

The Tipping Point: Methadone as a Trigger for Serotonin Syndrome
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Learning Objectives:

1. To recall the clinical criteria for diagnosis of serotonin syndrome.
2. To recognize methadone as a precipitant for serotonin syndrome.
3. To be aware of the dangers of polypharmacy.

Case Presentation: A 39-year-old white woman with a history of hypothyroidism, migraine headaches, depression, pseudotumor cerebri, and chronic pelvic pain, presented with fever, tremors and altered mental status. Four days prior to admission, she started methadone for treatment of chronic pelvic pain. Two days prior to admission, she was somnolent and developed dysuria, and was prescribed trimethoprim/sulfamethoxazole (TMP/SMX). One day prior to admission, her family noticed she was anxious and tremulous, answered questions inappropriately and was unable to perform usual activities. On the day of admission, her mental status significantly worsened and she developed fevers and tremors. The patient was taking 19 medications, including citalopram, buspirone, quetiapine, amitriptyline, levothyroxine, zonisamide, gabapentin, metformin, pravastatin, meclizine, promethazine, prochlorperazine, TMP/SMX and methadone. No recent changes in medications had been made with exception of the addition of TMP/SMX and methadone. On examination, temperature was 101.9°F with a heart rate of 122 beats per minute. She was diaphoretic, difficult to arouse, and her speech was unintelligible. Pupils were dilated, but reactive. Fundoscopic, cardiac, pulmonary, and abdominal exams were unremarkable. Extremities were tremulous and rigid with inducible clonus. CT head was unremarkable. Laboratory studies revealed sodium 132, glucose 239, white blood cell count 20, creatine phosphokinase 567, urine drug screen positive for methadone, and urinalysis positive for leukocyte esterase and nitrites. Antibiotics were given for her urinary tract infection, and intravenous fluids and benzodiazepines were given for treatment of serotonin syndrome. The patient's mental status, rigidity, and tremors improved within hours of benzodiazepine administration.

Discussion: Serotonin syndrome is an under-recognized and potentially life-threatening condition. Diagnosis is made using the Hunter Serotonin Toxicity Criteria (sensitivity 84%; specificity 97%), which requires one of the following after exposure to a serotonergic agent: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature above 100.4°F (38°C), and ocular or inducible clonus. Serum serotonin levels do not correlate with clinical findings,

however elevated white blood cell count and creatine phosphokinase or low serum bicarbonate may be seen. Medications that may induce serotonin syndrome include amphetamines, selective serotonin and/or norepinephrine reuptake inhibitors, antipsychotics, antiemetics, anti-migraines, and linezolid. In addition, certain synthetic opioids including methadone, pethidine, tramadol, dextromethorphan and propoxyphene act as weak inhibitors of monoamine reuptake. Our patient was concomitantly using seven of these medications, and the addition of methadone likely precipitated the syndrome. Treatment includes removal of offending agent(s), supportive care, and benzodiazapines for agitation and tremor. Cyproheptadine, a serotonin 2A antagonist, can be used to control continued autonomic instability. In summary, this case is a reminder that as the arsenal of medications at our disposal multiplies rapidly, we must be increasingly aware of the dangers of polypharmacy.