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# Illicit drugs and anaesthesia

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## Introduction

About 13.3% of South Africans meet the criteria to be diagnosed with a substance use disorder (SUD) according to the United Nations Office's Drugs and Crime World Drug Report of 2022.[1] The international prevalence of SUD is around 5.5% according to the World Health Organization (WHO). Compared to the rest of the world, this indicates that South Africa's substance use problem is nearly two and a half times larger.[2]

The understanding of addiction has undergone recent changes. SUD is now recognised as a medical disease and is no longer considered merely a symptom of poor self-control or a lack of moral fibre. Removing the stigma of addiction has improved both patient access to rehabilitation and rehabilitation success rates. Much of this shift has come about because of the opioid use disorder (OUD) epidemic in the United States, which has progressively worsened since 2017.[3,4] If one considers that the prevalence of asthma and diabetes mellitus in Africa both are around 12%, then the scale of the SUD epidemic can be appreciated.[5]

After nicotine, alcohol is the most used substance in South Africa. Following these, the list of commonly used substances in South Africa includes cannabis, methaqualone (Mandrax), 3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy), cocaine, methamphetamine (crystal meth/Tik), and heroin.[6] Newer "designer drugs" are constantly being added to the menu of options. Because nicotine and alcohol are not illicit substances, they will not be discussed here.

## Classification

It is clinically useful to classify substances as stimulants, depressants, and hallucinogens. Tables I–XI below summarise these and other substances' actions, pharmacokinetics, chemical structure, pharmacodynamics, and adverse effects.

### *Stimulants*

Stimulants usually increase the release or block the reuptake of catecholamines.[7]

**Table I:** Cocaine[7–12]

| | |
|---|---|
| Action | Dual mechanism (local anaesthetic and a reuptake inhibitor).<br>Ester local anaesthetic.<br>Presynaptic reuptake inhibitors of adrenaline, noradrenaline, dopamine, and serotonin.<br>Also facilitates catecholamine release. |
| Pharmacokinetics | Administration: Inhaled or intravenous.<br>Absorption: Bioavailability 30–40% orally and 80–90% inhaled.<br>Metabolism: Plasma and liver cholinesterase.<br>Excretion: Renal.<br>Onset of action: 5–10 minutes inhaled or intravenous.<br>Duration of action: 15 minutes to 1 hour. |
| Chemical structure | Alkaloid, ester. |
| Pharmacodynamics | Class 1C Na channel blocker (local anaesthetic effect).<br>Blocks monoamine oxidase inhibitors.<br>Reuptake inhibitor.<br>Central nervous system: Euphoria and excitement. |
| Adverse effects | Physical and psychological dependence.<br>Nasal septum and soft palate destruction with chronic use could cause airway management challenges.[13]<br>Sympathetic stimulation, anxiety, restlessness, and seizures.<br>Hypertension and myocardial ischemia.<br>Hypotension due to catecholamine depletion after chronic use.<br>Takotsubo cardiomyopathy after chronic use. |

**Table II:** Amphetamines and methylphenidate (Ritalin)[7,9,10,14,15]

| | |
|---|---|
| Action | Central nervous system stimulant, prescribed for attention-deficit/hyperactivity disorder and narcolepsy.<br>Causes the release of noradrenaline, dopamine and serotonin into the synaptic cleft.<br>Monoamine oxidase inhibitor. |
| Pharmacokinetics | Administration: Oral, inhaled, or intravenous.<br>Metabolism: CYP2D6 enzyme metabolism.<br>Onset of action: 30 minutes orally, immediately inhaled or intravenous.<br>Duration of action: 4 hours. |
| Chemical structure | D- and L-isomer. (D-isomer is more potent and more clinically effective). |

| | |
|---|---|
| Pharmacodynamics | Euphoria.<br>Increased energy levels.<br>Increased ability to concentrate (methylphenidate). |
| Adverse effects | Hypertension, tachycardia, panic attack, and paranoid psychosis.<br>Serotonin syndrome or rhabdomyolysis if used in conjunction with other serotonergic agents or CYP2D6 inhibitor agents.<br>Contraindicated within 14 days of any monoamine oxidase inhibitor use.<br>Prescription methylphenidate should be continued perioperatively to avoid haemodynamic instability from acute withdrawal.[13] |

**Table III:** Methamphetamine/crystal meth (Tik)[7,13]

| | |
|---|---|
| Action | Catecholamine reuptake inhibitor. |
| Pharmacokinetics | Administration: Oral, inhaled, or intravenous.<br>Metabolism: Metabolised to amphetamine.<br>Onset of action: 3 hours orally, 5–10 minutes inhaled or intravenous.<br>Duration of action: 6–12 hours. |
| Chemical structure | Synthesised from ephedrine and pseudoephedrine. |
| Pharmacodynamics | Euphoria. |
| Adverse effects | Airway difficulty due to poor oral hygiene ("meth mouth").<br>Nasal septal necrosis if "snorted".<br>Dysrhythmias, acute coronary syndrome, and aortic dissection.<br>Pulmonary hypertension.<br>Most abused substance in the Western Cape, South Africa.[10] |

**Table IV:** MDMA (Ecstasy)[7,10,13]

| | |
|---|---|
| Action | Empathogen and entactogen (enhanced social connectivity).<br>Primarily causes serotonin release into the synaptic cleft. |
| Pharmacokinetics | Administration: Oral.<br>Onset of action: 30–60 minutes orally.<br>Duration of action: About 6 hours. |
| Chemical structure | Amphetamine. |
| Pharmacodynamics | Euphoria, sociability, and potential psychedelic effects. |
| Adverse effects | Serotonin syndrome.<br>Fever, hyponatremia, rhabdomyolysis, renal failure, and liver failure while intoxicated.<br>Low energy ("crash"), low catecholamine levels for days post-use. |

## *Depressants*

**Table V:** Heroin (diacetylmorphine)[10,16,17]

| | |
|---|---|
| Action | Mu, kappa and delta agonist.<br>Mu1: Analgesia, euphoria, respiratory depression.<br>Mu2: Miosis, ⇓ GIT motility, dependence.<br>Kappa: Analgesia.<br>Twice as potent as morphine. |
| Pharmacokinetics | Administration: Oral, inhaled, intravenous, or subcutaneous.<br>Absorption: Orally absorbed and then deacetylated to morphine.<br>Metabolism: In central nervous system to monoacetylmorphine; peripherally to 6-monoacetylmorphine; metabolised in plasma, liver, and other tissues.<br>Excretion: 90% renally cleared.<br>Onset of action: 10-20 minutes orally, 3 minutes inhaled, 1 minute intravenous, 5 minutes subcutaneous.<br>Duration of action: Several hours. |
| Chemical structure | Diacetylmorphine, a semisynthetic derivative of morphine. |
| Pharmacodynamics | Analgesia, sedation, and respiratory depression. |
| Adverse effects | Physical dependence.<br>Narrow therapeutic index for respiratory depression.<br>Opioid-induced hyperalgesia complicates analgesia.<br>Withdrawal can present within 6–18 hours after the last dose. Withdrawal will require oral or intravenous opioids.<br>Agonist-antagonist agents such as nalbuphine or antagonists such as naloxone must be avoided to prevent withdrawal.[13] |

**Table VI:** Oxycodone[18]

| | |
|---|---|
| Action | Mu, kappa and delta agonist.<br>Oxycodone: Morphine dose ratio 1:1.5–2. |
| Pharmacokinetics | Administration: Oral or inhaled.<br>Metabolism: In the liver by CYP3A4 & CYP2D6 to noroxycodone and oxymorphone.<br>Excretion: Metabolites are excreted renally.<br>Onset of action: 10–30 minutes orally, 2-5 minutes inhaled.<br>Duration of action: 3–6 hours. |
| Chemical structure | Semisynthetic opioid. |
| Pharmacodynamics | Analgesia, sedation, and respiratory depression. |
| Adverse effects | Physical dependence.<br>Nasal septum and soft palate necrosis in patients who "snort" crushed tablets. |

**Table VII:** Methaqualone (Mandrax)[10]

| | |
|---|---|
| Action | Gamma-aminobutyric acid stimulant.<br>Barbiturate-like central nervous system depressant. |
| Pharmacokinetics | Administration: Oral.<br>Excretion: Renal.<br>Onset of action: 30 minutes.<br>Duration of action: 4–8 hours. |
| Pharmacodynamics | Euphoria, anxiolysis, and sedation. |
| Adverse effects | Withdrawal: 12–24 hours after the last dose. |

## *Hallucinogens*

**Table VIII:** Phencyclidine (PCP, "angel dust")[9,19,20]

| | |
|---|---|
| Action | N-methyl-D-aspartate antagonist.<br>Dopamine agonist, partial adrenergic agonist, and serotonin antagonist. |

| | |
|---|---|
| Pharmacokinetics | Administration: Oral or inhaled.<br>Metabolism: Hepatic.<br>Excretion: Renal.<br>Onset of action: 30–60 minutes orally, 2–5 minutes inhaled.<br>Duration of action: 4–8 hours. |
| Chemical structure | Precursor of ketamine. |
| Pharmacodynamics | Causes a dissociative state. |
| Adverse effects | Tachycardia, hypertension, psychosis, nystagmus, cerebral haemorrhage, and a depressed level of consciousness. |

**Table IX:** Lysergic acid diethylamide (LSD)[9,10,13,21]

| | |
|---|---|
| Action | Hallucinogen. |
| Pharmacokinetics | Administration: Oral.<br>Onset of action: 30–60 minutes.<br>Duration of action: 6–10 hours. |
| Chemical structure | Similar to serotonin.<br>R- (more potent) and S-isomers. |
| Pharmacodynamics | Direct stimulation of serotonin receptors (5HT2A and 5HT2AR). |
| Adverse effects | Significant variation in effects may cause anxiety, fear, panic and hallucinations ("bad trip").<br>Psychological dependence and antisocial behaviour. |

### *Other agents*

**Table X:** Marijuana[9,13,22,23]

| | |
|---|---|
| Action | Muscarinic inhibitor.<br>(No longer illicit for private consumption at home). |
| Pharmacokinetics | Administration: Usually smoked or ingested orally (edibles).<br>Metabolism: Hepatic (CYP enzymes).<br>Onset of action: Orally 30 minutes to 2 hours, inhaled 3–10 minutes.<br>Duration of action: Oral for up to 24 hours, inhaled 1–3 hours. |
| Chemical structure | Delta-9-tetrahydrocannabinol. |
| Pharmacodynamics | Euphoria, sedation and drunken feeling. |
| Adverse effects | Chronic cough with chronic smoking (less compared to cigarette smoking).<br>Enhances the effect of stimulants or depressants if used in combination. |

**Table XI:** Nyaope[24,25]

| | |
|---|---|
| Action | Similar to marijuana, heroin and other additives. |
| Pharmacokinetics | Administration: Intravenous, smoked, often with marijuana. |
| Chemical structure | Mostly heroin, plus any of several additives such as Zidovudine (ARV), codeine, opiates, caffeine, and amphetamines. |
| Pharmacodynamics | Euphoria. |
| Adverse effects | Highly addictive (heroin).<br>Respiratory depression.<br>Severe withdrawal with abdominal pain, and seizures. |

## Anaesthetic implications

While a SUD patient may present for surgery having only used one substance, it is not uncommon for these patients to have been exposed to a cocktail of stimulants and depressants simultaneously, complicating the clinical picture. Up to 83% of SUD patients who present for surgery have used at least two agents, commonly alongside alcohol.[26]

Among substances encountered by the anaesthesiologist, OUD is particularly in the spotlight in America.[4] While there is a strident call to improve opioid stewardship in the primary care setting, it is recognised that the perioperative prescription of opioids has little effect on long-term addiction.[27]

When patients with SUD, including OUD, present for elective surgery, a multidisciplinary perioperative analgesia plan, with patient input, is recommended.[4,7]

### *Acute intoxication*

Wherever possible, the patient who presents acutely intoxicated should be postponed until the substance has been cleared to avoid haemodynamic instability.[13] The management of acute toxicity is largely supportive. Any additional agents required will depend on the substance involved and the clinical picture.

Stimulant intoxication will present with a sympathomimetic clinical picture, with the differential diagnosis of thyrotoxicosis, malignant hyperthermia, neurolept malignant syndrome, and opioid withdrawal.[7] In the case of toxicity from stimulants, acute central nervous system and cardiovascular system toxicity can be managed with a variety of agents. Dexmedetomidine (alpha-2 agonist) has recently gained popularity for this role.[28] Other commonly used agents include benzodiazepines, direct-acting vasodilators, calcium channel blockers, and mixed alpha and beta antagonists.[7] The use of selective beta blockers, which would leave the patient exposed to unopposed alpha stimulation, is controversial and generally not recommended.[7] The successful use of intravenous lipid emulsion to counteract the toxicity of lipid-soluble agents, such as psychotropic agents and cocaine, is also described.[11,28]

In the case of a depressant substance toxicity, the management is again supportive, (especially in terms of respiratory depression) with the additional options of naloxone and flumazenil as antidotes for opioids and benzodiazepines, respectively.[26]

### *Acute withdrawal*

The clinical picture will depend on whether the patient is suffering withdrawal from a stimulant or a depressant agent. The patient may present with a spectrum from mild tremors, fever, and electrolyte derangement to haemodynamic instability, altered consciousness, and seizures. Psychostimulant agent withdrawal may present with depression, a decreased consciousness level, lethargy, and haemodynamic depression or potentially with anxiety, agitation, and psychosis.[7]

Dexmedetomidine and benzodiazepines form the mainstay of the management of withdrawal from depressant agents such as alcohol or opioids in conjunction with further supportive management, such as inotropic support where required.[13,29]

### *Chronic SUD*

All patients presenting for surgery, including the SUD patient, must be assured that they will be offered adequate and appropriate analgesia. The 2022 Centers for Disease Control and Prevention (CDC) clinical practice guideline recommends the maximised use of multimodal analgesic agents and regional techniques to reduce opiate requirements as much as possible in chronic SUD patients. However, where necessary, it is not recommended to withhold opiates.[30,31] The use of opioids in these patients should be at the lowest effective dose and for the shortest required duration. These patients may exhibit hyperalgesia and it may be difficult to control their pain with opioids alone. Hence the recommendation is to use multimodal analgesia, including regional techniques, as far as possible. Where opioids are used, the more potent, shorter-acting agents such as sufentanil and fentanyl are recommended.[4] If opioids are used for longer than a few days, their dose should be tapered and not stopped abruptly.[31]

A patient being rehabilitated for OUD may present for surgery on methadone (Table XII) or buprenorphine (Table XIII). It is recommended that these are continued through the perioperative period. The SUD patient may also present additional challenges, such as difficult intravenous access, a difficult airway, an altered level of consciousness, and a stormy haemodynamic perioperative course.[13]

The chronic cocaine SUD patient may present with catecholamine depletion and fewer postsynaptic receptors, which require the use of higher doses of direct-acting vasopressors or inotropes, as indirect-acting agents will not be able to facilitate the release of endogenous catecholamines.[7,11] Refractory hypotension in these patients may require the use of vasopressin.[7]

### *Medications for OUD*

**Table XII:** Methadone[4,9,13,32]

| | |
|---|---|
| Action | Mu agonist and N-methyl-D-aspartate receptor antagonist.<br>Also, serotonin and noradrenaline reuptake inhibitors.<br>Prescribed for chronic opioid rehabilitation in patients with OUD and for chronic pain patients. |
| Pharmacokinetics | Administration: Oral, intravenous, or subcutaneous.<br>Metabolism: Hepatic (CYP enzymes).<br>Excretion: Stool and urine.<br>Onset of action: 60 minutes.<br>Duration of action: 6–8 hours (t1/2 8–59 hours). |
| Chemical structure | Synthetic opioid. |
| Pharmacodynamics | Analgesia. |
| Adverse effects | Withdrawal begins 24–48 hours after the last dose.<br>Prolonged QT and possible torsade de pointes.<br>Respiratory depression in overdose, may be lethal in combination with other sedative/depressant agents. |

**Table XIII:** Buprenorphine[4]

| | |
|---|---|
| Action | Opioid agonist-antagonist (partial mu agonist, kappa antagonist). |
| Pharmacokinetics | Administration: Oral, sublingual, intravenous, or transdermal.<br>Onset of action: 30–60 minutes.<br>Duration of action: 6–12 hours. |
| Chemical structure | Morphinan alkaloid. |
| Pharmacodynamics | Potent analgesia with less respiratory depression and euphoria. |
| Adverse effects | Nausea, vomiting, drowsiness, orthostatic hypotension, and urinary retention. |

## Conclusion

Managing a SUD patient in the perioperative space requires an understanding of the potential effects and drug interactions of the substance used. It is a valuable contact time for postoperative referral for counselling, but not the time for rehabilitation. Furthermore, inadequately managing a patient's pain may do more harm and potentially push a recovering SUD patient to relapse.[31]

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