WEST VIRGINIA Department of Health & Human Resources
Bureau for Medical Services

DUR Capsules

News and Information for West Virginia Providers from the West Virginia Bureau for Medical Services (WVBMS)

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Topics Covered in This Issue

TARDIVE DYSKINESIA

Introduction

- Tardive dyskinesia is a movement disorder characterized by hyperkinetic movements that occurs with a delayed onset, typically after prolonged use of dopamine receptor-blocking agents such as antipsychotics and metoclopramide. Noted symptoms of tardive dyskinesia include chorea, athetosis, dystonia, akathisia, stereotyped behaviors, and tremor.
- The disorder is reversible in up to 90% of patients when identified and treated early, but complete remission can take years to occur, making prevention and early detection of the disorder highly important.
- The only certain method of tardive dyskinesia prevention is to avoid treatment with antipsychotic drugs and metoclopramide. If use of these drugs is unavoidable, providers should educate patients on the risks of tardive dyskinesia prior to initiating therapy, monitor patients closely while on therapy, and discontinue the dopamine receptor-blocking agent (if possible) as soon as symptoms of tardive dyskinesia are present in the patient.

Recent Advancements in Care

- Previously, there were no medications carrying an FDA approved indication for the treatment of tardive dyskinesia, leaving treatment options to off-label therapy with a variety of agents such as benzodiazepines, botulinum toxin, anticholinergic drugs, and tetrabenazine, all of which have limited evidence of efficacy for the treatment of tardive dyskinesia.
- In 2017, both Ingrezza® (valbenazine) and Austedo™ (deutetrabenazine) were the 1st and 2nd drug respectively to receive an FDA approval for the treatment of tardive dyskinesia. Both of these agents, as well as tetrabenazine, are in a class of drugs called vesicular monoamine transporter 2 (VMAT2) inhibitors. They achieve their therapeutic effects in tardive dyskinesia by acting centrally and causing the release of dopamine storage in presynaptic vesicles, resulting in an increase in synaptic dopamine available in the central nervous system.
- The FDA approval for the treatment of tardive dyskinesia of both Ingrezza® and Austedo™ was based on results from a randomized, double-blind, placebo-controlled trials of varying sizes and durations. The primary efficacy endpoint in all trials of both agents was the reduction in involuntary movement as measured by the Abnormal Involuntary Movement Scale (AIMS) relative to placebo after treatment.
    - The efficacy of Ingrezza® was demonstrated in a 6-week trial of 234 patients, the results of which showed a statistically significant reduction in AIMS score of 1.8 to 3.1 in patients treated with Ingrezza® versus placebo.
    - In two 12-week trials in a total of 222 patients, treatment with Austedo™ resulted statistically significant reduction in AIMS score of 0.7 to 1.9, when compared to placebo.
- Both agents are oral formulations that have not been evaluated for use in pediatric patients. The initial recommended dose of Ingrezza® is 40 mg once daily, which should be titrated to response and tolerability weekly to a maximum dose of 80 mg daily. Recommended dosing of Austedo™ is 6 mg once daily, which should be titrated to response and tolerability weekly to a maximum dose of 48 mg (daily doses >6 mg should be divided into 2 daily doses).

Safety Comparison of Newer Agents

- **Boxed Warnings**:
    - There is no boxed warning on the label for Ingrezza®. Austedo™ carries a boxed warning on its label regarding increased risk of depression and suicidality when used in patients with Huntington disease.
- **Contraindications**:
    - There are no contraindications listed on the label for Ingrezza®. Use of Austedo™ is contraindicated in patients with hepatic impairment as well as patients with Huntington disease who are suicidal or have inadequately treated depression. Co-administration of Austedo™ with tetrabenazine, valbenazine, within 14 days of taking an MAOI, or within 20 days of taking reserpine is also contraindicated.
- **Warnings/Precautions**:
    - Both agents carry a warning regarding their ability to cause an increase in depression/suicidal ideation, as well as their ability to prolong the QT interval. Additional warnings for Austedo™ include precautions about the drug's ability to cause akathisia, Neuroleptic malignant syndrome (NMS), increased prolactin levels, Parkinsonism symptoms, and possible accumulation and toxic effects in ophthalmic tissue.

- **Adverse Effects**:
  - The most common adverse reactions experienced (≥10%) by patients taking these agents were drowsiness (both agents), as well as fatigue and sedation (Ingrezza® only).
- **Special Populations Requiting Dose Adjustments**:
  - Patients who are cytochrome 2D6 (CYP2D6) poor metabolizers taking either agent may require a dose reduction, and these patients taking Austedo™ have a reduced maximum recommended dose. Austedo™ is contraindicated in patients with hepatic impairment, and Ingrezza® should be used with caution in patients with moderate or severe hepatic impairment, as they may require a dose reduction. Use of Ingrezza® is not recommended in patients with severe renal impairment.

PRESCRIPTION STIMULANT ABUSE AND ADD/ADHD TREATMENT

Introduction

- Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood disorders, affecting ~8% of children 4-17 years old, and can continue into adolescence and adulthood. Currently, the most commonly prescribed drugs to patients for the treatment of ADHD are stimulants such as dextroamphetamine/amphetamine (Adderall®) and methylphenidate (e.g. Concerta®), and others. While these drugs have been proven to be effective in the treatment of ADHD, healthcare providers should recognize that they also have a potential for abuse and addiction.
- Stimulants are most commonly abused by being taken at higher than prescribed doses or crushed and used in ways other than orally (intravenously or snorted). There are many reported reasons for the abuse of prescription stimulants, the most common of which are their effects on mental alertness, energy, weight loss, and for their potential to produce euphoria when abused.
- Stimulant medications work by promoting the release of the neurotransmitters dopamine and norepinephrine from their storage sites in nerve terminals.
  - Even when stimulants are used therapeutically for ADHD, they cause slow and steady increases in dopamine, a neurotransmitter often associated with addiction due to its ability to cause feelings of pleasure in the reward pathway of the brain.
  - When stimulants are abused, the dopamine levels in the brain rise much more rapidly, resulting in a feeling of euphoria due to the neurotransmitter's pleasure/reward actions, which also greatly increases the potential for addiction to these drugs.
    - Through this understanding of how and why stimulants are commonly abused, over the years, manufacturers have developed newer stimulant formulations and explored new pharmacotherapy options for the treatment of ADD/ADHD.

Overview of Treatment Options

- It should be noted that no medication indicated for the treatment of ADHD has been proven to be more effective than others, but some drugs carry a reduced potential for addiction (non-stimulant treatments) and may be less easily abused (extended release formulations and pro-drugs) relative to standard immediate-release stimulants.
    - The selective norepinephrine reuptake inhibitor atomoxetine (Strattera®), and the alpha 2-adrenergic receptor agonists clonidine (Kapvay®) and guanfacine (Intuniv®) are all non-stimulant medications indicated for the treatment of ADHD.

- While the exact mechanism of how these medications exert their effects in ADHD has yet to be determined, they have all been proven to be effective in the treatment of ADHD. Because these medications act differently from stimulants, they are considered to have little or no abuse potential and are not controlled substances.

- Prodrugs such as lisdexamfetamine (Vyvanse®) require the medication to be metabolically converted to the active drug in order to elicit its effects and, as the name implies, extended-release (ER) formulations of stimulants are released and able to be absorbed at over an extended period of time. Although achieved by different methods, both of these formulations of stimulants results in a delayed rise and fall of active drug levels in the brain relative to standard, immediate-release formulations.
    - This delay results in a slower increase in dopamine release which is why these medications are thought to carry a reduced abuse potential than the other stimulant formulations.

Immediate Release Stimulants for ADD/ADHD Treatment	**Extended Release Stimulants for ADD/ADHD Treatment**
· Adderall (dextroamphetamine/amphetamine) · Ritalin, Methylin (methylphenidate) · Dexedrine, Procentra, Zenzedi (dextroamphetamine) · Evekeo (amphetamine) · Focalin (dexmethylphenidate) · Desoxyn (methamphetamine)	· Mydayis, Adderall XR (dextroamphetamine/amphetamine) · Metadate ER, Ritalin LA, Concerta, Cotempla XR-ODT, Aptensio XR, Quillivant XR, Quillichew ER (methylphenidate) · Dynavel XR, Adzenyz XR-ODT (amphetamine) · Focalin XR (dexmethylphenidate) · Vyvanse (lisdexamphetamine)
Non-Stimulants for ADD/ADHD Treatment	
· Strattera (atomoxetine) · Kapvay (clonidine) · Intuniv (guanfacine)	

- Healthcare providers can help to reduce and prevent prescription stimulant abuse in many ways, such as;
    - Individualizing all pharmacotherapy to the patient
    - Considering the abuse and addiction risk factors of <u>both</u> the patient and the therapy choices when determining the best option for their patient.
    - Prescribing the lowest effective dose when stimulants are used to reduce the opportunity for misuse
    - Informing patients and their caregivers of the risks associated with stimulant use, and providing proper education on how to use them correctly

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.
2. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? Mov Disord 2006; 21:589.
3. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther 2010; 31:11.
4. Bhidayasiri R, Fahn S, et al. Evidence-based guideline: treatment of tardive syndromes report of the guideline development subcommittee of the American Academy of Neurology. Neurology. 2013 Jul 30;81(5):463-9.
5. Substance Abuse and Mental Health Services Administration. Results from the 2014 National Survey on Drug Use and Health: Detailed Tables. 2015. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.pdf
6. ATTENTION-DEFICIT, SUBCOMMITTEE ON. "ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents." Pediatrics (2011): peds-2011.
7. Greydanus, Donald E. "Stimulant Misuse: Strategies to Manage a Growing Problem." ACHA Professional Development Program: 1-22. Apr. 2012.
8. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed February 24, 2018.

The DUR Capsules is a quarterly newsletter published for West Virginia Medicaid Providers. Information concerning West Virginia Medicaid can be accessed online at http://www.dhhr.wv.gov/bms/.

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