The Prescribing Cascade: A case of polypharmacy and its unintended effects
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Story from the Front Lines:

A middle aged man with history depression and generalized anxiety disorder was discharged from the hospital to a skilled nursing facility after an episode of pneumonia. The physician at the rehab, while doing his intake, noted that the patient had been on stable, though higher than usual, doses of sertraline and trazodone for the last 5 years. In an attempt to minimize the patient’s risk of developing serotonin syndrome, he tapered the patient off the sertraline over the week and a half he stayed in rehab.

On returning to his assisted living the patient began complaining of severe, uncontrolled anxiety. He was seen by a new primary doctor (PCP) around that time, who started him on clonazepam to help these symptoms.

Although this helped some, he then began experiencing severe restless leg symptoms, and was subsequently referred to a neurologist. Over the course of two visits, he was started on pramipexole, gabapentin, and amantadine. At his follow up visit with his PCP, he again complained of uncontrolled anxiety, and was eventually seen by a psychiatrist.

Based on psychiatry notes reviewed, it is not clear that a medication reconciliation was done; the notes in fact referred to a prior medication list (sans pramipexole, gabapentin or amantadine). Due to concerns that the patient’s anxiety was perhaps due to mania, the patient was started on his 5th new medicine in two months, valproic acid 1500mg BID.

Within a month of these medication changes, staff at his assisted living noted a marked change in the patient’s personality. He was much more short-tempered, often going into rages. These episodes were interspersed with periods of somnolence, where he would miss meals due to his lethargy. When a nurse confronted him about his odd behavior, he made physical threats against her. The police were then called, and the patient was admitted to the hospital out of concern for acute psychosis.

Over the course of several weeks he was weaned off the valproic acid, clonazepam, pramipexole, gabapentin and amantadine, and restarted on a stable dose of sertraline. He reported feeling like he had “finally come out of a months-long fog” and felt “back to himself”. He was eventually discharged to a different assisted living facility after an extensive review process.

Teachable Moment:

As medical providers, one of our main tenets is to do no harm. While many types of harm are obvious, others are more subtle, and may occur even when we feel we are acting in the patient’s best interests. One such harm is adverse drug events (ADEs) which are not only an important cause of morbidity and mortality, but are in many cases avoidable. One study found that as many as 28% of hospital admissions in the United States of older people are a result of drug related problems, up to 70% of which are attributed to adverse reactions to drugs.¹ Adverse drug events are never far from a physician’s mind; one can hardly prescribed a medication via an Electronic Medical Record (EMR) without being warned of the many interactions and risks associated with that drug.
As a result, it is not surprising that our patient’s rehab physician was concerned about serotonin syndrome. As a recent review in the British Medical Journal explains “Severe toxicity occurs ... with a combination of two or more serotonergic drugs (even when each is at a therapeutic dose)”. Although this is true, it is also very important to note that one of these drugs is usually a monoamine oxidase inhibitor (MAOi), and that the absence of this class of drug makes serotonin syndrome rare. In fact, one review found no reports of serotonin syndrome with the combination of trazodone and sertraline, unless a third agent (in this case tramadol) was also added.

However, fear of an ADE is only half the story. Although discontinuing the sertraline was a likely contributor to his increased anxiety, it was the polypharmacy that followed that was especially risky and probably triggered his mood lability. In analyzing the factors that contributed to polypharmacy, several things become clear. First, it is very difficult to keep on top of medication changes when a patient is seen in several different care settings. This was demonstrated after review of his many provider notes, where incomplete medication reconciliations may have enabled the addition of new drugs without stopping those that were problematic. Second, reading through other clinicians’ notes is time consuming, and nearly impossible to do in a single clinic visit (which, on average is around 20 minutes). Third, unless a patient has good health literacy and is a vocal advocate for their care, side effects can often be mistaken for an entirely different health condition, leading to unneeded pharmacotherapy. This exact effect was coined the ‘prescribing cascade’ in an article by Rochon et al, published in the BMJ in 1997. As these authors note, “when assessing a patient who is already taking drugs, a doctor should always consider the development of any new signs and symptoms a [sic] consequence of the patient’s drug treatment”.

References:

2. Buckley N, Dawson A, Isbister G. Serotonin syndrome- Practice Pointer. BMJ. 2014;348:g1626