Antioxidants for the Treatment of Tardive Dyskinesia: AIMing to Find the Best Treatment Option

O. Greg Deardorff, PharmD, BCPP[a,*]; Kimberly A. Ehrhard, PharmD[a]; Jason Cafer, MD[a]; and Beth M. Hall, PharmD, BCPP[a]

Tardive dyskinesia (TD), a neurologic disorder of involuntary movements, most commonly occurs in 15%–30% of patients taking antipsychotic drugs for many years; however, in some cases, TD may occur after a brief exposure to the offending agent.[1] The Abnormal Involuntary Movement Scale (AIMS)[2] can detect TD and measure the severity of dyskinesias over time. An AIMS score of 2 in ≥2 movement categories or a score ≥3 in a single movement category is considered a positive AIMS score.[2]

The cause of TD is not entirely known; however, multiple theories exist. Currently, the 2 most accepted hypotheses are upregulation of postsynaptic dopamine receptor responsiveness and oxidative stress.[1] This report will mainly focus on the oxidative stress theory. TD has been suggested to occur as a result of the blockage of dopamine receptors by antipsychotic drugs, leading to increased dopamine metabolism and turnover and resulting in free radicals causing neuronal damage.[1,3,4]

Recently, new pharmacologic discoveries for the treatment of TD have occurred, which include deutetrabenazine and valbenazine. Both agents are vesicular monoamine transporter 2 inhibitors.[3] While clinical studies[5–7] have found these medications to cause a statistically significant decrease in a patient's AIMS score, their use comes with a large price tag. The wholesale acquisition cost of deutetrabenazine and valbenazine is $90,071 and $75,789, respectively.[5] While wholesale acquisition costs are quite large for these medications, assistance programs are provided through Shared Solutions[8] for deutetrabenazine and INBRACE[9] for valbenazine that may reduce copays for both patients and practitioners if qualifications are met. However, for mild cases of TD, clinicians may want to seek out more cost-effective options that may also treat or prevent TD. It has been postulated that antioxidants serve a role in the prevention and treatment of TD due to the oxidative stress hypothesis.[10]

[a]Fulton State Hospital Pharmacy, Fulton, Missouri

*Corresponding author: O. Greg Deardorff, PharmD, BCPP, Fulton State Hospital, 600 East 5th St, Fulton, MO 65251 (Greg.Deardorff@dmh.mo.gov).

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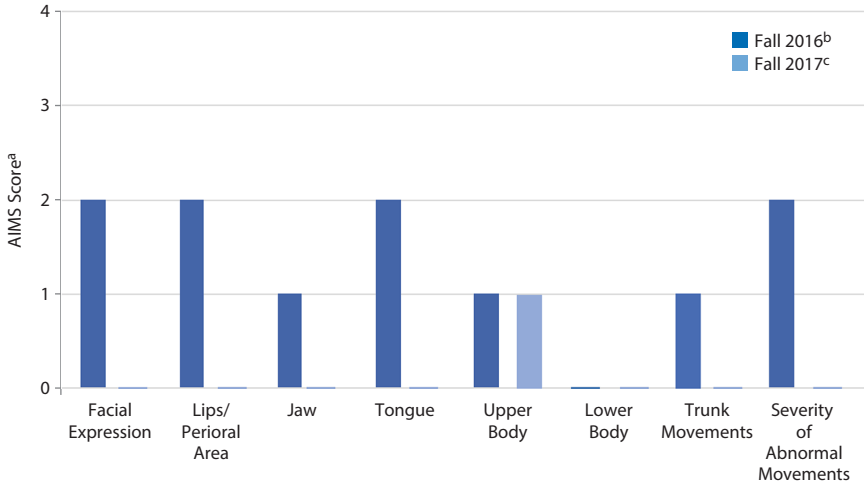
Antioxidants are stable molecules capable of donating an electron to a free radical, which results in its neutralization and thus decreases its ability to cause damage.[10] Studies have analyzed the use of high doses of melatonin, omega-3, and vitamin B_6 and their possible role in the prevention or treatment of TD. All 3 of these agents have shown beneficial effects in possibly reversing the symptoms of TD.[11–14]

Case Report

Mr A is a man in his 30s with a diagnosis of schizoaffective disorder, bipolar type residing at a long-term state psychiatric facility. In the summer of 2016 during a monthly evaluation, the psychiatrist noted possible involuntary movements of the patient's tongue. Current medications at the time were *N*-acetylcysteine 2,400 mg/d, melatonin 3 mg/d, mirtazapine 60 mg/d, olanzapine 30 mg/d, propranolol 20 mg/d (recently decreased from 40 mg/d), and vitamin D_3 2,000 IU/d. Laboratory results at the time were unremarkable. Due to concern for possible TD, Mr A's olanzapine dose was decreased to 25 mg on the same day and omega-3/DHA/EPA/DPA 1,050–1,200 mg twice daily was initiated. Eight days later, the psychiatrist performed a formal AIMS examination, which was positive with a score of 2 in at least 2 different movement categories (Figure 1). The psychiatrist was concerned with mild TD in those 2 categories, and treatment was optimized to prevent worsening of the TD and improve symptomatology. Over the course of 6 months, omega-3/DHA/EPA/DPA 1,050–1,200 mg twice daily was continued and other antioxidants were added including vitamin B_6 800 mg/d; melatonin was increased to 12 mg/d. Propranolol 40 mg/d was also reintroduced in an attempt to further reduce symptoms and then was discontinued.

Over the next 12 months, observance of involuntary movements of the tongue, lips, and truncal area had decreased as changes in medications including increases in antioxidant dosages were made. Certain increases in antioxidant dosages may have been higher than normally anticipated due to drug-drug interactions. Specifically, the reintroduction of propranolol may have caused a higher dosage of melatonin to be used due to propranolol's dose-dependent ability to intrinsically deplete melatonin levels.[15] A second AIMS evaluation was performed in the Fall of 2017, and results did not meet criteria for a positive AIMS score, with only minimal involuntary movement in the upper limbs observed with a score of 1 (Figure 1). See Table 1 for a timeline of medication changes and AIMS scores.

Figure 1. Difference in Involuntary Movements in AIMS Evaluation



[a]AIMS scoring: 4 = severe movements, 3 = moderate, 2 = mild, 1 = minimal, 0 = no movements.
[b]Medications during Fall 2016 AIMS scoring: *N*-acetylcysteine 2,400 mg/d; melatonin 3 mg/d; mirtazapine 60 mg/d; olanzapine 25 mg/d; omega-3/DHA/EPA/DPA 1,050–1,200 mg twice daily; and vitamin D_3 2,000 IU/d.
[c]Medications during Fall 2017 AIMS scoring: *N*-acetylcysteine 2,400 mg/d; melatonin 12 mg/d; mirtazapine 45 mg/d; olanzapine 20 mg/d; omega-3/DHA/EPA/DPA 1,050–1,200 mg twice daily; propranolol 40 mg/d; and vitamin B_6 800 mg/d.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, DHA/EPA/DPA = docosahexaenoic acid/eicosapentaenoic acid/docosapentaenoic acid.

Table 1. Timeline of AIMS Tests and Medication and Supplement Changes

Time	Observation	Medications and Supplements
Admission, Summer 2016	Baseline AIMS examination did not meet criteria for a positive AIMS results	*N*-acetylcysteine 2,400 mg/d Melatonin 3 mg/d Mirtazapine 60 mg/d Olanzapine 30 mg/d Propranolol 40 mg/d Vitamin D_3 2,000 IU/d
Summer 2016	Concerns about worsening depression	Propranolol decreased from 40 mg/d to 20 mg/d
10 Days later	Licking of upper lip was noted	Propranolol discontinued
2 Months later	Prominent involuntary movements noted; concern for possible tardive dyskinesia	Omega-3/DHA/EPA/DPA 1,050–1,200 mg twice daily started Olanzapine decreased to 25 mg/d
8 Days later[a]	AIMS administered; results signify TD with a positive score of 2 in 2 or more movements	Melatonin increased to 6 mg/d Olanzapine decreased to 20 mg/d
15 Days later	Involuntary movements continued	Melatonin increased to 9 mg/d
3 Months later	Attempt to manage continued TD symptoms	Propranolol restarted at 40 mg/d
3 Months later	Involuntary movements continued	Melatonin increased to 12 mg/d
15 Days later	Involuntary movements continued	Mirtazapine decreased to 45 mg/d
20 Days later	Involuntary movements continued	Vitamin B_6 200 mg/d started
18 Days later	Involuntary movements continued	Vitamin B_6 increased to 400 mg/d
4 Days later	Involuntary movements continued	Vitamin B_6 increased to 800 mg/d
5 Months later[b]	AIMS administered; results did not meet criteria for a positive AIMS	*N*-acetylcysteine 2,400 mg/d Melatonin 12 mg/d Mirtazapine 45 mg/d Olanzapine 20 mg/d Propranolol 40 mg/d Vitamin B_6 increased to 800 mg/d Omega-3/DHA/EPA/DPA 1,050–1,200 mg twice daily

[a]Timepoint seen in Figure 1 as Fall 2016.
[b]Timepoint seen in Figure 1 as Fall 2017.
Abbreviation: AIMS = Abnormal Involuntary Movement Scale, DHA/EPA/DPA = docosahexaenoic acid/eicosapentaenoic acid/docosapentaenoic acid, TD = tardive dyskinesia.

Discussion

This case report illustrates the importance of the utilization of antioxidants for treatment of TD. While initial agents did not provide complete improvement of involuntary movements, combining antioxidants had a beneficial effect in lowering symptom severity. This report also suggests that propranolol may have a role in the treatment of TD. Since movements only became apparent after the propranolol dose was lowered, this may indicate that, above a certain threshold, propranolol may also provide beneficial effect in masking, but not worsening, symptoms of TD or the adrenergic system affects modulation of the dopaminergic/cholinergic balance in the striatum.[16–18] On the basis of the observations of this case, alternative treatment options may be considered before use of more expensive US Food and Drug Administration–approved agents for mild cases of TD.

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