South Afr J Anaesth Analg. 2023;29(5 Suppl 1):S153-157
https://doi.org/10.36303/SAJAA.3043

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

FCA REFRESHER COURSE

Neuropsychiatric pharmacology for the anaesthetist

C Redelinghuys

Department of Anaesthesia, School of Clinical Medicine, Faculty of Health Sciences, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: *carared003@gmail.com*

Neuropsychiatric conditions are placing an increasing burden on healthcare systems around the world, including South Africa. Providing anaesthesia to patients who are treated with neuropsychiatric agents is becoming a regular occurrence. Emphasis needs to be placed on understanding the pharmacological interactions of these various drug classes with anaesthetic drugs. This review includes antidepressants, anti-anxiety, mood stabilisers, and antipsychotics, and highlights new emerging treatments. Within each class, focus is placed on the physiological alterations related to the drug, the drug interactions, and rare but fatal conditions, such as serotonin syndrome (SS) and neuroleptic malignant syndrome.

Keywords: neuropsychiatric pharmacology, neuropsychiatric conditions, pharmacological interaction

Introduction

In South Africa, neuropsychiatric conditions rank third in their contribution to the burden of disease, after acquired immune deficiency syndrome (AIDS) and other infectious diseases.[1] The pharmacology and anaesthetic implications of these drugs in the perioperative setting are often underappreciated.[2]

Antidepressants

Depression is the most common psychiatric disorder affecting up to 40% of South Africans.[3,4] Pharmacological management is aimed at correcting deficiencies of dopamine, noradrenaline, adrenaline, and serotonin within the brain. Antidepressants can be divided into four groups, discussed below.

Tricyclic antidepressants (TCAs)

TCAs are relatively old antidepressants. The dose-dependent side effects of TCAs have decreased their use as antidepressants. They are now more common in the management of chronic pain. Lower dosages are used for analgesia than used to treat depression, hence they have a more favourable side effect profile.[5]

Mechanism

TCAs act on roughly five different neurotransmitter pathways; its antidepressant effect is due to blocking serotonin and noradrenaline reuptake in presynaptic terminals. The other neurochemical pathways include histaminergic and cholinergic systems, which cause a wide range of side effects.[6]

Anaesthetic implications

TCAs cause multiple ECG changes, nonspecific T-wave abnormalities, widening of the QRS complex, prolongation of QT interval, bundle branch block, and other conduction abnormalities. Unstable tachydysrhythmias are usually seen in overdose but also with drugs such as halothane and pancuronium.[6,7]

Exaggerated blood pressure responses can be expected following the administration of indirect-acting vasopressors. Direct-acting drugs such as phenylephrine are recommended to treat hypotension and one should consider avoiding or reducing the dosage of vasopressors and ketamine to avoid this response.[7] Patients may also exhibit exaggerated responses to sedative agents, so consider dosage reduction. Pancuronium, ketamine, pethidine, and adrenaline-containing solutions should be avoided.[7,8] TCAs should be continued in the perioperative period, as abrupt discontinuation risks withdrawal and relapse.[5,7]

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

SSRIs are the first-line treatment for depression and anxiety and the most widely prescribed class of antidepressants. This class of antidepressants is highly efficacious, their side effect profile is well tolerated and is relatively safe in overdose.[5,9] SSRIs are indicated not only for depression but also anxiety disorders, eating disorders, menopausal hot flashes, obsessive-compulsive disorders, post-traumatic stress disorder, premature ejaculation, premenstrual dysphoric disorder, and somatic symptom disorder.[2,9]

Mechanism

SSRIs block the presynaptic reuptake of serotonin to allow increased serotonin levels post-synaptically. There are other delayed therapeutic effects including receptor down-regulation and decreased neuronal firing. SSRIs increase the production of neuroprotective proteins and possess anti-inflammatory

properties.[2,9] SNRIs inhibit the reuptake of both serotonin and noradrenaline with minimal direct effects on other neurotransmitters or receptors.

Anaesthetic implications

The SNRIs do not significantly inhibit cytochrome P450 (CYP) enzymes.[8] SSRIs are inhibitors of the CYP2D6 enzyme. This causes altered metabolism of codeine and tramadol to their active metabolites causing inadequate analgesia. Fentanyl, morphine, and oxycodone are more effective.[9] SNRIs can cause tachycardia and hypertension and may require tighter blood pressure control.[8] SSRIs can also affect platelet aggregation, which is worsened by the concomitant use of other anticoagulants.[2,8] There is less evidence for an increased bleeding risk with SNRIs.[8]

SSRIs/SNRIs should not be stopped perioperatively to avoid discontinuation syndrome. Discontinuation syndrome is caused by the abrupt withdrawal of antidepressants and is associated with nausea, abdominal pain, diarrhoea, sleep disturbance, as well as somatic and affective symptoms. This syndrome starts within a few days of cessation and can last up to three weeks. The treatment is the reintroduction of the antidepressant.[6]

Table I: Serotonin Syndrome (SS)[5,9]

Clinical
The Hunter Criteria for SS is a serotonergic agent plus one of the following: Spontaneous clonus. Inducible clonus and agitation or diaphoresis. Ocular clonus and agitation or diaphoresis. Tremor and hyperreflexia. Hypertonia. Temperature above 38 °C and ocular clonus or inducible clonus.
Differential diagnosis
Neuroleptic malignant syndrome. Anticholinergic toxicity. Malignant hyperthermia. Sympathomimetic toxicity. Meningitis or encephalitis.
Treatment
Discontinue serotonergic agents.
Sedate using benzodiazepines. The aim is to eliminate agitation, neuromuscular abnormalities, and elevations in heart rate and blood pressure; titrate dose to effect.
Provide oxygen (maintain $SpO_2 \geq 94\%$), intravenous fluids, and continuous cardiac monitoring.
If benzodiazepines and supportive care fail to improve agitation and abnormal vital signs, give cyproheptadine (serotonin 1_A and 2_A antagonist). Adult dose: 12 mg orally.
Treat patients with temperature > 41.1 °C with immediate sedation, paralysis, and endotracheal intubation. Treat hyperthermia with standard measures. Avoid antipyretics such as paracetamol.
Complications
Metabolic acidosis, rhabdomyolysis, renal impairment, disseminated intravascular coagulation, seizures, coma, and death.

Serotonin Syndrome (SS)

SSRIs/SNRIs are both associated with the risk of SS.[5] This syndrome can occur when serotonin levels increase due to either an increased dosage of SSRI/SNRI or the introduction of a new serotonergic agent. Concomitant use of pethidine, tramadol, pentazocine, and dextromethorphan should be avoided due to the SS risk.[8] SS is a clinical diagnosis and can manifest a wide range of clinical symptoms, from mild tremors to life-threatening hyperthermia and shock.[8,9] See Table I for a summary of SS.

Monoamine oxidase inhibitors (MAOIs)

MAOIs are not common in clinical practice and are reserved for treatment-resistant depression and atypical depression.[8] The development of newer agents such as SSRIs/SNRIs and the severe food and drug interactions have decreased its usage worldwide.[2]

Monoamine oxidase (MAO) exists as two isoenzymes, MAO_A and MAO_B. MAO_A preferentially deaminates serotonin, adrenaline, noradrenaline, and melatonin. MAO_B preferentially deaminates phenylethylamine, phenylethanolamine, tyramine, and benzylamine. Dopamine and tryptamine are deaminated by both isoenzymes.[2] MAOIs can be classified as reversible or irreversible. They can also be classified according to isoenzyme inhibition, namely selective or non-selective. Moclobemide is a selective inhibitor for MAO_A and selegiline is selective for MAO_B.

Mechanism

MAOIs act by inhibiting MAO, increasing the availability of monoaminergic transmitters. Irreversible MAOIs bind and permanently inactivate MAO, leading to prolonged effects.[8]

Anaesthetic implications

The anaesthetic implications are numerous and some are fatal. Patients taking MAOIs are at risk of hypertensive crisis precipitated by indirect sympathomimetics, like ephedrine or ketamine.[7] Direct-acting sympathomimetics, such as phenylephrine, are preferable.[5,7] Exaggerated responses can be expected and dosages need to be titrated due to receptor hypersensitivity.[8]

Pethidine and dextromethorphan must not be used concurrently with MAOIs. They can precipitate a serotonergic crisis due to synergistic inhibition of serotonin reuptake, termed a Type I/ excitatory reaction.[6–8] Opioids such as tramadol, fentanyl, alfentanil, sufentanil, and remifentanil, as well as methadone, have also been associated with perioperative serotonergic toxicity.[2] MAOIs interact with the CYP enzymes, notably CYP3A4 and CYP2C19.[8] Type II/depressive reactions are due to MAO inhibition of hepatic enzymes resulting in enhanced effects of all opioids. These enhanced effects are reversed by naloxone.[6,7] Pancuronium should also be avoided as it releases stored noradrenaline.[8]

The benefits and risks should be weighed when deciding to discontinue MAOIs. Irreversible MAOIs need to be stopped two

weeks before elective surgery. Reversible MAOIs should be discontinued 24 hours before elective surgery.[7,8]

Dietary interactions

MAOIs inhibit the breakdown of dietary amines and eating foods containing tyramine can lead to severe hypertensive crisis. Tyramine is transported via vesicular monoamine transporter (VMAT) into synaptic vessels and displaces noradrenaline, precipitating the hypertensive crisis.[7] Patients using oral MAOIs must adhere to dietary restrictions, avoiding foods such as cheese, sausage meats, and red wine.[2]

Atypical antidepressants

Bupropion

Bupropion is used in the treatment of depression, hypoactive sexual desire disorder, and smoking cessation. The mechanism of action is inhibition of dopamine and noradrenaline reuptake. Patients are at increased risk of seizures and neuroleptic malignant syndrome. There are no precautions needed with the use of adrenaline perioperatively. Bupropion may reduce the effectiveness of codeine and tramadol due to CYP2D6 inhibition.[2,8]

Trazadone

Trazodone blocks serotonin reuptake, histamine, and alpha-1-adrenergic receptors and is used as an antidepressant and a sleep agent. Trazadone can cause QT prolongation, especially in combination with other drugs that have a similar effect. It may impair platelet aggregation, especially in combination with antiplatelet agents. Patients on trazodone are also at risk of excess somnolence, which is more significant with other sedative agents. Trazadone must not be used with MAOIs due to the associated SS risk. Despite these concerns, it can be continued perioperatively.[2,8]

Ketamine

Ketamine acts on multiple receptors, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), opioid, nicotinic and muscarinic acetylcholine receptors (Ach), gamma-aminobutyric acid (GABA), and monoaminergic receptors.[7] Esketamine, the S-enantiomer of ketamine, is a fast-acting intranasal treatment used in adults with major depressive disorder with or without acute suicidal ideation. Other indications include treatment of refractory migraines and acute agitation. The rapid antidepressant action lasting two weeks is due to the rapid synthesis of neuroprotective proteins and anti-inflammatory effects.[10,11] To avoid ketamine poisoning, patients should be carefully screened for ketamine prescriptions and recreational use to confirm the overall dosage used. High doses cause systemic and pulmonary arterial pressure increases, tachycardia, and respiratory arrest.[8]

Psilocybin

Psychedelic drugs, including psilocybin, N,N-dimethyltryptamine (DMT), and lysergic acid diethylamide (LSD), are being examined as potential psychiatric therapies.[10,12] In South Africa, psilocybin is criminalised in terms of the Drugs and Drug Trafficking Act and the Medicines and Related Substances Act.[13] Psychedelic microdosing is used for the management of depression and it is gaining popularity due to the faster onset action, improved side effect profile, and sustained action after a single administration.[11] In 2019, psilocybin was granted the "FDA Breakthrough Therapy" designation, which is a process designed to expedite the development and review of drugs based on the potential therapeutic benefit of psilocybin for treating depression and anxiety.[10]

Psilocybin is the prodrug of psilocin, the active metabolite. Psilocin is a 5-hydroxytryptamine (5-HT2A) agonist.[12] LSD displays unusual binding and activation of 5-HT2B receptors, which may be associated with drug-induced valvular heart disease.

Anti-anxiety

Benzodiazepines

Benzodiazepines have a wide spectrum of uses due to their sedative, hypnotic, amnesic, anxiolytic, anticonvulsant, and muscle relaxant properties.[2,8] They are used for the initial treatment of panic disorder, generalised anxiety disorder, and insomnia. Benzodiazepines are used in the treatment of SS and perioperative alcohol withdrawal.[7,8]

Remimazolam is a relatively new addition to this class as of 2021. Remimazolam is a rapidly metabolised benzodiazepine with organ-independent elimination and has no active metabolites. It has a more favourable cardiorespiratory side effect profile compared to propofol and midazolam, which may be of benefit in paediatric, geriatric, and obese patients.[8]

Mechanism

Benzodiazepines bind to the alpha (α) and gamma (γ) subunits of the $GABA_A$ receptor. This binding site is different from the binding of endogenous GABA, which binds between the α and beta (β) subunits. Anxiolysis is associated with greater relative affinity for the α2 subunit.[2,8]

Anaesthetic implications

Benzodiazepines have sedative effects that are additive with other sedative agents and opioids; a dosage reduction may be appropriate. Even though many benzodiazepines are metabolised by CYP3A4, they are not strong inducers or inhibitors.[2] Emergence agitation occurs more commonly after benzodiazepine premedication and in patients with long-term benzodiazepine use. Paradoxical reactions are rare (< 1%) and may be caused by genetically heterogeneous $GABA_A$ receptors and alcohol use. The abuse potential of benzodiazepines is an important consideration for anaesthetists.[8] Perioperative

benzodiazepine use is associated with persistent benzodiazepine use in the postoperative period.[14] The American Geriatric Society also recommends avoiding benzodiazepines in elderly patients for the treatment of insomnia due to the risks of cognitive impairment and falls. Similar consideration should be taken for their use in the perioperative period.[8]

Mood stabilisers

Lithium

Lithium is the third element of the periodic table and exists as a monovalent cation. It interferes with other univalent ions, iodine, sodium, potassium, and hydrogen.[2,7]

Mechanism

Lithium affects multiple molecular pathways. Lithium affects sodium transport in nerve and muscle cells and inhibits inositol monophosphate, decreasing inositol and affecting adrenergic, serotonergic, and cholinergic signalling. It is not metabolised and is renally excreted.[2,8]

Anaesthetic implications

Lithium inhibits the release of thyroid hormones and can result in hypothyroidism. Perioperative thyroid function testing is essential for patients taking lithium.[7] Lithium prolongs the duration of action of both depolarising and non-depolarising neuromuscular blocking agents. Neuromuscular monitoring is recommended in all patients taking lithium. Due to lithium's exclusive renal excretion, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors can all increase serum lithium levels. Similarly, renal dysfunction and dehydration cause lithium levels to rise dramatically.[6] Toxicity occurs when levels are > 1.5 mmol/l and manifests with altered mental state, ataxia, arrhythmias, renal impairment, and coma. Management is supportive with hydration to enhance lithium excretion, discontinuation of lithium, and avoidance of diuretics.[5,6] Lithium should be discontinued at least 48–72 hours before surgery and is safe to discontinue abruptly.[8]

Anticonvulsants

Table II summarises the anaesthetic implications of a patient treated with anticonvulsant agents for mood disorders.

Antipsychotics

Antipsychotic drugs used are classified into two groups, neuroleptic and typical antipsychotics, which cause extrapyramidal side effects like acute dystonia, akathisia, parkinsonism, and tardive dyskinesia. Atypical antipsychotics do not tend to cause extrapyramidal side effects.

Mechanism

They act via dopamine 2 receptor blockade but also act on other receptors like histamine, serotonin, acetylcholine, and alpha-adrenergic receptors.

Anaesthetic implications

Antipsychotics potentiate the sedative and hypotensive effects of anaesthetic drugs. However, patients should continue their antipsychotics preoperatively as abrupt withdrawal may result in the recurrence of psychotic symptoms.[6] Drugs with antidopaminergic effects, such as metoclopramide and prochlorperazine, increase the risk of extrapyramidal side effects

Table II: Summary of anticonvulsants used to treat mood disorders[2,5,8]

Valproic acid	
Mechanism	**Anaesthetic implications**
Increased GABAergic transmission, reduced protein kinase C activity, and inositol cycling.	Continue in the perioperative period. Highly protein-bound and competitive inhibition of CYP3A4 causes increased levels of propofol. Recommended preoperative screening for bleeding risk: • Platelet count. • Bleeding time. • PT and activated partial thromboplastin time. • Fibrinogen and von Willebrand levels.
Carbamazepine	
Mechanism	**Anaesthetic implications**
Binding and inactivation of voltage-gated sodium channels.	Carbamazepine can be continued perioperatively. Strong CYP enzyme inducer. Aminosteroid neuromuscular blocker duration of action is shortened, more frequent dosing or a higher dose may be needed. Decrease plasma concentration of amiodarone, beta blockers, and calcium-channel blockers. Increased metabolism of midazolam, alfentanil, fentanyl, methadone, and tramadol.
Lamotrigine	
Mechanism	**Anaesthetic implications**
Blockade of voltage-gated sodium-channels and decreased release of excitatory neurotransmitters such as glutamate.	Continue in the perioperative period. The dissociative effects of ketamine can be decreased.

and neuroleptic malignant syndrome. Many antipsychotics can prolong the QTc interval. This is potentiated with concomitant use of other drugs that prolong QTc intervals, such as ondansetron.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is rare but potentially life-threatening. Table III summarises the cause, diagnosis, and management.[8]

Table III: Summary of neuroleptic malignant syndrome[8]

Neuroleptic malignant syndrome	
Associated drugs	Typical antipsychotics and antiemetic drugs.
Mechanism of action	Unknown but likely a dopamine receptor blockade leading to parkinsonian-type symptoms.
Symptoms	Classic tetrad: fever, rigidity, mental status change, and autonomic instability.
Diagnosis	Clinical with a history of antipsychotics or other associated medications.
Laboratory tests	Elevated creatine kinase, leucocytosis, low serum iron, hypocalcaemia, and hyperkalaemia.
Management	Stop the offending agents. Supportive care within an intensive care unit. If severe, consider dantrolene, benzodiazepines, bromocriptine, or amantadine.

Conclusion

Optimal perioperative outcomes for patients using neuropsychiatric agents require a good understanding of all the pharmacological classes, as well as the physiological effects of the various treatments. As psychiatry treatments continue to advance, new agents are introduced and explored. It is expected that the anaesthetist is up to date with the various agents and their implications in the perioperative period.

ORCID

C Redelinghuys https://orcid.org/0000-0002-8506-1106

References

1. Bagwathpersad N. Antidepressant prescribing in Gauteng: a public sector drug utilization review [Internet]. University of the Witwatersrand; 2016. Available from: http://hdl.handle.net/10539/21197. Accessed 11 August 2023.
2. Pryor KO, Storer KP. Drugs for neuropsychiatric disorders. In: Hemmings H, Egan T, editors. Pharmacology and physiology for anesthesia: foundations and clinical application. Elsevier; 2013. https://doi.org/10.1016/B978-1-4377-1679-5.00011-9.
3. Craig A, Rochat T, Naicker SN, et al. The prevalence of probable depression and probable anxiety, and associations with adverse childhood experiences and socio-demographics: a national survey in South Africa. Front Public Health. 2022;10:986531. https://doi.org/10.3389/fpubh.2022.986531.
4. Nguse S, Wassenaar D. Mental health and COVID-19 in South Africa. S Afr J Psychol. 2021;51(2):304-13. https://doi.org/10.1177/00812463211001543.
5. Ho S, Wong A. Perioperative management considerations in patients taking prescribed psychoactive medications (including those for depression and Parkinson's disease). Curr Opin Anaesthesiol. 2021;34(5):582-9. https://doi.org/10.1097/ACO.0000000000001041.
6. Attri JP, Bala N, Chatrath V. Psychiatric patient and anaesthesia. Indian J Anaesth. 2012;56(1):8-13. https://doi.org/10.4103/0019-5049.93337.
7. Moodley A, Kuhn M, Milner A. Central nervous system and neurotransmitters: clinical applications. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. Johannesburg: Milner and Welch (Pty) Ltd; 2019. p. 118-57.
8. Martinez-Baladejo M, Liongson FAZ, Wong D, et al. Anesthetic concerns in psychiatric disease. In: Ng-Pellegrino A, Stawicki SP, editors. Updates in anesthesia: the operating room and beyond. Rijeka: IntechOpen; 2023. https://doi.org/10.5772/intechopen.110173.
9. Hirsch M, Birnbaum RJ. Selective serotonin reuptake inhibitors: pharmacology, administration, and side effects [Internet]. UpToDate; 2022. Available from: https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects?search=Selective%20serotonin%20reuptake%20inhibitors:%20Pharmacology,administration,%20and%20side%20effects&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 20 July 2023.
10. McClure-Begley TD, Roth BL. The promises and perils of psychedelic pharmacology for psychiatry. Nat Rev Drug Discov. 2022;21(6):463-73. https://doi.org/10.1038/s41573-022-00421-7.
11. Scuteri D, Corasaniti MT, Tonin P, Nicotera P, Bagetta G. New trends in pharmacological control of neuropsychiatric symptoms of dementia. Curr Opin Pharmacol. 2021;61:69-76. https://doi.org/10.1016/j.coph.2021.09.002.
12. Mayet S. A review of common psychedelic drugs. S Afr J Anaesth Analg. 2020;26(6):S113-7. https://doi.org/10.36303/SAJAA.2020.26.6.S3.2554.
13. Foster SW. The right to privacy in the decriminalisation of psilocybin mushrooms in South Africa. Law Democr Dev. 2023;27:1-30. https://doi.org/10.17159/2077-4907/2023/ldd.v27.1.
14. Tai C-Y, Liu H-Y, Cata JP, et al. The association between general anesthesia and new postoperative uses of sedative-hypnotics: a nationwide matched cohort study. J Clin Med. 2022;11(12):3360. https://doi.org/10.3390/jcm11123360.