emerged only
No authores listed.[14]	2008	1 M	65	Schizophrenia	Haloperidol (10 years), quetapine (400 mg/day, 3 years)	Blinking and a bucco-lingo-masticatory syndrome	30 mg/day	Significant improvement
Shan *et al.*[15]	2009	1 M	31	Psychotic symptoms	Risperidone (2 years), olanzapinje (not stated)	Oral-buccal-lingual dyskinesia	30 mg/day	Disappeared
Osorio *et al.*[16]	2010	2 F, 1 M	84, 85, 82	Agitation, mood swings, paranoid delusions (1), delusional disorder (1), bipolar disorder (1)	Haloperidol (2 mg, 10 years) (1), haloperidol (3 mg/day, 2 years) (1), haloperidol and thioridazine (30 years) (1)	Involuntary jwa movements (1), involuntary movements of mouth, face, trunk and limbs (1), orolingual dyskinetic movement (1)	5 mg/day (1), 10 mg/day (2)	Gradually disappeared (1), Significant improvement (2)
Sharma *et al.*[17]	2005	1 M	52	Schizophrenia	Ziprasidone (120 mg/day, 2 month)	Buccal-oral dyskinesia	15 mg/day	Full remission
Witschy *et al.*[18]	2005		45	Schizoaffective disorder, bipolar type	Haloperidol (for many years), risperidole (4 mg/day)	Not stated (AIMS 26)	15 mg/day	Dramatically reduced
Lykouras *et al.*[19]	2007	1 F	57	Schizoaffective disorder, bipolar type	Quetapine (400 mg/day, 3 month), Ziprasidone (60 mg/day)	Abnormal movements of the jaw, lips, tongue, mouth, the upper extremities	15 mg/day	Full remission
Caykoylu *et al.*[20]	2009	1 F	44	Schizophrenia	Risperidone (4 mg/day, 4 month)	Abnormal movements of the jaw, lips, mouth, tongue, low extremities	15 mg/day	Full remission

reversing the symptoms of the condition; however, their role in TD remission is unclear and controversial. Aripiprazole, an atypical antipsychotic, has a unique mechanism of action: it acts as a partial agonist at the D_2 receptor and is a 5-HT_{2A} receptor antagonist and a 5-HT_{1A} receptor partial agonist.[11] Several case studies have suggested that aripiprazole can improve TD caused by typical[12-16] and atypical antipsychotics (Table 1).[17-20]

Caykoylu *et al.*[20] reported that a patient received risperidone at a dose of 4 mg and then, 4 months after the treatment dose was increased to 6 mg/day, abnormal movements of the jaw, lips, mouth, tongue, and lower extremities developed. The treatment regimen was changed from risperidone to aripiprazole. After 6 months of aripiprazole treatment (15 mg/day), the patient showed significant improvement in the severity of the TD. The authors suggested that the improvement was mediated by partial agonistic activity at the D_2 receptors and proposed that aripiprazole be used to treat atypical antipsychotic-induced TD.

Another case study reported by Osorio *et al.*[16] supported the role of aripiprazole as an effective treatment for TD. The patient was prescribed 5 mg/day aripiprazole and over the following month, the involuntary jaw movement

Table 2. Cases of aripiprazole-associated tardive dyskinesia reported in the literature

Author	Year	Number of patients	Age (years)	Dose/day (mg)	Underlying disorder	Treatment duration with aripiprazole	Other drugs	Type of dyskinesia	Improvement alter sopping aripiprazole
Maytal *et al.*[23]	2006	1 F	62	5-15 mg/day	Major depression, generalized anxiety disorder, agoraphobia	Not stated	Bupropion	Lingual-facial-buccal movements	Yes
Abbasian *et al.*[24]	2009	1 F	24	15 mg	Paranoid psychosis	9 months	None	Akathisia, repetitive chewing movements of lips, jaw, tongue	Yes
Evcimen *et al.*[25]	2007	1 F	54	15 mg/day	Schizoaffective disorder	6 weeks	None	Tongue protrusion and lingual writhing movements	Yes
Zaidi *et al.*[26]	2008	1 F	25	Not stated	Psychotic illness & acute brain injury	15 days	None	Oral buccal dyskiesia, akathisia	Yes
Lungu *et al.*[27]	2009	1 F, 1 M	40.5 (19-62)	7.5-15 mg	Anxiety and Violent outbursts PTSD	18 months-3 years	None	Cervical dystonia and upper lims (1), involuntary movements of tongue, mouth, neck and trunk (2)	Yes-1, No-1
Wang *et al.*[28]	2009	2 F	46.5 (41-52)	10-15 mg	Schizophrenia	2-15 months	Amisulpirid, sulpiride	Oral buccal dyskinesia (2), finger athetosis (1)	Better after treatment
Schwartz *et al.*[29]	2007	1 F	46	5-15 mg/day	Major depressive disorder	15 months	Duloxetine	Involuntary lateral jaw movements	Yes
Sajbel *et al.*[30]	2005	1 M	35	20 mg/day	Schizoaffective disorder	7 weeks	None	Rolling/writhing	Yes

PTSD, post-traumatic stress disorder.

gradually disappeared. When the patient stopped treatment, TD symptoms re-emerged after 3 months, but disappeared once again when treatment was re-started. However, in these cases, it is difficult to determine whether the improvement was the result of the therapeutic action of aripiprazole or the effect of withdrawing a high-potency neuroleptic agent.

The prevalence of aripiprazole-associated TD has been reported to be between 0.2 and 3.4%.[21,22] Cases of aripiprazole-induced TD have also been reported (Table 2),[23-30] but these reports have some limitations, such as a small number of cases.

In summary, reports on the effectiveness of aripiprazole as a treatment for TD are mixed, and no systematic review of this topic has been reported. Thus, we reviewed the mechanism of action of aripiprazole according to the known pathophysiology of TD.

METHODS

A search of MEDLINE from 2000 to 2010 was conducted using the terms “aripiprazole”, “tardive dyskinesia”, “pathophysiology”, and “treatment”. Twenty-nine articles were selected, and related articles were also reviewed for additional information. In total, 74 articles were selected.

Tardive Dyskinesia Pathophysiology

The pathophysiology of TD is not fully understood and no single theory can account for all of the manifestations of the condition. The most widely accepted explanation is the dopamine receptor hypersensitivity hypothesis, which states that chronic neuroleptic treatment supersensitizes striatal dopamine receptors.[31-33] However, several inconsistencies indicate that this hypothesis cannot fully explain the pathogenesis of TD. Nevertheless, D_2 receptor hypersensitivity may be a necessary first step in the pathway that ultimately leads to the development of TD.[32]

An earlier hypothesis suggested that TD resulted from neuroleptic-induced alterations in gamma-amino-butyric acid (GABA) transmission within the basal ganglia; it proposed that striatal GABA-containing neurons might be damaged.[34] This explanation may be consistent with neuroleptic-induced degeneration of the striato-pallidal and/or striato-nigral GABAergic pathways.

McGeer EG and McGeer PL[35] suggested that striatal excitotoxicity might play a role in the development of TD. Later studies showed that long-term treatment with neuroleptics increased striatal glutamate release and possible excitotoxicity,[36-39] but the exact mechanisms underlying the excitotoxicity in chronic neurodegeneration and TD remain unclear.

Neurotransmitters in the serotonergic system may play a modulatory role in the pathogenesis of TD.[40] The serotonin system interacts directly with dopaminergic neurons in the substantia nigra and ventral tegmental area.[41] Serotonin (5-HT) modulates striatal dopamine release and can influence dyskinetic movements.[42,43]

Spontaneous jaw movements in rats may be influenced by activation of the brain 5-HT system, particularly via 5-HT_{1A}, 5-HT_{2C}, and 5-HT_3 receptors.[44-46] Acute treatment with the 5-HT_{1A} agonist, 8-OH-DPAT, reduced haloperidol-induced vacuous chewing movements in rats in a dose-dependent manner, indicating that the serotonergic system is involved in haloperidol-induced dyskinetic movements in the rat model.[46]

Putative Therapeutic Action of Aripiprazole in Tardive Dyskinesia

D_2 Dopamine Receptor Partial Agonist Activity

Chronic blockade of D_2 dopamine receptors is associated with the development of TD in patients with chronic schizophrenia.[47] This can be explained by the dopamine hypersensitivity hypothesis. As a dopamine D_2 receptor partial agonist, aripiprazole can stabilize dopamine activity: it acts as a dopamine agonist in the hypodopaminergic state and as a dopamine antagonist in the hyperdopaminergic state.[48] A dopamine D_2 receptor partial agonist blocks the dopamine D_2 receptor, but does not up-regulate it; thus, this property makes aripiprazole useful for patients who suffer from schizophrenia.[49] Similarly, partial agonist activity at the D_2 receptor does not up-regulate the D_2 binding site or D_2 mRNA.[50] Thus, aripiprazole may prevent the development of TD and extrapyramidal side effects.[20]

Because aripiprazole has been reported to normalize dopamine D_2 up-regulation, the antipsychotic may improve the symptoms of TD induced by typical or atypical, antipsychotics.[17,51] In effective doses of 15-30 mg daily, aripiprazole occupies more than 80% of the striatal D_2-like dopamine receptors; more than 90% occupancy at 30 mg daily has been reported in some cases.[52] For most antipsychotics, high striatal D_2 occupancy ($>90\%$) is associated with the development of extrapyramidal side effects; however, aripiprazole does not increase the incidence of extrapyramidal side effects beyond that observed with placebo at this level of occupancy.[53,54] This observation indicates that even at high striatal dopamine D_2 receptor occupancy, aripiprazole blockade of D_2 receptor-mediated neurotransmission is less than that of full antagonists because of its unique property as a partial dopamine agonist.[24]

The rapid dissociation of aripiprazole could further explain this phenomenon. In contrast to typical antipsychotics, atypical antipsychotics dissociate rapidly from the D_2 receptor. Rapid dissociation has been characterized as "hit-and-run" binding.[55] The D_2 receptor binding site of the atypical antipsychotics is smooth, and the drug fits loosely into the D_2 receptor (the "hit"), so it slips off readily after binding only briefly and leaves (the "run"). This indicates that atypical antipsychotic drugs block D_2 receptors only long enough to produce an antipsychotic effect, then dissociate before extrapyramidal side effects develop. It has been suggested that before the next pulse of the drug, endogenous dopamine in the nigrostriatal dopamine system may bind the receptor and prevent motor side effects.[55] Thus, although aripiprazole has a high D_2 receptor occupancy, rapid dissociation means that the antipsychotic binds to the D_2 receptor for a short period of time. Rapid dissociation can explain the lower incidence of tardive dyskinesia, but it does not explain the therapeutic effect of aripiprazole on tardive dyskinesia.

5-HT_{1A} Receptor Partial Agonist Activity

The 5-HT_{1A} and 5-HT_{2A} receptors have different effects on dopamine and glutamate release. Activation of the 5-HT_{1A} autoreceptors disinhibits the dopamine neuron, thereby increasing dopamine release. The partial agonist action of aripiprazole stimulates 5-HT_{1A} receptor-mediated release of dopamine in the striatum and alleviates extrapyramidal side effects.[55]

Aripiprazole's low level of catalepsy is partially reversed by 5-HT_{1A} antagonists, indicating that the partial agonist activity of aripiprazole at the 5-HT_{1A} receptor plays an important role in the low incidence of ex-

trapyramidal symptoms.[56-59] Eskow *et al.*[60] reported in a preclinical study that buspirone, a partial 5-HT_{1A} agonist, improved l-3,4-dihydroxyphenylalanine (l-DOPA)-induced dyskinesia and motor fluctuations, indicating that a partial 5-HT_{1A} agonist may be beneficial in the treatment of tardive dyskinesia. The authors suggested two possible explanations for their results: stimulation of postsynaptic 5-HT_{1A} receptors in the corticostriatal glutamatergic pathway reduced excessive glutamate release in the striatum, or presynaptic 5-HT_{1A} receptors within the striatal striosomes inhibited glutamate release into the striatum and decreased the pathological striatal output responsible for dyskinetic movement.

These findings indicate that the 5-HT_{1A} partial agonist property of aripiprazole may mediate the drug's beneficial effect on dyskinetic movements[61] and suggest that drugs targeting 5-HT_{1A} receptors provide a promising non-dopaminergic therapy for dyskinetic movement.[60] Although several studies indicate that 5-HT_{1A} partial agonists decrease the incidence of extrapyramidal side effects, including tardive dyskinesia, evidence that they play a role in the remission of tardive dyskinesia is not convincing.

5-HT_{2A} Receptor Antagonist Activity

Aripiprazole acts as an antagonist at the 5-HT_{2A} receptor and releases dopamine by disinhibiting dopaminergic neurons.[55] Atypical antipsychotic drugs cause fewer extrapyramidal side effects, including TD, than do typical antipsychotics; however, drugs with low anti-dopaminergic (D_2) affinity and high anti-serotonergic (5-HT_{2A}) affinity are associated the fewest extrapyramidal symptoms, particularly tardive dyskinesia. Tarsy *et al.*[62] ranked antipsychotic drugs according to the risk of extrapyramidal symptoms in the following order: clozapine < quetiapine < olanzapine=ziprasidone < risperidone. However, aripiprazole had not yet been approved for clinical practice when that review was published.

Second-generation atypical antipsychotics differ from typical antipsychotics in that they have a high 5-HT_2 : D_2 affinity ratio and a low affinity for the dopamine D_2 receptor.[54] In contrast, aripiprazole has a low 5-HT_2 : D_2 affinity ratio and a high affinity for the dopamine D_2 receptor. Because aripiprazole is a partial dopamine agonist, it seems unlikely that the drug's high D_2 receptor affinity is the result of higher dopamine receptor antagonist activity than other atypical antipsychotics.[63] Previous research suggests that aripiprazole-induced moderate 5_{2A} receptor blockade accounts for the drug's low incidence of extrapyramidal symptoms, including tardive dyskinesia, and its beneficial therapeutic effect, but this association remains unproven.

Putative Mechanisms Underlying Aripiprazole-induced TD

Recently, Peña *et al.*[22] reported that eight of the 236 patients had aripiprazole-associated TD. Of these, five patients were classified as having definite aripiprazole-associated TD because their movement disorder occurred after exclusive exposure to aripiprazole, and three patients were classified as probable. However, most previous case reports of TD associated with aripiprazole either failed to show a convincing temporal correlation of symptom onset with administration of the drug or concerned patients who had been previously exposed to conventional antipsychotics.[25]

The finding that the incidence of aripiprazole-induced TD is similar to that of a placebo led us to examine non-drug related risk factors for tardive dyskinesia. Risk factors for tardive dyskinesia include older age, preexisting movement or neurodegenerative disorders, female gender, the presence of affective illness, and exposure to neuroleptic drugs for more than 6 months.[4,64] Several case reports of aripiprazole-induced tardive dyskinesia indicated that the patients had at least one of these risk factors.[26,29]

Furthermore, an association has been reported between a specific D_3 receptor polymorphism and the risk of TD. Ser9Gly homozygosity or heterozygosity for the DRD3-gly allele of the D_3 genetic locus has been reported with antipsychotic medications.[65] This suggests that the development of TD may be the result of vulnerability due to this polymorphism, rather than the action of aripiprazole itself. Alternatively, aripiprazole-induced TD may be explained by the drug's mechanisms of action.

High Dopamine Receptor Occupancy and Partial Agonist Effect on Dopamine Hypersensitivity

Kapur *et al.*[66] reported that extrapyramidal side effects increase significantly when D_2 occupancy exceeds 78%. Mamo *et al.*[64] recently reported that the striatal D_2 receptor occupancy of aripiprazole was high in the putamen, 87%; caudate, 93%; and ventral striatum, 91%.

Partial agonists have the intrinsic ability to act as both agonists and antagonists, depending on neurotransmitter levels. Thus, it is possible that the partial dopamine receptor agonist action of aripiprazole might induce mild extrapyramidal symptoms in patients who had no prior exposure to D_2 antagonists or were on an initiation dose.[55]

In cases where the dopamine receptor is up-regulated or hypersensitive following chronic antipsychotic treatment, the high dopamine receptor occupancy and partial agonist action of aripiprazole might enhance hypersensitivity in the nigrostriatal dopaminergic system, leading to TD.[67)]

Balance between Dopamine D_1 and D_2 Receptors

Studies of the basal ganglia and movement disorders suggest that the final common pathway for dyskinesia is increased activation of the D_1-mediated striatonigral (or "direct") pathway and blockade of the inhibitory D_2-mediated striatopallidal (or "indirect") loop. Stimulation of these pathways may cause D_1 receptor overactivation.[68-70)]

In the presence of D_2 receptor blockade, repetitive stimulation of the D_1 receptor sensitizes D_1-mediated striatal output. The kindling model suggests that this mechanism may cause the development of tardive dyskinesia (including tardive dystonia).[71)]

While D_2 receptors are occupied by chronic antipsychotic medication, endogenous dopamine may stimulate D_1 receptors. Thus, despite aripiprazole's D_2 partial agonist activity, chronic treatment with the drug may disrupt the balance of D_1- and D_2-mediated striatal outputs by selectively blocking D_2 receptors.[72)]

Lack of Anticholinergic Activity

Muscarinic receptor blockade may protect against the extrapyramidal side-effects associated with antipsychotic drug use.[73)] Aripiprazole has not been found to have anticholinergic activity at clinically effective doses, and this may play a role in aripiprazole-induced TD.[74)]

Limitations of the Present Review

The pathophysiology of tardive dyskinesia is not well understood and no randomized, placebo-controlled, double-blind study has been reported examining the therapeutic efficacy of aripiprazole for the treatment of tardive dyskinesia. Thus, this review is based primarily on case reports of tardive dyskinesia treated with aripiprazole. The limited information available did not allow us to determine whether any improvement was the result of the therapeutic action of aripiprazole or an effect of withdrawing a high-potency neuroleptic agent.

CONCLUSION

Aripiprazole has a unique mechanism of action as a partial agonist at the D_2 receptor, a 5-HT_{2A} receptor antagonist, and a 5-HT_{1A} receptor partial agonist. Despite limitations in the data, we conclude that the unique pharmacological profile of aripiprazole underlies the low incidence of tardive dyskinesia and the therapeutic effects associated with this antipsychotic agent.

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