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InterACT Rx™ PHARMACODYNAMIC INSIGHTS: A BRIEF LOOK AT QTc PROLONGATION, SEROTONIN SYNDROME, AND TARDIVE DYSKINESIA

Introduction

Some combinations of medications can lead to serious pharmacodynamic interactions with clinical effects that can be life-threatening in some cases. Patients taking multiple medications may need to be evaluated for drug-drug and drug-food interactions (collectively abbreviated as DDIs) in an objective manner to allow for consideration of recently ingested substances. Traditional methods of identifying DDIs typically consider patient-reported home medication lists, data from paper or electronic medical and pharmacy records, information from prescription drug monitoring programs, and/or pharmacy claims data. However, these sources may be incomplete, allowing unknown medications to continue to contribute to unevaluated drug interactions. Unfortunately, a drug interaction is not identified in some cases until the resulting adverse drug event (ADE) occurs. In this summary, three serious pharmacodynamic ADEs will be discussed: QTc prolongation, serotonin syndrome, and tardive dyskinesia.

QTc Prolongation

The QT interval, a portion of the heart rhythm measurable using an electrocardiogram (ECG), represents ventricular function of the human heart.[1] This measure is expressed in milliseconds, and when the value is corrected using a patient's heart rate, it is referred to as a corrected QT (QTc). QTc prolongation, a measure of delayed ventricular repolarization, may be indicative of patients at risk for potentially life-threatening arrhythmias.[2] The ventricular arrhythmia most often associated with QTc prolongation is known as Torsades de Pointes (TdP), which may result in sudden cardiac death.[3] A variety of factors may influence a particular patient's risk for QTc prolongation including sex, genetic predisposition, age, and medications.[4] Identifying potential causes of drug-induced QTc prolongation during treatment may allow providers to mitigate risk of life-threatening arrhythmias.

Determining if a patient has been affected by drug induced QTc prolongation can be accomplished through clinical assessment. A QTc interval >500 milliseconds (msec) is considered to be a warning sign for patients, especially when a baseline QTc for that patient has been established as normal (Men: 440 msec; Women: 460 msec). A change of >30-60 msec from baseline occurring after initiation of a new medication or following a dosage increase may also be indicative of a patient at risk for arrhythmias.[4]

The Arizona Center for Education and Research on Therapeutics (AZCERT) has developed an online database (CredibleMeds) to compile information about drug-induced QTc prolongation.[5] This database stratifies individual drugs into four categories based on level of risk and defines those categories as follows:[6]

- Known Risk of TdP: These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended.
- Possible Risk of TdP: These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.
- Conditional Risk of TdP: These drugs are associated with TdP BUT only under certain conditions of their use OR by creating conditions that facilitate or induce TdP.
- Drugs to Avoid in Congenital Long QT Syndrome (CLQTS): These drugs pose a high risk of TdP for patients with CLQTS and include all those in the above three categories PLUS additional drugs that do not prolong the QT interval per se but which have a Special Risk because of their other actions.

First Databank, Inc., the third-party vendor supporting the Aegis InterACT Rx database, utilizes information from CredibleMeds alongside case reports, published reviews, and FDA package inserts to assign risk for QTc prolongation to DDIs identified by InterACT Rx testing. All DDI descriptions provided by InterACT Rx testing have undergone rigorous review and meet inclusion criteria for both CredibleMeds and MedKnowledge, the First Databank drug information database.

Apart from medications known to cause QTc prolongation, there are other factors that may increase the risk of this negative cardiac event. These include:[7]

- Female sex
- Reduced heart rate (bradycardia)
- Electrolyte abnormalities
- Renal dysfunction

These risk factors are important to consider during the process of evaluating a patient's current therapeutic regimen. Healthcare systems have attempted to implement clinical decision support to alert providers of patients that are at the highest risk for adverse effects associated with drug-induced QTc prolongation.[7] Unfortunately, comprehensive review of risk factors for QTc prolongation is likely difficult in the outpatient setting. For this reason, utilizing a tool such as InterACT Rx to determine the presence of medications capable of causing QTc prolongation can assist in managing drug interactions as well as reduce the incidence of co-prescribing medications with additive adverse effect profiles.

Drug interactions identified by InterACT Rx reports are solely meant to supplement the knowledge base of the healthcare provider when making patient-related decisions. If an interaction is identified that may place a patient at risk for QTc prolongation, a comprehensive review of all home medications and other predisposing risk factors may be warranted. In those patients that appear to be at high risk for cardiac events associated with this adverse effect, an ECG may be required.[4] The risks and benefits of each medication involved in the drug-drug interaction should be assessed prior to any change to a patient's medication regimen. The required duration of therapy should also be determined. For example, interactions involving antimicrobial or antifungal medications may cause severe or contraindicated interactions with drugs prescribed to treat chronic disease states. By assessing length of therapy for interacting medications, a provider will be able to make an informed decision about the need for changes to prescribed drugs.

Serotonin Syndrome

Serotonin syndrome is an ADE precipitated by ingestion of substances that increase serotonin concentrations in the central nervous system. Symptoms related to this ADE include the following:[8]

- Neuromuscular excitation (muscle spasms and rigidity)
- Autonomic nervous system excitation (increased body temperature and heart rate)
- Altered mental state (agitation, confusion)

Prevalence and severity of this interaction are often influenced by the medications or drugs that are involved. Behavioral health medications that specifically target serotonin receptors may escalate the risk of these adverse effects. Patients that are prescribed multiple medications to treat psychiatric illnesses should be carefully evaluated for serotonin syndrome at the initiation of therapy or when medication doses are titrated.[9]

Due to their mechanism of action, behavioral health medications such as selective serotonin reuptake inhibitors (SSRIs) may be implicated as the major causative factor in serotonin syndrome. Serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), anti-migraine medications, some over-the-counter medications, and some illicit drugs have also proven capable of causing serotonergic toxicity.[10]

In addition to the medication classes listed above, some opioid analgesic medications have also been found to potentiate serotonin syndrome. Certain drugs within this class are more likely than others to be involved in this ADE. The opioids are grouped below based on the strength of literature characterizing their potential to cause serotonin syndrome:[9]

- Most Reported: tramadol, meperidine, fentanyl, methadone
- Case Reports: hydromorphone, buprenorphine, oxycodone
- No Case Reports: hydrocodone, codeine, morphine

The occurrence of serotonin syndrome is directly tied to the concentration of serotonin in the central nervous system. For this reason, polypharmacy involving serotonergic medications may increase the risk of dynamic drug interactions and associated adverse effects.[11] In addition to considering how concurrent usage of medications that cause release of serotonin may evoke adverse effects, one must also be aware of how drug interactions or genetic predispositions affecting metabolism may also factor into the occurrence of this ADE. Reduced metabolism of active drug, and resulting elevated concentrations, may lead to an increased potential for adverse effects.[12]

When evaluating an individual's risk for serotonin syndrome at initiation of therapy or when adjusting the dosage of a serotonergic drug, it is important to understand which drug classes may place patients at the highest risk for adverse effects. Monoamine oxidase inhibitors (MAOIs) are most often identified in serious cases of serotonin syndrome.[9-10] These drugs that were once a mainstay for the treatment of depression have fallen out of favor due to a high risk for adverse effects. A few examples of MAOIs are listed below:

- Phenelzine
- Tranylcypromine
- Isocarboxazid
- Linezolid

When an interaction that may potentially result in serotonin syndrome is identified by InterACT Rx testing, patients should be assessed for each of the previously discussed signs and symptoms. It is also important to rule out other potential drug-induced syndromes with similar adverse effect profiles, particularly neuroleptic malignant syndrome (NMS).[11] Although NMS and serotonin syndrome present similarly, the treatment and risk of adverse outcomes differ. Severe toxicity associated with either syndrome is considered a medical emergency and will likely require intensive medical treatment.

Milder cases of toxicity associated with serotonin syndrome generally resolve with removal of the offending agent.[8] It is important to understand that symptoms of serotonin syndrome are most likely to appear shortly after the initiation of therapy or an increase in dose of a serotonergic agent.[10] If an interaction is identified, and a patient has been stable on each drug that is part of the interaction, then changes to currently prescribed medications may not be necessary. The identification of the interaction may be especially helpful to providers that are preparing to adjust dosages of medications, specifically in patients that are on multiple serotonergic agents.

Tardive Dyskinesia

The term tardive dyskinesia (TD) literally means a slow onset (tardive) movement disorder (dyskinesia) with a range of possible movements, severities, and permanency. The involuntary muscle movements associated with this phenomenon can be a slight tremor or involve uncontrollable movement of the entire body.[13] Any part of the body may be involved including the face, lips, tongue, trunk, and extremities. TD is most often associated with dopaminergic antagonist medications such as antipsychotics, but it can also develop with many other classes of medications as well. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) further specifies that TD "persists despite discontinuation or change of the medications" and that diagnostic confirmation can take place after symptoms have persisted for $\geq$1 month following discontinuation of the medication.[14]

There are additional risk factors that may further predispose a patient toward the development of TD, although there is not equal agreement in the literature about the contribution of these, such as:[13,15]

- Use of both typical and atypical antipsychotics (reported cumulative annual incidence of 0.8%−3.0% with second-generation/atypical antipsychotics vs. 5.4%−7.7% with first-generation/typical antipsychotics[16])
- Older age (3.2-fold higher risk)
- Female sex (incidence rates as high as 30% after 1 year of cumulative exposure to antipsychotics)
- Previous brain injury
- Cognitive disturbance
- Dementia
- Early extrapyramidal symptoms
- African and African American Race
- Preexisting mood disorder
- Use of lithium or antiparkinsonian agents
- Diabetes
- HIV

There are several pathophysiologic pathways that have been proposed as contributing to TD, however none are considered universally accepted, and the etiology may be mulitfactorial:[13,15,16]

- Prolonged blockade of postsynaptic dopamine receptors leading to dopamine receptor hypersensitivity
- Gamma-aminobutyric acid (GABA) depletion
- Altered amino acid metabolism and GABA-containing neuron activity
- NMDA receptor excitotoxicity
- Cholinergic deficiency
- Oxidative stress (from increased dopamine metabolism and subsequent free radical production)
- Altered synaptic plasticity
- Neurotoxicity
- Defective neuroadaptive signaling
- Some evidence to suggest genetic predisposition to TD

Clinical assessment of TD is supported by the Abnormal Involuntary Movement Scale (AIMS) and the Schooler-Kane research criteria, the latter being used to identify probable anti-psychotic induced TD. The Schooler-Kane criteria require that three conditions be met:

1. Symptoms occur after >3 months of treatment with an antipsychotic
2. Abnormal, involuntary movements must occur in $\geq$2 body regions (if mild), or 1 body region (if moderate/severe) as determined by a rating scale such as AIMS
3. There are no other conditions that may be causing the abnormal movement patterns

When InterACT Rx testing identifies interacting medications with the clinical effect of an increased risk of TD, the clinician may evaluate the therapeutic indication for each medication. Some DDI scenarios resulting in increased risk for TD may come from duplicate therapies. The DDI scenario may also involve a medication that was prescribed for a short-term need, and the patient has not understood the limited timeframe they were directed to take the medication. Reviewing the patient's InterACT Rx results against their medication list with the patient to help match up current prescriptions with current diagnoses is essential to help resolve duplicate therapies and provide optimal patient medication education. Then any changes to the medication regimen to help resolve DDIs and address TD symptoms can be made with consideration of the correct and current medication list.

Putting It Into Practice

InterACT Rx testing allows providers to add on definitive testing for commonly prescribed medications in urine or oral fluid to allow for analysis of the positive results alongside positive results from medication adherence testing.

This analysis, in conjunction with data from First Databank allows for at-a-glance review of interacting pairs of medications, the severity of the interaction, and a description of the clinical effects of the interaction, which may include an increased risk for QTc prolongation, serotonin syndrome, tardive dyskinesia, and many other pharmacodynamic or pharmacokinetic DDIs. The Aegis clinical team is available to assist with the interpretation of InterACT Rx results. These results are intended to be used as tool within a comprehensive approach to ensure that optimal medication reconciliation and review is achieved.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

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