

Atypical opioids

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Opiates and opioids remain the main pillars of analgesia. Their use is, however, limited by abuse potential as well as their side effect profile. Thus, there is a need for the development of newer opioids. The atypical opioids tramadol, tapentadol, dextromethorphan (DXM), and buprenorphine are newer synthetic opioids. These opioids do not solely depend on mu-receptor agonism for their analgesic effects. Except for DXM, atypical opioids are now being used more than conventional opioids as part of chronic pain management.

Keywords: atypical opioids, chronic pain management

Introduction

Atypical opioids, also known as synthetic opioids, are a class of opioids that differ from traditional opioids in structure, function, and adverse effects. This class of drug aims to decrease negative opioid effects commonly seen with traditional opiates, like morphine, as well as provide adequate analgesia.¹ This review aims to highlight the pharmacology of atypical opiates such as tramadol, tapentadol, DXM, and buprenorphine. An understanding of traditional opiate pharmacology is imperative as part of our understanding of atypical opiates.

The terms opiates and opioids are used interchangeably but they differ:²

1. Opiates are natural opioids, derived from or related to the poppy plant, such as heroin, codeine, and morphine.
2. Opioids are a compound resembling opium, attached to opioid receptors that are partially or fully synthetic, such as fentanyl, hydrocodone, and oxycodone.

Physiology of opioids

Opioid receptors are G-protein-coupled receptors that mediate the body's response to hormones, neurotransmitters, and drugs. Three major receptors were discovered that were designated mu, kappa, and delta. Currently, they are termed mu-opioid receptor (MOR), kappa-opioid receptor (KOR), delta-opioid receptor (DOR), and the nociceptin/orphanin FQ peptide (NOP) receptor. The endogenous ligands for these receptors are the neuropeptides β -endorphin (MOR), dynorphin (KOR), and methionine enkephalin (DOR).³

Opioid receptors are located throughout the central nervous system and within peripheral tissue of neural and non-neural origin. Centrally, the periaqueductal grey (PAG), locus coeruleus, rostral ventromedial medulla, and limbic system show high concentrations of opioid receptors. Opioid receptors are also present in the substantia gelatinosa of the dorsal horn of

the spinal cord. Peripherally, receptors are distributed in the gastrointestinal tract, nerve fibres vas deferens, knee joints, gastrointestinal tract, heart, and immune system.^{3,4}

Classification of opioids^{3,4}

There are several opioid classifications. Below are tables highlighting the classification systems either via origin (Table I) or receptor type (Table II).

Table I: Classification of opioids via origin

Naturally occurring compounds	Semi-synthetic compounds	Synthetic compounds
Morphine	Diamorphine	Fentanyl, alfentanil, remifentanil
Codeine	Dihydromorphone	Methadone
Thebaine	Oxycodone	Pethidine
Papaverine	Buprenorphine	Tramadol
		Tapentadol

Table II: Classification of opioids via receptor action

Agonists	Morphine, pethidine, fentanyl, sufentanil, remifentanil, alfentanil, oxycodone
Antagonists	Naloxone, methyl naltrexone, nalmefene
Mixed agonists-antagonists (dualists)	Buprenorphine, pentazocine, nalbuphine
Atypical	Tramadol, tapentadol, DXM

Morphine – the prototype opiate

Morphine is considered the prototype opiate against which other agents are measured for their analgesic effects as well as adverse side effects. The effects of opiates and opioids are often compared to morphine for analgesic potency, side effect profile, as well as dependency or abuse potential.

Morphine is a mu-agonist administered orally, intravenously, or intramuscularly. Metabolism is via the liver, where it undergoes

extensive first pass metabolism to morphine-3-glucuronide (less potency) and morphine-6-glucuronide (increased potency compared to morphine).⁴

Uses include analgesia, cough suppression, sedation, anti-diarrhoeal, and perioperative analgesia.⁴

The side effect profile is important because other opiates are compared to morphine. The side effects include somnolence, nausea, vomiting, constipation, pruritus, hypotension, and bradycardia.⁴ Abuse potential is high with the naturally occurring opiates.

Atypical opioids

The atypical opioids show different profiles compared to conventional opioids with regard to efficacy, safety, tolerability and risk of abuse. These include Tramadol, DXM, tapentadol and buprenorphine and will be discussed below.

Tramadol

Tramadol is the prototype of the atypical opiate family. It is a centrally acting analgesic structurally similar to morphine and codeine. It is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for opioid receptors.⁵ Its potency is one-tenth that of morphine.⁴ Tramadol is available as an intravenous preparation, orally, and in sustained-release formulations.⁶

Structure

The chemical name for tramadol is 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol. Its molecular formula is $C_{16}H_{25}NO_2$ (Figure 1).

Indications

The main indication for tramadol is for perioperative pain or mild to moderate pain. This is usually part of a multimodal strategy. Due to its abuse potential, its use should be limited. The immediate-release formulation is usually reserved for pain lasting less than one week. The sustained-release formulation is reserved for pain that needs 24-hour management.

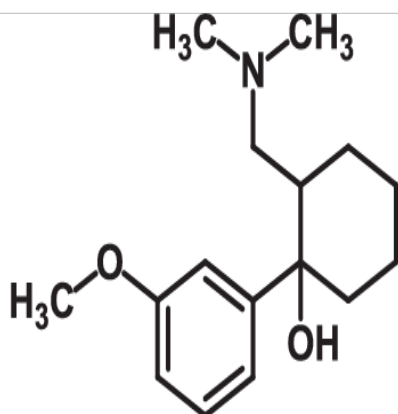


Figure 1: Structure of tramadol⁷

Tramadol may be found in a combination form with paracetamol for additive analgesia.

Off-label indications for tramadol are for restless legs syndrome as well as for the treatment of premature ejaculation. It has also been described for use in anxiety and depression and postoperative shivering.⁸

Mechanism of action⁹

Tramadol differs from traditional opiates. It has a two-fold effect. It works on the mu-receptor as a μ -opioid agonist where it has up to 4 500 times less affinity compared to morphine and affects monoamines by modulating the effects of neurotransmitters involved in the modulation of pain, such as serotonin and noradrenalin, which activate descending pain inhibitory pathways. Tramadol's effects on serotonin and norepinephrine mimic the effects of other serotonin noradrenergic receptor inhibitor (SNRI) antidepressants, such as duloxetine and venlafaxine.

Tramadol exists as a racemic mixture. It consists of two pharmacologically active enantiomers. These contribute to its analgesic property through different mechanisms: (+)-tramadol and its primary metabolite (+)-O-desmethyl-tramadol. The (+)-tramadol inhibits serotonin reuptake, and (-)-tramadol inhibits norepinephrine reuptake. These pathways are complementary and synergistic, improving tramadol's ability to modulate the perception of and response to pain.⁹

Absorption

Tramadol has an oral absorption of 100%, with a mean bioavailability of 70% due to a 20–30% first pass metabolism after a single oral dose. After multiple oral dosing, the bioavailability may increase by 90–100%, which may be the result of a saturated first pass hepatic metabolism. The bioavailability of tramadol after food intake, although increased, does not seem to be clinically relevant.⁹

Distribution⁸

Tramadol has a volume of distribution of approximately 2.7 L/kg and is only 20% bound to plasma proteins.

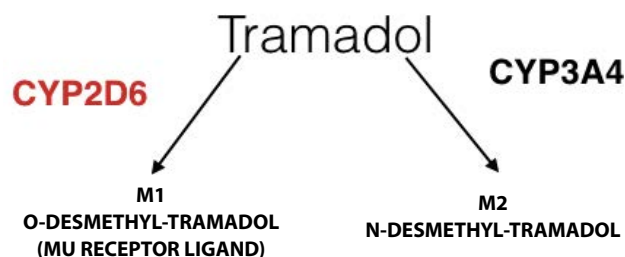
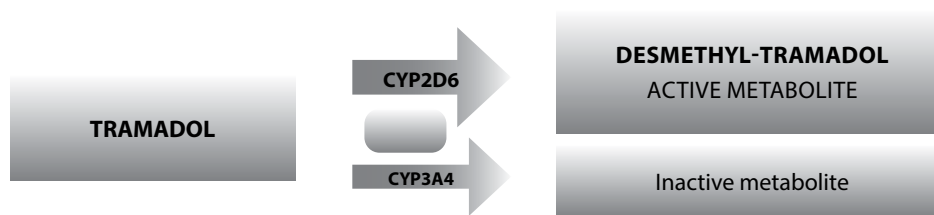


Figure 2: Hepatic metabolism of tramadol (cytochrome pathway)
CYP2D6 – cytochrome P2D6, CYP3A4 – cytochrome P3A4



CYP2D6 ultra-rapid metaboliser – increased concentration of desmethyl-tramadol – increased side effects
CYP2D6 poor metaboliser – lower concentration of desmethyl – tramadol decreased analgesia

Figure 3: Pharmacogenomics of tramadol

Metabolism and elimination⁹

Tramadol is extensively metabolised in the liver by *O*- and *N*-demethylation and by conjugation reactions to form glucuronides and sulfate metabolites. The *O*-demethylation of tramadol to its main active metabolite, *O*-desmethyl-tramadol (M1), is catalysed by cytochrome P450 (CYP) 2D6 and *N*-desmethyl-tramadol is catalysed by the enzyme CYP3A4 (Figure 2).

Pharmacokinetic-pharmacodynamic characterisation of tramadol is difficult because of the differences between tramadol concentrations in the plasma and at the site of action, and because of the pharmacodynamic interactions between the two enantiomers of tramadol and its active metabolites.⁹

The major route of excretion for tramadol and its metabolites is through the kidneys. About 30% of the dose is excreted in the urine as the parent drug and the rest are excreted as metabolites.⁹

Pharmacogenomics of tramadol⁹

CYP2D6 is one of the major CYP450 enzymes in drug metabolism via the liver. CYP2D6 converts tramadol to its more active metabolite, *O*-desmethyl-tramadol (Figure 3). Therefore, alterations in the metabolism of tramadol have a profound impact on the analgesic effect and risk of side effects. There have been reports of life-threatening respiratory depression in children who received tramadol following tonsillectomy and/or adenoidectomy, due to the ultra-rapid metabolism of tramadol caused by a CYP2D6 polymorphism. The Food and Drug Administration (FDA) has placed a black box warning on the use of tramadol in children younger than 12 years old and in patients who have other risk factors that may increase sensitivity to the respiratory depressant effects of the drug.

Dosage⁴

Oral formulations are dosed like intravenous formulations.

The different formulations include oral 50 mg capsules or oral 20 drops, equal to 50 mg, sustained release (between 50–200 mg tablets and 100 mg suppositories for adults, and 15–50 mg for paediatric patients).

Suppositories are not available in South Africa. Tramadol can be used in a parenterally controlled pump. Doses suggested include

a loading dose of 3 mg/kg followed by a bolus of 20–30 mg/kg and a lockout time of 10 minutes.⁴

Adverse effects

Between 1997 and 2017, there were 730 tramadol cases reported to the FDA's Adverse Event Reporting System. Seizures and serotonin syndrome accounted for 7% and 3% of the cases, respectively.¹⁰

Side effects are dose dependent. Nausea and vomiting are problematic on tramadol along with commonly reported side effects such as headache, somnolence, dyspepsia, sweating (due to monoaminergic effects), dry mouth, and postural hypotension.⁴

Serious adverse effects include respiratory depression. Adolescents aged 12–18 years may have additional risk factors for respiratory depression, obstructive sleep apnoea, obesity, severe lung disease, and neuromuscular disease.^{6,10}

Serotonin syndrome occurs due to the inhibition of adrenalin and serotonin by tramadol in the central nervous system. Patients on monoamine oxidase inhibitors, serotonin-releasing drugs, and serotonin reuptake inhibitors should not be prescribed tramadol. They are at increased risk of serotonin syndrome. The classic triad of symptoms includes neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status. Complications from serotonin syndrome include rhabdomyolysis, myoglobinuria, renal failure, disseminated intravascular coagulation, metabolic acidosis, and acute respiratory distress syndrome.¹¹

Toxicity can also predispose patients to seizure activity and cardiac dysrhythmias, such as prolongation of the QT interval.⁹

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome.

An overdose of tramadol leads to respiratory depression and seizures. Naloxone can be used to treat respiratory depression or tramadol-induced apnoea. A recent meta-analysis showed that naloxone administration does not increase the risk of seizure in patients with tramadol toxicity. Seizures due to tramadol do not respond to naloxone but are relieved with benzodiazepines. A combination of diazepam/naloxone is reported as an efficient antidote to reverse tramadol-induced central nervous system toxicity.¹² Table III highlights usage of tramadol in special

populations including paediatrics, renal and hepatic dysfunction, geriatric usage, pregnancy and breastfeeding.

Table III: Tramadol use in special populations

Special population	Precaution
Paediatrics	Off-label drug use can cause respiratory depression. Controversial in children < 12 years old.
Renal dysfunction	Creatinine (Cr) clearance < 30 ml/min, increase dosing interval to 12 hours.
Hepatic dysfunction	A dosing interval of 12 hours is recommended.
Geriatrics	If aged > 75 years, a maximum daily dose of 300 mg.
Pregnancy/ breastfeeding	May be teratogenic and cause somnolence or withdrawal in neonates if taken during breastfeeding.

Tapentadol

Tapentadol is a synthetic, centrally acting atypical opiate with both opioid and non-opioid mechanisms of action; mu-opioid receptor agonist and noradrenaline reuptake inhibition. As an active compound and not a prodrug, it is not reliant on enzyme systems and it is also devoid of active metabolites. It was developed in the 1980s to address the adverse effects associated with tramadol's serotonin reuptake inhibition.¹³

Structure

Tapentadol is a unique, centrally acting opioid of the aromatic hydrocarbon benzenoid class with a chemical formula of $C_{14}H_{23}NO$ (Figure 4).¹⁴

Mechanism of action¹⁴

Tapentadol is a non-racemic molecule and is not a prodrug. It is a synthetic opioid that is centrally acting. It has a two-fold analgesic action:

1. Selective mu-opioid receptor agonist (greater affinity than for delta and kappa receptors).
2. Increases noradrenaline levels by inhibiting noradrenaline uptake and activating alpha-2 receptors.

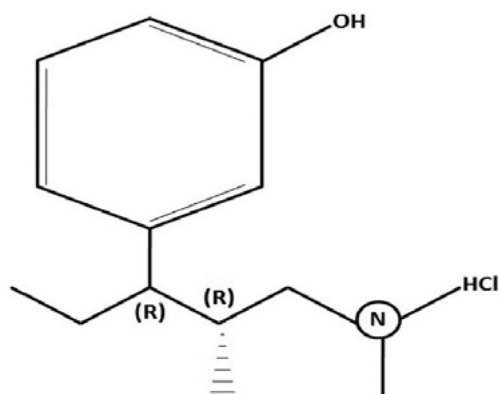


Figure 4: Structure of tapentadol

Tapentadol is a weak serotonin reuptake inhibitor; however, this action does not contribute to its analgesic effect.

Indications¹³

The indications of tapentadol include acute pain, chronic pain, as well as neuropathic pain, especially in diabetic neuropathy. It has also been used in cancer pain. Similar to tramadol, there is a risk of abuse potential with tapentadol. In this regard the tablet is difficult to crush, decreasing the ability to use it for recreational purposes.

Absorption and distribution¹³

The mean absolute bioavailability is 32% due to extensive first pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing. Dose-proportional increases in the C_{max} and area under the curve (AUC) values of tapentadol occur over the 50–150 mg dose range. Tapentadol may be given with or without food. The plasma protein binding of the drug is approximately 20%. Thus, the potential for drug interactions is less and the volume of distribution is 540 ± 9.8 L/kg.

Metabolism and elimination¹³

Tapentadol metabolism mainly occurs via the liver via phase II pathways. A very small amount is metabolised via phase I pathways. Therefore, unlike tramadol, the CYP pathway plays a very limited role in tapentadol metabolism. Tapentadol is mainly metabolised via conjugation with glucuronic acid to glucuronides. In the urine, 70% is excreted as O-glucuronide and sulfate metabolites.

Tapentadol is also metabolised via the CYP2C9 and CYP2C19 pathways where demethylation to form N-desmethyl-tapentadol occurs. Approximately 2% of tapentadol undergoes CYP2D6-mediated hydroxylation to form hydroxy-tapentadol. The metabolites of tapentadol are not pharmacologically active. The terminal half-life is about four hours after oral administration. The extended-release formulation has a mean terminal half-life shown to range between 4.4 and 5.9 hours.

Dosage¹³

Tapentadol is available in extended or immediate-release formulations at doses of 50, 75, or 100 mg formulations. Limited evidence exists for its intravenous use; however, it has been used via the intravenous route. In mild renal or hepatic impairment, no dose adjustment is required and the drug should be avoided in severe renal or hepatic impairment. In the elderly, first look at the renal function and dose accordingly and as conservatively as possible.

Adverse effects¹³

Tapentadol produces peripheral and central side effects. Peripherally, tapentadol may cause nausea and vomiting. Centrally, it may cause headaches, dizziness, and somnolence.

It is less likely to cause life-threatening situations associated with delirium, neuromuscular rigidity, and hyperthermia when combined with selective serotonin reuptake inhibitors (serotonin syndrome). Tapentadol should be used cautiously in patients with a history of seizures because it reduces the seizure threshold in patients. Serotonin syndrome has been reported when tapentadol is used in combination with serotonergic antidepressants, but less so than with tramadol.

Dextromethorphan (DXM)^{14,15}

DXM is the D-isomer of levorphanol, a synthetic analogue of codeine. DXM also contains an alkylated amine adjacent to a cyclohexane ring, a chemical structure similar to dissociative agents like ketamine and phencyclidine. Unlike the other atypical opiates, its mechanism of action is antagonism at the N-methyl-D-aspartate (NMDA) receptor and sigma-1 receptor.

DXM is indicated as a non-sedating antitussive and is being considered as part of a multimodal perioperative opiate-sparing technique for analgesia due to its NMDA antagonism.

The volume of distribution is estimated to be 5–6.7 L/kg.

DXM undergoes metabolism in the liver via cytochrome (CYP2D6) to dextrorphan (primary active metabolite) and 3-methoxymorphinan. The average half-life of the parent compound in therapeutic use is approximately three hours in individuals who are rapid metabolisers, and 30 hours in slow metabolisers, due to genetic polymorphism. DXM and its metabolites, dextrorphan and 3-methoxymorphinan, are almost exclusively renally excreted.^{14,15}

DXM is a drug with great abuse potential. Toxicity presents as nausea, vomiting, respiratory depression, seizures, tachycardia, hyperexcitability, psychosis, cerebellar signs, dystonia, blurred vision, and serotonin syndrome.^{14,15}

Buprenorphine

Buprenorphine is a mu-opioid receptor agonist and a weak kappa- and delta-opioid receptor antagonist, thus classing it as an opioid dualist (opioid partial agonist-antagonist). It underwent development in the late 1960s. It is a synthetic analogue of thebaine, an alkaloid compound derived from the poppy flower.¹⁶

Although buprenorphine is traditionally classified as a partial agonist, the notion that it behaves as a full agonist in analgesia (occupying only 5–10% of MOR to obtain the analgesic effect) is widely accepted nowadays.¹⁷

Indications

Buprenorphine was initially developed for the treatment of opioid use dependency, especially if methadone is contraindicated. It has now become common in the treatment of acute and chronic pain.

The ceiling effect of buprenorphine¹⁷

Partial agonists show a partial response compared to a full agonist. This manifests as a plateau effect, referred to as a ceiling effect. Consequently, increasing the dosage of a drug is not proportional to its increased pharmacological effect.¹⁷ A ceiling effect is observed in respiratory depression. Therefore, buprenorphine is used for a better side effect profile compared to other opioids, although respiratory depression can occur. Buprenorphine has anti-hyperalgesic properties, most likely due to its kappa-receptor antagonism.

Pharmacokinetics^{16,17}

Buprenorphine is metabolised via the liver via the CYP3A4 system. It has poor first pass metabolism with only 10–15% oral bioavailability. This led to the sublingual formulation where bioavailability is similar to intravenous preparations.

Buprenorphine is metabolised to norbuprenorphine via CYP3A4/3A5-mediated N-dealkylation. Buprenorphine and norbuprenorphine both undergo glucuronidation to the inactive metabolites buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, respectively.

Elimination is via the faeces and urine.

The mean elimination half-life of buprenorphine in plasma ranges from 31 to 42 hours.

Adverse effects¹⁶

Buprenorphine exerts some anticholinergic-like effects and may cause hypotension, QT prolongation, and a lower seizure threshold.

Other side effects of buprenorphine include nausea, vomiting, drowsiness, dizziness, headache, memory loss, sweating, dry mouth, miosis, orthostatic hypotension, sexual side effects, and urinary retention.

Newer atypical opioids in development:

CEBRANOPODOL:¹⁸

Due to adverse effects like respiratory depression, tolerance and physical dependence with the atypical opioids currently available, cebranopodol is being evaluated as a novel atypical opioid that acts at the mu opioid receptor as well as the nociceptin/orphanin receptor (NOP) with a better side effect profile and less addictive potential. It may in the future become an alternative to all the currently available opioids.

Conclusion

Despite the increase in opioid abuse worldwide, opioids remain an integral part of our analgesia armamentarium. When compared to the opiate prototype, morphine, the atypical opioids and the advent of new drugs in this field aim for fewer adverse effects, a better analgesia profile, and less abuse potential.

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