Bruno Riou, M.D., Ph.D., Editor

Case Scenario: Opioid Association with Serotonin Syndrome

Implications to the Practitioners

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CHRONIC pain is a complex and subjective experience reflecting interactions of sensory, affective, cognitive, behavioral, and social factors.[1] The complexity of chronic pain necessitates multidimensional therapies; however, complex analgesic regimens pose risks for adverse drug interactions.[1] Analgesic regimens frequently include different classes of analgesics: nonopioids (acetaminophen, nonsteroidal antiinflammatory agents), opioids, and/or adjuvants (antidepressants, anticonvulsants, *etc.*). Effective and streamlined management of chronic pain is further confounded by associated comorbidities,[2] especially depression, which is present in more than 60% of chronic pain patients.[1,2] Medications modulating serotonergic pathways, such as tricyclic antidepressants (*e.g.*, amitriptyline, desipramine), selective serotonin reuptake inhibitors (SSRIs, *e.g.*, fluoxetine, citalopram), or serotonin norepinephrine reuptake inhibitors (*e.g.*, duloxetine, venlafaxine) are frequently used in the treatment of depression.[2,3] As a result, it is common for patients with chronic pain to be prescribed opioid analgesics along with antidepressant medications either for the analgesic and/or antidepressant effect.[3] Less common is the awareness that opioids may significantly affect serotonin kinetics in the presence of other serotonergic agents, causing increased intrasynaptic serotonin level.[4] The following case scenarios illustrate the concern of potential iatrogenic adverse interactions of serotonergic drugs with commonly prescribed opioids in chronic pain patients.

Case One

SA was a 45-yr-old male with long-standing abdominal pain attributed to Crohn's disease, as well as low back and neck pain with associated insomnia and depression. For several years he maintained a stable regimen of 30 mg oral methadone three times a day, 60 mg duloxetine once a day, and 10 mg desipramine at bedtime.

He presented to the pain clinic for an unscheduled follow-up per his request, with new complaints of increased tremulousness, fatigue, and weakness in the bilateral upper and lower extremities. He also reported worsening insomnia and anxiety over the past week. On history, he admitted to taking more than his prescribed dose of methadone during the last 2 weeks for acute, severe renal colic pain secondary to nephrolithiasis.

On exam, SA was hypertensive, diaphoretic, and tremulous, and had stiff extremities with passive range of motion without clonus, as well as 3+ patella reflexes. This constellation of symptoms along with his history met the diagnostic criteria for serotonin syndrome. Subsequently, he was instructed to discontinue duloxetine and reduce his methadone to his prescribed dose. The low-dose desipramine was continued, as it had been effective in managing insomnia. Over the following 2 days, his symptoms resolved.

Case Two[5]

RB was a 58-yr-old male with a long history of back pain following vertebral fractures sustained in a motor vehicle

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Table 1. Timeline of Development of Symptoms and Management in Case Two

Time	Health Care Visits	Management
Day 0	Inadequate pain control.	Increase frequency of fentanyl patch replacement to every 48 h.
Day 7	Outpatient visit: Anxiety, tremulous, fever, and sweating.	Diagnosed as anxiety, started on 0.2 mg oral clonidine every 4 h.
Day 8	(24 h later) Persistence of symptoms.	Self-discontinuation of fentanyl patch.
Day 9	(12–14 h later) Emergency room visit 1: additional symptom of mild confusion.	Treated with 5 mg haloperidol and 2 mg lorazepam for agitation and anxiety, and discharged home.
Day 9	(Within 12 h) Emergency room visit 2: additional symptoms of yawning and insomnia.	Urine drug screen negative for opiates; diagnosed as acute opioid withdrawal; treated with fentanyl patch reapplication (after no fentanyl for 30–32 h); and admitted to hospital.
Day 10	(Within 8 h) Pain consult: diagnosis of serotonin syndrome made.	Treated with discontinuation of fentanyl (within 8 h of reapplication), oxycodone, citalopram and mirtazapine. Supplement with intravenous morphine sulphate as needed.
Day 11	Complete resolution of symptoms, vitals stabilized.	Restarted 45 mg morphine sulphate extended release tablet twice a day and 15 mg instant release tablet every 6 h as needed; restarted citalopram and mirtazapine.

accident 40 yr ago. History revealed long-term stable doses of medications for management of his pain and depression. These included 75 μg per hour transdermal fentanyl patch replaced every 3 days, 5/325 mg oral oxycodone/acetaminophen twice daily, 200 mg celecoxib twice daily for pain, and 40 mg citalopram once daily and 50 mg mirtazapine at bedtime for depression. In addition, he was prescribed 4 mg doxazosin for benign prostatic hypertrophy and 12.5 mg zolpidem extended-release at bedtime as needed for insomnia.

Due to his complaint of inadequate pain control, RB's frequency for replacement of fentanyl patch was increased to 2 days rather than 3 days by his managing physician. A week after the increase in fentanyl, he developed anxiety, tremulousness, fever, and sweating. He was prescribed 0.2 mg oral clonidine every 4 h for management of anxiety, but this did not improve his symptoms by the next day. RB then decided to discontinue his fentanyl patch without informing his prescribing physician, as he believed the recent increase was the cause of his new symptoms.

With persisting symptoms, RB presented to the emergency department the next day and was found to be hypertensive, tachycardic with heart rate in the low 100s, tachypneic with respiratory rate in the 20s, anxious, unable to stand still, and mildly confused. Laboratory, electrocardiogram, and drug screen were unremarkable. RB was treated with 5 mg haloperidol and 2 mg lorazepam for agitation and anxiety and discharged home (table 1).

Continuing to have persistent symptoms, he returned to the emergency department later that night with new complaints of frequent yawning and insomnia. The emergency department physician suspected opioid withdrawal, given a negative urine drug screen for opiate metabolites. However, RB claimed that he took his oxycodone as prescribed. He was admitted to the hospital with a working diagnosis of opioid withdrawal, so his fentanyl patch, which he removed 2 days prior, was reapplied. The admitting team then consulted the pain service for further management (table 1).

Further questioning by the pain service revealed that RB had a similar, although less intense, presentation of symptoms shortly after initiating oxycodone. With regard to his current symptoms, an increase in replacement frequency of his fentanyl patch was the only recent change in his medication regimen. Based on current and past symptoms being preceded by opioid medication changes in the setting of other agents affecting the serotonin pathways, the pain service diagnosed RB with serotonin syndrome. Increased fentanyl was thought to be the precipitating factor, even though he had been without his fentanyl patch for 30 h, since peripheral stores of fentanyl are cleared slowly after discontinuation of a transcutaneous patch. After making the diagnosis of serotonin syndrome, haloperidol, fentanyl patch, oxycodone/acetaminophen, citalopram, and mirtazapine were discontinued. RB had complete resolution of symptoms by the following day. For chronic pain, he was prescribed 45 mg extended-release oral morphine sulfate every 12 hours in place of the fentanyl patch, with reported good pain control and no recurrence of earlier symptoms on follow up. Since his depression had been stable on citalopram and mirtazapine before the recent increase in fentanyl, RB was discharged from the hospital with instructions to restart these antidepressants (table 1).

Case Discussion. Both of these cases highlight the limitations/complexities in the diagnosis of serotonin syndrome. They expose the consequences of polypharmacy and limited knowledge of the interactions among prescribed medications. The lack of awareness among clinical practitioners led to a misdiagnosis/missed diagnosis on two occasions in case two. Mild symptoms, overlapping features between several syndromes, and limitations of clinical diagnostic criteria for serotonin syndrome are also other confounding factors in

missed diagnosis. These two cases affirm that upon early and accurate diagnosis, discontinuation of suspicious offending agents leads to resolution of symptoms within 24 h.

The symptoms of serotonin syndrome have a direct correlation with intrasynaptic serotonin level. Hence, choice of nonserotonergic medications, dose reduction, and discontinuation of the serotonergic agents will prevent recurrence of serotonin syndrome. In case one, decreasing the dose of methadone, and in case two, replacement of serotonergic opioids (oxycodone and fentanyl) by a nonserotonergic opioid (morphine) despite continuation of the other serotonergic agents (desipramine, mirtazapine), was helpful in managing the other symptoms. In both cases the serotonergic symptoms subsided shortly after these adjustments were made with no recurrence.

Serotonin Syndrome

Serotonin syndrome is a rare, but potentially life-threatening, iatrogenic complication[4,6] from therapeutic use or overdosage of serotonergic drugs alone or in combination *via* postsynaptic hyperstimulation of 5-hydroxytryptamine (5-HT) 2A and 1A serotonin receptors in the central and peripheral nervous system.[6] Serotonin syndrome presents as a constellation of symptoms including mental status changes, neuromuscular over-activity, and autonomic instability.[6,7]

Serotonin syndrome was first described in the1950s as a drug interaction of iproniazid with pethidine, and it was soon discovered thereafter that serotonin excess was the causative factor.[4,8] The true incidence is likely underestimated because of unrecognized milder symptoms and overlapping symptoms with other diseases, making the diagnosis challenging.[9,10,11] The incidence of serotonin syndrome is reported to be 14–16% in patients who overdose with SSRIs alone.[12] However, the incidence of serotonin syndrome has been on the rise in the past 20 yr due to development of diagnostic criteria, wide usage of SSRIs, emergence of newer SSRIs, and polypharmacy.[1,13]

Symptoms manifest predictably, with rising intrasynaptic serotonin concentration ranging from mild tremors and diarrhea to severe toxic symptoms such as hyperthermia and rigidity. Intentional misuse, overdosing, or concomitant use of multiple serotonergic drugs in therapeutic dosages may result in serotonin syndrome. Occasionally, monotherapy may also precipitate symptoms,[12] but most severe reactions are attributed to polypharmacy.

Serotonin Physiology

Serotonin is an essential neurotransmitter found in the central nervous system at the brainstem raphe nuclei and in the periphery within intestinal enterochromaffin cells and platelets.[7] It is generated by hydroxylation and decarboxylation of L-tryptophan.[14] Serotonin cannot cross the blood brain barrier but its precursor metabolites can.[10,15] Serotonin mediates excitatory neurotransmission through its action on the family of G protein-coupled/ligand-gated ion channel serotonin receptors, *i.e.*, 5-HT receptors.[11,12] There are seven main types of serotonin receptor (5-HT_1 to 5-HT_7) with several subtypes described.[14] Centrally serotonin regulates wakefulness, affective behavior, core temperature, vomiting, eating behavior, and sexual behavior, and mediates nociception/analgesia. Peripherally, it modulates gastrointestinal motility and vasomotor function.[7,12] After serotonin release, postsynaptic vesicles reuptake serotonin and metabolize it to 5-hydroxy indole acetic acid *via* monoamine oxidase enzymatic action.[14]

Serotonin Syndrome Pathophysiology

Pathophysiology of serotonin syndrome is complex. Excessive postsynaptic agonism of serotonergic receptors through increased intrasynaptic serotonin level or direct receptor stimulation resulting in increased postsynaptic excitatory neurotransmission at 5-HT_{2A} and 5-HT_{1A} receptors is responsible for the development of serotonin syndrome[16] (fig. 1). Intrasynaptic serotonin excess can result from its in-

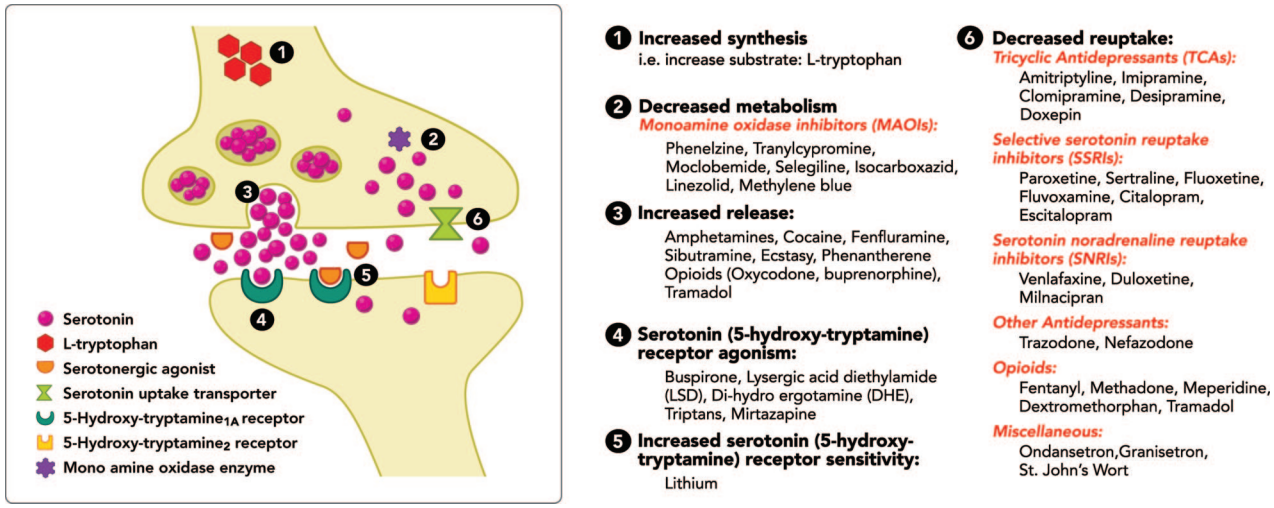

Fig. 1. Increase intrasynaptic serotonin levels: Mechanisms and associated serotonergic agents.

creased synthesis or release, as well as decreased reuptake or decreased metabolism.[12,16] There is an expanding list of agents through various mechanisms having potential to cause serotonin syndrome, as mentioned in figure 1. In addition to excessive 5-HT_{2A} and 5-HT_{1A} postsynaptic agonism,[16] there are several other factors predisposing serotonin syndrome, including:

1. Mutation of cytochrome isoforms CYP2D6 & CYP3A4, as they are key modulators of serotonin metabolism.[14]
2. Hypersensitivity of serotonin receptors from gene splices variants, allelic polymorphisms, and receptor mutations.
3. Inhibition of CYP2D6 and CYP3A4, which decreases serotonin metabolism.[14]
4. Inhibition of norepinephrine reuptake, blockage of *N*-methyl-*D*-aspartate, inhibition of γ-amino butyric acid, and antagonism of 5-HT_3 also play some role in serotonin syndrome precipitation.[7,11]

Serotonergic Opioids

Despite a limited-yet-growing armamentarium of medications to treat pain conditions, opioids remain a mainstay of pain management. Opioids are commonly used analgesics prescribed in conjunction with other serotonergic medications, thus affecting the pharmacodyanamics of serotonin. In recent years, opioids have been recognized as serotonergic agents that have been associated with serotonin syndrome.[4] Proposed mechanisms for opioids' serotonergic action include both a weak serotonin reuptake inhibition[6] and an increased release of intrasynaptic serotonin through inhibition of γ-amino butyric acid-ergic presynaptic inhibitory neuron on serotonin neurons.[3,10] Synthetic piperidine opioids are considered proserotonergic and include fentanyl,[17] methadone,[18] meperidine,[19] propoxyphene, dextromethorphan,[20] and tramadol.[21] The phenantherene morphine analogues, *i.e.*, oxycodone,[22] hydromorphone, oxymorphone, and buprenorphine[23] do not act as serotonin uptake inhibitors,[24] but may increase the intrasynaptic serotonin levels either through increased release of neurotransmitter or some unknown mechanism.[4,6,14] The list of opioids implicated in causing serotonin syndrome with other serotonergic agents is growing (table 2).

Oxycodone. Oxycodone is a centrally acting synthetic morphine analog acting on μ and κ receptors to provide analgesia. It lacks serotonin uptake inhibition property[24] but may cause increased serotonin-like activity at the synaptic level by direct action on postsynaptic membranes mimicking serotonin activity, or may release serotonin through an unknown opioid-mediated release.[24]

There are several case reports published in recent years showing synergism with other serotonergic agents to precipitate serotonin syndrome.

Fentanyl. Fentanyl is a synthetic phenylpiperidine opioid that binds with μ receptors to provide analgesia. It is a 5-HT_{1A} agonist, which augments serotonin release, and through weak serotonin reuptake inhibition, increases intrasynaptic serotonin levels.[4] There is no report of fentanyl causing serotonin syndrome as a sole agent; rather, it requires the additive action of other serotonergic agents or use in combination with SSRIs.[14] In our second case, RB had an imbalance of serotonin precipitated by an increase in fentanyl patch dosing.

Table 2. Serotonergic Opioids Association in Serotonin Syndrome

Opioid	Coadministered Agent
Tramadol	Paroxetine, fluoxetine
Oxycodone	Escitalopram, sertraline, fluvoxamine, citalopram
Fentanyl	Escitalopram, trazadone, paroxetine, venlafaxine, citalopram, sertraline, granisetron, dihydroergotamine
Methadone	Venlafaxine, sertraline, fluoxetine, linezolid
Dextromethorphan	Bupropion, methadone, citalopram, sertraline, escitalopram, chlorpheniramine, tramadol
Meperidine	Citalopram, fluoxetine, linezolid, moclobemide, venlafaxine
Codeine	Sertraline
Buprenorphine	Doxepin, amitriptyline

Methadone. Methadone, a synthetic piperidine opioid, is a racemic mixture of R/S methadone enantiomers. It exerts its analgesia through opioid receptor agonism by R enantiomer and *N*-methyl-*D*-aspartate antagonism by S enantiomer.[14] It is metabolized by hepatic enzymes and is a CYP2D6 enzyme inhibitor, which indirectly inhibits metabolism of tramadol to its active metabolite M_1, making tramadol less effective upon its concomitant usage.[25] *In vitro* studies of methadone show a greater tendency toward serotonin reuptake inhibition compared with other opiates, which may explain methadone-mediated precipitation of serotonin syndrome.[4] In our first case, SA's increased use of methadone was responsible for precipitation of serotonin syndrome.

Tramadol. Tramadol is a racemic mixture of RR and SS enantiomers. It is metabolized by liver enzymes to a more pharmacologically active metabolite, M_1.[14] The RR enantiomer is a μ receptor agonist, while the SS enantiomer inhibits reuptake of norepinephrine and releases serotonin.[25] Thus tramadol results in intrasynaptic serotonin excess when combined with other serotonergic drugs.[6]

Dextromethorphan. Dextromethorphan, a d-isomer of levorphanol, is a cough suppressant *via* action on σ opioid receptors. Its active metabolite, dextrorphan, antagonizes *N*-methyl *D*-aspartate receptors, whereas dextromethorphan itself binds 5-HT_{2A} receptors that may cause serotonin syndrome.[14,24,25] Since the hepatic enzyme, CYP2D6 metabolizes it; an inhibitor of CYP2D6 can also further increase serotonin levels.[14]

Diagnosis of Serotonin Syndrome

Serotonin syndrome is a diagnostic challenge because of its variable and overlapping clinical manifestations. This is further confounded by overall lack of awareness among physi-

cians,[7,26] limitations of diagnostic criteria, inaccurate diagnosis, and individual differences in serotonin metabolism.[26] In fact, milder forms of this disorder may go unrecognized.[14] Our second case report exemplifies all of these challenges, which led to two misdiagnoses before serotonin syndrome was correctly diagnosed and treated.

Serotonin syndrome should not be a diagnosis of exclusion but one made after careful history-taking, to glean information on changes in serotonin agents, and a focused physical exam. Index of suspicion should be high with a history of serotonergic agent intake and other medical and psychiatric conditions need to be excluded.[6,7,12] Patients with a history of known exposure to serotonergic agents may have a constellation of clinical symptoms described as a triad[4,7,10,11,26] of:

Mental status changes: Anxiety, agitation, confusion, hypomania, visual hallucinations, restlessness, disorientation, and coma.

Neuromuscular abnormalities: Muscle rigidity, tremors, nystagmus, myoclonus, ocular clonus, hyperreflexia, ataxia, and trismus.

Autonomic instability: hyper/hypotension, tachycardia, tachypnea, diarrhea, mydriasis, diaphoresis, and hyperthermia.

A predictable spectrum of symptom manifestation directly correlates with intrasynaptic serotonin level[6,11,27,28] (fig. 2). Milder forms may present with anxiety, akathisia, diarrhea, and tremors, but full-blown serotonin syndrome may present with altered mental status and myoclonus. Severe serotonin toxicity, however, may be a life-threatening crisis with muscular rigidity more pronounced in lower extremities, hyperthermia, and coma.[6,11] Symptoms with escalating toxicity, if left untreated, may result in more severe complications including metabolic acidosis, rhabdomyolysis, disseminated intravascular coagulation, seizures, and death.[3,7,10]

Typically, serotonin syndrome symptoms present soon after the offending medication regimen is initiated. Usually symptoms appear within 6 h of ingestion of the drug or drugs (60% of cases). By 24 h, a majority (more than 75%) of patients are symptomatic.[7,10] In a subset of patients (7%), some of whom are older, the onset may be delayed for a few days because of a decreased neurotransmitter serotonin synthesis and decreased receptor density with age (18% fall in 5-HT_{2A} receptors per decade).[29] Although symptoms resolve within 24 h of stopping the offending agent, in 60–70% of

Fig. 2. Spectrum of serotonin syndrome and their management strategies.

serotonin cases, there is still a 2–12% mortality risk associated with serotonin toxicity.[7,15]

No specific lab abnormality is diagnostic of serotonin syndrome.[7,12] Blood serotonin level does not correlate with the severity of the disease since it does not reflect intrasynaptic serotonin level. Some observed lab abnormalities include electrolyte derangements, metabolic acidosis, increased creatinine, and increased serum aminotransferase.[10,12,15] These are associated with muscular hypertonicity and possible rhabdomyolysis, which may be seen in cases of severe serotonin toxicity.[6,7,11]

Due to lack of specific laboratory tests, several clinical diagnostic criteria for serotonin syndrome have been established.[3,7,30] Of course, a history of recent exposure to serotonergic agent(s) is a prerequisite to considering serotonin syndrome and utilization of these criteria. The two most commonly used criteria for diagnosing serotonin syndrome are shown in table 3. They are Sternbach's Criteria, (sensitivity 75%, specificity 96%),[11,30] and Hunter Serotonin Toxicity Criteria, (sensitivity 84%, specificity 97%).[30]

Several medical conditions, some involving toxicity, can mimic serotonin syndrome.[4] Many of these can be ruled out by careful, thorough history and physical examination. The clinical mimics include: neuroleptic syndrome, malignant hyperthermia, anticholinergic syndrome, opioid withdrawal, and acute opioid toxicity[31] (table 4).

Neuroleptic syndrome can be precipitated by use of antipsychotic medications and may present with similar symptoms, such as hypertension, tachycardia, tachypnea, pallor, stupor, and coma. The two entities differ in onset of symptoms, hyporeflexia, decrease or normal bowel sounds, lead-pipe rigidity, and hyperthermia of more than 41°C.[14,31]

Malignant hyperthermia is differentiated by exposure to inhaled halogenated anesthetics or depolarizing paralytic agents with associated hyperthermia of 42–46°C, hypercarbia, acidosis, muscular rigidity, hyporeflexia, decreased bowel sound along with hypertension, tachycardia, tachypnea, mottled skin, and agitation.[14,31]

Anticholinergic syndrome carries a history of tricyclic antidepressant or anticholinergic agent use and is associated with dry mouth, blurred vision, delirium, decreased bowel sounds along with tachycardia, tachypnea, and hyperthermia of 40°C.[31]

Table 3. Diagnostic Criteria for Serotonin Syndrome

Sternbach's Criteria	Hunter Serotonin Toxicity Criteria
A. Recent addition or increase of serotonergic agent	History of serotonergic agent usage
B. No recent addition or increase of neuroleptic agent	
C. Rule out other etiologies, such as infections, substance abuse or withdrawal	
At least three of the following:	At least one or more of following:
1. Altered mental status (confusion, hypomania)	1. Clonus: spontaneous, inducible, ocular
2. Agitation	2. Agitation
3. Myoclonus	3. Autonomic dysfunction (*i.e.* hyperthermia)
4. Hyperreflexia	4. Tremor
5. Diaphoresis	5. Hyperreflexia
6. Shivering	
7. Tremor	
8. Diarrhea	
9. Poor coordination	
10. Fever	

Management and Prevention

Serotonin syndrome has a favorable prognosis with symptoms resolving in the majority of cases within 24 h of stopping the serotonergic agent[10]; however, in 30–40%, symptoms persist beyond 24 h and require more intense care[15] (fig. 2). Anxiety and agitation can be managed with anxiolytics. Moderate to severe presentation may require serotonin receptor antagonists, *i.e.*, cyproheptadine (per oral form in 2 mg incremental doses for a maximum of 12–32 mg in 24 h) or chlorpromazine, a phenothiazine derivative, (available in oral and intravenous formulation in a dose of 50–100 mg) to decrease intrasynaptic serotonin level through 5-HT blocking action.[4,7,10] Cyproheptadine is only available in oral form, which limits its usage if oral intake is not possible or activated charcoal is already used in management of toxic agent ingestion. Chlorpromazine is the preferred alternative as it can be administered in intravascular form, but the patient needs to be well hydrated to prevent significant hypotension from its use.[4,9] Severe symptoms require intensive care for neuromuscular paralysis and subsequent ventilatory support[4,10,27] to decrease rigidity, hyperthermia, and complications of rhabdomyolysis. Succinylcholine and physical restraints should be avoided due to detrimental effect in the setting of rhabdomyolysis. The symptoms can also be managed by nitroglycerine through its conversion to nitric oxide,[32] short-acting benzodiazepines (*i.e.*, Lorazepam) for agitation, anxiety and hyperexcitatory symptoms,[10,12] and β blockers (*i.e.*, propranolol) for autonomic symptoms of serotonin syndrome.[11,12] A recent case report suggested some promise in the use of Intralipid for severe serotonin toxicity for its transient ability to draw tissue and receptor bound serotonergic drugs into lipid-expanded intravascular compartment, trapping them in a lipid phase[33] (fig. 2).

It is undeniably easier to prevent than to have to treat serotonin syndrome. Prescribing physicians should strive to identify at-risk patients by maintaining clear and frequent communication with other prescribing physicians regarding changes and addition of new medications. Patients in an older age group, with multiple comorbidities or polyphar-

Table 4. Differential Diagnosis of Serotonin Syndrome

Clinical Conditions	Distinguishing Features
Serotonin syndrome (serotonin excess)	Cognitive: anxiety, agitation, confusion, hypomania, visual hallucinations, restlessness, disorientation, and coma. Autonomic: hyper/hypotension, tachycardia, tachypnea, diarrhea, mydriasis, diaphoresis, and hyperthermia. Neuromuscular: muscle rigidity, tremors, nystagmus, myoclonus, ocular clonus, hyperreflexia, ataxia, and trismus
Neuroleptic malignant syndrome (dopamine antagonism)	Extrapyramidal symptoms, "lead pipe" rigidity, gradual onset, bradykinesia, absence of gastrointestinal hyperactivity, myoclonus, and hyperreflexia
Anticholinergic syndrome (cholinergic antagonism)	History of anticholinergic agent use (such as tricyclic antidepressants), widened pulse pressure, dry skin and mucus membranes, normal reflexes, absence of myoclonus, and gastrointestinal hyperactivity
Malignant hyperthermia	History of halogenated anesthetic and depolarizing muscle relaxant exposure, hyporeflexia, and absence of myoclonus
Opioid toxicity	History of opioid exposure, miosis, hypotension, hypothermia, bradycardia, hypopnea, and hyporeflexia
Opioid withdrawal	History of sudden opioid discontinuation or intake of opioid antagonist agents, piloerection, joint pains, "flu-like" symptoms, absence of hyperreflexia, and myoclonus

macy along with serotonergic drugs (fig. 1), or on monoamine oxidase inhibitors, should be considered as relatively high risk for development of serotonin syndrome. Physicians should also select the less toxic anticonvulsants, acetaminophen, and morphine, over morphine analogues and piperidine opioids, when appropriate. Upon switching serotonergic agents, care should be given regarding their half-life to provide enough washout periods before trying newer serotonergic agent.[7]

Knowledge Gap

Serotonin syndrome is a complication of polypharmacy that has been described in the literature for decades. Its occurrence is attributed to missed and inaccurate diagnosis. Factors responsible for the missed diagnosis include lack of awareness and knowledge among health professionals regarding its clinical presentation and clear understanding of interactions among the multiple serotonergic medications. Variations in serotonin metabolism, overlapping clinical presentation, mild symptoms, and limitation of diagnostic criteria often make the diagnosis challenging. The common offending agents have been well characterized but there needs be a shift in attention to the commonly prescribed opioids as a possible trigger for the potentially deadly serotonin syndrome.

Anesthesiologists need to be aware of the increased risk of serotonin syndrome in the perioperative setting, where high dose opioids are often administered. Similarly, practitioners in chronic pain management, where use of opioids in conjunction with other serotonergic agents is the norm, must also have heightened sense of awareness. Patient history should be carefully evaluated for concomitant use of serotonergic agents including mono-amine-oxidase inhibitor, SSRIs, and several nonprescribed agents, such as herbal medications, St. John's wort,[34] the street drug ecstasy,[27,35] commonly used cough syrup ingredient dextromethorphan, and weight loss drugs fenfluramine[35]and sibutramine. In addition, methylene blue[37] dye, which is commonly used intraoperatively to delineate lymphovascular channels, has also been shown to be associated with severe serotonin syndrome. Thus, seemingly unrelated classes of pharmacological agents have the potential to cause serotonin syndrome with simultaneous use of serotonergic agents. Opioids have now been recognized to be such an agent.

The mechanism of increased serotonin levels caused by commonly used opioids is still being studied, and treatment options involve mostly supportive care of manifesting symptoms. Future therapy may be directed toward identifying the molecular and pharmacological variables and specific receptor action and/or antagonism, but the most effective treatment is likely preventive medicine. Polypharmacy needs to be carefully selected, monitored, and avoided where possible to achieve better patient care and decrease the risk of excessive socioeconomic burden to society.[1] As more research and physician awareness is directed toward serotonin syndrome, our insight into the condition will invariably expand, and both morbidity and mortality will be reduced.

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