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What anesthesiologists need to know about Antidepressants and other Psychotropic Drugs

Abstract

Psychotropic medications are widely prescribed and are a mainstay treatment for various mental health disorders. A significant portion of patients undergoing surgery or various procedures take these medications. With the rising prevalence of mental health conditions, anesthesiologists increasingly find themselves encountering patients who depend on these medications, making the understanding of potential interactions with anesthetic agents crucial during the perioperative period. Appreciating the adverse-effect profiles and familiarity with the clinically relevant drug interactions that may occur in the perioperative setting are imperative to ensure the best possible outcome in delivering patient care. This review focuses on various classes of psychotropic agents, including antidepressants, antipsychotics, mood stabilizers, and anxiolytics. It covers the pharmacodynamics and pharmacokinetics of these medication classes and their interactions with agents commonly used in anesthesia.

Keywords: Antidepressants, antipsychotic, anxiolytics, psychotropic drugs, mood stabilizers, anesthetic consideration, serotonin syndrome, regional anesthesia

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Aminat Haruna MD MPH,[1] Iyesogie Ojo MD,[2] Rebecca Rusnak BA,[3] Hilmi Ibtesam MBCHB, FRCA[1]

[1]Department of Anesthesiology and Perioperative Medicine University of Pittsburgh, USA
[2]Department of Anesthesiology, Yale New Haven Hospital, USA
[3]SUNY Upstate Medical University, USA

Correspondence: Ibtesam Hilmi. MBCHB, FRCA, Professor of Anesthesiology and Perioperative Medicine, Professor, Clinical and Translational Science Institute, University of Pittsburgh, School of Medicine, USA, Email hilmiia@upmc.edu

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Abbreviations

SSRI, serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, MAO-inhibitors; FDA, Food and Drug Administration; CNS, central nervous system; SARI, serotonin antagonist reuptake inhibitor; SERT, serotonin reuptake transporter; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder; TdP, torsades de pointes; EPS, extrapyramidal symptoms; FGA, first generation antipsychotic; SGA, second generation antipsychotic; NMS, neuroleptic malignant syndrome; VPA, valproic acid; SIADH, symptoms of inappropriate antidiuretic hormone; LAST, local anesthetic systemic toxicity.

Introduction

Psychotropic medications are widely prescribed and are a mainstay treatment for various mental health conditions. A considerable portion of the surgical population rely on these medications to manage conditions such as depression, anxiety, bipolar disorder, schizophrenia, and chronic pain. These medications can have important interactions with agents typically used in anesthesia, leading to potential side effects and complications. This is of growing concern for anesthesia providers, as more Americans are taking psychotropic medications every year. In 2020, 16.5% of all Americans reported having used a prescription for their mental health in the past year.[1] Antidepressants are the most commonly used medication, followed by anxiolytics.[2] Other less commonly used medications included hypnotics, antipsychotics, and sedatives.[2] This usage rate may be higher among the surgical population, with some studies reporting that as many as 43% of surgical patients endorse psychotropic drug usage.[3] These numbers may be increasing, as data from the CDC has shown a 34% increase in antidepressant use among women between 2010 and 2018.[4]

Although historical articles have been written as guidance for anesthesia providers.[5,6] This article aims to provide an updated and more comprehensive review of the commonly encountered psychotropic medications. Medications reviewed will include antidepressants, antipsychotics, mood stabilizers, and anxiolytics. The pharmacodynamics and pharmacokinetics of these medications will be covered, as well as their key interactions with anesthetic agents, including inhaled agents, intravenous induction, agents used in the maintenance of anesthesia, analgesic medications, and paralytics. Moreover, few articles have explored the relationship between psychotropic medications and regional anesthesia,[7] so attention will be given to these potential considerations as well.

Material and methods

A comprehensive literature review was conducted using PubMed and Google Scholar, with the following keywords: Psychotropic drugs, Antidepressants, Anxiolytics, Antipsychotics, Mood stabilizers, Benzodiazepines, 'Barbiturates, Anesthetic considerations/ interactions, Perioperative considerations, Regional anesthesia, Neuraxial anesthesia, Peripheral nerve blocks, and Local anesthetics. Relevant references within the retrieved articles were examined and reviewed for additional sources. Specific side effects and interactions were additionally searched.

Antidepressants:

Depression is a prevalent mental health disorder, often characterized by imbalance in neurotransmitter levels like serotonin, norepinephrine, and dopamine. Antidepressant medications, which modulate these neurotransmitters, are central to the treatment of depression.[8,9] The main classes of antidepressants include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and Monoamine Oxidase Inhibitors (MAOIs).

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs selectively inhibit the reuptake of serotonin (5-HT), with minimal effects on norepinephrine, dopamine, or acetylcholine. The 5-HT reuptake increases serotonin transmission in the central nervous system (CNS).[10] Currently available SSRIs in the United States include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine,

and sertraline, with citalopram being the most selective. Side effects of SSRIs reported include nausea, headaches, restlessness, decreased sexual arousal, and insomnia.

Most SSRIs are highly protein bound, with varying durations of action. They are metabolized by the liver via the CYP (cytochrome P450) system and eliminated via the kidneys and feces. Certain SSRIs inhibit the CYP450 enzyme, which can alter the plasma concentrations of benzodiazepines, barbiturates, and other anesthetic agents, potentially leading to prolonged sedation or increased sensitivity to these medications. Additionally, SSRIs reduce the metabolism of pro-drugs such as tramadol, codeine, and oxycodone, potentially diminishing their analgesic efficacy. Genetic polymorphisms in CYP systems (CYP2D6, CYP2C19, and CYP2B6) can further influence the metabolism of SSRIs, affecting dosing and effectiveness.[11] Notably, fluoxetine and fluvoxamine increase the risk of perioperative bleeding in patients simultaneously using NSAIDs, anticoagulants, or antiplatelet therapies.[12,13] The bleeding effect can theoretically be attributed to SSRI's inhibition of serotonin reuptake by platelets, which impairs platelet aggregation and hemostasis.[13-16]

Serotonin syndrome is a potentially life-threatening condition characterized by a triad of neuromuscular hyperactivity (clonus, hyperreflexia, myoclonus), autonomic instability (hyperthermia, tachycardia, diaphoresis), and altered mental status.[16] This syndrome can occur in the perioperative setting when multiple serotonergic medications, i.e., linezolid, ondansetron, metoclopramide, fentanyl, and methadone, are administered in quick succession or when serotonergic drugs already present in the system interact with these agents.[17] Intraoperative recognition of serotonin syndrome can be challenging due to overlapping signs with other conditions such as neuroleptic malignant syndrome (NMS), malignant hyperthermia, or thyroid storm.[18] Cyproheptadine, a 5-HT2 receptor antagonist, can be used as an antidote to serotonin syndrome, often producing rapid resolution of symptoms.[19] A repeat dose may be necessary if symptoms recur.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs commonly used in treating major depressive and anxiety disorders and are known for their efficacy and good safety profile. SNRIs exert their action by blocking serotonin and norepinephrine reuptake, leading to elevated levels of aforementioned neurotransmitters in the synaptic cleft.[20] Current Food and Drug Administration (FDA) approved SNRIs in the market include Venlafaxine, Duloxetine, Desvenlafaxine, milnacipran, and levomilnacipran. SNRIs are routinely prescribed for other medical conditions outside of depression and anxiety. Duloxetine, in particular, has gained widespread use for treating chronic pain, fibromyalgia, and neuropathy.[20] Venlafaxine and Duloxetine are metabolized via the cytochrome P450 system leading to potential drug-drug interactions i.e., abnormal bleeding in warfarin.[21] Though uncommon, the reuptake of norepinephrine in this class of medication can increase blood pressure and further precipitate a hypertensive crisis even at lower doses when inhibitors of the CYP3A4 enzyme (cimetidine, amiodarone, diltiazem, ciprofloxacin) are administered concomitantly.[22] Levomilnacipran and milnacipran have a stronger norepinephrine effect with a higher risk of hypertension.[23,24] Similarly to SSRIs, the perioperative administration of other serotonergic agents carries the risks of increased bleeding and serotonin syndrome.

Anesthetic considerations

The relationship between SSRIs and anesthetic requirements remains complex and variable. Anesthesia providers should closely monitor and have a high index of suspicion for serotonin syndrome when administering other serotonergic drugs.[16] Serotonin mediated vasopressin release is linked to symptom of inappropriate antidiuretic hormone (SIADH) and several cases with SSRI mediated SIADH have been reported in the literature.[25] SIADH if not appropriately managed can cause life threatening seizures, coma and in severe cases death. This emphasizes the importance of a thorough preoperative evaluation and labs. Mainstay treatment includes fluid restriction, vasopressin antagonist and hypertonic saline in extreme cases.[25,26] SSRIs and SNRIs are potent inhibitors of the CYP50 systems and can cause drug -drug interaction with drugs such as warfarin, benzodiazepines, phenytoin. These interactions can be fatal in renally or hepatically impaired individuals or aberrant CYP metabolizers.[21] Anesthetic management should be individualized, with attention paid to potential drug interactions, bleeding risks, and the possibility of SIADH and serotonin syndrome.

Tricyclic Antidepressants (TCAs)

TCAs non-selectively inhibit the reuptake of serotonin, norepinephrine, and dopamine, leading to increased levels of these neurotransmitters in the brain, improving mood, attention, and pain.[27] Due to the nonselective action of this class, antagonism of alpha adrenergic, muscarinic, and histaminergic(H1) receptors is observed which can lead to anticholinergic and sedative side effects. TCA's exhibit high protein binding with a large volume of distribution, and mostly undergo CYP 450 hepatic metabolism and are excreted via the renal system.[28] Despite their initial widespread use, TCAs have fallen out of favor, limiting their current use due to their narrow therapeutic index and the risk of significant toxicity and side effects, including cardiovascular, neurological, and anticholinergic complications limit their current use. They are now second line in the treatment of depression.[29]

The current FDA approved medications in this class for treating depression include amitriptyline, doxepin, nortriptyline, imipramine, desipramine, amoxapine, trimipramine, and protriptyline. Clomipramine is FDA approved for treating obsessive-compulsive disorder (OCD). We also see increasing off-label use of TCAs in the management of chronic pain, migraines, and neuropathy.[30,31] Nortriptyline and desipramine have the most favorable side effect profile of this class. TCA crosses the blood-brain barrier and can cause CNS depression, delirium, disorientation, and seizures, particularly in geriatric patients. The elderly are also more sensitive to anticholinergic side effects such as confusion, urinary retention, and blurry vision. TCAs should not be discontinued abruptly but gradually tapered off over two weeks, given their potential for withdrawal symptoms (malaise, chills, rhinorrhea).[32]

Anesthetic considerations

Careful consideration should be taken in using TCAs with centrally acting anticholinergic agents to decrease the risk of postoperative sedation and delirium.[27] In patients with underlying cardiovascular disease, TCAs should be avoided as they increases the sensitivity of adrenergic receptors to catecholamines, altering cardiac conduction, affecting cardiac chronotropy, worsening ischemic heart disease in the acute period following a myocardial infarction and causing

sudden cardiac death.[33] Sympathomimetic agents like ketamine, pancuronium, and epinephrine containing medications warrants cautious use in patients on TCA to avoid the risk of exaggerated sympathetic response. Elevated levels of catecholamines within the CNS can increase anesthetic requirements during surgery. The enhancement of brain catecholamines necessitates careful attention during perioperative management. Conversely, catecholamine depletion due to chronic TCA use can lead to hypotension due to the unopposed cardiac depressant effects of anesthetic agents in the absence of sufficient catecholamine counterbalance.[33]

Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors are a class of antidepressants that inhibit the breakdown of monoamines (serotonin, norepinephrine, dopamine) and bind irreversibly to the enzymes, thereby prolonging their effects after discontinuation.[34] It was initially used for the treatment of unipolar depression and is now used in the management of treatment-resistant depression. Its use has expanded to the management of neurocognitive disorders such as dementia and Parkinson's.[34] Phenelzine, isocarboxazid, tranylcypromine, and selegiline are selective MAOI currently available in the USA. There are two types of monoamine oxidase, A and B. MAO-A increases the levels of certain neurotransmitters, including serotonin, norepinephrine, and dopamine, which is beneficial in the treating mood disorders. MAO-B primarily targets dopamine levels, providing benefit in Parkinson's disease.[35-37] Selegiline, a selective MAO-Binhibitor approved for treating Parkinson's.[35] Although efficacious, this class has fallen out of favor and has been less prescribed over the last few decades due to unfavorable side effect profiles and dietary restrictions.[37] This class of drugs are metabolized hepatically and excreted renally.[34] They have long lasting effects due to the irreversible enzyme inhibition, which has severe implications for perioperative management. Severe interactions, particularly with tyramine-containing foods (aged cheese, unpasteurized beer) or sympathomimetic agents, can potentially lead to lethal hypertensive crises.[38] Sympathomimetics such as ephedrine, oxymetazoline and serotonergic agents i,e., SSRIs, SNRIs, TCAS, linezolid, methylene blue, and synthetic opioids should be avoided in these patients.[19]

Anesthetic considerations

The perioperative use of MAOIs requires extreme caution, and anesthetic agents that pose risks for hypertensive episodes should be avoided. Overdoses of MAOIs may result in severe CNS excitation and increased sympathetic outflow, which can manifest as neuromuscular irritability, hyperthermia, hypertension or hypotension, and arrhythmias.[36,39] Conversely, MAOI can predispose patients to hypotension during anesthesia; direct acting vasopressors i.e phenylephrine, are the preferred treatment for managing hypotension in these cases.[40] Prolonged sedation with opioids, barbiturates, and other CNS depressants can be observed. As with other classes of antidepressants, the risk of serotonin syndrome is increased when combined with serotonergic agents i.e., Tramadol, meperidine, dextromethorphan, and methadone, and they are contraindicated in patients on MAOIs.[19] While it is recommended for a two-week washout prior to surgery, abrupt discontinuation can also lead to withdrawal symptoms. Selegiline at doses less than 10mg daily can be continued perioperatively.[39] Caution should still be observed after 14 days of discontinuation during anesthetic management in patients, as some patients may need a longer washout period.[41]

Atypical antidepressants: Trazodone, Bupropion, and Mirtazapine

Bupropion

Bupropion, an aminopropiophenone, is a medication that exerts its effect via selective reuptake inhibition of dopamine, and to a lesser extent, norepinephrine.[42] It is used in the treatment of anxiety and depression, but its use has expanded to the management of smoking cessation, off-label use in the treatment of ADHD, and sexual dysfunction.[42-44] The half-life is 10 hours, and it is metabolized via the Hepatic cytochrome P450 system, specifically CYP2B6 isoenzyme, into active metabolites excreted in the urine.[42] It should be renally and hepatically dosed in patients with renal or hepatic impairments.

Anesthetic considerations of Bupropion

Bupropion has a good safety profile and should be avoided in combination with MAOI. Extreme caution is advised when administering drugs that induce or inhibit its metabolism via the CYP2B6 system as the activity can alter the plasma concentrations of bupropion or other agents,[44] potentially leading to CNS toxicity, seizures, and cardiovascular collapse.[45] Index of suspicion should be high in patients presenting with CNS excitability and cardiotoxicity. Intralipid emulsion has been successfully reported to improve outcomes in the treatment of bupropion overdose,[45-47] and in extreme cases, initiation of Veno-Arterial Extracorporeal Membrane Oxygenation has been used.[48]

Mirtazapine

Mirtazapine is a non-adrenergic, serotonergic medication with antagonists of 5-HT_2 and 5-HT_3 receptors and central α- 2 receptor increasing serotonin and norepinephrine neurotransmitters approved for the treatment of unipolar depression.[49-51] It is known to have antidepressants, antianxiety, orexigenic, and antiemetic effects used off-label in the treatment of post-traumatic stress disorder (PTSD), OCD, panic disorders, adjuncts in the treatment of schizophrenia, chronic pain, and insomnia.[52-54] Mirtazapine has a highly plasma protein binding with a peak plasma concentration reached within 2 hours and elimination half-life that ranges from 20 to 40 hours. It is metabolized hepatically via glucuronide conjugation, demethylation, hydroxylation, and cytochrome P450 enzymes; it is excreted majorly via the kidneys (75%) and feces (20%).[49,50]

Anesthetic considerations

Mirtazapine should be avoided in patients currently on MAO inhibitors, with extra caution in administering other serotonergic agents such as linezolid because of an increased risk of serotonin syndrome.[17,19,55] Concurrently administering other CNS depressants without care considerations can potentiate the sedative effects.[53,55]

Trazodone

Trazodone is a tetracyclic antidepressant that acts as a weak serotonin antagonist reuptake inhibitor (SARI). They exert their effect by inhibiting the serotonin reuptake transporter (SERT) and blocking 5HT2A and 5HT1A receptors, increasing serotonin levels in the synaptic cleft.[55] They also have an affinity for histamine and α-1-adrenergic receptors, responsible for the sedative and anticholinergic effects.[56] They are used in the treatment of depression and off-label for insomnia, anxiety, chronic pain, sexual dysfunction, fibromyalgia, and nightmares in PTSD.[57,58] Trazodone unique side effect is priapism. This drug has a high plasma protein binding with peak

plasma concentration within 2 hours, a large volume of distribution. It is metabolized via the hepatic CYP2D6 system, with metabolites excreted via the kidneys.[57]

Anesthetic considerations

Similarly, with SSRIs and MAOis, the risk of serotonin syndrome is elevated when combining trazodone with other serotonergic agents, i.e, methylene blue, methadone.[59] The α-1-adrenergic receptors affinity of trazodone can potentiate sedative synergy and increased somnolence when combined with other medications such as opioids and benzodiazepines.[56,57] The risk of QT prolongation and torsade de point (TdP) is increased, particularly in trazodone overdose, but has been reported in normal levels.[60,61] The risk is more pronounced with underlying electrolyte imbalance and conduction abnormalities.[61] Careful monitoring of the patient is indicated as trazodone is an inhibitor CYP2D6 enzyme involved in the metabolism of many drugs, i.e. antipsychotics, SSRIs, TCAs, MAOi, digoxin[61] altering their levels leading to toxicity and can slow the breakdown of trazodone leading to toxic levels precipitating arrhythmias[60,61] and increase the risk of serotonin syndrome.[59] Although the level of evidence is limited, case reports and observational studies have suggested that trazodone may decrease the anticoagulant effect of warfarin.[13,63,64]

Anxiolytics:

Anxiety is one of the most common mental health disorders, making anxiolytics one of the most prescribed medications, at least in the Western world.[65] Anxiolytics are used in the management of varying types of anxiety disorders, from generalized anxiety, social anxiety, phobias, and panic disorders, and in the perioperative setting as a perioperative intervention for sedation and anxiolytics in patients without anxiety disorders.[66-68] SSRIs, SNRIs, are first line in the treatment of anxiety disorders.[67] This section will discuss anxiolytic agents: Benzodiazepines, buspirone, hydroxyzine, and non-benzodiazepine hypnotics.

Benzodiazepines

Benzodiazepines is a sedative-amnestic-hypnotic used in the perioperative period. Its use extends as an anticonvulsant in the treatment of seizures and epilepsy. It exerts its effect by serving as an allosteric modulator of GABA, thus enhancing the inhibition of GABA synapses.[69] There are two types of GABA receptors: $GABA_A$ and $GABA_B$. Benzodiazepines exert their effect by binding it to the BZ receptor and increasing the Cl- conductance of the $GABA_A$ receptor, causing increased inhibitory neurotransmission.[70,71] Commonly used benzodiazepines include midazolam, lorazepam, diazepam, and alprazolam. This class of medication has high lipid solubility but varying duration of action, with midazolam having the most rapid onset, diazepam with fast onset, alprazolam with intermediate onset, and lorazepam with the slowest onset.[69] Most benzodiazepines are metabolized via the CYP450 system. The potential for abuse and dependence makes this drug class less favorable.[71]

Anesthetic considerations

Benzodiazepines have a synergistic effect with other commonly used anesthetic agents, such as opioids and propofol, and can lead to respiratory depression, CNS depression, or profound sedation.[72] Chronic benzodiazepine use can increase anesthetic requirements, and acute use decreases anesthetic requirements. Some studies associate preoperative use of benzodiazepine with an increased risk of postoperative delirium particularly in frail and elderly patients.[73] Additionally, abrupt discontinuation of patients chronically on benzodiazepines can result in withdrawal, potentially leading to agitation and seizures perioperatively.[68,71]

Barbiturates

Barbiturates are sedative hypnotics that exert their effect by enhancing GABA signaling by potentiating GABA receptors. Its use varies from procedural sedation, antiepileptics, treatment of headaches, treatment-resistant status epilepticus, and alcohol withdrawal syndrome.[74,75] Current FDA-approved barbiturates in the United States include methohexital (ultra short-acting), pentobarbital (short-acting), butalbital (intermediate-acting), phenobarbital, and primidone (long-acting).[74] Butalbital is used in the treatment of headaches; methohexital is used in procedural sedation and, less commonly, induction and maintenance of anesthesia. Phenobarbital is used as an anticonvulsant, and pentobarbital is used in sedation and seizure management.[74-77] The time-to-peak concentration is 2 to 4 hours. It is highly lipid-soluble and crosses the blood-brain barrier rapidly, with rapid redistribution and a low volume of distribution. Barbiturates undergo hepatic metabolism via oxidation, n-glycosylation, and by the cytochrome P450, and excreted via the kidneys.[75] They were historically used as anticonvulsants, sedatives, and anxiolytics, but their current use is limited due to their adverse effects profile, elevated risk of dependence, and respiratory and CNS depression.[74]

Anesthetic considerations

Acute barbiturate decreases minimum alveolar concentration (MAC) and overall anesthetic requirements, while chronic use will increase requirements. The CNS and respiratory depression effects can potentiate the effects of other anesthetic agents.[76-78] Barbiturates should be avoided in patients with blunted or absent baroreceptor reflex i.e., hypovolemia, cardiac tamponade, beta-adrenergic blockade, as it can drop cardiac output without the ability to compensate.[76,77] Methohexital can depress airway response, leading to bronchospasm in status asthmaticus from histamine release when used alone.[78,79] It should also be avoided in patients with acute intermittent porphyria as it increases porphyrin production and precipitates a crisis.[80] Barbiturates can enhance the metabolism of other drugs due to CYP450 enzyme induction. Barbiturates should not be abruptly discontinued to avoid withdrawal symptoms, agitation, and in severe cases, life-threatening seizures.[74]

Buspirone

Buspirone is an azaspirodecanedione compound and a non-benzodiazepine, non-sedative anxiolytic approved for the treatment of anxiety and depression. It is a partial agonist of the serotonin 5HT1A receptor with moderate affinity for dopamine D2 receptors.[81] It has a short half-life, primarily metabolized by the liver and excreted via the kidneys. Buspirone has a favorable safety profile and can be continued in the perioperative period.

Hydroxyzine

Hydroxyzine is an antihistamine H1 antagonist with mild muscarinic receptor and 5-HT2 serotonergic receptor activity used as a second-line treatment in the management of anxiety disorders.[82,83] Hydroxyzine has a good pharmacological safety profile, with a long half-life of 20 hours, and it is metabolized hepatically and excreted renally. It is often used as a pre-anesthetic agent due to its sedative effects, particularly in pediatrics.[84]

Anesthetic considerations for Buspirone and Hydroxyzine

Buspirone has a favorable safety profile, but the serotonergic mechanism of action raises concern about the potential for serotonin syndrome in the perioperative period.[19] Although safe, hydroxyzine has been reported to contribute to the development of QT prolongation or torsade de point in patients with underlying risk factors of cardiovascular rhythm disturbance and concomitant administration of drugs that are known to contribute to the development of QT prolongation and TdP.[85,86] The sedative effects can be enhanced in combination with opioids and other CNS depressants.[87] Extra precaution is warranted in patients with renal or hepatic failure to avoid prolonged sedation.[88]

Non benzodiazepines hypnotics (z drugs)

Zolpidem, zopiclone and zaleplon are nonbenzodiazepine sedative-hypnotics. Similarly to benzodiazepines, these drugs act on the GABA-A receptors by selectively binding the alpha (α) 1 subunit, which is associated with sedation.[89] It is prescribed for insomnia but with off-label use for anxiety.[90] Due to their selectivity and short half-life, they are deemed to have better safety profiles and long-term use can be associated with dependence. Zaleplon has the shortest half-life (1 hour), zolpidem (2-3 hours), and eszopiclone with the longest half-life (6 hours).[73]

Anesthetic consideration:

Z drugs are metabolized by the CYP system and can interact with other drugs that rely on this pathway. The sedative effects of this drug class can potentiate the actions of other anesthetic agents, contributing to prolonged postoperative sedation and increased risk of overdose, especially in the elderly.[72,73,90] Combination with alcohol and other sedatives can potentiate CNS depression increasing risk of delirium and impair mental and psychomotor function.[91]

Antipsychotics:

Antipsychotics are a class of medications used to treat a wide variety of personality and mood disorders. Most notable among the personality disorders is the class A type including schizophrenia and schizoaffective disorder. Specifically, these medications help to improve positive psychotic symptoms such as agitation, delusions, and hallucinations.[92] Mood disorders can range from manic to depressive episodes. Antipsychotics are also used in the treatment of acute agitation, delirium and dementia. There are two main classes of antipsychotics, first generation and second generation with the second generation being termed atypical and more commonly used in current times. The driving thought regarding the neuro pharmacodynamics of modern antipsychotic drugs is that blocking dopamine D2 receptors at the postsynaptic membrane provides treatment against psychotic and manic symptoms by decreasing the activity of dopamine.[92] The blockade of dopamine receptors leads to increased risks of extrapyramidal symptoms (EPS) and tardive dyskinesia. Extrapyramidal symptoms occur as dopamine transmission in the nigrostriatal tract is disrupted, it can present as rigidity, tremors and bradykinesia similar to Parkinson's disease symptoms.[93] Many atypical antipsychotic drugs also act on other receptors, i.e., clozapine. Clozapine loosely binds dopamine receptors with a greater affinity for serotonin receptors, but its complexity is found in the other receptors that it also acts on, including histamine, acetylcholine muscarinic, and alpha-1 adrenoreceptors.[92] Clozapine is used in treatment-resistant schizophrenia. These atypical antipsychotic medications exhibit anticholinergic effects, which in turn limits the risk of extrapyramidal symptoms.

First generation antipsychotics

First generation antipsychotic (FGA) work most efficiently at D2 receptors at 60-80% occupancy while 75-80% leads to EPS and more adverse effects.[94] Among the FGAs there are high potency medications, including haloperidol and perphenazine that have low activity at histamine and muscarinic receptors. This leads to having less side effect profiles of sedation or anticholinergic activity. Low potency FGAs include chlorpromazine and thioridazine, have high histamine and muscarinic activity, thus increased anticholinergic activity and weight gain/sedation in contrast to high potency.[93] High anticholinergic activity leads to less risk of developing extrapyramidal symptoms. Of note, low potency FGAs are known to have greater adverse effects, including orthostatic hypotension, QT prolongation, and changes in vision compared to their counterpart.[93] The liver metabolizes all FGAs, and specifically, it has been shown that slow metabolizers of the CYP-2D6 enzyme lead to a higher risk of side effects from some of these medications, such as haloperidol.[93]

Second generation antipsychotics

Second generation antipsychotics (SGA) include medications like clozapine, quetiapine, olanzapine and risperidone. This class is known as the atypical or modern class of antipsychotic medications. The implementation of these medications changed the narrative that EPS was unavoidable in the treatment of psychosis. The subsequent development of other SGAs built upon this by creating even safer drug profiles than clozapine, which is known to cause many adverse effects, most notably agranulocytosis.[92] By acting on serotonin receptors with a higher affinity than dopamine receptors, the risk of EPS was limited although not eliminated. Similar to FGAs, SGAs are primarily metabolized by the liver.[94,95]

Metabolic syndrome, characterized by weight gain, dyslipidemia, and hyperglycemia, in some cases leading to type 2 diabetes, are common adverse effects of some SGAs, mostly due to sedation and inactivity.[92] Acutely, some of these antipsychotic medications have been known to cause orthostatic hypotension secondary to alpha adrenergic blockade.[95] The cardiovascular effects of some antipsychotics increase the risk of developing hypertension and can cause prolonged repolarization of potassium channels, leading to QT prolongation and, in rare cases sudden cardiac death.[92] The blockade of dopamine in many antipsychotics may lead to neuroleptic malignant syndrome (NMS), one of the rarest but most serious adverse effects that can occur. NMS can occur after a single administration or even after years of use; it presents with dysautonomia, rigidity, fever, and altered mental status. Treatment is supportive care, cessation of the offending agent, and, in more severe cases, dantrolene with recovery usually necessitating an intensive care unit stay.[96]

Anesthetic considerations

Antipsychotics should not be discontinued abruptly in the perioperative period as this may lead to increased post-op confusion, as well as emergence delirium.[96] Due to dopamine receptor blockade, antipsychotics interfere with the hypothalamic regulation of temperature.[96] This can be important when considering the pharmacokinetics of anesthetic medications as some can have prolonged effects when hypothermic, and some become more effective at higher temperature such as local anesthetics. Hypothermia can also lead to many adverse effects by influencing coagulation, platelet function, catecholamine levels, etc.[97] Patients on antipsychotics tend to be more prone to developing postoperative ileus. Neuraxial anesthesia should be considered where appropriate as this would

block the sympathetic system. Antipsychotic use can increase the risk of infection due to immunosuppression.[96] Antipsychotic medications are primarily metabolized by the liver, most notably via the CYP450 enzymes and thus experience numerous drug interactions when CYP450 enzymes are inhibited or enhanced.[98] Antipsychotics have also been known to lower the seizure threshold; careful consideration must be taken into account with medications used so as not to cause further seizure.[98]

Mood stabilizers

Mood Stabilizers are generally used to treat bipolar disorder, a mood disorder with symptoms ranging from manic episodes to depressive episodes affecting nearly 2% of the world.[98] This section will cover lithium, valproic acid, topiramate, lamotrigine, Carbamazepine and oxcarbazepine.

Lithium

The most commonly used treatment for bipolar disorder is lithium, whose mechanism of action is not well understood. The current hypothesis is that as a monovalent cation, lithium mimics sodium and limits the release of neurotransmitters in the nervous system, while others hypothesize that it is neuroprotective by inhibiting the NMDA receptor.[99] Lithium has no active metabolite and is renally excreted unchanged with a very narrow window of therapeutic use. There is no need to taper when discontinuing Lithium.[98,100]

Anesthetic considerations

Medications that impair kidney function can increase lithium toxicity, ex. NSAIDs, diuretics, and dehydration. Lithium toxicity usually presents as lethargy, restlessness, altered mental status, AV blockade, tremors, and gastrointestinal symptoms: nausea, emesis, and vision changes. Lithium can cause prolongation of neuromuscular blockade and decrease MAC requirements, and appropriate dose considerations should be given.[101-103] Lithium can cause electrolyte imbalance, primarily sodium, increasing the risk of cardiac complications during anesthesia. EKG changes such as T wave inversion can also be observed and, in rare cases, can cause arrhythmias.[104,105] Current guidelines are to stop lithium 72 hours prior to surgery due to its long half-life, given the likelihood of renal impairment secondary to perioperative hemodynamic instability.[98,103]

Topiramate

Topiramate is an antiepileptic drug approved for use in mood disorders refractory to other treatments, migraines and neuropathic pain.[106] Its precise mechanism of action is not well understood, although it is hypothesized that it enhances the activity of GABA while also inhibiting the activity of glutamate at NMDA receptors.[106,107] Additional evidence suggests that topiramate blocks sodium channels in a voltage-sensitive, use-dependent manner and weakly inhibits carbonic anhydrase II and IV.[107] Topiramate is poorly bound to proteins and undergoes minimal metabolism before being excreted unchanged in the urine.[107] The average elimination half-life is approximately 21 hours.[107] Common side effects of topiramate include weight loss, ataxia, somnolence and dizziness.[108]

Anesthetic considerations

Topiramate weakly inhibits carbonic anhydrase enzymes II and IV which can lead to metabolic acidosis.[108] In a study of patients taking topiramate for at least three months prior to surgery and no preexisting renal impairment, blood gas analyses revealed of metabolic acidosis in 60% of patients, with six experiencing severe hyperchloremic metabolic acidosis.[108] This acidosis is typically compensated for through respiratory mechanism, with patients either spontaneously hyperventilating or providers adjusting ventilatory settings by increasing their tidal volume and respiratory rate to correct the acidosis. Metabolic acidosis may impair cerebral metabolism and blood flow[108] making it advisable to consider preoperative blood gas analysis on patients taking topiramate.

Valproic Acid (VPA)

Valproic Acid (VPA) is used in the treatment of mania in bipolar disorder. It is also widely used as an antiepileptic to treat different types of seizure, including focal and generalized seizures[103]. VPA's mechanism of action is not yet fully understood; one accepted method is that it inhibits voltage-gated sodium channels, reducing neuronal excitability, and limiting the abnormal electrical impulses which cause seizures. VPA is also known to enhance the effect of gamma-aminobutyric acid (GABA)[109] by inhibiting the GABA transaminase enzyme and stimulating its synthesis by upregulating glutamic acid decarboxylase (GAD). In essence, VPA decreases excitatory neurotransmission by blocking GABA's breakdown and by increasing the conversion of glutamate to GABA via GAD.[110] It has also been shown to inhibit histone deacetylase, essentially influencing the transcription of genes, which is thought to allow for better mood regulation, neurodevelopment, and cognition; but this property also contributes to the teratogenicity of this medication. Lastly, VPA has been shown to affect various calcium channels (types L, T, and N) influencing neuronal signaling and neurotransmitter release.[111] Some notable side effects of this drug include pancreatitis, weight gain, thrombocytopenia, and leukopenia.[109] The pharmacokinetics of valproic acid are complex. The drug is highly plasma-protein bound, with a binding rate of approximately 90%. VPA is primarily metabolized by the liver via glucuronidation, oxidation and beta-oxidation. Glucuronidation is the primary method of excretion, with 20-70% of the drug being metabolized and later excreted in the urine.[112] Studies have shown that CYP450 plays a minor but important role in the metabolization.[113]

Anesthetic considerations

VPA can be continued in the perioperative period, but if discontinued, it has no rebound effect. However, abrupt discontinuation without a taper when used as an anticonvulsant can increase risk of perioperative seizures.[114] VPA can enhance the sedative effects of anesthetic agents particularly opioids and propofol. A decreased dose of propofol may be required due to VPA being highly plasma-protein bound, increasing the free concentration of propofol.[103] Other perioperative considerations include the risk for valproate-induced coagulopathy, which is secondary to thrombocytopenia as well as a reduction in coagulation factors like factors VII and VIII.[112,113]

Carbamazepine and oxcarbazepine

Carbamazepine is used as a mood stabilizer in the treatment of mania as well as an anticonvulsant in the treatment of epilepsy.[115] This drug works via blockade of voltage-gated sodium channels and increases GABA activity, which decreases hyperexcitability in the nervous system and contributes to its antiepileptic properties.[116] Oxcarbazepine is a derivative of carbamazepine with a similar mechanism of action.[117] It is FDA approved for the treatment of seizures and epilepsy but used off-label as a mood stabilizer.[118] Some side effects of both of these medications include hyponatremia, nausea, vomiting, headache, Steven-Johnson's syndrome, coagulopathy, thrombocytopenia, and aplastic anemia.[103,117] Generally, oxcarbazepine is better tolerated as it has fewer drug interactions.[118]

The pharmacokinetics of carbamazepine and oxcarbazepine differ greatly, despite their similar chemical structure. Carbamazepine undergoes oxidation in the liver by the CYP3A4 enzyme and hydrolysis by the epoxide hydrolase enzyme, creating a metabolite called 10, 11-Dihydro-10, and 11-DHD.[119] This metabolite is thought to be responsible for the majority of the side effects seen in patients taking this medication. Carbamazepine also acts as an inducer of the CYP3A4,5 group, and it inhibits CYP2C19.[120] Oxcarbazepine is first metabolized by cytosolic arylketone reductase in the liver. The derivative is then metabolized through glucuronide conjugation by UDP-glucuronyltransferase and excreted by the kidneys.[119] This drug has fewer interactions, because it only mildly induces CYP3A4,5 group and requires high doses to inhibit CYP2C19.[120]

Anesthetic considerations

Anesthetic considerations for carbamazepine largely stem from its induction of the CYP3A4,5 group, which increases the metabolism of several anesthetic classes.[5] The agents affected include opioids, benzodiazepines, and nondepolarizing neuromuscular blockers such as vecuronium. Higher and more frequent dosing of neuromuscular blocking agents might be needed due to the rapidity of the metabolism.[103] This effect must also be considered when treating perioperative pain in individuals on these medications. Because oxcarbazepine induces this enzyme to a lesser degree,[120] the metabolism of anesthetic agents is likely only mildly affected, although the relationship between the two has not clearly been studied. Lastly, carbamazepine and oxcarbazepine are associated with SIADH; perioperative electrolytes, in particular sodium, should be monitored to avoid arrhythmias and seizures from sodium imbalance.[104]

Lamotrigine

Lamotrigine is a mood stabilizer used in the treatment of bipolar disorder, including acute mania and bipolar depression. It is also an anticonvulsant that is widely used to treat both focal and generalized seizures.[121] Similar to other drugs in this category, lamotrigine is known to decrease glutamate release and act on voltage-gated sodium channels, which may underlie its efficacy as a mood stabilizer.[122] Lamotrigine has not been found to have any significant GABAergic effect.[122,123] Side effects of lamotrigine include: nausea, vomiting, weight changes, dysmenorrhea, and most severely, Stevens-Johnson syndrome. Lamotrigine is primarily metabolized via glucuronic acid conjugation, which may be induced by other drugs, including carbamazepine, phenytoin, and phenobarbital.[124,125]

Anesthetic consideration

Lamotrigine is largely regarded as safe to continue in the perioperative period. Abrupt discontinuation in patients taking it for its antiepileptic properties can cause rebound seizure, although this effect is diminished in lamotrigine compared to other antiepileptics like carbamazepine.[126] However, because lamotrigine decreases the release of glutamate, caution should be used when considering ketamine as an anesthetic adjunct.[5] Ketamine causes dissociation predominantly due to disinhibition of pyramidal neurons and enhanced glutaminergic firing.[127] Thus, in patients who take lamotrigine and have reduced glutamate release, the dissociative effects of ketamine will be diminished.[128]

Regional anesthesia:

Regional anesthesia is gaining increased utilization with the advent of ultrasound. It is used in clinical practice, either as surgical anesthesia or for analgesia. Common approaches include neuraxial anesthesia (epidural and spinal anesthesia) and peripheral nerve blocks (e.g., adductor canal, supraclavicular, and transversus abdominis plane blocks). Peripheral nerve blocks are generally considered safe and effective for most patients, although there remains a theoretical risk of local anesthetic systemic toxicity—a concern common to all regional techniques.[129] When administering neuraxial anesthesia, special attention should be given to patients taking certain psychotropic medications due to the physiological effects of neuraxial blocks (e.g., transient hypotension) and potential complications, such as bleeding, infection, and nausea. These considerations are especially important in the context of psychotropic medications, which can affect anesthetic management.

Hypotension

Epidural and spinal anesthesia can cause transient hypotension through the blockade of presynaptic sympathetic fibers, which lowers systemic vascular resistance.[130,131] If the block extends high enough, decreased stroke volume and bradycardia may also be observed from blockade of cardiac accelerator fibers.[131] Treating neuraxial anesthesia induced hypotension with indirect sympathomimetics like ephedrine can lead to excessive sympathetic responses in these patients. An example is discussed in a case report of a 21-year-old female receiving spinal anesthesia for knee arthroscopy experiencing severe hypertension 245/124 following administration of ephedrine. She had been taking phenelzine and selegiline, both MAOIs, which likely potentiated the hypertensive response.[132] Other case reports highlight similar risks, including subarachnoid hemorrhage due to hypertensive crises triggered by the combination of ephedrine and MAOIs.[133] Direct-acting vasopressors like phenylephrine are the preferred agents for treating hypotensive episodes during regional anesthesia.

Hematology and infectious

Epidural hematoma formation, though rare, is a feared complication of neuraxial anesthesia. Current literature estimates the incidence to be 1:168,000[134] in women, with a mortality rate around 3.5%.[135] Other potential complications of neuraxial anesthesia include bleeding, infection, with epidural abscesses occurring in approximately 1:1000 cases and meningitis in 1:50,000.[136]

Certain psychotropic medications, particularly tricyclic antidepressants (e.g., nortriptyline) and selective serotonin reuptake inhibitors (SSRIs) (e.g., escitalopram), have been shown to impair platelet aggregation,[137] increasing the risk of bleeding and hematoma formation. A report of epidural hematoma in a patient taking nortriptyline is detailed in the literature.[138] Similarly, antipsychotics like clozapine, risperidone, and haloperidol have also been associated with reduced platelet aggregation, increasing the risk of bleeding.[139] Clozapine is also known to cause agranulocytosis, which significantly increases the risk of infection.[140] Although no specific case reports link clozapine to infections following neuraxial anesthesia, its potential to increase the risk of complications like epidural abscess or meningitis is a theoretical concern.

Nausea and vomiting

Nausea is a common side effect of neuraxial anesthesia, with incidence rates as high as 80% in cesarean section performed under spinal anesthesia.[140] However, this rate varies significantly by procedure, with rates as low as 3.5% reported in patients undergoing hip arthroplasty.[141] Multiple antiemetics are available to treat intraoperative nausea, including serotonin antagonists (ondansetron, granisetron), dopamine antagonists (metoclopramide, haloperidol), neurokinin 1 antagonist (aprepitant), anticholinergics (scopolamine),

histamine antagonists (perphenazine, diphenhydramine), and dexamethasone. However, for patients on psychotropic medications, caution is required when administering certain antiemetics due to the potential for adverse interactions. Metoclopramide acts as an antiemetic by antagonizing D2 and 5HT-3 receptors in the chemoreceptor trigger zone.[142] Because it crosses the blood-brain barrier, it can block dopamine in the nigrostriatal pathway, resulting in acute dystonia, tardive dyskinesia, and drug-induced parkinsonism.[143] Since antipsychotics also antagonize D2 receptors,[92] concurrent use of metoclopramide and other antiemetics within this class with antipsychotics significantly increases the risk of extrapyramidal symptoms. A case report highlights this risk, describing a patient who developed prolonged extrapyramidal symptoms after receiving standard doses of olanzapine and metoclopramide.[144]

In patients already taking SSRI or SNRI, ondansetron and other serotonin antiemetics can enhance serotonergic effects,[145] which, although sometimes beneficial,[146] also poses a risk of serotonin syndrome. This risk is documented in a case involving a patient on fluoxetine who developed serotonin syndrome after receiving a standard dose of ondansetron.[147]

Local anesthetic metabolization

The most commonly used local anesthetics for neuraxial anesthesia include amides, such as bupivacaine, ropivacaine, and lidocaine, and esters, like chloroprocaine. *E*ster anesthetics are metabolized by plasma cholinesterases,[148] while amide anesthetics undergo hepatic clearance via phase I and phase II hepatic cytochrome p450 metabolism.[149]

Certain SSRIs can inhibit specific cytochrome P450 enzymes, potentially affecting the metabolism of amide anesthetics. Fluoxetine and paroxetine are potent CYP2D6 inhibitors, while sertraline has mild CYPD6 inhibition and escitalopram has no inhibitory effect.[150] In patients taking potent CYP2D6 inhibitors, such as fluoxetine or paroxetine, there is a theoretical risk of prolonged blockade or local anesthetic systemic toxicity (LAST) due to delayed clearance of amide local anesthetic. Therefore, consideration should be taken when administering local anesthetics in patients taking one of these potent inhibitors. A case report of this is noted in the literature, where a patient who took sertraline and flurazepam developed symptoms of LAST from standard dosing of lidocaine injected during a liposuction procedure.[151]

Increased risk of LAST is seen with concomitant use of drugs decreasing P450 activity accumulating lidocaine in the blood. Antipsychotics have variable effects on CYP450 isozymes. The first generation and some second-generation antipsychotics, including clozapine and risperidone, have been shown to inhibit CYP2D6.[152] The combination of these drugs with amide anesthetics presents a theoretical risk of LAST. In contrast, aripiprazole may reduce the duration of local anesthetic efficacy due to its enzyme inducing properties. Lastly, barbiturates are known to induce cytochrome p450 isozymes, particularly CYP2B.[153] This mechanism could theoretically lead to more rapid clearance of amide anesthetic, shortening the duration of effect.[154] However, no reports have been identified in the literature that documenting this interaction.

Conclusion

With the increasing prevalence of mental health disorders, the use of psychotropic medications has become a common occurrence seen in patients presenting for surgery and other procedures necessitating heightened vigilance during perioperative planning. The hepatic metabolism of many psychotropic drugs via CYP enzymes can alter the pharmacokinetics of drugs concurrently administered, affecting their duration and potency. Furthermore, the current literature on the interactions between psychotropic drugs and regional anesthesia is sparse, highlighting the significant gap in our understanding despite the increasing use of regional anesthesia. Given the limited data available, further studies are needed to explore these interactions. To optimize patient safety, anesthesiologists must tailor their management strategies while accounting for the effects of psychotropic medications on hemodynamics, bleeding, infection risk, and other adverse reactions. Thorough preoperative assessment is critical to minimizing risks of serotonin syndrome, neuroleptic malignant syndrome, hypertensive crises, electrolyte abnormalities causing cardiac and neurological complications, acute dystonia, and other extrapyramidal symptoms when administering other agents commonly used in anesthesia. Ultimately, it is the anesthesiologist's responsibility to stay informed on these medications and develop an appropriate intraoperative plan based on the patient's psychotropic drug use.

Conflict of interest

The authors of this article declare no conflict of interest.

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