Anesthetic Considerations for Patients on Antidepressant Therapy – Part II

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Millions of patients take antidepressant medications in the United States for the treatment of depression or anxiety disorders. Some antidepressants are prescribed off-label to treat problems such as chronic pain, low energy, and menstrual symptoms. Antidepressants are a broad and expansive group of medications, but the more common drug classes include tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors. A miscellaneous or “atypical” category covers other agents. Some herbal supplements that claim to have antidepressant activity will also be discussed. Part I of this series reviewed antidepressant pharmacology, adverse effects, and drug interactions with adrenergic agonists. In part II, drug–drug interactions with sedation and general anesthetics, bleeding effects, and serotonin syndrome will be discussed.

Part I of this series discussed antidepressant pharmacology and interactions with adrenergic agonists. In part II, we will focus on Sedation and General Anesthetic Drug Interactions, Serotonin Syndrome, and other anesthetic concerns with antidepressants.

SEDATION AND GENERAL ANESTHETIC DRUG INTERACTIONS

Tricyclic Antidepressants (TCAs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

As noted in part I, both the TCAs and the SNRIs inhibit the reuptake of both serotonin and norepinephrine. The tertiary amine TCAs (eg, amitriptyline,* imipramine, clomipramine, doxepin,* trimipramine) tend to inhibit the reuptake of serotonin more than norepinephrine while the secondary amines (eg, desipramine, nortriptyline, protriptyline) tend to inhibit the reuptake of norepinephrine preferentially. Sympathetic nervous system activation and use of adrenergic agonists, both direct and indirect, may lead to exaggerated symptoms of hypertension and tachycardia, particularly for the more

noradrenergic TCAs. This is likely dose related such that lower doses less than 25 mg/day may not exhibit significant interaction. Recall as well that several tertiary amine TCAs have active metabolites that are secondary amines: amitriptyline to nortriptyline; doxepin to nortoxepin; and imipramine to desipramine.¹ Therefore, even the “serotonergic” TCAs likely possess some norepinephrine reuptake inhibition. These same considerations apply to the SNRIs, which tend to be more selective for norepinephrine reuptake inhibition than for serotonin. Metabolism of TCAs is generally via the cytochrome P450 system with CYP 3A4, 2D6, 1A2, 2C9, and 2B6 commonly involved. Inhibition of various CYP enzymes by TCAs is variable and should be reviewed during preoperative evaluation. For the SNRIs, venlafaxine is a weak inhibitor, and duloxetine a moderate inhibitor, of CYP 2D6. Genetic polymorphism of this enzyme system may affect metabolism.²

Due to adrenergic agonist concerns noted above, ketamine, a dissociative anesthetic that likely has indirect acting sympathomimetic effects, should be used cautiously and carefully titrated, particularly in those with cardiovascular compromise.^{3,4} As noted in part I, chronic TCA therapy may lead to depletion of catecholamine stores and adrenergic downregulation minimizing these unwanted cardiovascular effects. Vagolytics, such as pancuronium, should be avoided, particularly if resting tachycardia is noted.³ Serotonin syndrome concerns are addressed below.

Although unlikely to be encountered in anesthesia practice, flumazenil is contraindicated in TCA overdose.⁵ TCA overdose may cause seizures that may then be treated

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Figure 1. Analgesic prodrugs, codeine and tramadol, require metabolism by CYP 2D6 to their active metabolites, morphine and o-desmethyltramadol, respectively. CYP2D6 inhibition by SSRIs (fluoxetine, paroxetine) may result in inadequate analgesia. From Hersh EV, Moore PA. *JADA*. 2004;135:298–311.

with benzodiazepines.¹ Respiratory depression and over sedation may result from benzodiazepine administration, and this may occur synergistically in the postictal state during a TCA overdose. Administering flumazenil can worsen seizures in the setting of a TCA overdose.⁵

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs may be involved in several notable drug interactions such as cytochrome P450 inhibition, synergistic effects with anticoagulants, and serotonin syndrome. Several SSRIs are potent CYP inhibitors, including fluoxetine, paroxetine, and fluvoxamine.¹ Venlafaxine, an SNRI, is both an inhibitor and substrate of CYP 2D6.⁶ A notable interaction with CYP 2D6 in the postoperative period concerns the administration of analgesics for postoperative pain containing codeine or tramadol (Figure 1). Both codeine and tramadol are prodrugs that require metabolism by CYP 2D6 to their active metabolites, morphine and o-desmethyltramadol, respectively. Inhibition of CYP 2D6 will reduce the amount of prodrug that is converted to active drug, resulting in inadequate analgesia.^{7,8} The prescription of such prodrugs should be avoided in patients taking known CYP 2D6 inhibitors, including some SSRIs, some SNRIs, and some TCAs, which produce clinically relevant inhibition.

Monoamine Oxidase Inhibitors (MAOIs)

As noted in part I, due to increasing stores of presynaptic norepinephrine in sympathetic nervous

Bottom Line: SSRIs + NSAIDs = Increased Bleeding Risk

Figure 2. Increased risk of bleeding with selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drug (NSAIDs). Pinto A, Farrar JT, Hersh EV. *Compend Contin Educ Dent*. 2009;30:142–151.

system neurons associated with MAOIs, indirect acting sympathomimetic agents should also be avoided. Ketamine, a dissociative anesthetic that likely has indirect acting sympathomimetic effects should be avoided.³ Meperidine is contraindicated with MAOIs due to triggering of serotonin syndrome. See below for a full discussion of serotonin syndrome.

St John's Wort is a potent CYP 3A4 inducer such that oral midazolam is likely to exhibit less effectiveness.

Bleeding and Antidepressants

Patients taking SSRIs and SNRIs may be at risk for bleeding through the reduction of platelet levels of serotonin. This antiplatelet effect enhances this effect caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and increases bleeding risk in patients taking warfarin and other nonvitamin K antagonist oral anticoagulants (NOACs).^{1,6,9–12} Serotonin is released by platelets and plays a role in their aggregation and clot formation. There may be less serotonin available for uptake by platelets with concomitant SSRI and SNRI use (Figure 2).^{9,11,13} Additionally, serotonin reuptake inhibition may also cause a decrease in serotonin receptor density on the platelet surface.¹³ Patients taking SSRIs have a three-fold increased risk of a serious upper gastrointestinal (GI) bleeds. NSAIDs, and particularly aspirin, interfere with platelet aggregation and enhance the risk of bleeding, especially in older patients.^{10,11} The addition of NSAIDs to SSRIs synergistically increases the risk of an upper GI bleed 15-fold as compared to an individual taking neither of these medications.^{8,13} SSRIs with relatively higher degrees of serotonin reuptake

inhibition such as fluoxetine, paroxetine, and sertraline (as well as the very highly serotonergic TCA, clomipramine) induce a higher risk of bleeding episodes.^{10,11} SSRIs may also inhibit the metabolism of NSAIDs, which may increase plasma levels of NSAIDs, elevating the risk for GI perforations, ulcerations, and bleeds. SSRIs such as paroxetine, sertraline, and fluvoxamine are CYP 2C9 inhibitors of enzymes that metabolize various NSAIDs including ibuprofen, naproxen, diclofenac, and celecoxib.⁸

SSRIs and warfarin are both highly plasma protein bound drugs. A potential for a plasma protein competition (protein bumping) interaction may occur when drugs such as paroxetine binds albumin as avidly as warfarin and displaces the warfarin resulting in increased free serum warfarin concentrations.¹ Warfarin is a CYP substrate as well. The more potent S-warfarin isomer is a substrate of 2C9, while the less potent R-isomer is a substrate of 1A2, 2C19, and 3A4. SSRIs, including fluoxetine and paroxetine, may interfere with the metabolism of the S-warfarin isomer by inhibiting CYP 2C9 and therefore increasing the plasma concentration of warfarin.^{3,6}

While a thorough discussion on anticoagulant therapy management is outside the scope of this paper, the practitioner should pay particular attention to patients being prescribed warfarin and the NOACs particularly when also prescribed antidepressants. The practitioner should review PT/INR and other applicable tests to determine whether the patient is therapeutically anticoagulated. Any changes to warfarin treatment should be made in collaboration with the patient's prescribing physician.

Serotonin Syndrome

Serotonin syndrome is a potentially fatal consequence of excessive central nervous system serotonergic activity, which may occur with therapeutic doses of medications, but is more likely attributable to overdose or drug–drug interactions that contribute synergistically to increased serotonergic activity.^{3,14–16} The most publicized case of serotonin syndrome is the death in 1984 of Libby Zion, a patient in New York City, which highlighted the fatal drug interaction of meperidine and phenelzine (an MAOI) precipitating serotonin syndrome, as well as calling attention to the need to improve medical resident work hours to prevent such an avoidable and tragic error.^{15,17} The incidence of serotonin syndrome in patients taking serotonergic drugs at therapeutic doses is 0.2 to 0.5%. In SSRI overdose, the incidence rises to 14 to 16%.^{15,18,19} The actual incidence may be higher

than reported and likely to rise with increased antidepressant prescriptions; increased potential for polypharmacy and drug–drug interactions; and increased awareness of serotonin syndrome with improved diagnostic criteria.^{14,20} Serotonergic transmission is usually terminated by the presynaptic reuptake of serotonin and subsequent metabolism by MAO in the presynaptic neuron.²¹ Agents capable of increasing serotonin levels and precipitating serotonin syndrome include antidepressants (SSRIs, SNRIs, TCAs, MAOIs) alone or in combination with other proserotonergic medications such as phenylpiperidine opioids (particularly meperidine, but potentially fentanyl and its derivatives) tramadol, dextromethorphan, ondansetron, metoclopramide, methylene blue, erythromycin, metronidazole, the antimigraine medications “triptans,” selegiline, the second generation (atypical) antipsychotics (eg, aripiprazole, clozapine, olanzapine, quetiapine, risperidone) St. John's wort, and 3,4-methylenedioxy-methamphetamine (MDMA or ecstasy).^{1,3,9,12,14–16,20,22–24} It should be noted that serotonin antagonists, such as the 5-HT₃ antagonist antiemetics, may inhibit binding of serotonin to this subset of receptors thus increasing availability of serotonin to other serotonin receptors. In this way, serotonin syndrome may be precipitated. Furthermore, administration of drugs that inhibit cytochrome P450 2D6 and 3A4 may hinder metabolism of some SSRIs and SNRIs, resulting in supratherapeutic levels of these antidepressants increasing serotonergic activity.¹⁵

Serotonin syndrome manifests with a triad of symptoms: autonomic instability, neuromuscular abnormalities, and changes in mental status. Autonomic instability may present as mydriasis, diaphoresis, diarrhea, tachypnea, tachycardia, hyperthermia, hypertension, or hypotension. Neuromuscular abnormalities may manifest as tremors, hyperreflexia, myoclonus, trismus, ataxia, muscle rigidity, or myoclonus. The myoclonus is typically described as “cogwheel” with a rigid and jerking motion on flexion of an extremity. Changes in mental status may present as agitation, anxiety, confusion, disorientation, restlessness, visual hallucinations, or coma.^{1,12,14–16,20,22} Serious complications may include disseminated intravascular coagulation, hyperthermia, metabolic acidosis, renal failure, rhabdomyolysis, seizures, coma, and death.^{1,12,15,16,20,22}

There is no diagnostic test for serotonin syndrome, but it is rather a clinical diagnosis underlied by an exposure to proserotonergic medications, over the counter (OTC) agents, herbal substances, or recreational drugs.¹⁵ The Hunter Serotonin Toxicity Criteria outlines diagnostic criteria including a history of taking serotonergic medications in the last 5 weeks and at least one of the following signs or symptoms: hyperreflexia and tremor; spontaneous clonus; inducible or ocular clonus with

agitation or diaphoresis; inducible or ocular clonus with hypertonia and elevated body temperature (over 38°C).^{14,16,20,25} Severe muscle rigidity may obscure the observation of hyperreflexia and clonus.¹⁵

This clinical diagnosis is confounded by the fact that not all patients present with the exact same constellation of symptoms and degree of severity.^{14,22} One case report highlights the subtlety of the presentation of this toxidrome: an otherwise healthy patient who was taking fluoxetine for severe depression and anxiety, underwent orthopedic surgery with regional anesthesia and total intravenous anesthesia (TIVA) consisting of fentanyl and propofol for induction and maintenance with remifentanyl and propofol. He had mild clonus at the ankles, diaphoresis, and nystagmus. Fortunately, neuromuscular blockers (NMB) were not administered, as they might have masked some of these signs. Inadequate anesthesia was ruled out as there was no hemodynamic response indicating light anesthesia. The symptoms subsided once the remifentanyl infusion was discontinued. Upon further investigation, the patient disclosed that he had a similar episode of involuntary “tremors and muscle contractions” and agitation after taking opioid analgesics 6 months earlier. It was short lived and the patient discontinued the opioid use.²² Clonus has been noted in some patients only following reversal of the NMB.

In another reported case, a patient taking SSRIs had presented with serotonin syndrome after an uneventful extraction and incision and drainage of an abscess. It is important to note that the patient had not received sedation or any precipitating medications from the oral surgeon. He recently had an SSRI dose increase and then self-administered oral dextromethorphan, an OTC cough medication the prior day. Dextromethorphan (an opioid analog), although approved for OTC use, can inhibit serotonin reuptake. The patient’s symptoms began with autonomic instability, mental status changes, and lower limb clonus but escalated through his 7-day hospital admission and management. Treatment included management of severe hyperthermia, arrhythmias, and subsequent intubation.¹⁶ During procedural sedation, serotonin syndrome should be considered in the differential if the patient on serotonergic medications presents with clonus, especially in the lower limbs.^{15,16}

A retrospective analysis of patients who were administered fentanyl while also taking a serotonergic medication found that serotonin syndrome can occur, although the incidence is low. It may be possible that there is a higher incidence of serotonin syndrome with fentanyl but that it is confounded by underdiagnosis or underreporting, highlighting the need for additional research in this area.²³ It is important to note that

serotonin syndrome may occur with opioid analgesics prescribed for postoperative analgesia.²² There are also reports of serotonin syndrome occurring with tramadol therapy with or without other serotonergic medications.^{26,27} Tramadol, a DEA schedule IV substance, is a weak opioid agonist that has serotonin reuptake inhibition. Ultimately, the prescribing dentist must be aware of the proserotonergic activity and potential adverse effects of this drug before prescribing it.

Treatment of serotonin syndrome consists first of recognition, then discontinuation of any serotonergic medications, and early transfer to a hospital facility for supportive care to manage symptoms.^{12,14–16,22} Prevention and avoidance of serotonin syndrome in the perioperative period is the best approach and begins with a proper preoperative history and physical to identify patients taking any serotonergic medications (including recent dosage adjustments), herbal supplements including St. John’s wort, and OTC products. Should serotonin syndrome be suspected, supportive care may include benzodiazepines to treat agitation.^{15,16} Autonomic instability should be managed with direct-acting alpha and beta adrenergic agonists to treat hypotension and bradycardia, respectively, and nitroprusside and esmolol for hypertension and tachycardia, respectively.^{12,15} Indirect-acting adrenergic agents, such as ephedrine, should be avoided if there is concomitant TCA, SNRI, or MAOI administration.^{1,15} Propranolol, a nonspecific beta blocker, should not be used as it can cause both hypotension and bradycardia, resulting in cardiovascular collapse in patients with autonomic instability.¹⁵ In severe cases, the patient may require neuromuscular blockade, endotracheal intubation, and mechanical ventilation to control myoclonus and hyperthermia.^{15,22} Succinylcholine should be avoided as the hyperkalemia secondary to succinylcholine administration combined with the hyperkalemia associated with rhabdomyolysis increases the risk of arrhythmias.¹⁵ Cyproheptadine, a 5-HT_{1A} and 5-HT_{2A} antagonist antihistamine, is available to mitigate the effects of excessive serotonergic transmission in mild to moderate presentations of serotonin syndrome.^{12,15,16,20,22} Hyperthermia is a result of severe myoclonus, and therefore, antipyretic therapy is not indicated nor efficacious in reducing body temperature.^{14–16} The onset of serotonin syndrome usually occurs within 1 day of exposure to the precipitating agents and resolves within 1 day of discontinuing the agents and initiating supportive care.^{12,14–16} However, some patients may need prolonged monitoring and intervention if the precipitating agents have long half-lives or active metabolites.¹⁶

CONCLUSIONS

All patients and especially those with mood disorders may experience heightened anxiety prior to dental and/or maxillofacial procedures. It is generally accepted that it is safe to administer anesthetics to patients on antidepressants; however, the anesthesia provider must be aware of the risk of potential drug–drug interactions; serotonin syndrome; hemodynamic changes; and/or bleeding issues. It is imperative for the anesthesia provider to take a thorough medical history, including all medications, OTC products, herbal supplements, and recreational drugs as well as their duration of use and any recent changes in dosing regimens.^{12,16}

In the perioperative setting, benzodiazepines are the drug of choice for anxiolysis. There is a correlation between increased postoperative pain scores and chronic depression. Patients may benefit from ketamine (approximately 1 mg/kg), administered intraoperatively for improvement in both postoperative pain scores and mood, assuming cardiovascular effects are considered.¹² The decision to hold or continue antidepressant medications preoperatively should be carefully considered, taking in to account any potential withdrawal symptoms and/or relapse of psychiatric disease due to discontinuation with the risk of any serious perioperative events such as drug–drug interactions or hemodynamic events due to continuation.^{9,12} Stopping an antidepressant for 1 day due to surgery, or delaying administration to after surgery, is unlikely to affect mood but may mitigate some unwanted cardiovascular effects.

Serotonin syndrome is a potentially lethal consequence of excessive serotonergic activity, and presents with a triad of symptoms: autonomic instability, neuromuscular abnormalities, and changes in mental status.^{1,12,14–16,20,22} Providers must take a careful history for any potentially proserotonergic agents as this is a clinical diagnosis that can be made if the provider is aware of the patient's medication history. Proserotonergic agents should be administered cautiously to patients on antidepressant therapy during anesthesia care and postoperatively. Profound local anesthesia and multimodal regimens have many merits including a reduction in total opioid consumption and risk of opioid-induced serotonin syndrome.^{1,28}

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CONTINUING EDUCATION QUESTIONS

This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and utilize the information appropriately in providing patient care.

The American Dental Society of Anesthesiology (ADSA) is accredited by the American Dental Association and Academy of General Dentistry to sponsor CE for dentists and will award CE credit for each article completed. You must answer 3 of the 4 questions correctly to receive credit.

Submit your answers online at www.adsahome.org. Click on “On Demand CE.”

1. Which one of the following medications is specifically used to treat serotonin syndrome:
 - A. Cyproheptadine
 - B. Dantrolene
 - C. Epinephrine
 - D. Succinylcholine
2. Patients taking SSRIs and SNRIs may be at risk for bleeding through the reduction of platelet levels of serotonin. With respect to the administration of, or prescription for, analgesics, which drug class has the least concern for excessive bleeding in an otherwise healthy patient?
 - A. Acetaminophen
 - B. Ibuprofen
 - C. Naproxen
 - D. Tramadol
3. Which analgesic is most appropriate for a patient who is chronically taking paroxetine for depression?
 - A. Codeine
 - B. Oxycodone
 - C. Tramadol
 - D. All of the above
4. Serotonin syndrome is a potentially fatal consequence of excessive CNS serotonergic activity which may occur with therapeutic doses of medications, but is more likely attributable to overdose or drug–drug interactions which contribute synergistically to increased serotonergic activity. With respect to administration of analgesics, which of the following drugs is least likely to contribute to serotonergic activity?
 - A. Alfentanil
 - B. Meperidine
 - C. Morphine
 - D. Tramadol