CURESZ FOUNDATION
Newsletter
SPECIAL EDITION
Comprehensive Understanding via Research and Education into SchiZophrenia
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After Decades of Research

Discovery of New Treatments for Tardive Dyskinesia

A Late-Onset Serious Movement Disorder Caused by Antipsychotic Medications

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Antipsychotic medications are widely used for the treatment of schizophrenia, bipolar mania, bipolar depression and major depressive disorder. It is well known that the antipsychotic effect is mediated by blockade of dopamine D2 receptors in a region of the brain called *"mesolimbic dopamine tract."* However, when persons receive antipsychotic drugs, the dopamine receptors are blocked in all other brain regions that contain dopamine receptors including *"the nigro-striatal dopamine tract,"* which is responsible for coordinating muscle movements throughout the body. This is why abnormal muscle movements occur as a side effect of antipsychotic medications. These abnormal movements are of 2 types:

Short-Term Movements

The short-term abnormal movements that occur when dopamine activity is reduced in the nigro-striatal are called *"extra-pyramidal symptoms"* or EPS. These include too many movements (akathisia and dyskinesia) or too few movements (dystonia and Parkinsonism). The EPS movements can occur within hours of taking antipsychotic drug (such as dystonia) or within a few days (akathisia). The rigidity, slow gait and rhythmic tremor, triggered by antipsychotic drugs, are all symptoms resembling Parkinson's Disease, usually appear after several weeks when dopamine activity is drastically reduced in the nigrostriatal tract. All those EPS side-effects have traditionally been treated with anticholinergic medications (like cogentin or artane) or simply by reducing the dose of antipsychotic medication by 10-15%.

Long-Term Movements

The long-term abnormal movements that can emerge from antipsychotic drug treatment are called Tardive Dyskinesia (which means late-onset movements). It is called TD for short. TD usually appears after months or years of antipsychotic therapy, and they are different from the short-term EPS movements. TD movements usually affect the muscles of the face, especially the tongue, lips, jaw and eyes. Those affected develop random mouth movements that may resemble chewing or lip-smacking or grimacing, as well as tongue movements in and out of the mouth. These movements can be very embarrassing to the affected individual because of their disfiguring effect on the face. Other body regions can also show random movements including the neck, arms, fingers, legs, toes or trunk (body swaying movements). TD can even affect the diaphragm, causing grunting or barking sounds when it contracts randomly. Those TD movements can progress from mild to severe, and anticholinergic medications that are used for acute EPS (such as Cogentin) worsen TD.

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Several follow up studies have shown that about 5-6% of persons receiving the older antipsychotic drugs and 2-3% of those receiving the newer antipsychotics, develop TD each year. After many years of taking antipsychotic medications (which cannot be stopped because psychosis or bipolar mania may re-emerge), the prevalence of TD can be around 20-30% of patients. It is estimated that ~500,000 persons in the United States suffer from TD.

TD must be differentiated from other neurological disorders such as:

- Huntington's disease
- Senile Chorea
- Wilson's disease
- Meige Syndrome
- Blepharospasm
- Sydenham Chorea
- Tourette Syndrome
- Basal Ganglia Calcification
- Restless-Leg Syndrome

Recognized Risk Factors of TD

- Long-duration of antipsychotic treatment
- Older age
- Female gender
- Diagnosis of a mood disorder
- Post-menopaused status
- Abusing drugs & alcohol
- Past history of EPS
- Diabetes

Measuring the Severity of TD

A rating scale called the AIMS (Abnormal Involuntary Movement) Scale was developed in 1976. It scores the severity of TD movements in the face, upper and lower extremities. The AIMS measurements of TD are used in clinical trials that assess the efficacy of potential treatments for TD, including FDA trials.

Lengthy Search

For over 50 years, TD has been untreatable and often irreversible. Numerous attempts to find a drug to treat TD have failed. The author of this article spent several years conducting federally funded TD research in the 1980's, but could not find an effective drug to treat TD.

Exciting Breakthrough

Fortunately, research finally paid off and efficacious treatment for TD has been discovered. Valbenazine was the first drug approved by the FDA in April 2017 for the treatment of TD. Another agent, deutetrabenazine, was subsequently approved in August 2017. Both drugs have the same mechanism of action which is to inhibit a protein called VMAT2 (vesicular monoamine transporter 2). By inhibiting VMAT2, dopamine is prevented from being stored inside protective vesicles, and is destroyed in the cytoplasm of the neuron by an enzyme called MAO (monoamine oxidase). This reduces the activity of dopamine hypersensitive receptors in the nigrostriatal tract where muscle movement is initiated, leading to suppression of the abnormal movements of TD. The medications have to be taken on an ongoing basis because if stopped, the TD will return (just as hypertension will return if an antihypertensive drug is discontinued).

"The era of hopelessness and suffering is now behind us."

In summary, TD will still emerge among persons receiving antipsychotic drugs, but the era of hopelessness and suffering is now behind us because FDA-approved medications have finally been developed to treat TD. This is great news for both patients and the psychiatrist who treat psychosis and mood disorders. The discovery of treatment for TD underscores how research leads to medical advances that reduce suffering and improve the quality of life for countless people who suffer from various diseases, including TD.

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VIDEO HIGHLIGHT

Tardive Dyskinesia

4-Part Video Series

Dr. Henry Nasrallah and Bethany Yeiser talk about tardive dyskinesia.

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