Chapter

Anesthetic Concerns in Psychiatric Disease

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Abstract

As the prevalence of mental health illnesses rises worldwide, the use of psychotropic medications follows. Undoubtedly, many patients using psychotropic medications will undergo procedures requiring anesthesia both in the operating room and outside of it. This chapter focuses on psychotropic medications that may complicate the surgical and postoperative course of patients undergoing anesthesia. Toward this aim, we performed a literature review using targeted key terms. Relevant articles were cited, and findings are summarized in this narrative review. We begin with discussing psychotropic medication pharmacology, drug-drug interactions, and side effects, emphasizing their interaction with anesthetic agents. We summarize the current recommendations for managing these medications in the perioperative period. In the discussion section, we focus on highlighting future directions for the intersection between psychotropic medications and anesthesia. Overall, we provide insight into the perioperative management of patients taking psychotropic medications, the point of intersection between the fields of psychiatry and anesthesia.

Keywords: antidepressants, antipsychotics, anxiolytics, stimulants, substances, ketamine, dexmedetomidine, samidorphan, lumateperone, medication-assisted treatments, herbal supplements

1. Introduction

As of 2022, an estimated nearly one billion people around the globe carry a diagnosis of at least one mental health condition or substance dependence disorder [1]. Focusing on the United States, there has been an increase of psychiatric disease prevalence over the last 30 years [2]. Subsequently, there has been a rise in the consumption of psychotropic medications with the greatest increase seen for antidepressants, which are commonly long-term medications [3]. This fact is supported by a

study in 2017 finding that in a sample of surveyed patients taking psychotropic medications, 84.3% responded that they had taken their medication for at least 3 years [4].

Given the increase in mental health disorders and subsequent rise in utilization, we expect an increased number of patients presenting for outpatient or inpatient procedures requiring anesthesia. Some of these drugs, if taken in conjunction with sedatives, can have dangerous interactions, and some of these interactions can be life threatening. Thus, anesthesiologists and anesthesia professionals must be informed of the potential side effects, drug-drug interactions, and management of these drugs in the perioperative setting. Furthermore, if discontinued, various psychotropic medications will cause withdrawal symptoms and can impact the patient's well-being and management.

This chapter describes the most used psychotropic medications and herbal supplements used by psychiatric patients. In addition to more commonly known medications, newer agents are discussed, such as dexmedetomidine, the combination of olanzapine and samidorphan, and lumateperone. In the sections that follow, pharmacology, side effects, and drug-drug interactions are discussed and recommendations during the perioperative period from relevant societies and governing bodies.

2. Antidepressants

Depression is one of the most prevalent mental health disorders in the United States. In 2020, an estimated 21.0 million adults in the United States had at least one major depressive episode, roughly 8.4% of all U.S. adults [5]. Per the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a major depressive episode is defined as a period of at least 2 weeks of experiencing depressed mood or loss of interest or pleasure and symptoms of affected sleep, eating, energy, concentration, or self-worth without the root cause stemming from a medical illness, substance use disorder, or medication [6]. Of those with major depressive episodes, an estimated 66% of U.S. adults received treatment in 2020 [5]. Treatment of depression includes medications, non-pharmaceutical modalities such as electroconvulsive therapy (ECT), or a combination of both. Five major classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. Though the primary mechanism of action is relatively known for each of these medication classes, off-target and secondary mechanisms are relatively unknown despite significant investigation. The effectiveness of these medications requires both downregulation of synaptic receptors and activation of secondary messengers to cause a response over the course of time. The process is not immediate, supporting why antidepressants may take two or more weeks for patients to notice clinical improvements [7].

2.1 Selective serotonin reuptake inhibitors

SSRIs are first-line treatment for depression and anxiety and the most widely prescribed class of antidepressants, with examples that include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. The drug is popularly used because it has little effects on the adrenergic, cholinergic (except paroxetine), or histaminergic systems, which minimize its side effect profile by almost

exclusively blocking presynaptic reuptake of serotonin to allow increased serotonin levels [8]. Two newer medications, vortioxetine and vilazodone, are considered SSRIs but are hypothesized to also block serotonin uptake through direct modulation of various serotonin receptors. SSRIs should not be stopped perioperatively to avoid discontinuation syndrome. Careful consideration should be taken when monitoring for serotonin syndrome (SS), a life-threatening drug reaction that can lead to autonomic dysfunction (symptoms of hyperthermia, tachycardia, labile blood pressure, diarrhea) and can cause seizures, rhabdomyolysis, renal failure, arrhythmia, coma, and potentially death. Serotonin syndrome can occur when serotonin levels are increased, such as changes in dosages or introducing a new serotonergic agent. Recommendations to avoid pethidine/meperidine, tramadol, pentazocine, and dextromethorphan should be taken to reduce serotonin syndrome risks [8]. Of note, SSRIs are metabolized and interact with the CYP-450 enzymes. Thus, special consideration should be taken when prescribing antiarrhythmics, benzodiazepines, and neuromuscular blocking medications in patients who are taking SSRIs. Some SSRIs are inhibitors of CYP2D6, such as escitalopram, fluoxetine, sertraline, paroxetine, and citalopram [9]. Fluvoxamine and fluoxetine inhibit CYP2C19, while fluvoxamine inhibits CYP1A2 [9]. Finally, QT prolongation can occur (particularly with citalopram) and can affect platelet function resulting in abnormal bleeding [10].

2.2 Serotonin-norepinephrine reuptake inhibitors

The mechanism of action for SNRIs is through inhibiting the reuptake of both serotonin and norepinephrine in the synaptic cleft while minimizing effects to other neurotransmitters. This class includes desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine. SNRIs should not be stopped perioperatively to avoid discontinuation syndrome. Primarily due to their norepinephrine reuptake inhibition, SNRIs can cause tachycardia and hypertension and may require tighter blood pressure control. SNRIs can also cause side effects of sexual dysfunction, mydriasis, urinary constriction, dry mouth, dizziness, and sedation. Like SSRIs, SNRIs have a potential of causing serotonin syndrome and are linked with inhibition of platelet aggregation. It is recommended to avoid pethidine/meperidine, tramadol, pentazocine, and dextromethorphan to reduce serotonin syndrome risks [8]. Likewise, venlafaxine inhibits the CYP-450 enzymes, but desvenlafaxine (active metabolite) will not [10]. Thus, it is important to keep this fact in mind when prescribing antiarrhythmics, benzodiazepines, and neuromuscular blocking medications during anesthesia in patients who are taking SNRIs.

2.3 Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are relatively older antidepressants, having been discovered earlier than SSRIs and the newer SNRIs. TCAs are so named after their chemical structure containing three rings. Specific medications in the TCA class include amitriptyline, amoxapine, doxepin, desipramine, nortriptyline, protriptyline, imipramine, and trimipramine. TCAs act on roughly five different neurotransmitter pathways, but receive its antidepressant effects by blocking serotonin and norepinephrine reuptake in presynaptic terminals [11]. Attached to its ring structure is either a secondary amine (desipramine, nortriptyline, protriptyline) that causes greater norepinephrine uptake blockade or tertiary amine (amitriptyline, clomipramine, doxepin, imipramine, trimipramine) that causes greater serotonin reuptake blockade.

Since these medications are also competitive antagonists of alpha-1 adrenergic, alpha-2 adrenergic, muscarinic, and histaminergic receptors, they can lead to unwanted side effects of dizziness, memory impairment, and drowsiness among other symptoms [12].

Though TCAs have displayed efficacy in treating depression (arguably equivocal efficacy to SSRIs), their side-effect profile has dissuaded many providers from using them first line. One of the feared complications with TCAs includes cardiac conduction changes that include QT prolongation, Torsade de Pointes, and sudden cardiac death [13]. Special consideration and caution should be taken when prescribing sympathomimetics (such as ketamine, ephedrine, or metaraminol) in patients taking TCAs to avoid hypertensive crises. TCAs are also known to reduce seizure threshold, and when taken in combination with tramadol, clomipramine, and maprotiline, they may place patients at higher risk for seizures [14, 15]. Notably, TCAs can have sedative properties (particularly amitriptyline and doxepin), which may augment anesthetic sedatives. Abruptly discontinuing the medication can lead to rhinorrhea, muscle aches, chills, and malaise [14]. In *in vitro* studies, TCAs have shown mild inhibitory effects on the CYP450 enzymes CYP1A2, CYP2D6, and CYP2C19 [16]. Interaction with CYP1A2 can cause a theoretical alteration in clearance rate of ropivacaine, a local anesthetic, but this interaction has not been studied extensively clinically [17]. CYP2D6 causes activation of anesthetic medications such as codeine and tramadol to their active form and, if disrupted, can lead to less pain control [18]. CYP2C19 enzymes can affect the clearance of diazepam, which is commonly utilized perioperatively [19]. These interactions are important to keep in mind when a patient taking TCAs is to undergo anesthesia for an upcoming procedure.

2.4 Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are a relatively older class of antidepressants. They are not used as commonly in clinical practice in comparison with SSRIs or SNRIs due primarily to their side effect profile. Monoamine oxidases are enzymes that break down serotonin and norepinephrine. Inhibition of these enzymes leads to a reduced decline in serotonin and norepinephrine levels. MAOIs can be reversible (moclobemide) or irreversible (phenelzine, tranylcypromine, isocarboxazid). If an irreversible MAOI binds, the enzyme is permanently inactivated, leading to prolonged effects; therefore, more caution should be taken with individuals on irreversible MAOIs before initiating anesthesia.

The primary anesthesia concern for patients taking MAOIs is concern for hypertensive crisis as sympathomimetics like phenylephrine or ketamine can precipitate these crises. Additionally, meperidine and dextromethorphan should be avoided for patients on MAOIs as it can precipitate a serotonergic crisis due to synergistic inhibition of serotonin reuptake [15]. The MAOI phenelzine can prolong neuromuscular blockade and should be cautioned with administration of succinylcholine. The benefits and risks should be weighed when deciding between discontinuing MAOIs, but are often discontinued perioperatively and would recommend a 2-week washout prior [8]. MAOIs are also known to interact with several liver enzymes, most notably CYP3A4 and CYP2C19 [20]. As mentioned above, interactions with anesthetic medications may occur with CYP2D6 (codeine and tramadol), CYP1A2 (ropivacaine), and CYP2C19 (diazepam) [17–19].

2.5 Atypical antidepressants

There are several antidepressants used in clinical practice that are not part of the other classic families, as they have alternative mechanisms of action. Three of these atypical antidepressants are mirtazapine, trazodone, and bupropion.

Mirtazapine has both 5-HT2 and 5-HT3 antagonistic effects, which provides both anxiolytic and antiemetic properties. It also has antihistaminic properties that help with insomnia at low doses and commonly utilized is its side effect to increase appetite and promote weight gain. Mirtazapine may also help postoperative nausea and vomiting [21]. It is also extensively metabolized by CYP2D6, CYP3A4, and CYP1A2 [22].

Trazodone blocks serotonin reuptake, histamine, and alpha-1-adrenergic receptors; therefore, it is used as an antidepressant but also commonly as a sleep agent. Trazodone has a risk of QT prolongation and can lead to excess somnolence during procedures and, however, can be continued perioperatively [23].

Bupropion inhibits dopamine and norepinephrine, and has a chemical structure similar to amphetamines. It increases risk of seizures and neuroleptic malignant syndrome [24]. Notably, atypical antidepressants do not significantly interact with epinephrine and can be perioperatively continued [25].

2.6 Ketamine

Ketamine was first synthesized in the 1960s and initially approved as an anesthetic agent. Though ketamine continues to be used in treatment-refractory migraines and acutely agitated patients, it was recently approved for antidepressant use with potent anti-suicidal effects [26]. Esketamine, the S-enantiomer of ketamine, is clinically indicated for adults with major depressive disorder with or without acute suicidal ideation or behavior [27]. It functions as a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. Ketamine has sedative, anesthetic, amnesia, and analgesic properties [28, 29]. Ketamine may also interact with other medications utilized in the psychiatric patient and have lower efficacy as an antidepressant, notably the mood stabilizer lamotrigine [30]. The mechanism of action of lamotrigine is believed to be inhibition of sodium and calcium channels in presynaptic neurons and decreased glutamine, and increased GABA release. The decreased glutamate release can reduce ketamine anesthetic response in patients [31].

Anesthetic providers should carefully screen patients for ketamine prescription or recreational use and confirm with primary/consulting teams whether ketamine was used during patient care. It is important to accurately determine the overall amount of ketamine administered to avoid ketamine poisoning. High doses may cause an increase in systemic and pulmonary artery pressure, increase in cardiac outpatient, tachycardia, and respiratory arrest [28].

2.7 Discontinuation syndrome

When preparing for the use of anesthetics, abruptly discontinuing a patient's antidepressants can result in discontinuation syndrome or withdrawal symptoms. Rarely do symptoms become serious but discontinuing antidepressants with anticholinergic effects can lead to symptoms of cholinergic rebound, such as nausea, vomiting, abdominal cramping, sweating, headache, and muscle spasms. Discontinuing MAOIs can result in flu-like symptoms, dysphoria, restlessness,

tachycardia, hypertension, and a delirium-like state. Discontinuing serotoninergic antidepressants may cause dizziness, weakness, nausea, headache, lethargy, insomnia, anxiety, poor concentration, and paresthesia [32]. Because the discontinuation symptoms may be worse than possible interactions with anesthetics, the recommendations provided can help guide individuals in the discussion of risks and benefits for each of their medications.

Please refer to Summary Table for a summarized view of side effects and recommendations at the end of the chapter.

3. Anxiolytics

Anxiolysis is of particular concern both to psychiatrists and to anesthesiologists. In practice, both specialties share several medications that they can prescribe to achieve this desired effect in their patients. Perhaps the most historically used anxiolytics are the benzodiazepines. In addition to benzodiazepines, other anxiolytics include buspirone and hydroxyzine, among others.

3.1 Benzodiazepines

Several examples of medications within the benzodiazepine class include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flunitrazepam, flurazepam, loflazepate, lorazepam, midazolam, oxazepam, quazepam, temazepam, and triazolam. Benzodiazepines work primarily as positive allosteric modulators on the gamma amino butyric acid (GABA)-A receptor, which is a chloride channel [33, 34]. This association between benzodiazepines and the $GABA_A$ receptor has been well established, so much so that before known as $GABA_A$, this receptor was known as the "benzodiazepine receptor" [35]. The receptor itself is a pentamer of two alpha, two beta, and a gamma subunit. Benzodiazepines are allosteric modulators, which bind to the extracellular domain making the receptor adopt the pore conformation. Additional receptor subtypes confer differential responsivity to benzodiazepines [35].

Beyond anxiolysis, benzodiazepines are used for other reasons in anesthesia. Notable is their use as amnestic and premedication for procedures, from those requiring general anesthesia to procedures of shorter duration. Benzodiazepines are thought to impair memory formation by impairing new information acquisition [36]. A meta-analysis found that for general anesthesia and general anesthesia with inhalational maintenance, benzodiazepine premedication seemed to have a protective role in preventing implicit memory formation. However, the result was not significant for benzodiazepine premedication and general anesthesia with intravenous maintenance. The reason may be that the intravenous maintenance administration of propofol is already impacting memory and confounding the effect [37]. During surgery, benzodiazepines reduce awareness compared to thiopental, ketamine, and placebo [38]. A meta-analysis found that while benzodiazepines do increase time to recover, time to discharge is unaffected while the incidence of postoperative side effects is reduced. Psychological outcomes are not significant [39]. It is important to mention that the benzodiazepines triazolam, alprazolam, brotizolam, and midazolam are primarily metabolized by CYP3A4 [40]. As mentioned above, specific antidepressants like MAOIs and mirtazapine are metabolized by CYP3A4, leading to a potential interaction between benzodiazepine administration in the perioperative period and home antidepressant use.

Two additional considerations for the use of benzodiazepines in anesthesia are the treatment of serotonin syndrome and perioperative alcohol withdrawal. Benzodiazepine infusions are used to prevent rhabdomyolysis in serotonin syndrome-associated increased muscle tone [41]. Intravenous benzodiazepines are used for acute withdrawal syndrome in the perioperative context; it is important that the anesthetist distinguishes the syndrome from delirium, which is notably not treated with benzodiazepines [42].

3.2 Remimazolam

A relatively new benzodiazepine, remimazolam, was approved for use by the United States Food and Drug Administration (FDA) in 2021 and its effects in the perioperative setting are less studied. Remimazolam is a rapidly metabolized benzodiazepine with high organ-independent elimination clearance and no active metabolites. Remimazolam does not seem to have a prolonged sedative effect. It was shown to be non-inferior to midazolam for providing adequate sedation when co-administered with opioids, and non-inferior to propofol for induction and maintenance of general anesthesia [43]. It has smaller effects on the respiratory and circulatory systems than propofol and midazolam, and may be a potentially safer option for pediatric, geriatric, and obese populations and those with multiple comorbidities. However, additional work is needed to determine safety of long-term use and use in ICU sedation, and to determine optimal dosing for specific indications [44, 45].

3.3 Benzodiazepine-associated risks and adverse events

Benzodiazepines are associated with some risks in anesthesia, for short and long term. In immediate use, emergent agitation, allergy, and paradoxical reaction should be kept in mind. Paradoxical reactions occur at a frequency of <1% and are possibly associated with alcohol use. This phenomenon is thought to be caused by genetic predisposition due to $GABA_A$ subunit expression generating heterogeneous receptor isoforms [46]. Considering emergence agitation, benzodiazepine premedication increases the risk of emergence agitation and may be a greater risk in patients with long-term benzodiazepine use [47]. Also considering patients with long-term benzodiazepine use, it was shown that the amount of propofol required for intravenous sedation was significantly lower in those with long-term benzodiazepine use compared to the control; this finding was not influenced by preoperative oral benzodiazepine administration on the day of procedure [48]. Finally, benzodiazepine allergy is exceedingly rare and difficult to assess due to the likelihood of multiple other exposures occurring. If a benzodiazepine allergy is documented, alternatives for anxiolysis and sedation do exist [49].

A 2022 study discussed the important consideration for abuse potential. First, general anesthesia was associated with new postoperative benzodiazepine use that occurred 90–180 days post-surgery. General anesthesia was also more associated with new postoperative benzodiazepine use than neuraxial anesthesia. Perioperative benzodiazepine use was associated with postoperative persistent benzodiazepine use. Additionally, 15.2% and 4.9% of patients with new benzodiazepine prescriptions continued to use benzodiazepines for 1 and 8 years after, respectively. Additional risk factors for new postoperative use of benzodiazepines were orthopedic surgery, preexisting malignancy, anxiety disorder, concurrent systemic steroid use, postoperative complications, and admission to ICU, among others [50].

3.4 Considerations for the geriatric population

There is no formal defining age of "geriatric" or "elderly." Study designs may define onset as early as 50 years, however 65 years is frequently seen. The American Geriatric Society Beers Criteria recommend that elderly patients avoid benzodiazepines in the treatment of insomnia due the risks of cognitive impairment and falls [51]. Although the risks of benzodiazepine use in the elderly are common knowledge, their use remains disproportionately high in the elderly. In a United States national survey, prevalence of benzodiazepine use in non-institutionalized adults was 3.8%, while in a Dutch survey of the elderly, prevalence approached 8% [52]. One systematic review measured the prevalence of potentially inappropriate prescription (PIP; percentage of cohort taking at least one potentially inappropriate medication) of multiple drug classes in elderly patients with dementia. The authors found the most prescribed potentially inappropriate medications were anxiolytic-hypnotic and anticholinergic medications. Rates of anxiolytic-hypnotic use ranged from 5 to 38% [53]. One meta-analysis associated their use with falls in the elderly and found an odd ratios of 2.00 for short-acting benzodiazepines, 2.16 for long-acting, and 1.67 for any benzodiazepine use compared to elderly patients not taking benzodiazepines [54]. Therefore, continued work to publicize the danger of benzodiazepine use in the geriatric population is indicated.

3.5 Non-benzodiazepine anxiolytics

In addition to benzodiazepines, buspirone and hydroxyzine are used as anxiolytics. Buspirone is a serotonin 1A preceptor partial agonist that is effective in treating generalized anxiety disorder but is not first line [55]. Buspirone is thought to be safe intraoperatively but should be avoided in the context of administration with meperidine or tramadol due to a theoretical risk of serotonin syndrome [56, 57]. Hydroxyzine is an antihistamine medication with anxiolytic and sedative effects [58]. Hydroxyzine has been studied in the context of preventing preoperative anxiety in the pediatric population but has been shown to have limited resulting efficacy [59]. It has been FDA approved for perioperative sedation, but it has been largely replaced by alternative agents for this purpose.

4. Mood stabilizers

Bipolar disorder is a chronic psychiatric illness characterized by episodes of alternating mania or hypomania and depression, or mixed features of depression and mania. The lifetime prevalence is estimated to be approximately 3–7% and annual incidence of 3–10 cases per 100,000 population [60]. The diagnosis of Bipolar I Disorder is made if there is any lifetime episode of mania, whereas Bipolar II Disorder is diagnosed if there is at least one lifetime episode of hypomania and one lifetime episode of depression. Many patients with bipolar disorder are treated with mood stabilizers which can affect preoperative, perioperative, and postoperative outcomes. Some of the medications interact with the commonly used anesthetic agents and require a decision whether they need to be continued or held prior to a surgical procedure. There are many mood stabilizers on the market today, including lithium, antipsychotics, and anti-epileptic Drugs (AEDs) such as valproic acid, carbamazepine,

and lamotrigine. This section will focus on lithium and AEDs as they are the most commonly used mood stabilizers.

4.1 Lithium

Lithium is commonly used as a first-line mood stabilizer in people suffering acute manic episodes in bipolar disorder, as well as mixed and depressive episodes. Its exact mechanism of action is uncertain but is believed to affect multiple molecular pathways involved in neurotransmission. Lithium enters cells, modifies sodium transport in nerve and muscle cells, and impacts secondary messenger systems *via* inhibition of inositol monophosphate (IMP), which affects phosphatidylinositol and neurotransmission. It also decreases protein kinase C, which alters gene expression involved in neurotransmission [61].

Lithium has a narrow therapeutic index, ranging from 0.6 mmol to 1.2 mmol/L. Dosing is guided by plasma lithium levels. Above 1.5 mmol/L concentration, lithium induces dose-related intoxication, including tremors, vomiting, confusion, diarrhea, increased deep tendon reflexes, hypotension, seizures, and death [62]. As it is renally excreted, plasma lithium levels are sensitive to changes in patient's renal function and volume status. Medications that affect renal function, such as diuretics, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs, can increase lithium concentration and lead to toxicity [63]. For these reasons, caution must be taken pre- and postoperatively to monitor patient's volume status and renal function.

Ideally, patients on lithium therapy should have lithium discontinued at least 48–72 hours prior to a surgical procedure owing to its half-life off 24–36 hours [8]. As lithium does not have discontinuation side effects, it is safe to discontinue abruptly. For anesthesia purposes, administration of lithium prolongs depolarization and polarization phase of neuromuscular blockade by acting additively with depolarizing neuromuscular agents and synergistically with non-depolarizing neuromuscular agents. [63] As a result, it can prolong neuromuscular blockade [64, 65]. As a precaution, all patients treated with lithium undergoing neuromuscular blockage should be monitored appropriately.

4.2 Valproic acid

Valproic acid is a commonly prescribed anti-epileptic agent used for mood stabilization alone or with another medication to treat manic, mixed, or depressive episodes of bipolar disorder. It exerts its anti-seizure activity by blocking voltage-gated sodium channels, thereby decreasing the frequency of neuronal firing [66]. It also increases levels of GABA in the CNS. Side effects can include sedation, tremors, dizziness, thrombocytopenia, elevated liver enzymes. Serious side effects include Steven Johnson Syndrome, hyponatremia, syndrome of inappropriate anti-diuretic hormone release (SIADH), encephalopathy, and coma. Abrupt discontinuation can cause withdrawal seizures [66].

In general, valproic acid (VPA) can be continued peri-operatively for patients treated with bipolar disorder and does not need to be stopped, although it can interact with anesthetic agents. Some research shows that VPA is highly plasma protein bound and presence of other highly protein bound medications can increase free VPA plasma concentrations [67]. Certain highly protein bound anesthetics such as propofol can have their levels increased in the presence of VPA

[68]. Similarly, VPA can decrease clearance of propofol by competing for the same liver enzymes (CYP3A4) that metabolize them [69, 70]. Another consideration is increased bleeding risk, which is thought to be caused by platelet dysfunction and associated decrease in platelet count, fibrinogen, protein C, factor VII, and factor VIII [67]. It is therefore recommended to assess preoperative bleeding risk and to obtain baseline hemostasis and coagulation factors such as bleeding time, platelet count, Prothrombin Time (PT), Activated Thromboplastin Time (aPTT), von Willebrand factor, and fibrinogen.

4.3 Carbamazepine

Carbamazepine is another AED that is used as a mood stabilizer to treat manic or mixed episodes of bipolar disorder. Carbamazepine exerts its effect primarily *via* binding and inactivation of voltage-gated sodium channels, thereby decreasing neuronal action potential and neurotransmission. Side effects of carbamazepine include dizziness, sedation, dry mouth, ataxia, nausea, and vomiting. Serious side effects include hyponatremia, agranulocytosis, hepatotoxicity, confusion, and serious dermatologic reaction [71].

Carbamazepine can be continued perioperatively. But it is a strong cytochrome p450 inducer. Medications that use CYP450 can have their levels reduced in the presence of carbamazepine, including neuromuscular blocking agents. Specifically, the duration of effect of non-depolarizing aminosteroid neuromuscular blockers such as vecuronium is shortened [15]. Therefore, neuromuscular blockade may need to be administered more frequently or at a higher dose. A structurally similar mood stabilizer, oxcarbazepine, is associated with lesser CYP450 induction and is considered safer in terms of interactions (refer to Summary Table section for preoperative recommendations) [72].

4.4 Lamotrigine

Lamotrigine is another mood stabilizer found to be effective in treating depression associated with bipolar disorder [73]. Its mechanism of action is not entirely clear but is believed to stabilize presynaptic neuronal membrane *via* blockade of voltage gated sodium channels and decrease the release of excitatory neurotransmitters such as glutamate. Side effects include visual disturbance, headaches, dizziness, tremors, agitation, and in rare cases, serious dermatological side effects such as Steven Johnson Syndrome [74].

In general, lamotrigine can be continued and does not need to be held for surgery or anesthesia. However, some data suggest that the dissociative effects of ketamine anesthetic can be decreased in the presence of lamotrigine since ketamine's dissociative effects are thought to be due to augmentation of glutamate neurotransmission [75]. The implication of this effect is important to consider since ketamine is commonly used as a procedural anesthetic.

Medications used to treat bipolar disorder can be safely continued perioperatively but sometimes pose a challenge to potential drug-drug interactions. Of the mentioned medications, it is recommended that lithium be discontinued prior to procedures requiring anesthesia or sedation, and appropriate patient monitoring is important if the decision is made to continue lithium.

The summary of side effects and recommendations can be found in the Summary Table at the end of the chapter.

5. Antipsychotics

Approximately 0.25–0.64% of people living in the United States have schizophrenia and related disorders, which are characterized by psychosis [76–78]. Psychosis itself is characterized by the presence of hallucinations, delusions, or both in such a way that disrupts a patient's capacity to meet the ordinary demands of life [79]. Antipsychotics, classified as first-generation antipsychotics (FGAs), and second-generation antipsychotics (SGAs), are pharmacologic treatment options for bipolar disorder, acute psychosis, psychotic disorders such as schizophrenia, agitation, and schizoaffective disorder. In this section, we will briefly discuss FGAs and SGAs, their mechanism of action, adverse effects, and considerations for anesthesia or perioperative use.

5.1 First- and second-generation antipsychotics

The proposed mechanism of action of antipsychotics is post-synaptic blockade of dopamine D2 receptors in the brain. Adverse effects in this medication class include tardive dyskinesia (TD), extrapyramidal symptoms (EPS), hyperprolactinemia, neuroleptic malignant syndrome (NMS), weight gain, insulin resistance, QT prolongation, and sudden death, among others. Many of these agents are metabolized *via* the cytochrome P450 (CYP450) system, so drug-drug interactions and altered plasma medication levels when used in individuals with altered hepatic function or with agents that act on the CYP450 system. Of note, CYP gene polymorphisms can alter metabolism of antipsychotics. For example, individuals with CYP-2D6, a cytochrome gene polymorphism, are slow metabolizers and typically have higher plasma levels of antipsychotics, which lead to increased risk of more severe adverse effects [80].

First-generation antipsychotics (neuroleptics, conventional or typical antipsychotics, FGAs) include fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, trifluoperazine, chlorpromazine, and thioridazine. Although the agents in this class act *via* D2 dopamine blockade, they vary based on their effects on neuronal 5-HT2, alpha-1 sympathetic, histamine, and anticholinergic receptors, which can correspond to the differences in their adverse effect profiles as seen in **Table 1**.

Second-generation antipsychotics (atypical antipsychotics, SGAs) include aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, and ziprasidone. Generally preferred over FGAs due to their side effect profile seen in **Table 1**, most medications in this class of antipsychotics differ from FGAs due to their increased affinity for serotonin 5HT2 receptors relative to dopamine D2 receptors. Decreased risk of EPS in SGAs compared to FGAs is thought to be due to 5HT2 activity.

In the perioperative setting, the adverse effect profile of antipsychotic medications should be considered. The four key adverse effects in focus are anticholinergic effects, orthostatic hypotension, QT prolongation, and sedation. Direct inhibition of the cardiac delayed potassium rectifier channels is the proposed mechanism for the increased risk of QT prolongation, Torsade de Pointes, and sudden death with all antipsychotics [81]. Thioridazine and quetiapine are the FGA and SGA, respectively, associated with the highest risk of QT prolongation. Olanzapine, an SGA, has been suggested to cause some of the least changes in QTc [82]. When preparing for anesthesia clearance, a

	Anticholinergic effects	Orthostatic hypotension	QTC prolongation	Sedation
First-generation antipsychotics (GFA, typical, conventional)				
Chlorpromazine	↑↑	↑↑	↑↑	↑↑
Fluphenazine	↑	↑	↑	↑
Haloperidol	↑	↑	Oral: ↑ IV:↑↑	↑
Loxapine	↑	↑	—	↑
Perphenazine	↑	↑	—	↑
Pimozide	↑	↑	↑	↑
Thioridizine	↑↑	↑↑	↑	↑↑
Thiothixene	↑	↑	—	↑
Trifluoperazine	↑	↑	—	↑
Second-generation antipsychotics (SGA, atypical)				
Aripiprazole	↑	↑	—	↑
Asenapine	↑	↑	↑	↑
Brexipiprazole	↑	↑	—	↑
Cariprazine	↑	↑	—	↑
Clozapine	↑↑	↑↑	↑	↑↑
Iloperidone	↑	↑↑	↑	↑
Lumateperone	↑	↑	—	↑
Lurasidone	↑	↑	—	↑
Olanzapine	↑	↑	↑	↑↑
Paliperidone	↑	↑	↑	↑
Pimavanserin	↑	↑	↑	↑
Quetiapine	↑	↑	↑	↑↑
Risperidone	↑	↑	↑	↑
Ziprasidone	↑	↑	↑↑	↑

In this table, the "↑" sign is used to signify mild- to moderately increased risk of side effect. The "↑↑" sign is used to signify severely increased risk of side effect. The "-" is used to indicate no clinically significant increased risk.

Table 1.
Side effect profile of antipsychotics.

standard pre-operative electrocardiogram (ECG) is recommended to determine if a patient has prolonged QTc [15]. Since many antipsychotics cause sedation due to H1 receptor antagonism, a decreased anesthetic requirement may be considered during surgery. Chlorpromazine and thioridazine are the most sedating of the FGAS, and clozapine and olanzapine are the most sedating of the SGA. In general, SGAs are typically less sedating than FGAs and would be preferable when planning for anesthetic intervention [83].

First- and second-generation antipsychotics should be continued in the perioperative setting in order to avoid exacerbation of underlying psychiatric disorder, postoperative delirium, and discontinuation syndrome as described in Section 5.2. Due to the

effects of antipsychotics on blood pressure, seizure threshold, and temperature regulation, enflurane should be avoided due to increased risk of hypotension, arrhythmias, and seizures if used concurrently [84].

5.2 Discontinuation syndrome

Dopamine blockade from antipsychotics over a prolonged period of time can cause hypersensitivity of dopamine receptors. When the dopamine antagonists are abruptly stopped, the body's own physiologic dopamine can cause overstimulation of these receptors, causing the symptoms of withdrawal. Thus, to discontinue the use of antipsychotics, the recommendation is to taper them off gradually over at least 6–12 months. Abrupt discontinuation of first- or second-generation antipsychotics can cause tachycardia, anxiety, diaphoresis, insomnia, dyskinesia, hyperkinesia, myalgia, dry mucus membranes, in addition to GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain [85]. These symptoms can last up to one to 4 weeks, and the only way to prevent them is to slowly taper the dose of antipsychotics if cessation is required [86].

5.3 Postoperative concerns

There are postoperative concerns with continued use and abrupt cessation of antipsychotics. Antipsychotics have been implicated in causing paralytic ileus due to the drugs' anticholinergic and noradrenergic effects. In a database review of 26,720 patients, one study showed statistical significance in clozapine causing postoperative ileus [85] which can be concerning especially in patients with schizophrenia due to potential decreased pain awareness and subsequent decreased awareness of symptoms that lead to ileus. Also, antipsychotic drugs can increase risk of hypotension due to α-adrenergic blockade. Of the FGAs, thioridazine and chlorpromazine are most commonly associated with postoperative hypotension [81, 87]. Conversely, abrupt discontinuation of antipsychotics can increase incidence of delirium and further supports recommendations to continue this medication perioperatively [88].

5.4 Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening neurological emergency associated with antipsychotic use during which decreased serotonin inhibition and dopaminergic blockade in the anterior hypothalamus led to sympathetic dysregulation [87, 88]. The clinical picture consists of hyperthermia, muscle rigidity, altered mental status, motor abnormalities (bradykinesia), and autonomic dysfunction (blood pressure and heart rate lability) [89]. Although commonly associated with use of FGAs such as haloperidol or fluphenazine, all neuroleptic drugs have been implicated, including low-potency drugs such as chlorpromazine [90, 91]. NMS has also been seen with use of antiemetic medications such as metoclopramide or promethazine [92–94]. Frequently seen following medication initiation or dosage changes, NMS can also occur up to several weeks after starting treatment NMS can persist a week after the causal agent has been discontinued [95–97]. Although most patients with NMS are young adults, the syndrome has been described in all age groups from 0.9 to 78 years, and age is not considered a risk factor for its development, although infection, severe trauma, and surgery may precipitate NMS [98].

It is important to distinguish the clinical presentation of NMS from malignant hyperthermia (MH) and serotonin syndrome (SS). MH can be distinguished by two primary features in clinical history: spasms in the masseter muscles with the administration of succinyl choline, as its earliest indicator. Subsequently, the development of tachypnea, tachycardia, increased carbon dioxide concentrations, and acidosis occur during the induction or maintenance of anesthesia [99]. This causes hyperthermia and cyanosis, which can lead to stiffness and rhabdomyolysis [95]. If left untreated or misdiagnosed, MH can be fatal. NMS can also be confused with serotonin syndrome (SS), but they can be differentiated by onset time. SS starts within hours or a day of initiation or dose change of the drug, while NMS typical symptoms progress over one to three days and have a later onset (1–44 days) compared to SS [100, 101]. The pathophysiology of NMS, MH, and SS is different. Misdiagnoses and, subsequently, mistreatments can be prevented with a detailed medical history. See **Table 2** for a more detailed evaluation of NMS in contrast to malignant hyperthermia and SS.

6. Stimulants

Central nervous system (CNS) stimulants comprise a drug class that causes excitation of the cerebral cortex, brain stem, and spinal cord [102]. This drug class is widely used in the clinical setting and is also often used recreationally. Stimulants are commonly used in the clinical setting for attention deficit hyperactivity disorder, depression, chronic fatigue, and narcolepsy. Stimulants can cause side effects such as euphoria, anxiety, insomnia, psychosis, and seizures.

Recent evidence supports that approximately 17.2 million American adults or 6.6% of the American adult population used prescription stimulants from 2015 to 2016 [103]. Commonly used stimulants include amphetamines, caffeine, cocaine, methylphenidate, and modafinil. As a drug class, stimulants are considered to have high potential for misuse due to their euphoric properties [104]. In fact, there were 1.1 million users of recreational stimulants among persons 12 years or older in the United States as of 2010 [105]. Due to the prevalence of stimulant use in the population, it is probable that some of the individuals who use stimulants, prescription or recreational, will undergo anesthesia. Subsequently, it is imperative that practitioners understand how to manage the pharmacologic interactions and effects of stimulants with anesthetics to ensure optimal care.

6.1 Amphetamines

Amphetamines are synthetic methylphenethylamine derivatives that act by inhibiting monoamine reuptake by the norepinephrine transporter (NET) and the dopamine active transporter (DAT), reversing their normal activity and increasing neurotransmitter displacement from neuronal vesicles in the cortex, motor nuclei, and reticular-activating system [106]. Acute stimulant intoxication results in sympathetic activation including agitation, hypertension, hyperthermia, tachycardia, and tachypnea [107]. Methylenedioxymethamphetamine, MDMA or ecstasy, is a stimulant that may present with a toxidrome or fever, hyponatremia, rhabdomyolysis, renal injury, and liver injury [108].

This group includes mixed amphetamines, methamphetamine (“crystal meth”), and MDMA. MDMA also is a weak agonist of the 5-hydroxytryptamine/serotonin 1A (5-HT1A) receptor, which may be responsible for its hallucinogenic properties [106].

	Neuroleptic malignant syndrome	Malignant hyperthermia	Serotonin syndrome
Associated drugs	First-generation antipsychotics, antiemetic drugs	Administration of inhaled anesthetics (ex: halothane, isoflurane, sevoflurane, desflurane) with or without succinylcholine	Combination of any of the following: SSRI's, SNRI's, MAOI's, TCA's, Linezolid, oxycodone, morphine
Mechanism of action	Unknown but likely dopamine receptor blockade (hypothalamic dopamine blockade leading to dysautonomia and nigrostriatal dopamine blockage leading to parkinsonian-type symptoms)	Dihydropyridine (DHP) receptors and Ryanodine (RYP) receptors within the muscle cells normally regulate the movement of calcium into the intracellular space. In MH-susceptible patients, there is a mutation in the DHP or RYP1receptors, and thus unregulated movement of calcium from the sarcoplasmic reticulum. The accumulation of calcium causes the classic symptoms.	Serotonin Syndrome (SS) results from the concomitant use of drugs that have the net effect of increasing serotonin release (stimulation of the post-synaptic 5-HT1A and 5-HT2A)
Symptoms	Classic Tetrad: fever, rigidity, mental status change, autonomic instability Later onset-days	Sustained muscle contractions causing muscle rigidity, tachycardia, tachypnea, hyperthermia	Hyperthermia, hyperreflexia, clonus Earlier onset-within hours
Diagnosis	Clinical with history of antipsychotics or other associated medications	Clinical diagnosis, also suspect with hypercarbia, when the end-tidal CO2 continues to increase despite increasing minute ventilation	Clinical diagnosis can use the Hunter Toxicity Criteria Decision Rules: must have the presence of a serotonergic agent and have one of the following: • Spontaneous clonus • Inducible clonus plus agitation or diaphoresis • Ocular clonus plus agitation or diaphoresis • Tremor plus hyperreflexia • Hypertonia plus temperature above 38°C PLUS ocular clonus or inducible clonus
Lab findings	Elevated CK, leukocytosis, low serum iron, hypocalcemia, hyperkalemia	Hypercarbia, mixed respiratory/metabolic acidosis, hyperkalemia, myoglobinuria	Leukocytosis, elevated CPK, decreased serum bicarbonate
Treatment	1. Stop offending agent 2. Supportive Care 3. If severe manifestations, dantrolene, benzodiazepines, bromocriptine, or amantadine	Dantrolene ASAP—it binds to ryanodine receptors to stop the release of calcium, acts as a skeletal muscle relaxant. Treat electrolyte abnormalities, institute cooling, cardiovascular support Make sure to take a good family history to prevent an episode.	1. Stop offending agent 2. Supportive Care 3. Sedation with benzodiazepines to control agitation, which can worsen the muscle contractions/hyperthermia 4. If nothing helps, use Cyproheptadine, a 5-HT1A, and 5-HT2A antagonist

Table 2.
Comparison of neuroleptic malignant syndrome, malignant hyperthermia, and serotonin syndrome.

As a group, amphetamines lead to euphoria, wakefulness, increased concentration, and tachycardia. Prescription amphetamines are commonly used for attention deficit hyperactivity disorder and narcolepsy [102]. They may also be used for appetite suppression, depression, or management of Parkinson's disease symptoms. Some physiologic effects of amphetamines include increased systolic and diastolic blood pressure, weak bronchodilation properties, and respiratory stimulation [109].

6.2 Methylphenidate

Methylphenidate is a synthetic piperidine derivative that is thought to stimulate CNS activity through inhibiting dopamine and norepinephrine reuptake, thus increasing their quantities in the extra neuronal space [102]. This medication leads to increased attention and wakefulness. Prescription methylphenidate is commonly used for attention deficit hyperactivity disorder and narcolepsy. Adverse drug reactions include psychosis, anxiety, difficulty sleeping, palpitations, and mydriasis. In setting of overdose, methylphenidate can lead to delirium, hyperthermia, rhabdomyolysis, convulsions, and coma [110].

6.3 Modafinil

Modafinil is a synthetic benzhydryl sulfinyl compound that is thought to increase dopamine neurotransmission through DAT inhibition, although the mechanism is unclear [102]. The compound appears to have affinity for norepinephrine and serotonin receptors, to promote histamine and orexin release, and to act as a partial agonist at the D2 receptors. This medication causes wakefulness and is commonly used for the treatment of narcolepsy. Modafinil is an inducer of CYP3A4, CYP1A2, and CYP2B6 as well as a potent suppressor of CYP2C19 and CYP2C9, so caution should be maintained in patients for drug interactions associated with the pharmacokinetic profile of the medication [111].

6.4 Caffeine

Caffeine is a methylated xanthine alkaloid derived from *Coffea* plant seeds (coffee beans), *Camellia sinesis* leaves (tea), and the kola nut. It acts as an adenosine receptor antagonist and as a phosphodiesterase inhibitor (PDEi). Caffeine causes improved concentration and reduced fatigue. Caffeine is often used recreationally in the form of coffee or tea to increase energy levels, focus, and attention. Clinical uses of caffeine include the treatment of apnea of prematurity in newborns [102]. There is evidence that caffeine may provide symptomatic relief of post-dural puncture headache, although the evidence is limited and does not decrease the number of patients who need an epidural blood patch [112].

6.5 Anesthetic considerations

Repeated or chronic use of stimulants has been reported to blunt dopamine neurotransmission in the striatum through depletion of catecholamine receptor storage, a mechanism that may be responsible for increasing the reward threshold and driving drug consumption of stimulants [113]. This attenuation of dopaminergic signaling has been demonstrated even after longer periods of withdrawal [114, 115]. Reduced

endogenous catecholamine stores produce a blunted physiologic and sympathetic response to hypotension associated with anesthetic use [113].

It is worth noting that the blunted response associated with stimulant use may cause limited to poor response to sympathomimetic medication in patients. Ephedrine is noted to have a reduced pressor response in patients with chronic stimulant use, although it is traditionally used as a first-line agent for intraoperative hypotension [116]. Due to the altered pressor response after stimulant use, direct-acting vasopressor agents such as epinephrine and phenylephrine are recommended for intraoperative management of refractory hypotension or bradycardia in patients using stimulants [113].

Although the literature is unclear as to whether stimulants should be discontinued prior to surgery to improve patient outcomes, there are case reports supporting that patients on stimulants maintained cardiac and hemodynamic stability intraoperatively with general anesthesia [116].

For a summary of the side effects and recommendations, please refer to the Summary Table at the end of the chapter.

7. Recreational substances

Substance use disorder is defined as an individual's inability to control their use of these substances, legal or illegal. Substance use disorders have an estimated prevalence of 13.24% (43.63 million) of the population aged 12 years or greater in the United States per the 2020 National Survey on Drug Use and Health [117]. In addition, there are individuals who use substances recreationally without meeting criteria for substance use disorder. Commonly used recreational substances include tobacco, alcohol, benzodiazepines, opioids, cocaine, amphetamines, marijuana, hallucinogens, and inhalants. These substances affect the physiologic status of a patient and can interact with other medications, notably anesthetic agents.

Preoperatively, providers should assess patients for substance use, emphasizing the questions asked are to provide better and safer care to the patient and not to judge [108]. Urine drug screens and other toxicology screens are helpful to determine the presence of one or more substances pre-operatively/pre-procedurally. Screening should be utilized in the unconscious patient, altered patient, and in those patients with clinical symptoms consistent with substance intoxication or withdrawal.

7.1 Tobacco

Tobacco contains thousands of ingredients including nicotine and carbon monoxide. Nicotine activates nicotinic cholinergic receptors resulting in sympathetic stimulation. This stimulation can cause an increase in heart rate, blood pressure, and respiratory rate. Carbon monoxide binds hemoglobin with increased affinity compared to oxygen. This binding creates carboxyhemoglobin, lowers stores of oxyhemoglobin, and results in decreased tissue oxygenation [118]. Long-term smoking is associated with chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), peripheral vascular disease (PVD), and stroke.

Pulmonary system effects which are important to consider peri- and intraoperatively are increased airway irritability and decreased mucociliary clearance. Smoking also increases the risk of postoperative complications including pulmonary complications of laryngospasm, pneumonia, respiratory failure, impaired tissue

oxygenation, and impaired wound healing. Smoking cessation is encouraged prior to elective surgery, with a minimum recommendation of 72 hours before surgery with significant pulmonary benefit seen with cessation 4–8 weeks before surgery [118].

7.2 Alcohol

Alcohol is a central nervous system depressant believed to act at GABA-A receptors. Acute intoxication causes disinhibition, impaired motor control, and altered mentation. Alcohol can delay gastric emptying time and therefore increase the risk of aspiration. Chronic use is associated with gastritis, cirrhosis, chronic pancreatitis, Wernicke's encephalopathy, Wernicke-Korsakoff Syndrome, and cardiac beriberi [118].

Anesthetic requirements are decreased during acute alcohol intoxication due to CNS depression. Conversely, anesthetic requirements tend to be higher in chronic alcohol use disorder patients due to alcohol inducing liver enzymes. Aspiration risk is increased in acute intoxication and chronic use. Chronic users have increased airway colonization of pathologic bacteria which increases their risk for pneumonia [119]. Dehydration, cardiomyopathy, and decreased adrenocortical response to stress from chronic alcohol use may result in hypotension [108]. Thiamine (vitamin B1) and folate (vitamin B9) replacement should be initiated in alcohol use disorder patients.

Alcohol withdrawal is potentially life threatening with seizure and delirium tremens as possible effects. Withdrawal symptoms can begin within 12–24 hours following discontinuation, with seizures possible 24–48 hours after discontinuation, and delirium tremens possible after 48–72 hours after discontinuation. Symptoms can be mild to severe and can vary from autonomic symptoms to delirium tremens. Some mild symptoms include diaphoresis, palpitations, headaches, nausea, vomiting, and anorexia. More severe symptoms include tachycardia, hypertension, anxiety, insomnia, tremors, hallucinations, and hyperreflexia. [120] Alcoholic hallucinosis may present with intact consciousness, but the patient may experience auditory, visual, or tactile hallucinations and delusional thinking. Delirium tremens, on the other hand, may present with altered mental status, hallucinations, psychomotor agitation, and autonomic instability.

Treatment of alcohol withdrawal symptoms may include tapers of benzodiazepines, phenobarbital, or gabapentin. Alcohol withdrawal seizures are treated with intravenous benzodiazepines. The preferred benzodiazepines for the treatment are lorazepam, oxazepam, and temazepam. These are selected over other benzodiazepines due to their decreased hepatic metabolism. Importantly, supportive care is recommended, including hydration and electrolyte repletion. Folate and thiamine supplementation is also recommended, and for patients with Wernicke encephalopathy, high-dose thiamine should be initiated [42, 121].

Alcohol cessation before anticipated or elective surgery is recommended at least 1–2 weeks before surgery. Evidence demonstrates some organ dysfunction improves after the 1–2 weeks from cesation and that intervention programs starting 3–8 weeks prior to surgery significantly reduce the incidence of postoperative complications [122].

7.3 Cocaine

Cocaine is a naturally occurring benzoic acid ester derived from *Erythroxylon* coca leaves that acts as a dopamine, norepinephrine, and serotonin reuptake inhibitor

[102]. At high concentrations, cocaine can also inhibit voltage-gated sodium and potassium channels. This substance is a stimulant with vasoconstrictor and anesthetic properties. Peak effects of cocaine occur in 1–5 minutes, and the half-life is 60–120 minutes. Intoxication can lead to complications including hyperthermia, severe cardiovascular events such as hypertension, arrhythmias, myocardial infarction, prothrombotic events, coronary artery dissection, aortic dissection, heart failure, and cardiomyopathy [123]. Typically used recreationally, it leads to euphoria, perceptual disturbances, and convulsions and can also cause confusion and coma. In the United States, there are approximately 5 million people who use cocaine regularly. Cocaine addiction develops due to psychological and physiological tolerance, and rapid discontinuation of use results in drug craving, depressive symptoms, and fatigue.

Due to possible unopposed alpha-adrenergic receptor activation in combination with effects of cocaine, beta-blocker use is contraindicated in patients with acute cocaine toxicity due to unopposed alpha-adrenergic stimulation, coronary vasoconstriction, reduced nitric oxide production, and increased endothelin-1 levels [31, 123]. It is recommended to utilize nitric oxide mediated vasodilators, calcium channel blockers, and non-selective beta-blockers to manage hemodynamic instability in acute cocaine intoxication [31]. Acute intoxication causes sympathetic stimulation and may result in increased anesthetic requirements. Cocaine intoxication may also result in an exaggerated hypertensive response to ephedrine and ketamine. In chronic users, depletion of neurotransmitters results in decreased need for anesthetic agents and decreased response to ephedrine [117].

In individuals who use cocaine, there is risk of compromised oxygenation and supply due to the vasoconstrictive properties and vasospasm associated with use. When intubating or placing adjuvant airways in cocaine use disorder patients, caution should be taken due to chronic intranasal use causing septal and soft palate destruction [124]. Chronic smoking or crack-cocaine can lead to pulmonary complications that may result in difficult oxygenation or ventilation [108].

Due to changes in circulating catecholamines, patients may become hypertensive or hypotensive intraoperatively and should be monitored closely for pressure changes and arrhythmias. It may be valuable to also obtain a platelet count in patients with cocaine use to manage cocaine-induced thrombocytopenia that takes place due to platelet activation from vasospasm or autoimmune response [28]. Discontinuation of cocaine may cause withdrawal symptoms of increased anxiety, psychomotor agitation, and tremors [108]. Some of the other adverse effects of cocaine use include anxiety, papillary dilation, asthma, pulmonary hemorrhage, angina, and myocardial infarction [28].

7.4 Amphetamines and methamphetamines

Acute intoxication and chronic use may lead to cardiac complications including arrhythmias, aortic dissection, acute coronary syndrome, and cardiomyopathy [108]. It is recommended to obtain an electrocardiogram in acute and chronic users.

Due to increased sympathetic stimulation during acute intoxication, anesthetic requirements may be increased. Chronic users will demonstrate decreased anesthetic requirements [117]. Chronic amphetamine/methamphetamine users may experience poor oral hygiene resulting in damaged and loose teeth. Caution should be taken as such poor oral hygiene may result in dislodged teeth during intubation [108]. Chronic intranasal use may result in septal destruction and caution should be taken in use of nasogastric tubes. Smoking route of use can lead to pulmonary complications of

arteriole remodeling and pulmonary hypertension [108]. It is recommended to continue prescription amphetamines perioperatively to prevent hemodynamic instability, which may result from chronic stimulant use. Amphetamine withdrawal may result in decreased energy, sleep disturbance, changes in appetite, mood changes, notably dysphoria and anxiety, as well as the emergence of suicidal ideations (for more information about the mechanism of action refer to stimulants).

7.5 Marijuana

Marijuana has become increasingly accessibly in the United States with the legalization for medical and recreational use in multiple states. Marijuana contains cannabinoids and the active ingredient is tetrahydrocannabinol (THC). Inhalation effects of marijuana include bronchodilation in acute intoxication with possible airway obstruction in chronic use [108]. Cardiovascular effects of marijuana are dose dependent. At low doses, sympathetic stimulation results and at high dose sympathetic inhibition results [125]. Withdrawal from marijuana causes mild physiologic effects and may result in increased anxiety, increased appetite, irritability, and mood changes.

There is limited evidence regarding marijuana cessation prior to anticipated or elective surgery. If a patient utilizes marijuana *via* smoking or other inhalation methods, it would be beneficial to discontinue use at minimum of 72 hours prior to surgery with consideration of 4–8 weeks prior to surgery as is recommended in tobacco use due to the benefits on the pulmonary system.

7.6 Hallucinogens/lysergic acid diethylamide/phencyclidine

Acute intoxication with hallucinogenic substances typically manifests as hallucinations, tachycardia, hypertension, hyperthermia, and gastrointestinal symptoms. Patients using lysergic acid diethylamide (LSD) may experience mydriasis, tachycardia, tachypnea, fever, hyperglycemia with effects lasting from 6 to 10 hours after use [108].

Patients using phencyclidine (PCP) may present with nystagmus, tachycardia, hypertension, psychosis, agitation, and cerebral hemorrhage with effects lasting from 4 to 8 hours [108]. Avoid ketamine use in patients intoxicated with PCP as it is a derivative of the substance.

7.7 Inhalants

There are various substances including organic solvents and volatile agents used as inhalants. Toluene is one of the more commonly utilized inhalants and its acute intoxication may cause cardiac arrhythmias, bronchial irritation, acute respiratory distress syndrome, liver toxicity, pulmonary hypertension, methemoglobinemia, cerebral edema, and pulmonary edema [28]. Chronic use may lead to cerebellar degeneration and brain atrophy. General anesthesia may be the preferred option for patients acutely intoxicated with inhalants/solvents due to respiratory compromise and aspiration risk [28].

7.8 Opioids

Opioids continue to be an important pharmacologic agent in the management of certain types of pain, and it is important to acknowledge that this class of medications

has significant potential for misuse. Natural and synthetic opioids bind mu receptors: u1, which plays a role in analgesia and u2, in respiratory depression. Acute intoxication causes sedation, reduced respiratory rate, hypoxia, and pupillary miosis. It also causes delayed gastric emptying time and increases aspiration risk [117]. Chronic use can cause constipation. Use *via* snorting may result in septal and soft palate destruction.

Tramadol, commonly used in chronic pain management, is linked to psychiatric symptoms including altered mood, hallucinations, confusion, sleep disturbance, and nightmares [8]. Notably, when Tramadol is combined with selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in the risk of serotonin syndrome, it reduces the seizure threshold.

Opioid overdose causes respiratory depression and can be life threatening. Additionally, opioid intoxication and overdose may result in pulmonary edema [117]. Opiate overdose is most often reversed with the opioid antagonist, naloxone, which can be administered intranasally or intravenously in the pre-, intra-, and postoperative period. Repeated intravenous access for use may result in difficult access in the peri- and intraoperative period and should be considered in intravenous users [108].

Patients in recent or sustained opioid use disorder recovery may request induction agents other than fentanyl, in such cases ketamine may be a favored option. Patients in recovery may be utilizing medical assisted therapy to maintain sobriety and it is important to assess for such use including methadone, buprenorphine-naloxone combinations in sublingual form, naloxone in oral or injectable form, or buprenorphine in sublingual or injectable form. Patients on buprenorphine/naloxone combination medication should consider tapering prior to surgery to prevent the opioid antagonist from counteracting postoperative opioids for pain [117].

It is recommended to continue opioids perioperatively to avoid withdrawal and to decrease the need for scheduled additional pain medications in the perioperative setting. It is recommended to use a multimodal pain regimen in patients including but not limited to acetaminophen, non-steroidal anti-inflammatory drugs, gabapentin, regional anesthesia (including nerve blocks) where appropriate [108]. Opiate withdrawal onset varies based on amount used and type of opioid. For example, heroin withdrawal may begin in 6–18 hours, methadone withdrawal in 24–48 hours.

Opioid withdrawal may result in sympathetic hyperactivity, including tachycardia, hypertension, anxiety, insomnia, irritability, mydriasis, yawning, lacrimation, hyperreflexia, and muscle cramps. Rhinorrhea, piloerection, chills, myalgia, and arthralgia are common occurrences in opioid withdrawal. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea may also occur. Supportive management is recommended, including hydration and electrolyte repletion. Clonidine is often used to help alleviate autonomic symptoms of opioid withdrawal [126].

7.9 Medication-assisted treatments (MATs)

MAT uses a combination of counseling, psychotherapy, and medications to assist patients with substance use disorders. Special care should be taken with patients who have a history of opioid use dependence as they are at high risk of relapse. In patients with this history, it may be beneficial to order a substance use disorder consult in addition to careful preoperative planning, which includes active patient participation in the weighing of the risks and benefits of different forms of pain management and frank discussion on the risk of relapse. Patients with a history of opioid abuse can benefit of becoming part of a MAT program as it has been shown to improve patient

retention, increase abstinence, and decrease illicit opiate use [127–129]. There are many patients with opioid use dependence who are currently participating in MAT including methadone, suboxone, and naltrexone.

Methadone is a synthetic opioid that has been in use since 1972 [130]. It binds to the mu-opioid receptor and prevents opioid withdrawal for 24 hours or more. Methadone is available in several formulations, but it is advised to avoid switching formulations to decrease the chances of eliciting withdrawal symptoms. It can be continued at the outpatient dosage, which is notably not sufficient for pain management in the perioperative setting. If a patient is on methadone treatment, avoid using partial agonist opioids such as buprenorphine or butorphanol as this can also precipitate withdrawal symptoms.

Suboxone is a combination of buprenorphine and naloxone. It is used to treat opioid use disorder. Buprenorphine is a partial mu-receptor agonist and suppresses cravings and withdrawal symptoms while blocking the receptor against other opioids. Naloxone is a non-selective and competitive opioid receptor agonist. Per a review by Kohan *et al.* in *Regional Anesthesia Pain Medicine* in 2021, buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel, the most recently published recommendation is to continue buprenorphine throughout the perioperative period [131].

Naltrexone is an opioid antagonist that binds competitively to mu-receptors and therefore blocks endogenous and exogenous opioids. Thus, opioid intoxication and dependence is reduced, and increases patient abstinence. Since this medication inhibits analgesia, a "wash out" period is recommended. For injectable versions of naltrexone such as Vivitrol, it is recommended to wait 4 weeks from the last dosage prior to surgery. For oral naltrexone, a 72-hour washout prior to surgery is recommended [130].

For a general overview of side effects and recommendations, please refer to the Summary Table at the end of the chapter.

8. New psychotropic medications and considerations

This section contains some of the newer psychiatric medications that were recently approved by the FDA and released into the market. The new medications are of interest as there are limited data on potential drug-drug interactions with commonly used anesthetic agents. Regardless as they generally can cause various side effects, it is not unreasonable to speculate that the patients taking these medications would need to be monitored closely during procedures that require sedation, anesthesia, or analgesia.

8.1 Dexmedetomidine sublingual film (IGALMI™)

This formulation of alpha-2 adrenergic agonist received FDA approval in 2022 for acute treatment of agitation associated with Bipolar I or II Disorder or Schizophrenia [132]. Most common adverse effects reported from clinical trials include somnolence, dry mouth, hypotension, and dizziness [133]. There is a possible serious adverse effect such as orthostatic hypotension and QT prolongation. Since dexmedetomidine decreases sympathetic activity, hypotension and/or bradycardia can be pronounced in patients with hypovolemia, chronic hypertension, and patients who are elderly. Caution should be used if co-administered with other anesthetic agents.

8.2 Olanzapine and Samidorphan (LYBALVI®)

This combination of a second-generation antipsychotic and opioid antagonist was initially approved by FDA in 2021 for the treatment of schizophrenia, mania, or mixed episodes of Bipolar I Disorder as monotherapy or adjunct to lithium or valproate [134]. The medication is formulated to provide the efficacy of olanzapine and to mitigate the risk of olanzapine associated weight gain. Most common adverse effects reported during clinical trials were weight gain, somnolence, headaches, upper respiratory infections [135]. As with other antipsychotic medications, there is an increased risk for serious adverse reactions, such as neutropenia/agranulocytosis, lowering of seizure threshold, hypotension, and neuroleptic malignant syndrome [136]. Due to the opioid antagonist component, there is a risk of opioid intoxication if concurrent opioids are used to overcome the effect of antagonism. There is also a risk of precipitated withdrawal in those who are taking opioids. Thus, this medication is contraindicated in those using opioids and in those undergoing opioid withdrawal. Caution must be taken with regards to medication interactions, as CNS acting drugs such as anesthetics, sedatives, and hypnotics can potentiate the risk of orthostatic hypotension.

8.3 Lumateperone (Caplyta)

This is a new second-generation antipsychotic FDA approved for the treatment of schizophrenia in 2019 and Bipolar depression in 2022 [137]. It works as a presynaptic partial agonist and post-synaptic antagonist at D2 receptors and has high affinity for serotonin receptors [138]. Common side effects include fatigue, somnolence, sedation, constipation. Lumateperone shares serious side effects like other second-generation antipsychotics. Caution should be used when co-administering medications that affect CYP3A4: inhibitors require decrease in lumateperone dose and concomitant use of inducers should be avoided. Common agents that are CYP3A4 inducers are phenobarbital, primidone, fosphenytoin, and carbamazepine [139]. Like for other antipsychotics, vital signs should be monitored if anesthetic agents are administered.

9. Herbal supplements

Recent data show that more than 50% of U.S. adults aged 20 and use some form of dietary supplement. Its use was also found to increase with age, as 80.2% of U.S. adults 60 or older report using at least one form of dietary supplement [140]. Although concern has been raised by medical associations and physicians about the use of herbal remedies and supplements, most patients perceive herbal medicines as natural and safe products. As a result, many patients fail to disclose their current use of herbal remedies placing themselves in danger of potential side effects or even death.

Knowledge of herbal medicines is essential when the patient presents for a surgical procedure, elective or urgent, especially for the potential interactions with anesthetic agents and unexpected complications in the perioperative period. Herbs can cause hematologic, cardiovascular, and endocrine disturbances, hepatotoxicity, prolongation of anesthetic agents, and even organ transplant rejection. Even though the American Society of Anesthesiologists (ASA) advises that all herbal medicines and supplements must be stopped 2 weeks before surgery [141] anesthesiologists should

be aware of the potential drug-drug interaction of the most common herbal remedies used by the psychiatric population and advise patients, as necessary.

9.1 St John's wort

Various herbal supplements have been linked to the treatment of depression. Generally, these should be discontinued at least 2 weeks prior to surgery but can vary with supplements. A commonly used supplement is St. John's Wort, which notably inhibits dopamine, norepinephrine, and serotonin and has the potential for serotonin syndrome [142]. St. John's Wort induces CYP3A4, which therefore reduces the efficacy of oral midazolam [14].

9.2 Ephedra Sinica

Ephedra sinica, also known as ephedra or ma-huang, is a central nervous system stimulant (CNS) that contains alkaloids ephedrine, methyephedrine, pseudo-ephedrine, and nor-pseudo-ephedrine. It works by stimulating α- and β-adrenergic receptors and increasing the release of norepinephrine from presynaptic neurons [143]. Due to its sympathomimetic effects, it is marketed for memory enhancement, weight loss, and asthma treatment. However, it is also used in the illegal manufacture of methamphetamine known as "Cloud 9" or "Herbal Ecstasy" [144]. A few side effects include hypertension, tachycardia, seizure, and stroke [145].

The effects of ephedra on anesthesia are well understood. Fatal arrhythmias associated with the simultaneous administration of ephedra and inhalation of the anesthetic agent halothane have been reported [146]. In addition to arrhythmias, if combined with other sympathomimetics it can also cause hyperthermia and hypertension [145]. Patients who have used this agent long term may benefit from direct-acting sympathomimetics as their endogenous catecholamine stores may be depleted, which increases the risk of intraoperative cardiovascular instability.

9.3 Ginkgo Biloba

Ginkgo biloba is a supplement commonly used to improve memory, mental alertness, treat intermittent claudication, and other circulatory disorders. The two main active medicinal groups of ginkgo are terpene lactones and ginkgo flavone [147]. The terpene lactones are known to inhibit the platelet-activating factor (PAF), which predisposes the patient to increased bleeding [148]. A case report described an event of spontaneous hyphemia with the combined use of ginkgo and high-dose aspirin [149]. In another case, a patient developed spontaneous bilateral subdural hematoma [150]. Caution is advised on patients with previous history of bleeding disorders or who are taking anticoagulant drugs (especially with non-steroidal anti-inflammatory drugs (NSAIDs), heparin, and warfarin) [147].

The reported medicinal components of ginkgo, terpenes, and flavones do not significantly inhibit the CYP450 enzymes, but other components of this herbal supplement do inhibit the CYP1A2 and CYP3A4 [151].

9.4 Ginseng

Ginseng is advertised for several things, especially as an energy booster and lowering blood glucose agent. It is also used as a stress-relieving and homeostatic product

[152]. Its pharmacological properties come from the ginsenosides that act as steroidal hormones. Ginseng interacts with coagulation cascade and inhibits platelet aggregation [153]. Due to its glucose blood lowering effects, it is sometimes used concomitantly with other glucose-lowering agents in patients with type II diabetes [154]. Therefore, serum blood glucose concentrations should be closely monitored in diabetic surgical patients taking ginseng. Additional precautions should also be exercised in patients receiving anticoagulants or blood thinners. Finally, during surgery, it may precipitate rapid heart rate and high blood pressure [155].

9.5 Valerian

Valerian is used to treat sleep disorders, anxiety, headaches, depression, irregular heartbeat, and tremors. Its active compounds are called sesquiterpenes. Valerian acts similar to St. John's Wort as it modulates the Gamma Aminobutyric Acid (GABA) neurotransmitter and has hypnotic and sedative properties. As a sedative, it can potentiate the effects of general anesthesia [156]. Therefore, it may make it harder to wake up after general anesthesia and can cause irregular heart rhythms [155]. Lastly, the abrupt discontinuation of this product can produce benzodiazepine withdrawal symptoms [156, 157].

9.6 Kava

Kava, a CNS depressant, is used for religious and medicinal purposes in the South Pacific Rim and is known to be beneficial in treating anxiety [158, 159]. Research suggests that the primary active ingredient (kavalactones) modulates GABA activity and inhibits dopamine and noradrenaline reuptake [160, 161]. Kava is also a muscle relaxant and, in toxic doses, can induce paralysis and reversible muscle weakness but no loss of consciousness. This supplement may decrease the dosage needed for relaxants during surgery and increase the potency of antiemetics, antipsychotics, and CNS depressants [162]. It can also cause liver damage [163].

10. Electroconvulsive treatment

Electroconvulsive therapy (ECT) is defined as the "induction of a series of generalized epileptic seizures for therapeutic purposes." ECT may be utilized as a first line treatment for severe depressive episodes, catatonia, schizoaffective psychosis, and neuroleptic malignant syndrome [164]. ECT is also utilized as a treatment for mania as well as depressive or psychotic symptoms due to organic disease and has been employed as a last resort treatment for epilepsy, dyskinesias, and Parkinson's disease [164]. The procedure is brief, with an expected seizure duration of 30 to 90 seconds and administered two to three times per week, 6 to 12 treatments in total per series [165]. **Table 3** shows a list of common anesthetics used during ECT.

The mechanism of action by which ECT achieves therapeutic results is unknown; however, studies have discovered that ECT affects neurotransmitter pathways in the brain (increasing GABA neurotransmission and increasing plasma levels of tryptophan as well as glutamate), affects the hypothalamic pituitary adrenal axis, and results in an increase in cerebral blood flow [164]. In patients suffering from psychotic depression, 90% will achieve remission from ECT treatment, with relief of symptoms occurring within 10 to 14 days [164].

Drug	Mechanism of action	Purpose of drug for ECT	Onset of action	Half life	Potential post-procedural side effects	Effect on seizure duration
Dexmetomidine	Highly selective a2 receptor agonist	Sedative	4–5 minutes	2–2.5 hours	Hypotension, bradycardia, arrhythmias	No effect
Etomidate	$GABA_A$ receptor modulator	Sedative	30–60 seconds	2–5 hours	Adrenal suppression, nausea, vomiting, clonus	Increase
Ketamine	NMDA receptor agonist	Sedative	1–2 minutes	2.5–3 hours	Secretions, disassociation, hypertension, tachycardia	Increase
Methohexital	$GABA_A$ receptor modulator	Sedative	30–60 seconds	3–6 hours	Fatigue, confusion, nausea, vomiting	No effect
Propofol	$GABA_A$ receptor modulator	Sedative	30–60 seconds	Initial: 40 minutes Terminal: 4–7 hours	Hypotension, myoclonus, QT prolongation	Decrease
Remifentanil	Opioid	Sedative	1–3 minutes	1–20 minutes	Hypotension, bradycardia, nausea, vomiting	No effect
Rocuronium	Depolarizing Neuromuscular Blocker	Paralytic	3–5 minutes	20–45 minutes	Respiratory complications, anaphylaxis	No effect
Succinylcholine	Non-depolarizing Neuromuscular Blocker	Paralytic	30–60 seconds	30–60 seconds	Residual paralysis, apnea, bradycardia, malignant hyperthermia	No effect

Table 3.
Common anesthetic agents utilized during ECT.

As the procedure is brief, ideal sedating agents and paralytics for ECT have a fast onset of action and a short distribution half-life [166]. It is important to note that the goal of an ECT session is to achieve adequate seizure duration (between 30 and 90 seconds) and anesthetic agents can influence seizure threshold and duration [166]. Ideally, the anesthetic agent should also be easy to administer and have minimal postoperative side effects [166].

In preparation for the procedure, it is equally important to recognize that psychiatric medications can also have an impact on seizure duration and require management strategies in the setting of ECT administration. Mood stabilizing agents including lithium, valproic acid, and carbamazepine may require dosing adjustments [165]. **Table 4** shows a list of psychiatric medications and their potential effects in the setting of ECT Administration.

There are no absolute contraindications for ECT administration; however, there are several relative contraindications that require careful consideration before performing the procedure [164]. Relative contraindications include increased intracranial pressure, intracranial bleeding, recent cerebral infarction or myocardial

Drug	Class	Potential complications	Recommendations
Lithium	Mood Stabilizer	• Delirium • Postictal confusion • Lithium toxicity • Increases seizure duration • Serotonin syndrome • Prolonged effects of neuromuscular blocking agents	• Consider substituting an atypical antipsychotic for lithium during ECT treatment course. • Recommend adjusting the dose to maintain a blood lithium level in the lowest therapeutic range. • Recommend utilizing reduced doses of neuromuscular blocking agents.
Valproic Acid	Mood Stabilizer	• Increases seizure threshold • Decrease seizure duration	• Consider reducing the dose of valproic acid during ECT treatment course. • Consider utilizing a sedative agent such as etomidate that increases seizure duration.
Carbamazepine	Mood Stabilizer	• Increases seizure threshold • Decreases seizure duration • Decreases efficacy of neuromuscular blocking agents	• Consider reducing the dose of carbamazepine during ECT treatment course. • Consider holding doses prior to ECT procedure (holding the nighttime dose prior to the procedure or holding the morning dose prior to the procedure). • Studies suggest succinylcholine and mivacurium are preferred paralytic agents for patients receiving carbamazepine.
Lamotrigine	Mood stabilizer	Theoretically increases seizure threshold.	No medication adjustments are necessary.
Gabapentin	Mood stabilizer	Theoretically increases seizure threshold.	No medication adjustments are necessary.
Topiramate	Mood stabilizer	Theoretically increases seizure threshold.	No medication adjustments are necessary.
Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid	MAOI	Hypertensive crisis	• Recommend careful monitoring and avoidance of medications known to interact with MAOIs. • Consider switching patient to a reversible MAOI such as moclobemide.
Fluoxetine, Sertraline, Paroxetine, Escitalopram Citalopram	SSRI	Theoretically reduces seizure threshold.	• No medication adjustments are necessary. • Monitor for signs of serotonin syndrome.
Venlafaxine, Desvenlafaxine, Duloxetine	SNRI	Theoretically reduces seizure threshold.	No medication adjustments are necessary.

Drug	Class	Potential complications	Recommendations
Bupropion	NDRI	Theoretically increases seizure duration.	Consider reducing the dose of bupropion during ECT treatment.
Alprazolam, Clonazepam, Diazepam, Lorazepam, Midazolam, Temazepam	Benzodiazepines	• Increases seizure threshold • Decreases seizure duration	• Discontinue benzodiazepines or utilize sparingly during ECT treatment. • Long-acting benzodiazepines such as clonazepam should be discontinued days before ECT treatment.
Chlorpromazine, Loxapine, Haloperidol, Prochlorperazine, Perphenazine, Thiothixene	First-Generation Antipsychotics	Theoretically reduces seizure threshold.	• No medication adjustments are recommended • Monitor for anticholinergic and antiadrenergic side effects.
Clozapine	Second-Generation Antipsychotic	Clozapine reduces seizure threshold in a dose dependent manner.	Consider reducing the dose of clozapine during ECT treatment.
Methylphenidate	Stimulant	Theoretically increases seizure duration.	No medication adjustments are recommended.

Table 4.
Psychiatric medication management in the Setting of ECT administration.

infarction less than 3 months ago, intracerebral tumor, and vascular malformations [164]. Cardiac pathology (including coronary artery disease, unstable angina, cardiac arrythmias), orthopedic pathology (including severe osteoporosis), and respiratory pathology (including respiratory conditions such as severe COPD that would pose a life-threatening anesthesia risk as well as conditions that would predispose the patient to aspiration such as an esophageal hernia) are also relative contraindications [164].

11. Postoperative considerations for psychiatric patients

Several studies suggest that severe mental illness may suppress and dysregulate the immune system [167–169] and, thus, expose patients to higher risk of postoperative infection and mortality [167, 169]. Higher rates of postoperative infection have been reported for multiple surgeries including coronary bypass graft, hip surgery, total knee replacement, craniotomy, bariatric surgeries, and the implantation of ventricular assist devices [167, 170, 171]. Surgical procedures can also exacerbate cognitive impairment commonly associated with mental illness [8]. In addition, research has shown that depression and anxiety lower pain thresholds and that patients with these conditions prior to surgery have significantly higher postoperative pain and analgesic requirements. Depression and anxiety are also strong predictors of chronic surgical pain and are independent risk factors for postoperative delirium [8, 167].

Psychiatric patients undergoing surgery report a lack of mental health recognition, minimal discussion on the impact of surgery on mental health, a lack of specific mental health information prior to discharge, and inconsistent interaction with the mental health team. Surgeons report that they do not routinely ask their patients about their

mental health status prior to surgery. Reasons cited by surgeons include a lack of time and fear of being inappropriate or disliked by patients. Surgeons also reported feeling less confident about managing patients with severe mental illness compared to medical comorbidities. In addition, patients may be fearful to discuss topics of mental health, as there continues to be a stigma toward mental illness in healthcare and studies suggest that this stigma may impact surgical decisions [172, 173].

Due to these concerns, several hospitals and insurance companies now require a surgical clearance assessment from a psychiatrist before patients can undergo major elective surgeries [167, 171, 174, 175]. For example, most patients that undergo bariatric surgery receive psychiatric clearance prior to the surgery. This psychiatric assessment helps determine if the patient is psychologically and emotionally prepared to undergo the procedure and helps identify if there are any issues that might impede a successful surgical outcome. The assessment also addresses whether the patient can make adequate lifestyle changes and if mental health support is needed following the surgery. Psychiatric evaluations have been shown to result in more favorable outcomes when mental health issues are treated prior to surgery [167, 171, 175].

Psychiatric evaluations should include a diagnostic interview, observation, and thorough review of medical records. Psychiatric evaluation should focus on history of major mental illnesses, substance use, cognitive skills, and capacity to make decisions, ability to adhere to treatment, coping skills, level of social support, and safety assessment including assessment for active suicidal or homicidal ideations [175, 176]. Patients with uncontrolled psychiatric illness and poor social support are at higher risk for surgical complications. Patients with active substance use are also at an increased risk for surgical complications and efforts should be made to connect these patients with drug and alcohol treatment prior to undergoing major elective procedures [176]. Surgery is a significant life event that can exacerbate mental illness [167, 173]. The patient should fully understand the surgical risks and benefits. A history of compliance with medical instructions, medications, and keeping appointments is also important. Patients should have established internal and external resources for coping with stress, depression, and anxiety.

Following major surgeries, there is often some loss of normal functioning and the need to modify lifestyle and depend on others for assistance. Disruption of the patient's normal routine, combined with loss of independence, can have a debilitating effect on mental health and exacerbate existing psychiatric conditions [167, 175]. There is growing awareness among surgeons that general anesthesia may be responsible for delirium, confusion, hallucinations, depression, mania, and psychotic behavior [167]. Therefore, patients and families should be educated on the early signs of worsening mental health and an action plan should be developed prior to discharge.

12. Discussion

Optimal perioperative outcomes require a multidisciplinary team to provide comprehensive and individualized care. Teamwork, interprofessional communication, and quality improvement efforts continue to play a vital role in the advancement of healthcare. It is important to consider protocols to screen patients for mental illness and facilitate communication between anesthesiologists and mental health professionals particularly when to prevent treatment errors, avoid higher treatment costs, and improve patient experiences. Moreover, efforts to increase communication such as electronic health records, TigerConnect, and TelmedIQ can be implemented in the

hospital systems to ease the flow of information between providers and decrease the likelihood of sentinel events. In hospitals where access to these technologies is not possible, physician notes or letters can be given to the patient to share his/her personal health information across his/her health care providers.

As psychiatry continues to advance, it is expected to see new treatment methods and psychotropic medicines. One such new medicine is the novel recent FDA approved neurosteroid Zulresso® (brexanolone) injection for the treatment of postpartum depression. This medicine is administered as a continuous intravenous infusion, throughout 2.5 days, and is thought to work as a positive allosteric modulator of $GABA_A$ receptors [177]. Other common adverse effects are dizziness, vertigo, presyncope, and sedation [178]. Interactions with anesthetics or other sedatives have not been studied but caution is advised due to its mechanism of action.

Another promising new therapy is the use of propranolol for the reduction of posttraumatic stress disorder (PTSD) symptoms. In a randomized controlled trial, Bruner and colleagues found that patients taking propranolol had improved Clinician-Administered PTSD Scale (CAPS-5) scores compared to the placebo group [179]. Although these were exciting results, long-term follow-up studies and replication of this study are necessary to reach any conclusions.

The use of medical cannabis is growing in popularity across the U.S.A. but controlled studies in its efficacy and safety are lacking. An 8-week multicenter, double-blind randomized controlled trial on the use of cannabidiol (CBD) on patients with schizophrenia demonstrated that when compared to the placebo group, patients taking 1000-mg daily of CBD had decreased positive symptoms in the Positive and Negative Syndrome Scale (PANSS). Improvement in cognition was also documented and the treatment was well tolerated by the participants [180]. Although these results are promising the study had a small sample size, is pending replication, and to confirm these results a lasting phase-3 trial is necessary.

13. Conclusion

This chapter discusses the most common psychotropic medications, substances, and herbal supplements used by patients with psychiatric conditions. Anesthesiologists should exercise special caution to prevent discontinuation syndromes, withdrawal symptoms, or potentially lethal interactions with anesthetics. It is also essential to stay up to date with new drugs such as dexmedetomidine, olanzapine/samidorphan combination, and lumateperon for new data on anesthetic interactions. Lastly, anesthesiologists are encouraged to contact the patient's physician if questions about their psychotropic medications arise during the pre-operative examination (**Table 5**).

14. Summary table

Drug	Hold/continue	Interaction with anesthetics	Considerations
Antidepressants			
SSRI	Continue	Avoid serotonin crisis precipitants & methylene blue	Avoid pethidine, meperidine, tramadol, pentazocine, and dextromethorphan

Drug	Hold/continue	Interaction with anesthetics	Considerations
SNRI	Continue	Avoid serotonin crisis precipitants & methylene blue	Avoid pethidine, meperidine, tramadol, pentazocine, and dextromethorphan
MAOI	2-week Washout	Avoid indirect acting sympathomimetics (such as phenylephrine or ketamine), avoid serotonergic crisis precipitants such as meperidine or dextromethorphan	
TCA	Hold 2 days prior	Avoid sympathomimetics (ketamine, ephedrine, metaraminol, etc.)	May reduce seizure threshold and may augment anesthetic sedatives
Atypical Antidepressants (Mirtazapine, etc.)	Continue	Avoid serotonin crisis precipitants & methylene blue	
Ketamine	Continue		Potential decreased efficacy with lamotrigine
Anxiolytics			
Benzodiazepines	Continue		Avoid use with meperidine and tramadol
Buspirone	Continue		Avoid use with meperidine or tramadol
Hydroxyzine	Continue		Avoid anticholinergics
Mood stabilizer			
Lithium	Stop 72 hours prior	Prolongs depolarization and polarization phase of neuromuscular blockade by acting additively with depolarizing neuromuscular agents and synergistically with non-depolarizing neuromuscular agents.	Signs of toxicity: tremors, vomiting, confusion, diarrhea, increased deep tendon reflexes, hypotension, seizures. Obtain plasma lithium level if suspected toxicity
Valproic Acid	Continue	Can increase levels of highly protein bound anesthetics such as propofol.	Recommend preoperative screening for bleeding risk, as well as preoperative platelet count, bleeding time, PT, activated partial thromboplastin time, fibrinogen, and von Willebrand factor
Carbamazepine	Continue	Duration of effect of non-depolarizing aminosteroid neuromuscular blockers	Strong CYP450 Inducer, can decrease plasma concentration of many medications including

Drug	Hold/continue	Interaction with anesthetics	Considerations
		such as vecuronium can be shortened	cardiovascular drugs, such as amiodarone, β-blockers (metoprolol, propranolol), and calcium channel blockers (nifedipine, nimodipine, felodipine, and verapamil).
Lamotrigine	Continue	Can decrease Ketamine's dissociative effect	
Antipsychotics			
Antipsychotics	Continue	Avoid enflurane	Caution is advised with other seizure-threshold lowering drugs
Stimulants			
Amphetamines/Amphetamine-like substances	Continue	• Acute intoxication—anesthetic requirements increase • Chronic use—anesthetic requirements decrease	
Recreational drugs			
Tobacco	Stop at least 72 hours before elective surgery		
Alcohol	Stop 1–2 weeks prior to surgery	• Acute intoxication—anesthetic requirements decrease • Chronic use—anesthetic requirements increase	
Opioids	Continue prescription opioids for pain control as appropriate to avoid withdrawal		
Cocaine		• Acute intoxication—anesthetic requirements increase • Chronic use—anesthetic requirements decrease	• Acute intoxication—hypertension possible in response to ephedrine and ketamine • Chronic use—decreased response to ephedrine
Marijuana	Stop smoking use at least 72 hours prior to elective surgery		

Drug	Hold/continue	Interaction with anesthetics	Considerations
Inhalants			Acute intoxication—recommendation for general anesthesia due to respiratory compromise and aspiration risk
Medication assisted treatments (MATs)			
Methadone	Continue		Avoid buprenorphine or butorphanol, as it can precipitate withdrawal
Buprenorphine	Continue		Do not administer on patient on methadone
Naltrexone (oral)	Hold at least 72 hours prior to surgery	Inhibits anesthetics	
Naltrexone (Vivitrol)	Hold 4 weeks prior to surgery	Inhibits anesthetics	
New medications			
Dexmedetomidine Sublingual Film (IGALMI™)	Continue	Limited Data	Side effects can be similar to dexmedetomidine used intravenously
Olanzapine and Samidorphan (LYBALVI®)	Continue	Limited Data	Anesthetics, sedatives, and hypnotics can potentiate the risk of orthostatic hypotension.
Lumateperone (Caplyta)	Continue	Limited Data	Anesthetics, sedatives, and hypnotics can potentiate the risk of orthostatic hypotension.

Table 5.
Summary of recommendations.

Conflict of interest

The authors declare that the work for this book chapter was conducted in the absence of any commercial or financial relationships that could be considered a conflict of interest.

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