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Valbenazine has a small but meaningful benefit for tardive dyskinesia

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ABSTRACT A critical appraisal and clinical application of

Hauser RA, Factor SA, Marder SR, et al. KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia. *Am J Psychiatry*. 2017;174(5):476-484. <https://doi.org/10.1176/appi.ajp.2017.16091037>

and

Factor SA, Remington G, Comella CL, et al. The Effects of Valbenazine in Participants with Tardive Dyskinesia: Results of the 1-Year KINECT 3 Extension Study. *J Clin Psychiatry*. 2017;78(9):1344-1350. <https://doi.org/10.4088/JCP.17m11777>

exploring the efficacy of a newer therapy for tardive dyskinesia, and describing recommendations for a patient with acute medical problems and longstanding tardive dyskinesia.

Keywords: *tardive dyskinesia, valbenazine, therapy*

Clinical Context

Mary Cross [pseudonym], a 66-year-old Caucasian female, presented with nausea and vomiting. Ms. Cross was found to have acute kidney injury secondary to dehydration. Her past medical history was significant for schizoaffective disorder, hypertension, and stage 3 chronic kidney disease. Blood and urine cultures were positive for pan-sensitive *E. coli*. Her hospital course included treatment with antibiotics and steroids for hospital-acquired pneumonia and sepsis secondary to a complicated urinary tract infection. During her admission, Ms. Cross exhibited tardive dyskinesia (TD) with lip smacking and involuntary tongue movements. These symptoms have been present over the past several years resulting from her history of schizoaffective disorder treated with fluphenazine and quetiapine. The symptoms were severe enough to interfere with communication between the patient and healthcare providers. When asked, Ms. Cross expressed interest in beginning therapy to ameliorate her symptoms. After confirmation of her medication regimen with her community mental health provider, treatment of her TD was considered by our team because one of the doctors was aware of newer medications from direct-to-consumer advertising on television.

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Clinical Question

Is there a medication that would be appropriate for this patient with tardive dyskinesia?

Research Article

Hauser RA, Factor SA, Marder SR, et al. KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia. *American Journal of Psychiatry.* 2017;174(5):476-484. <https://doi.org/10.1176/appi.ajp.2017.16091037>

Factor SA, Remington G, Comella CL, et al. The Effects of Valbenazine in Participants with Tardive Dyskinesia: Results of the 1-Year KINECT 3 Extension Study. *Journal of Clinical Psychiatry.* 2017;78(9):1344-1350. <https://doi.org/10.4088/JCP.17m11777>

Related Literature

Using Google search, the terms “new drugs for tardive dyskinesia” allowed us to identify two new medications approved by the FDA for the treatment of tardive dyskinesia, valbenazine and deutetrabenazine. We then searched PubMed using the search term “valbenazine therapy” with the “best match” filter; it returned 55 articles. We manually scanned the titles and abstracts for relevant papers. Additionally, we reviewed the references from a systematic review¹ revealing no additional relevant citations.

Adding the clinical trial filter, only 9 papers were identified. The same group of authors published all of the papers; a phase two trial,² and two publications reporting data from the same research study.^{3,4} The phase two trial was not designed to determine efficacy. The KINECT 3 and the KINECT 3 Extension Study utilized the same patient cohort. The KINECT 3 was a randomized, controlled, triple-blind, 6-week trial to determine efficacy. The KINECT 3 Extension study followed the patients that completed the KINECT 3 trial for a total of 48 weeks with an additional 4-week wash-out period.

PubMed was searched for “deutetrabenazine therapy” using the clinical trials filter. Four studies were identified, two of which evaluated the medication for use in tardive dyskinesia. Both studies were conducted by the same group of authors. The first study was a 12-week, randomized, controlled, double-blinded trial with similar results (effect size) as the KINECT 3 trial.⁵ The second study was an equivalent, randomized, double-blinded phase 3 trial to find the correct dosage for tardive dyskinesia treatment; results were consistent with the KINECT 3 trial.⁶

Due to longer follow up with the KINECT 3 studies, we decided to use them for the critical appraisal.

Critical Appraisal

The KINECT 3 and 1-Year KINECT 3 Extension Study both used the same patient cohort and methodology but reported outcomes at two different intervals. Because we want the best assessment of harms and benefits, we will review both of these publications together.

The KINECT 3 was a triple-blind, randomized, placebo-controlled, prospective trial. This 6-week trial compared patients taking valbenazine at 40 mg, valbenazine at 80 mg, and similarly appearing placebo tablets. Patients were maintained on their psychiatric and medical therapy throughout the study. Randomization was accomplished with an interactive web response system. Baseline characteristics were similar in all three groups, including diagnosis category, degree of suicidal behavior, and type of antipsychotic. Sixty-six percent of patients had a diagnosis of schizophrenia or schizoaffective disorder.

Patients were eligible for the study if they had a diagnosis of moderate or severe tardive dyskinesia based on initial screening. Participants were required to be medically stable and between the age of 18 and 85 years of age. Underlying diagnoses included schizophrenia, schizoaffective disorder, or a mood disorder according to DSM-IV criteria. These diagnoses explain the exposure to dopamine receptor blockers as a cause for tardive dyskinesia. Exclusion criterion included unstable medical conditions, significant risk of suicide, a history of neuroleptic malignant syndrome, or other comorbid movement disorders.

The primary outcome measure was a change from baseline in Abnormal Involuntary Movement Scale (AIMS) over the 6-week trial.² The AIMS rates 7 observable areas of involuntary movements and utilizes a 0 to 4 scale to score, resulting in an overall score between 0 and 28. These 7 areas rated the severity of facial, oral, extremity, and trunk movements. The AIMS score was determined through video-recorded review. The reviewers were blinded to treatment and study visit sequence. Assessments occurred at baseline and weeks 2, 4 and 6. Each assessment was done by two reviewers and a consensus score for each item was used.

This multi-center trial assessed patients from 63 centers in North America recruited between October 2014 to September 2015. The researchers used International Conference on Harmonization Guidelines to enhance standardization of study protocol adherence. Recruitment procedures were not well-described.

Although there was some loss to follow-up for various reasons, the overall completion of the study protocol was 205 of 234 (87.6%) enrolled participants. The researchers did report an intention-to-treat analysis. Drop-out rates were comparable in all three groups.

Adverse events were similar in all three groups, suggesting that blinding was preserved throughout the study. For both the 40 mg and 80 mg valbenazine groups, there were progressive decreases in AIMS scores.

The mean baseline AIMS scores for the placebo, 40 mg, and 80 mg valbenazine groups were 9.9, 9.7, and 10.4, respectively, with an overall mean of 10.0 for all participants. On average, the 80 mg valbenazine group decreased their AIMS score by 3.1 compared to placebo, and 1.8 for 40 mg, from baseline to week 6.

According to the SORT criteria, the study quality of these publications is Level 1.⁸ The 1-Year KINECT 3 Extension Study included all of the patients that completed the KINECT 3 trial and reassigned them to 40 mg and 80 mg groups. This means that members of the placebo group that finished the original trial were reassigned to an active treatment group and followed for an additional 42 weeks. The effect size of benefit (change from baseline AIMS) was consistent with the KINECT 3 trial for both doses respectively. Again, additional benefit was identified with longer duration of treatment. For the 40 mg group, there was a change in baseline AIMS from -1 to -2.5. For the 80 mg group, it changed from -4 to -4.5.

Following the 48 weeks, there was an additional 4-week washout observation off study medication, which showed a progressive trend towards original baseline.

The advantage of a 1-year follow-up was to assess for additional adverse events. There was a 62% and 76% incidence of adverse events for the 40 mg and 80 mg groups, respectively. Adverse events included typical symptoms such as dry mouth, headache, vomiting, fatigue, etc. Severe adverse events included suicidal ideation, suicidal behavior, and hallucinations, which are not unexpected in this patient cohort.

A reduction of 50% or greater from baseline in the AIMS score was considered to be an efficacious response. The percentage of participants receiving valbenazine who achieved an AIMS response at 6 weeks was 40% for 80 mg and 23.8% for 40 mg. The placebo group's response at 6 weeks was 8.7%, yielding number needed to treat (NNT) values of 3.2 for 80 mg and 6.6 for 40 mg. The rates of adverse events during the 6-week trial for the placebo, 40 mg, and 80 mg valbenazine groups were 43.4%, 40.3%, and 50.6%, respectively. These rates yield a number needed to harm (NNH) value of 13.9 for 80 mg. Given the lower incidence of adverse events for the 40 mg group compared to placebo, the NNH for 40 mg is -32.2.

Clinical Application

Because Ms. Cross expressed an interest in possible therapy, our inpatient team explored the clinical research evidence during her hospital stay. We each independently scored Ms. Cross using the AIMS and our scores ranged from 13 to 17. This indicated her symptoms were more severe than patients in the KINECT 3 trial, where the average AIMS score was 10. This may support that Ms. Cross was likely to benefit from medication more than the patients in the KINECT 3 trial.

After reviewing the articles, we believe the effect size is real, mild to moderate, but meaningful. One of our largest concerns was that Ms. Cross' tardive dyskinesia interfered with speech and communication. She was admitted with multiple severe medical conditions that could have been treated earlier, assuming better communication would

have allowed her to relay her symptoms accurately. Upon discharge and return to care at community mental health, we included the following statement in her hospital discharge summary:

"Patient has a past medical history of schizoaffective disorder, anxiety, and depression taking multiple psychiatric medications. Patient was found to have tardive dyskinesia during this hospitalization. While the patient was hospitalized, we assessed her interest in treatment for her TD. She expressed interest in treatment secondary to bothersome symptoms of lip smacking. After reviewing the medical research evidence, it is reasonable to recommend a trial of valbenazine 80 mg when she resumes treatment with community mental health."

The decision to include these recommendations in her discharge summary rather than altering her medication regimen was based on the potential barrier of miscommunication between medical providers. Ms. Cross is a patient treated with psychotropic medications that have been carefully managed by her community physician. Our hospitalist team felt that the best decision for Ms. Cross' health was to defer to her physician for any changes in her treatment regimen.

Implications for Clinical Decision Science

The role of direct-to-consumer advertising taught us that new medications exist for the treatment of tardive dyskinesia, promoting an educational discussion between patient and provider. Due to our focus on treating her medical conditions, we were inattentive to Ms. Cross' severe deficit in her ability to communicate (tardive dyskinesia). We now appreciate that addressing communication deficits can lead to improved quality of life and medical care. The application of clinical research in this scenario reaffirmed the importance of collaboration between physicians, as miscommunication is a potential barrier to managing complicated treatment regimens.

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