New Treatment Options for Tardive Dyskinesia

Haron N. Manwa

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Title: New Treatment Options for Tardive Dyskinesia

Department: Nursing

Degree: Master of Science

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Tardive dyskinesia (TD) is a movement disorder characterized by repetitive, abnormal, persistent, purposeless, and uncontrollable movements which occur as a result of long-term use of antipsychotic medications. Manifestations of this disorder include twisted tongue movements, jaw movements, eye blinking, and lip smacking/puckering/pursing (Mentzel et al., 2018). Uhlyar and Rey (2018) defined TD as a spectrum of hyperkinetic movement disorders which occur due to the use of dopamine receptor blocking agents. Antipsychotics and neuroleptics are considered dopamine receptor blockers and have been associated with TD.

The dopamine D2 receptor is the common target for antipsychotic medications which, according to Seeman (2011), occupy 60-80% of these receptors in patients. First generation antipsychotics have been implicated as posing a higher risk of developing TD than second generation antipsychotics (Freudenreich & Remington, 2017). They have high affinity for D2 receptors, a property which enables them to remain attached to these receptors for days hence preventing relapse. This attachment, however, can lead to TD hence the recommendation to image and desensitize these receptors in early stage psychosis. Clozapine and quetiapine are released from D2 receptors within 12 to 24 hours confirming why these two antipsychotic medications don’t elicit TD (Seeman, 2011).

The actual pathophysiology of TD is unknown but there have been investigations on dopamine receptor supersensitivity, gamma-aminobutyric acid hypofunction, and neurodegeneration (Uhlyar & Rey, 2018). Discontinuing use of any offending agents may not be an option especially for patients dependent on those agents to treat their underlying conditions, doing so would also not reverse TD symptoms and this might temporarily exacerbate TD symptoms (Atlas, Agboola, & Curfman, 2018). The Abnormal Involuntary Movement Scale
(AIMS) is commonly used for evaluating the severity of dyskinesia in patients receiving chronic antipsychotic therapies. According to Uhlyar and Rey (2018), incidence of TD is about 1% and patients receiving antipsychotic therapies have a prevalence of up to 30%. The elderly, women, African Americans, and patients receiving prolonged treatment with antipsychotics have a higher risk of developing TD. Hansen, Nausheen, Hart, and Kingdon (2013) contended that antipsychotics do not have to be given in large amounts to provoke high levels of extrapyramidal side effects (EPSs). Patients are likely to develop TD even at low doses of antipsychotic medication.

There has been no study conducted to investigate the connection between methamphetamine use and TD in humans. A recent study in mice indicated that methamphetamine may have long-term consequences on the nerve cells in the brain regions responsible for cognition, memory, decision-making capacity, and movement. The striatum, hippocampus, and the frontal cortex are the areas that are most commonly affected. It is assumed that if this drug kills nerve cells in the same human brain regions, there could be huge consequences. The researchers further asserted that movement disorders such as TD and huntington’s chorea are likely to arise as a result of loss of striatal cells and DNA fragmentation. Imaging studies on human brains of methamphetamine abusers have indicated extensive damage to nerve endings of cells that contain dopamine. This damage persists for at least three years after these individuals have stopped using the drug. This drug also leads to death of other nerve cells that produce other neurotransmitters in the brain (Mathias, 2000).

Alcohol and cannabis use have been found to contribute to TD and other EPSs in individuals with or without schizophrenia. These two, along with other illicit chemicals increase
vulnerability to movement disorders. Occasional alcohol use has not been found to contribute to TD symptoms but use that has reached the point of treatment has been found to be contributory not only to TD symptoms but also other negative schizophrenia symptoms (Swofford, Scheller-Gilkey, Miller, Woolwine, & Mance, 2000). Seeman (2011) noted that use of dopamine-like drugs such as cocaine lead to elevation of D2 receptors which consequently increase TD symptoms. No correlation has been found between smoking and EPSs (Hansen et al., 2013).

This case study focuses on a 53-year-old, Caucasian, divorced man admitted to the hospital from jail. He was adjudicated not competent to proceed with respect to felony charges of attempting to disarm a peace officer, fleeing a peace officer in a motor vehicle, and assault on a peace officer, 4th Degree. This stemmed from events that occurred in late May when the patient allegedly behaved in a suspicious manner, watching a woman and her children from his truck. When approached by law enforcement, he was noted to be pacing and behaving in an agitated manner, and then allegedly lashed out at officers in the course of attempts to detain him resulting in use of a taser. He was reportedly arrested after a high-speed chase involving multiple law enforcement agencies. While jailed, he was housed in administrative segregation, although his behavior was described as increasingly calm and pleasant following the initial period of disorganized behavior, refusal to follow directions from correctional officers and hostile, labile affect. He reportedly harbored delusional beliefs about the devil and believed he was vulnerable to receiving messages from spirits near him. Records documented a positive drug screen for methamphetamine and (tetrahydrocannabinol) THC upon arrest.

Records indicated a pattern of exacerbated psychotic symptoms, predominantly hallucinations, delusional thinking, disorganized speech and erratic, disorganized behavior with a primary diagnosis of schizophrenia. He had a history of significant mood symptoms, including
severe depression with suicidal ideation. Additional diagnostic considerations had included methamphetamine use disorder, cannabis use disorder, and alcohol use disorder by history. Records indicated that he first received psychiatric treatment at approximately age 20 and maintained good symptom control until he experienced significant depressive symptoms and suicidal ideation in 2012. Records documented multiple psychiatric hospitalizations since 2012 and civil commitment as mentally ill and chemically dependent. A history of marijuana and methamphetamine use was also documented. He had a history of suicidal ideation and behavior but had consistently denied any suicidal ideation, intent or plan to self-harm. In 2014, he reportedly attempted suicide by hanging which has a high potential for lethality.

He had a diagnosis of TD with severe abnormal jaw movement. He didn't remember when this started or what medication caused it. On admission, he was not on any medications but reported he had been on paliperidone before. He did not believe he had a mental illness hence saw no need for medications. His treating clinician petitioned the court for an order for involuntary treatment with antipsychotic medications and it was granted. To reduce risk of worsening TD, he was recently started on clozapine which requires weekly lab draws. Risks and benefits of clozapine were reviewed with him. The patient is afraid of needles and had initially been refusing lab draws. He was agreeable to blood draws and has been compliant with taking clozapine which has been gradually titrated to current dose of 450 mg a day.

He has been compliant and there has been noticeable improvement in his paranoia as well as lateral jaw movement especially after his dose was titrated to 350 mg a day. Even though this has been the case, he has been requesting different medications that don't require lab draws. This request has created an ethical dilemma since he is on medical assistance and the newer medications indicated for TD are expensive and would not be covered by his government issued
insurance. Weekly labs have been normal thus far. The effectiveness of clozapine and other
ewer medications/supplements in treating TD were researched. The findings are presented in
the following paragraphs.

Clozapine is considered the gold standard in treatment of refractory schizophrenia and
suicidal patients diagnosed with schizophrenia. When given in moderate doses, clozapine is
preferred in treatment of preexisting TD as it is safe and well tolerated. It has been demonstrated
as being effective in reducing abnormal movements due to its ability to bind loosely and
transiently to D2 receptors. Even though it presents serious side effects such as, agranulocytosis,
myocarditis, and seizures, its therapeutic gains have been shown to be maintained for extended
periods of time (Alam, Baruah, & Timungpi, 2015)

Clozapine is likely to increase the risk of type 2 diabetes mellitus and weight gain, in a
naturalistic study conducted on 82 patients on clozapine over a five-year period, 36.6% of
patients developed diabetes. A meta-analysis of short-term trials with clozapine indicated an
average weight gain of ten pounds over a period of ten weeks. Clozapine derives its effects from
its low D2 to serotonin ratio and also its selective preference for the mesolimbic dopamine
system (Alam et al., 2015). Mentzel et al (2018) recommended need to discontinue and replace
current antipsychotic treatment with clozapine monotherapy, a strategy that has been proved
effective in reducing TD symptoms.

Baptista and de Leon (2018) pointed out that there has not been decisive evidence to
support clozapine treatment, however, there is evidence of significant reduction in severity of TD
in many patients with moderate to severe TD. They admitted that it is unclear if clozapine treats
TD or merely suppresses its symptoms. The authors described a case where a 35-year-old
woman who developed a tardive movement disorder after starting on low dose risperidone to
augment fluoxetine ordered for severe non-psychotic obsessive-compulsive disorder (OCD). Improvement in OCS and abnormal movements was noted after risperidone was discontinued, and instead a low dose of clozapine (50 mg/day) was added to a combination of fluoxetine and clonazepam hence confirming effectiveness of clozapine in treating tardive dyskinesia.

In a retrospective study involving review of charts of 13 patients with TD who were being treated with clozapine, there was significant improvement especially in the chronically psychotic patients. The improvement, however, appeared to be dose-related, patients with TD at baseline receiving 554 mg a day of clozapine had their mean AIMS score decrease by 85% over a period of approximately 16 months (Dalack, Becks, & Meador-Woodruff, 1998). The researchers concluded that, the clozapine effect was greater for those who were treated with higher doses (around 300mg per day or above) and for longer periods of time, months as opposed to weeks (Dalack et al., 1998).

In a class IV study conducted on five patients with non-psychotic illness and TD or tardive dystonia who were put on clozapine, their AIMS reduced by at least 40% within three weeks of treatment. In another study comprised of six patients with severe TD whose offending medications were discontinued and clozapine in combination with clonazepam and tetrabenazine (TBZ) were used; marked reductions in abnormal movements were noted. A six-year follow-up using a Global Response Scale confirmed these results. Bhidayasiri, Jitkritsadakul, Friedman, and Fahn (2018) recommended initiating clonazepam at 0.5 mg and titrating it slowly to a maximum daily dose of 4.5 mg.

In another class IV open label, 12-month study meant to examine the effectiveness of quetiapine, 16 patients diagnosed with psychotic or mood disorders and tardive dystonia had their offending antipsychotics cross-tapered within the first three months. Significant
improvement of dystonia was observed at the end of the 12-month period and there was no loss in antipsychotic efficacy. Antipsychotics such as, haloperidol, thiopropazate, risperidone, and olanzapine are not recommended for treatment of TD or tardive syndromes as they are known to mask symptoms hence causing parkinsonism. It has also been noted that long-term use could worsen TD or tardive syndrome symptoms (Bhidayasiri et al., 2018).

TD patients especially those with a polymorphism in the (brain-derived neurotrophic factor) BDNF gene have shown great improvements after using supplement Ginkgo biloba extract EGb-761 which contains potent antioxidant properties. Research has shown that this supplement improves psychotic as well as EPSs when used together with haloperidol. In a study investigating effects of Ginkgo biloba on TD patients, 157 male patients under 60 years were started on a 12-week treatment with EGb-761 240 mg/day. Results indicated a significant decline in AIMS score in patients with TD and there was no worsening in cognition noted and no significant adverse effects. The researchers concluded that the antioxidant activity of extract EGb-761 makes this supplement effective in treating schizophrenia patients exhibiting TD symptoms (Lerner, Miodownik, & Lerner, 2015).

The maximum recommended daily dose of Ginkgo biloba is 240 mg. This supplement has an antiplatelet effect and can cause hemorrhage; therefore, it is not recommended in patients taking antiplatelets or anticoagulants. TBZ or amantadine is recommended as an adjuvant if symptoms persist with Ginkgo biloba, however, patients have to be monitored for adverse effects such as depression, parkinsonism, and visual hallucinations (Bhidayasiri et al., 2018). Vitamin E has also been noted to prevent further deterioration of TD symptoms (Mentzel et al., 2018).

There has been no well-studied treatment for TD but there are some new medications that have shown effectiveness. These medications include; valbenazine (Ingrezza), TBZ, and
Deutetrabenazine (Austedo). Deutetrabenazine and valbenazine are selective vascular monoamine transporter 2 (VMAT2) inhibitors that have been recommended as well tolerated by patients and they have longer half-lives compared to TBZ. These two medications are considered first-line therapy approved by FDA in treating adults with TD. Their long-term benefits and adverse effects are not known since the available clinical trials have been short-term. Atlas et al. (2018) argued that regardless of their effectiveness, majority of TD patients are unable to obtain them due to their high pricing.

A deuterated form of TBZ, deutetrabenazine (Deut-TBZ) has a slower breakdown of metabolites which is advantageous in terms of ensuring a pharmacokinetic profile with a longer metabolite duration of action. Deut-TBZ is formed through deuteration of tetrabenazine which requires replacing six hydrogen atoms with deuterium. The half-life of the principle active metabolite is extended, and peak plasma concentrations are reduced since deuterium bonds are more stable than hydrogen bonds; these properties allow for once or twice per day dosing. This also helps in tolerability that has been observed in short trials.

Tetrabenazine, on the other hand, requires frequent dosing and has been reported to have some problematic properties such as, orthostasis during titration, sedation, and induction of depression and suicidality (Cummings, Proctor, & Stahl, 2018). Bhidayasiri et al. (2018) suggested use of TBZ for those patients who have no access to Deut-TBZ or valbenazine even if there is not much evidence as there is for clonazepam or Ginkgo biloba. They further reasoned that clonazepam or Gingko biloba can be considered as alternatives for those who fail or cannot tolerate Deut-TBZ or valbenazine. Valbenazine was approved by FDA in 2017 as the first drug meant for treatment of adults with TD (Uhlyar & Rey, 2018).
In a study to examine effectiveness of Deut-TBZ in patients on antipsychotic medications, 117 patients with moderate-to-severe TD were randomly selected from a group of patients and then put on a 12-week treatment. A daily dose of 38.8 mg of Deut-TBZ or placebo was randomly administered to subjects. Fifty-nine random subjects got the placebo whereas 58 got Deut-TBZ. A blinded central video was used to record AIMS scores. Results revealed that AIMS scores decreased in patients receiving Deut-TBZ compared to those receiving placebo (Bhidayasiri et al., 2018).

Another double-blind placebo-controlled fixed dose study conducted on 298 randomly selected patients by European and US multicenter group meant to evaluate Deut-TBZ’s effectiveness at doses of 12 mg, 24 mg, and 36 mg/day revealed that Deut-TBZ was well tolerated. Significant changes in AIMS score were noted in the 24 mg and 36 mg dose groups compared to placebo. Results also demonstrated reduced rates of depression, somnolence, and akathisia (Bhidayasiri et al., 2018).

Deut-TBZ’s starting dose is 6 mg once per day. It is contraindicated in suicidal patients or those with untreated depression, hepatic impairment, or those that are on monoamine oxidase inhibitors. Adverse reactions include neuroleptic malignant syndrome, agitation, parkinsonism, QT prolongation, depression, and suicidality (Bhidayasiri et al., 2018). Despite the positive effects of Deut-TBZ as relates to TD treatment, the cost of this drug is too high for majority of patients to afford, the Institute for Clinical and Economic Review (ICER) fixed the wholesale acquisition cost (WAC) of a daily 36-mg dose of Deut-TBZ at $90,071 (Morrow, 2018).

Valbenazine metabolizes slowly hence minimizing high peak plasma concentrations, its half-life is long, approximately 20 hours, a property that makes it suitable to be administered
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Once daily. In a randomized study, 234 subjects with TD were subjected equally to either a placebo, 40 mg/day, or 80 mg/day of valbenazine. Persistent improvement in AIMS scores was noted with increasing dose, maximum effect was noted at 80 mg dose. According to Bhidayasiri et al. (2018), treatment with valbenazine did not have any effect on existing depressive symptoms. Also, even though this treatment was associated with side effects such as, somnolence, fatigue, headache, decreased appetite, and potentially prolonged QT interval, there was no evidence that it caused suicidal ideation in patients with a mood disorder, schizophrenia, or schizoaffective disorder.

Valbenazine should be avoided in patients with arrhythmias; initial dose is 40 mg once daily (Bhidayasiri et al., 2018). The starting dose is usually administered for one week and then increased to 80 mg, maximum dose administered once daily by mouth only. Valbenazine is very costly and it is found only in specialty pharmacies. Patients insured under governmental, federal, or state programs would not be able to get this medication as it is not covered. Most patients would need 30 capsules to last them one month and wholesale price for a 40-mg strength capsule of valbenazine is approximately $191 while that of 80-mg strength capsule goes for $208 (Uhlyar & Rey, 2018).

In a randomized, double-blind, placebo-controlled trial, 102 medically stable patients 18 to 85 years of age with clinical diagnoses of schizophrenia, schizoaffective disorder, or mood disorder were made to remain on a stable dose of dopamine antagonist for a minimum of 30 days before baseline. Medications such as, amantadine, tetrabenazine, anticholinergic, and benzodiazepines were prohibited. Patients were randomly divided into two groups; one group was started on valbenazine which was initiated at 25 mg and titrated 25 mg every two weeks to a maximum of 75 mg per day as tolerated. The second group was placed on a placebo. At six
weeks, researchers observed a mean reduction of 2.4 points on the AIMS in patients with moderate-to-severe TD taking valbenazine. After another six weeks, a mean reduction in AIMS score of 3.2 was noted in patients taking daily valbenazine dose of 80 mg (Uhlyar & Rey, 2018).

Financial dilemma for most patients presents a challenge to providers who are forced to make a decision to proceed with alternative treatment that costs less. There is need to advocate for safety net institutions where patients can receive subsidized or free treatment of their choice. Weiner (2001) noted that providers may unknowingly commit technical violations or be engaged in abuse or fraud in their efforts to accommodate patients with health insurance coverages that do not cover needed treatments or services. These violations may result from not billing at all, undercoding, waiving deductibles, or reducing charges below their usual fee.
References


