

Clinical Pharmacology

In this section you will...

- Gain an overview of opioid pharmacology and the actions and potential side effects associated with methadone and buprenorphine;
- Be provided with a comparison of treatment options; and
- Understand the Gateway Model.

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4.1 Basic Opioid Pharmacology

The term opioid is used to describe drugs whose actions resemble morphine but whose chemical structures are different from natural opiates derived from the opium poppy. The term describes all of the compounds that interact with stereospecific mu (μ)-opioid receptors in the central and peripheral nervous systems, including natural and synthetic compounds, as well as endogenous peptides. The principal effects of opioids are analgesia, sedation, respiratory depression and euphoria. Opioids have varying potency, bioavailability, speed of onset and duration of effect.

Opioids produce their effects by acting on a range of receptors at the molecular level of the nervous system. Figure 3.1 below demonstrates opioid effects according to dose. Opioid compounds can be classified into four groups: pure agonists, partial agonists, mixed agonist-antagonists and antagonists, which will be referred to when describing specific opioids later in this section.

- **A pure agonist** is a drug that has affinity for and binds to receptors to induce changes in the cell that stimulate physiological activity. The potency of a μ -opioid receptor agonist can be described by a dose-response relationship. This relationship is influenced by the drug's pharmacokinetic characteristics (absorption, distribution, metabolism and elimination), affinity for the receptor, and the level of intrinsic activity at the receptor level. Morphine, methadone, pethidine, hydrocodone, oxycodone and heroin are examples of opioid agonists.
- **A partial agonist** is a drug that binds to a receptor but does not produce maximum stimulation. Because it occupies the receptor, it can prevent a concurrently administered agonist with weaker receptor affinity from attaching to μ -opioid receptors and producing its full agonist effect. Buprenorphine is a partial agonist at the μ -opioid receptor.
- **Mixed agonist-antagonists** are drugs that have a mixed μ -opioid receptor action, stimulating one receptor type while antagonising another. Buprenorphine, pentazocine, butorphanol and nalbuphine are examples of agonist-antagonist opioids.
- **Antagonist** opioids have no intrinsic pharmacological action on μ -opioid receptors but can block the action of an agonist; thus they can reverse the effects of μ -opioid agonists. They are often used therapeutically to reverse the effects of opioid overdose. Naloxone and naltrexone are opioid receptor antagonists that can reverse the effects of agonists such as morphine and methadone.

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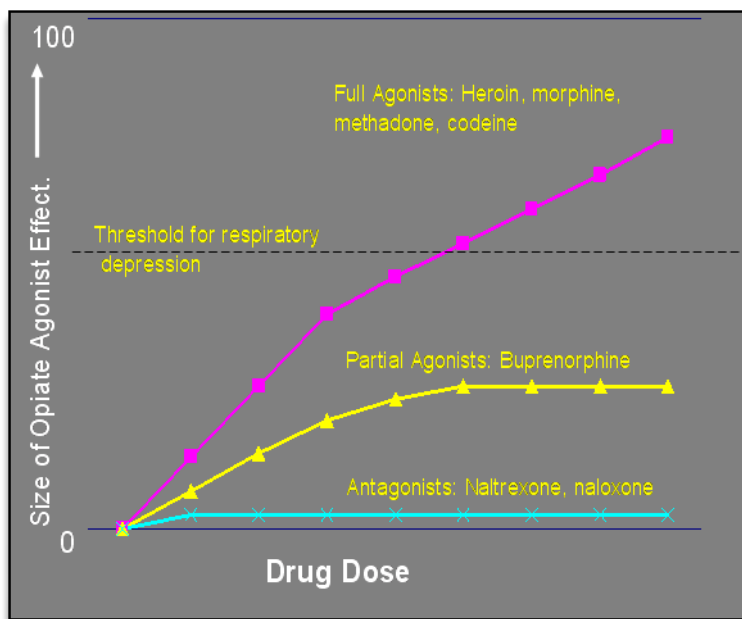


Figure 4.1: Opiate effects of full agonists, partial and antagonist

Note: Reproduced from *Induction into buprenorphine treatment*. Dr Nicholas Lintzeris. Presentation at Conference Safer options, Hamburg 19-21 April 2005.

4.2 Methadone

Methadone is a synthetic μ -opioid receptor agonist used to treat opioid dependence. In Tasmania its medical use is regulated under the Poisons Act 1971, as a 'controlled (S8) drug'. The effects of methadone are qualitatively similar to morphine and other pure agonist opioids. The clinical pharmacology of methadone makes it a very good agent for the treatment of opioid dependence (Vazquez, et al., 2006, Gowing et al., 2001).

The chemical name for methadone hydrochloride is: 6-dimethylamino-4,4-diphenyl-3-hepatone hydrochloride and is represented in Figure 3.2 below.

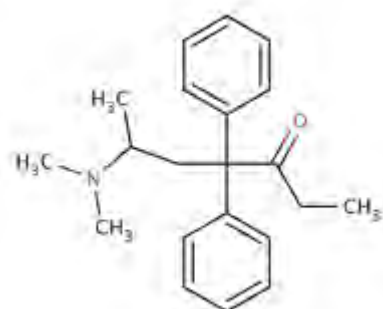


Figure 4.2: Methadone Molecule

Note: Adapted from *Subutex, Product Information, TGA Product and Consumer Medicine, 2003*. Retrieved September 22, 2011, from <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=methadone&r=/>

There appear to be two separate active sites in the molecule:

- the nitrogen atom with the hydrochloride bonded to it at one end - thought to act on the peripheral nervous system; and
- the 2 phenyl 'rings' - thought to be necessary for its opiate-like action on the central nervous system.

4.2.1 Methadone formulations

In the context of this document, the general term 'methadone' will be used when describing information that applies to both of the available methadone preparations for opioid dependence in Australia. These preparations are:

- (a) **Methadone Syrup.** This formulation contains 5mg/mL methadone hydrochloride, sorbitol, glycerol, ethanol (4.75%), caramel, flavouring, and sodium benzoate; and
- (b) **Biodone® Forte liquid.** This formulation contains 5mg/mL methadone hydrochloride and permicol-red colouring.

The two formulations are of equal strength and bioavailability. While pharmacies can choose to dispense either one, or both of these formulations, Alcohol and Drug Services (Tasmania) dispense Biodone® from its pharmacy in Southern Tasmania because:

- it is safer than the syrup if inappropriately injected by the patient;
- the sorbitol in the syrup can cause gastrointestinal problems;
- the aftertaste of Biodone® is easier to remove than the aftertaste of the syrup
- it contains no alcohol
- it is easier for pharmacists to use as it is less viscous; and,
- it is easier to clean equipment after dispensing Biodone®.

4.2.2 Methadone Pharmacokinetics

There is wide individual variability in the pharmacokinetics of methadone, however, in general blood levels rise for three to four hours following ingestion of oral methadone and then begin to fall. Methadone is rapidly absorbed from the gastrointestinal tract, with measurable concentrations in plasma within 30 minutes of oral administration, and a long half-life. The apparent half-life of a single first dose is 12 - 18 hours, with a mean half-life of 15 hours. With ongoing dosing, the half-life of methadone is extended to between 14 and 58 hours with a mean of 24 hours (Lugo, et al., 2005 and Eap, et al., 1999).

This prolonged half-life contributes to the fact that methadone blood levels continue to rise during the first week of daily dosing and fall relatively slowly between doses. The clinical implication is that missing one day's dose is not usually associated with significant withdrawal symptoms.

Sometimes patients report withdrawal symptoms if they are a few hours late for dosing. However, due to the long half-life of methadone, they are unlikely to be in withdrawal and their discomfort is more likely to be due to their anxiety about not receiving the

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dose on time. However, if a dose is missed, near steady state methadone blood levels may not be re-attained for a number of days following resumption of daily dosing.

Methadone reaches steady state in the body (where drug elimination equals the rate of drug administration) after a period equivalent to four to five half-lives of approximately three to ten days. Steady state does not automatically imply clinical stability of the patient.

Steady state refers to a point where the methadone plasma level has reached equilibrium.

Once steady state has been achieved, variations in blood concentration levels are relatively small and good suppression of withdrawal is achieved (Lugo, et al., 2005). For some, however, fluctuations in methadone concentrations may lead to withdrawal in the latter part of the inter-dosing interval. **A dose increase or split dosing may prevent this; however, constrained pharmacy resources in Tasmania, and clinical safety considerations, mean that split dosing cannot be made available.** In such circumstances, a switch to buprenorphine should be considered providing there are no identifiable contraindications.

Table 4.1: Summary of Methadone Pharmacokinetics

Onset of effects	30 minutes
Peak effects	Approx. 2-4 hours
Half life (in MMT)	14-58 hours
Time to steady state	5-10 days
Withdrawal onset	36-48 hours Peak intensity 5-7 days

Note: Adapted from Department of Health, Western Australia Government and the Drug and Alcohol Office, (2006). *Clinical policies and procedures for the use of methadone and Buprenorphine in the treatment of opioid dependence*, (p.11).

Methadone is fat soluble and binds to a range of body tissues including the lungs, kidneys, liver and spleen such that the concentration of methadone in these organs is much higher than in blood. Because of its good oral absorption and long half-life, methadone is taken in an oral daily dose.

Methadone is primarily broken down in the liver via the Cytochrome P450 3A4 enzyme system. Approximately 10% of methadone administered orally is eliminated unchanged. The rest is metabolised and the (mainly inactive) metabolites are eliminated in the urine and faeces. Methadone is also secreted in sweat and saliva.

Signs and symptoms of opioid withdrawal (see Section 2 for a definition and Section 5 for assessment) usually begin two to three half-lives (i.e. 36-48 hours) after the last dose of methadone.

4.2.3 Methadone actions and side effects

Most people who have used heroin will experience few side effects from methadone. Once on a stable dose, tolerance develops until cognitive skills and attention are not impaired (Gruber, et al., 2006). This may not be the case at very high doses or when other depressant drugs, including alcohol and benzodiazepines, are used. Symptoms including constipation, sexual dysfunction, and increased sweating, can continue to be troubling for the duration of methadone maintenance treatment. Table 4.2 contains a summary of the overall effects of methadone.

Table 4.2: Effects of Methadone

Main Actions	Analgesia Sedation Respiratory depression Euphoria (oral methadone causes less euphoria than intravenous heroin)
Skin Actions	Histamine release – may cause itching
Other physiological effects	Decreased blood pressure Constricted pupil Gastrointestinal tract actions, including: <ul style="list-style-type: none"> • Reduced gastric emptying • Reduced mobility • Elevated tone of Sphincter of Oddi, which can result in biliary spasm • Suppression of immune function
Endocrine actions	Reduced Luteinising Hormone Elevated Prolactin Reduced Adreno-Cortico-Trophic Hormone (ACTH) Elevated Anti Diuretic Hormone (ADH) Reduced testosterone (endocrine function may return to normal after 2-10 months).
Side Effects	Headaches Sleep disturbances Nausea, vomiting and constipation Lethargy Dry mouth and reduced salivary flow Increased sweating Vasodilatation and itching Menstrual irregularities in women Gynaecomastia in males Sexual dysfunction including impotence in males Fluid retention and weight gain

Note: Adapted from Queensland Health, (2008). Queensland Opioid Treatment Program Clinical Guidelines. (p.8).

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4.2.4 Methadone and Dental Health

Large proportions of opioid pharmacotherapy program patients report dental problems such as decayed teeth and periodontal disease (Graham & Meechan, 2005 and Nathwani & Gallagher, 2008). In the past, methadone syrup contained sugar, which was associated with tooth decay and dental caries. In 1993, the sugar in methadone syrup was replaced by sorbitol, a non-cariogenic sweetening agent.

More recently, Biodone®, another methadone formulation containing no additives apart from colourant (as required by the Commonwealth Government's Therapeutic Goods Administration), has been introduced and is commonly used. Nevertheless, dental problems may still occur in opioid pharmacotherapy patients for the following reasons:

- the acidic nature of methadone syrup can cause direct corrosion of the enamel;
- opioids, including methadone and buprenorphine, inhibit saliva production. Saliva is a natural defence against plaque;
- pre-existing dental problems;
- a high sugar diet;
- a history of poor dental hygiene during periods of dependent drug use;
- the analgesic effects of opioids, which can mask the existence of a tooth ache; and
- the route of use of other drugs, such as rubbing cocaine on the gums.

Researchers have noticed similar prevalence of dental problems in intravenous heroin users who are not on methadone (Laslett, et al., 2008 and Picozzi et al., 1972). This supports the conclusion that poor dental health is endemic among opioid users and that, in some instances, methadone may be exacerbating pre-existing problems rather than causing new ones.

A few simple countermeasures may assist in the management of dental health of opioid treatment program patients:

- examine the mouth and gums in the initial and subsequent physical examinations, and develop a management plan for any problems identified;
- if xerostomia (abnormal dryness of the mouth) is identified as a problem, recommend sugar-free gum or sugar-free candy to stimulate saliva production;
- recommend non-cariogenic diluents for take-away doses;
- provide information about low sugar diet and oral hygiene when appropriate;
- recommend treatment at community dental clinics for concession card holders, or by private dentists in other cases;
- recommend the use of aqueous-based, sugar-free methadone, especially in long-term methadone treatment;
- explain and encourage good dental hygiene;
- encourage regular check-ups;
- encourage regular brushing of teeth; and

- suggest rinsing the mouth immediately after taking methadone.

4.2.5 Drug Interactions with Methadone

Toxicity and death have resulted from interactions between methadone and other drugs. The following are a list of cautions and contraindications for prescribing and administering methadone maintenance treatment.

- **Sedatives:** including other opioids, alcohol, benzodiazepines, tricyclic antidepressants, anti psychotics, and sedating antihistamines. Combined with methadone, these drugs can lead to accidents, depression of respiratory drive, and fatal and non-fatal overdose;
- **Benzodiazepines:** in addition to the risks mentioned above, benzodiazepines combined with methadone are associated with impairment of memory (Barker et al., 2004).
- **Other opioid agonists:** combined with methadone increase the risk of overdose and death;
- **Naltrexone and Naloxone** (μ -opioid receptor antagonists) reverse or inhibit the effects of methadone;
- **Buprenorphine** (agonist/antagonist) can precipitate withdrawal symptoms in people taking methadone;
- **Interferon-alpha and ribavirin:** used in the management of Hepatitis B and C and other conditions Side effects of these medications may mimic opioid withdrawal symptoms; Hepatic enzyme inhibitors and inducers: Methadone is metabolised by the cytochrome P450 3A4 enzyme system in the liver. Drugs that induce this system can accelerate the metabolism of methadone and precipitate withdrawal while inhibitors of cytochrome P450 can slow the metabolism of methadone and increase risk of opioid toxicity particularly in the presence of other CNS depressant drugs. cause an overdose. Specialist advice and caution are required if medications affecting cytochrome P450 are to be prescribed to patients receiving methadone;
- **Highly active antiretroviral therapy (HAART).** Drugs used in the treatment of HIV infection alter methadone pharmacokinetics and caution must be exercised in patients receiving HAART (Neuman, 2006)). HIV anti-viral drugs are usually strong inhibitors of the Cytochrome P450 3A3,5,7 enzymes leading to delayed metabolism of methadone and the possibility of opioid toxicity if the dose is not adjusted in accordance with careful clinical assessment and review.

A full list of drugs interactions with methadone is presented in Appendix XX.

4.3 Buprenorphine

Buprenorphine is a synthetic opioid used to treat opioid dependence. In Tasmania its medical use is regulated under the Poisons Act 1971, as a 'controlled (S8) drug'.

Buprenorphine is derived from the morphine alkaloid thebaine, and is a partial μ -opioid receptor agonist at the μ -opioid receptors in the nervous system (Lintzeris, 2008).

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Although buprenorphine is a relatively potent μ -opioid receptor agonist at low doses, there appears to be a ceiling on its maximal opioid activity. Buprenorphine diminishes cravings for heroin and other unsanctioned opioids such as morphine, and prevents or alleviates opioid withdrawal in dependent opioid users. Therefore, it is suitable for opioid maintenance or withdrawal treatment.

Buprenorphine has a higher affinity for μ -opioid receptors than all full μ -opioid receptor agonists. In fact, naltrexone and naloxone are the only opioids with a similar receptor affinity for the μ -opioid receptors. Because of this, buprenorphine can block the effects of other opioid agonists in a dose-dependent fashion. At a dose of 16mg, most or all of the μ -opioid receptors are occupied by Buprenorphine (Greenwald et al., 2003). Through this dual effect of reducing craving and attenuating the response to administered heroin and other μ -opioid receptor agonists, buprenorphine assists in reducing use of heroin and other unsanctioned opioids.

Methadone, a full μ -opioid receptor agonist, also reduces the impact of additional μ -opioid receptor agonist use, but the effect of methadone is achieved primarily through its pharmacological action of inducing cross-tolerance to other opioids. This cross-tolerance is dose dependent. In contrast, at doses approaching 16 mg daily, buprenorphine achieves its effect primarily through its prolonged occupancy of a high proportion of μ -opioid receptors, blocking the action of other opioid agonists.

Unlike methadone, the effect of buprenorphine on respiratory depression reaches a ceiling at doses of between 8 and 16mg (Greenwald et al., 2003). Higher doses are not associated with increasing respiratory depression to any significant degree. Hence, buprenorphine is much safer than methadone and is associated with fewer deaths from overdose. However, if buprenorphine is used in combination with other central nervous system depressants such as alcohol or benzodiazepines, the combined effect on respiration can be life threatening. While respiratory depression from buprenorphine overdose is less likely than methadone, intravenous use of buprenorphine can be fatal due to complications caused by mode of administration (e.g. rapid increase in blood levels reaching the brain after injection).

Buprenorphine also exhibits antagonist effects at the kappa (κ) opioid receptor. The role of these receptors in humans is still poorly understood. Thus, buprenorphine acts as an agonist/antagonist.

Chemically, buprenorphine is 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol, hydrochloride [5 α ,7 α (S)]. Buprenorphine hydrochloride has the molecular formula C₂₉H₄₁NO₄ HCl and the molecular weight is 504.10 (Figure 3.3).

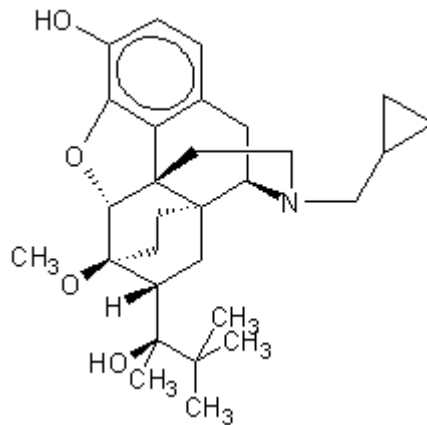


Figure 4.3: Buprenorphine Molecule

Note: Adapted from *Sigma Methadone Syrup, Product Information, 2008. TGA Product and Consumer Medicine, 2003. Retrieved September 22, 2011, from <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=buprenorphine&r/>*

4.3.1 Buprenorphine Pharmacokinetics

Peak plasma concentrations are achieved one to two hours after sublingual administration of buprenorphine. Buprenorphine undergoes extensive first pass metabolism when swallowed. The major metabolite, norbuprenorphine, has some opioid activity but the extent of its contribution to the pharmacological effects of buprenorphine is unknown.

Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-de-alkylation, mediated by the cytochrome P450 3A4 iso-enzyme. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and, to a lesser extent, in the urine.

Buprenorphine is a long-acting drug with a terminal elimination half-life of 24-37 hours. Peak clinical effects occur one to four hours after sublingual administration. Typically, effects will continue to be experienced for up to 12 hours at low doses (2 mg), but as long as 24-72 hours at higher doses (16 - 32 mg). The prolonged duration of effect at high doses enables alternate-day (double), and even 3-days-a-week (triple) dispensing regimes.

Table 4.3: Summary of Buprenorphine Pharmacokinetics

Onset of effects	30-60 minutes
Peak clinical effects	1-4 hours
Duration of effects	8-12 hours at low dose (<2mg) 24-72 hours at high dose (>16mg)
Time to steady state	7-10 days
Withdrawal onset	3-5 hours, symptoms generally milder than withdrawal from other opioids.

Note: Adapted from Department of Health, Western Australia Government and the Drug and Alcohol Office, (2006). *Clinical policies and procedures for the use of methadone and Buprenorphine in the treatment of opioid dependence*, (p.16).

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4.3.2 Buprenorphine Formulations for Opioid Dependence

In the context of this document, the general term 'buprenorphine' will be used when discussing both of the available buprenorphine preparations for opioid dependence in Australia. These preparations are:

- (a) **Subutex®**: a mono product containing buprenorphine hydrochloride in 0.4, 2, and 8 mg tablets; and
- (b) **Suboxone®**: a combination product containing buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio. Available in 2mg and 8 mg sublingual tablets and in 2 mg and 8mg sublingual film.

Both preparations are sublingual tablets and have approximately 30-50% of the bioavailability of intravenous buprenorphine preparations. The bioavailability of sublingual buprenorphine is largely dependent on the amount of time the drug is in contact with the oral mucosa.

Partly in response to the mono preparation of buprenorphine being easier to divert than methadone liquid, the combination product containing naloxone was developed. The naloxone is poorly absorbed via the sublingual route, however, if injected it will cause opioid withdrawal symptoms in a person who is neuro-adapted. It was expected that the combination product would be less likely to be diverted or injected than the mono preparation. However experience has shown that diversion still does occur. For this reason, in Tasmania, Suboxone® is the preferred preparation of buprenorphine.

In Tasmania, Suboxone® is the preferred preparation of buprenorphine.

Exceptions are:

- patients with a known sensitivity of naloxone (rare);
- pregnant and breastfeeding women; and,
- patients prescribed small daily doses or doses requiring the use of the 0.4mg strength that is presently available as Subutex® but not Suboxone®.

The **Suboxone® sublingual film** was introduced in September 2011 and is an alternative preparation that may overcome the disadvantages of sublingual tablets.

The sublingual film formulation of buprenorphine with naloxone is intended to make dosing easier. Buprenorphine sublingual tablets take approximately 2–10 minutes to dissolve and this can make supervision of dosing difficult, particularly in community pharmacies. The sublingual film dissolves faster under the tongue than sublingual tablets (approximately 30 seconds : <16 mg & 1 minute >16mg) and therefore requires less supervision time.

As the film rapidly adheres to the oral mucosa, this makes it more difficult to remove. It is anticipated that this may deter removal of the product and reduce the potential for diversion. The introduction of this preparation into clinical practice will assist in

determining if the film has a lower rate of abuse than the combination sublingual tablet or than methadone syrup.

Doctors must be trained and authorised to prescribe Subutex® and Suboxone® for opioid dependence; these two preparations are not available to pain medicine specialists or other doctors for the treatment of persistent pain alone. However, if an opioid dependent patient has a comorbid, chronic non-malignant pain condition, Subutex® and Suboxone® can be effective in treating both conditions.

4.3.3 Buprenorphine Formulations for Pain Management

Two buprenorphine preparations are available for treatment of pain in Australia:

- (a) **Temgesic®** available in 0.2 mg sublingual tablet and ampoules for intramuscular injection for the relief of short-term pain (up to 7 days). The usual dose is 1-2 tablets, 3-4 times daily; and
- (b) **Norspan®** available as a low dose weekly patch in 5, 10, and 20 (maximum dose) mcg/hr doses.

These two buprenorphine preparations are not suitable for the management of opioid dependence because the doses are too low. For further information on pain, see Section 12.

4.3.4 Buprenorphine Actions and Side Effects

Many patients report less sedation on buprenorphine than on methadone (Soyka, et al., 2008). Research evidence suggests that buprenorphine has minimal effect on psychomotor performance; less than methadone or slow release oral morphine (Lintzeris, 2008). Any effect on psychomotor performance is likely to be greatest during the early stages of treatment or following dose increases. During this time, patients should be advised to exercise caution in driving or operating machinery. The increased alertness commonly described by patients treated with buprenorphine may make it a more suitable pharmacotherapy than methadone for people who are working, studying or looking after young children.

Buprenorphine appears to have minimal impact on hepatic function, although there have been some reports of acute Hepatitis following very high doses (>32mg IV) (Hervé, et al., 2004). It should be noted however that there are some adverse side effects that have been observed with the sublingual film. These include a redness of the mouth, sore tongue and numb mouth. These symptoms are not reported for the sublingual tablet.

Because of its lower intrinsic activity and higher affinity with μ -opioid receptors than other opioids, when presently treated with full μ -opioid receptor agonists, buprenorphine may precipitate opioid withdrawal symptoms one to four hours after the first dose. It may do so by displacing the agonist opioid medication from μ -opioid receptors. In the short term, newly introduced buprenorphine may not produce sufficient agonist effects to compensate for the displaced methadone, morphine or heroin, producing opioid withdrawal as it reaches its peak effects (approximately 153535353 hours after initial administration).

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The phenomenon of precipitated withdrawal has particular clinical relevance during the induction of persons taking full agonist opioids, such as morphine, oxycodone and methadone. If precipitated withdrawal does occur, it is not life threatening and usually settles quite rapidly. This may nevertheless be distressing for patients and require treatment with Clonidine 150µg Stat. A summary of the effects of buprenorphine are included in Table 4.3.

Buprenorphine has similar actions and side effects to methadone, however, the sedative and euphoric effects of buprenorphine are not as pronounced as methadone.

4.3.5 Drug Interactions with Buprenorphine

The principal drug interactions with buprenorphine relate to its opioid activity. Drugs which interact with buprenorphine that are more likely to be observed in the opioid pharmacotherapy setting include:

- **Sedatives:** including opioids, alcohol, benzodiazepines, tricyclic antidepressants, antipsychotics, and sedating antihistamines, combined with buprenorphine, can lead to additive sedative effects, respiratory and CNS depression;
- **Opioid antagonists:** naloxone and naltrexone, can precipitate a withdrawal reaction in patients on buprenorphine, although the effect may be delayed by between 2 to 4 hours;
- **Opioid agonists:** effects can be blocked by buprenorphine, complicating the use of additional opioids for analgesia. Furthermore, the initial dose of buprenorphine can precipitate opioid withdrawal in patients who have recently used an opioid drug; and
- **Hepatic enzyme inducers and inhibitors:** Buprenorphine metabolism can be influenced by the presence of drugs and other compounds that are metabolised by, or affect the activity of the Cytochrome system. Patients who are concurrently prescribed or using inhibitors of Cytochrome P450 3A4 (e.g. ketoconazole, nifedipine, and erythromycin) may have increased buprenorphine blood concentrations, and those taking inducers may have decreased blood concentrations. Such interactions are unlikely to be clinically significant, but precaution should still be exercised (See Appendix X)

A full list of drugs interactions with buprenorphine is presented in Appendix X.

4.3.6 Clinical Policy on Buprenorphine in Pregnancy and Breastfeeding

At the time of writing, the Therapeutic Goods Administration (TGA) had not approved the use of buprenorphine pharmacotherapy during pregnancy and breastfeeding due to insufficient scientific support. Therefore, previous recommendations were to switch female patients who became pregnant while on buprenorphine to methadone. However, switching a patient from buprenorphine to methadone can cause opioid withdrawal in both mother and unborn baby (Vester & Buning, 2005). Therefore, the TOPP does not recommend switching female patients from buprenorphine to methadone if they become pregnant while in the program.

The Tasmanian Opioid Pharmacotherapy Policy and Clinical Guidelines do not recommend switching female patients from buprenorphine to methadone if they become pregnant while in the program.

This does not apply to the combination product, Suboxone®, which is absolutely contraindicated in pregnancy. Furthermore, pregnant patients cannot be inducted into the program on either buprenorphine preparation due to risks of precipitated opioid withdrawal, which can potentially lead to premature labour.

Therefore, the guidelines regarding buprenorphine and pregnancy are as follows:

For patients who become pregnant while receiving opioid pharmacotherapy

- if on Subutex®, continue on Subutex®; or
- if on Suboxone®, switch to equivalent dose of Subutex®.

For pregnant patients being inducted onto opioid pharmacotherapy

- DO NOT induct on either buprenorphine preparation; and
- induct on methadone only.

For patients who are breastfeeding:

- DO NOT induct on either buprenorphine preparation;
- induct on methadone only;
- if on methadone, continue breastfeeding; and
- if buprenorphine is the only viable treatment option, inform the mother of the limited research regarding the safety and effects on development of breastfed babies exposed to buprenorphine.

For a more detailed discussion on management of pregnancy and breastfeeding and buprenorphine, see Section 11.

4.4 Indication for Opioid Pharmacotherapy

Patients are suitable for opioid pharmacotherapy with either methadone or buprenorphine if they are opioid dependent and have been using opioids for an extended period time. Section 2 contains more detailed information about the criteria for opioid dependence.

For patients with an opioid use history of less than 6 months duration, the advice of an Addiction Medicine Specialist must be sought to review the possibility of other treatment options prior to commencing opioid maintenance treatment.

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4.5 General Contraindications and Precautions for Opioid Pharmacotherapy

There are several situations in which opioid pharmacotherapy may not be appropriate, require additional caution, or require approval through additional procedures. These include:

- (1) **When there are concerns about informed consent:**
 - (a) **Patients aged 16–17 years:** A second opinion by an Addiction Medicine Specialist in support of treatment must be obtained and fully documented before commencing pharmacotherapy. Buprenorphine may be preferred over methadone due to its lower risk of harm in overdose and less severe withdrawal syndrome;
 - (b) **Patients aged less than 16 years:** Opioid pharmacotherapy treatment is generally contraindicated. If wanting to commence treatment, the prescriber must request an exemption in writing from the Clinical Director, Alcohol and Drug Services. The request for an exemption should include a second opinion from a drug and alcohol medical specialist. Alternative dosing times may need to be considered for this special patient group so they are kept separate from adults in treatment;
 - (c) **Patients with reduced capacity to provide consent:** These include patients with an impaired mental state and reduced cognitive capacity. A second opinion from an Addiction Medicine Specialist is required to ensure legal requirements for consent are met.
- (2) **When there is a comorbid mental illness:** If the patient has a serious mental illness (e.g. schizophrenia or severe mood disturbance including mood instability), the general priority is to treat the mental illness; caution is required when prescribing opioid pharmacotherapy. A second opinion from an Addiction Medicine Specialist is required to authorise unsupervised dosing when the patient has a history of impulsive self-harm, a current risk of suicide or deliberate self-harm or thought disorder. In such cases, ongoing assessment of mental state is required to ensure that the patient can safely manage take-away doses. If there is any reason for concern or takeaway doses should not be provided.
- (3) **When there is poly substance use:** If the patient is using other drugs, especially sedatives including alcohol and benzodiazepines, caution should be exercised. Particular emphasis should be given to assessing the level of physical dependence on opioids, the likelihood of continued use of other sedative or psychoactive drugs, and the risk of overdose. Patients should be advised that commencing opioid pharmacotherapy is contingent on the patient's agreement to address other drug use through supervised daily dosing where appropriate (e.g. benzodiazepine dependence) and selective withdrawal management. Admission to the Inpatient Withdrawal Unit (ADS, Hobart) may be appropriate to facilitate safe induction and selective withdrawal management of other substance.

- (4) **When there is persistent pain:** Patients with persistent pain require specialist assessment and management. In the presence of co-occurring opioid dependence and persistent pain, safe and effective management of the pain is not possible unless and until the dependence is brought under control. Such patients are best managed by an Addiction Medicine specialist in consultation with a Pain Medicine specialist and a Multi-disciplinary Pain Unit team (See Appendix X for further details).
- (5) **When there is allergy or hypersensitivity:** If the patient has a known hypersensitivity or allergy to the proposed drug formulation, an alternative preparation needs to be prescribed.
- (6) **Certain medical conditions:** Some medical conditions and associated treatments can affect the pharmacokinetics of both methadone and buprenorphine. For example, in patients with advanced liver disease, doses of either medication may need to be significantly reduced. In cases of progressive liver disease, such as that seen in patients with Hepatitis C, previously tolerated doses may need to be reduced. Patients with respiratory disease may also be at increased risk of respiratory depression. In all these cases, and in patients with: acute alcohol dependence, head injury and raised intracranial pressure, ulcerative colitis, biliary and renal tract spasm, and for patients receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment, caution is required. Seeking advice from an Addiction Medicine Specialist is recommended.
- (7) **When there is no neuroadaptation:** Opioid pharmacotherapy is usually only suitable for individuals with opioid dependence accompanied with neuroadaptation: that is, patients who have developed tolerance and experience withdrawal symptoms when reducing or ceasing opioid use. However, some individuals with a long history of opioid dependence may benefit from opioid pharmacotherapy as a preventative measure following a long period of abstinence, for example, following incarceration. In such individuals, treatment induction must be cautious and a second opinion is recommended if treatment suitability is unclear. Such patients should be inducted on:
 - Start with 5-10mg methadone and increase to no more than 20 mg per day for the first two weeks (unless the patient is showing signs of sedation. If so dose should be reduced); or
 - Start with 2-4mg Buprenorphine and increase to no more than 8 mg of for the first two weeks (unless the patient is showing signs of sedation. If so dose should be reduced).

Section 6 outlines guidelines for safe treatment induction.

4.6 Comparing Treatment Options

With the availability of two major opioid pharmacotherapy treatment options, medical practitioners and their patients need to consider many factors when deciding on the most appropriate treatment. A thorough assessment will help clinicians identify risk and lifestyle

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factors that will influence the choice of pharmacotherapy for their patients, thus improving clinicians' ability to match treatment to assessment. It is important to remember that, despite the associated risks of both maintenance therapies, appropriate prescription and use of the medications is unlikely to lead to adverse consequences. The following section will offer comparisons between methadone and buprenorphine opioid pharmacotherapy on a variety of factors.

4.6.1 Pharmacology

A summary of the pharmacological comparisons is presented in Table 4.4 below.

Table 4.4: Pharmacological Comparisons between Methadone and Buprenorphine

	Methadone	Buprenorphine
Classification	Full μ -opioid receptor agonist Used for maintenance treatment	Partial μ agonist Used for maintenance or withdrawal treatment
Substitutes for heroin	+++ Reduces cravings for heroin	+++ Reduces cravings for heroin
Blocks effects of heroin	++ At high doses (e.g. >60mg)	++++ At low doses (e.g. >4mg)
Side effects	Opiate like	Less sedating Can precipitate withdrawal
Withdrawal on cessation	+++ Described as severe and prolonged	++ Less severe
Onset of effects	30-60 minutes	30-60 minutes
Peak effects	2-6 hours	1-4 hours
Duration of clinical effects	16-30 hours	2-3 days
Metabolism	Hepatic MES +++ affected by liver metabolism	Hepatic MES and conjugation Less clinical impact on liver metabolism
Mode of administration	Oral	Sublingual
Drug interactions	Sedatives, μ -opioid receptor antagonists, inducers/inhibitors MES	Sedatives, μ -opioid receptor agonists and antagonists

Note: Reproduced from Queensland Health, (2008). *Queensland Opioid Treatment Program Clinical Guidelines*, (p.27).

4.6.2 Safety

Diversion

Both buprenorphine preparations are easier to divert than methadone liquid since they are in tablet form. However, Suboxone® is less likely to be diverted than Subutex®

because the naloxone can precipitate withdrawal if injected (as discussed earlier). The recently released Suboxone® sublingual film may assist in reducing diversion.

Crushing the Subutex® tablets has been shown to have equal bioavailability to non-crushed tablets (Simojoki, et al., 2010) and is recommended to reduce the likelihood of diversion.

Injection of buprenorphine tablets is more likely to cause serious vascular damage and infection leading to the loss of limbs or digits than diverted methadone, which is already in a liquid form.

Polysubstance use

While polysubstance use is a risk factor for methadone and buprenorphine treatments, buprenorphine is generally safer when combined with other substances than methadone.

However, buprenorphine combined with benzodiazepines or alcohol, particularly in a non-opioid tolerant individual, can lead to fatal respiratory depression. Because of this risk, Gibson and Degenhardt (2005) recommend patients receiving the buprenorphine-naloxone combination should be warned of toxicity when the medication is combined with alcohol and benzodiazepines. The authors conclude that people dependent on alcohol or benzodiazepines should not receive unsupervised administration of buprenorphine.

Toxicity and Respiratory Depression

Dose response studies show that high buprenorphine doses (>16 mg daily) do not result in substantially greater peak opioid effects than lower doses (8 - 12 mg) (Walsh et al., 1995). Because buprenorphine is a partial μ -opioid receptor agonist, doses many times greater than normal therapeutic doses appear to be well tolerated in most individuals, and rarely result in clinically significant respiratory depression, except in individuals who are not opioid-tolerant. However, even low doses of buprenorphine can be toxic when combined with sedatives such as benzodiazepines and alcohol.

Methadone, however, is a full μ -opioid receptor agonist. Therefore, increasing the dose causes progressive depression of respiration and consciousness, which contributes to a higher risk-profile for methadone than buprenorphine.

Overdose

Either directly experiencing or witnessing an overdose is a common occurrence for many opioid dependent people. Route of administration, variable drug purity, variable tolerance, polydrug use, and poor general health, all contribute to the risk of accidental overdose. Furthermore, the mortality rate for opioid users who are recently released from prison and not in an opioid pharmacotherapy program is up to fifty times greater than comparison groups with age matched (Kamina, et al., 2007; and Krinsky, et al., 2009). High levels of psychiatric comorbidity in opioid users mean that the risk of intentional overdose is high.

Experience of a non-fatal overdose can be a traumatic experience for patients. Clinicians should attempt to improve patient engagement with treatment services following an overdose. It is important to establish the causes of the overdose: deliberate attempt at

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self-harm may require psychiatric assessment, potentially leading to scheduling the patient under the Mental Health Act.

Since buprenorphine is safer than methadone in overdose, it is the preferred treatment option, particularly in patients at risk of overdose or in situations in which children may accidentally consume stored or diverted medication. However, in the event of a high dose buprenorphine overdose higher doses of naloxone may be required (in conjunction with other medical interventions) in order to resuscitate the patient in comparison to overdose on methadone or other opioids with lower μ -opioid receptor affinity.

Mortality

A number of factors have been associated with death during the induction phase of methadone. These factors include:

- concurrent use of other drugs;
- inadequate assessment of tolerance;
- commencement dose too high;
- dose increase too rapid;
- inadequate understanding of cumulative effects of methadone;
- poor supervision during dosing; and,
- individual variation in the metabolism of methadone.

Furthermore, mortality rates associated with methadone treatment are higher than rates associated with buprenorphine treatment (Bell, et al., 2009a). Indeed, over one-fifth of all methadone deaths occur during the first week of treatment induction whereas international literature has recorded only two deaths during buprenorphine induction (Bell, et al., 2009b, Gibson & Degenhardt, 2005). More specifically, Australian research by Gibson and Degenhardt (2005) has shown that buprenorphine is associated with lower mortality (0.02/1,000 treatment episodes 95% CI 0.0005, 0.1) than methadone (2.7/1,000 treatment episodes: 95% CI 2.4, 3.1) and naltrexone (10.1/1,000 treatment episodes: 95% CI 6.9, 14.3). In other words, on the basis of this study, the risk of death per treatment episode is 135 times greater for methadone compared to buprenorphine, and 500 times greater for naltrexone compared to buprenorphine.

There are some concerns in the literature that buprenorphine deaths may be under-represented in Australian coronial databases (Gibson & Degenhardt, 2005); however, many of the deaths that have occurred in association with buprenorphine treatment outside of Australia have largely been due to patient's unsanctioned use of opioid drugs. Overall, however, when administered appropriately (with supervision), buprenorphine is safer during both the induction and the maintenance phases of opioid pharmacotherapy.

4.6.3 Abuse Potential

Although all opioids have abuse potential, people who are frequent users of heroin, methadone, or other μ -opioid receptor agonists that bind less tightly to opioid receptors than buprenorphine, are less likely to abuse Buprenorphine (Jones et al., 1999), especially if they are aware that this may cause precipitated withdrawal. The effects of

buprenorphine (taken sublingually or by intravenous injection) in people in naltrexone maintenance treatment remains unclear. It is salient to note once again that naltrexone has a higher affinity for the μ -opioid receptor. Administration of buprenorphine to this population may result in an attenuated agonist effect, particularly with low doses of naltrexone, as is generally the case with implanted preparations of naltrexone.

4.6.4 Accessibility

Both methadone and buprenorphine are available to patients and subsidised by the Pharmaceutical Benefits Scheme (PBS – Section 100).

Patients can be dosed on buprenorphine every second to third day once stabilised, whereas methadone must be dosed daily. Since there are very few 7 day dosing pharmacies in Tasmania, buprenorphine is usually the most convenient option for patients.

4.6.5 Administration

Methadone liquid is immediately consumable, whereas buprenorphine sublingual tablets take between 4-10 minutes to be absorbed sublingually. Although the rate of dissolution of buprenorphine can be increased (if the patient is given a lemon drink before the medication is placed under the tongue and the tablets rough crumbled), time taken to complete the procedure remains lengthier than the administering of methadone.

4.6.6 Evidence

Current evidence indicates that both methadone and buprenorphine are the most effective opioid pharmacotherapy treatment options and significantly reduce illicit opioid use and associated risks. Furthermore, they are both similarly effective on several measures (Gowing et al., 2001 and Mattick et al., 2004). Although many patients report preferring buprenorphine in comparison to methadone due to its subjective effects, some evidence indicates that treatment retention is more effective for methadone (Gowing et al., 2001 and Mattick et al., 2004). It is important to acknowledge that despite the documented benefits of buprenorphine, methadone has been available to practitioners for much longer; hence, methadone may be a more familiar option to both practitioners and patients.

4.6.7 Effects

The patient's personal and psychosocial circumstances will influence whether they prefer the effects of methadone or buprenorphine. It has been reported that patients generally prefer buprenorphine as it has fewer side effects and patients experience less sedation and often report feeling more energetic when receiving buprenorphine treatment in comparison to methadone (Pinto, Rumball & Holland, 2008). However, some patients with psychosocial problems may prefer the sedating effects of methadone, while others who are more active or have more responsibilities may prefer buprenorphine (White, et al., 2007). Finally, some patients wishing to continue unsanctioned opioids may prefer methadone as it is less likely to block the effects of unsanctioned opioid use than buprenorphine at higher doses.

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4.6.8 Withdrawal

During induction onto buprenorphine, there is a risk of precipitated withdrawal occurring (particularly if continuing to use full agonist opioids) as the buprenorphine displaces other agonist opioids from μ -opioid receptors (see section 4.3.4).

However, buprenorphine withdrawal is generally less severe than withdrawal from methadone- both in the severity of the symptoms and the duration of withdrawal. Buprenorphine is now favoured as the pharmacological agent of choice for opioid withdrawal management. A more rapid withdrawal from buprenorphine can be achieved than with methadone. It is also possible to immediately cease buprenorphine if necessary.

4.6.9 Switching treatment options

It is relatively easy to transfer from buprenorphine to methadone, but more complex transferring from methadone to buprenorphine, as this can precipitate withdrawal. (See section 8.12 for guidelines for switching).

4.7 Gateway Model - Buprenorphine as Induction Agent of Choice

As evidenced when comparing buprenorphine and methadone on a variety of outcomes, buprenorphine is safer, and overcomes access issues and patients can engage in treatment more readily. It also has a more favourable side-effects profile than methadone. This, combined with the restrictions of limited daily dosing pharmacies in Tasmania, make it the most desirable induction agent of choice. Therefore, Tasmanian Alcohol and Drug Services adopt and support a 'Gateway Model' for opioid pharmacotherapy induction. More specifically, the preferred agent for commencement and stabilisation of patients onto the Tasmanian Opioid Pharmacotherapy Program is the buprenorphine-naloxone preparation – Suboxone®. Exclusions from this model of treatment induction are:

- pregnant females;
- patients currently on methadone being transferred from another clinic;
- patients with a known allergy or hypersensitivity to buprenorphine and its available preparations;
- patients for whom a clinical evidence indicates methadone would be the most appropriate induction agent and where this is considered safe; and
- patients with clinically significant respiratory or hepatic insufficiency. For these clients both buprenorphine and methadone may pose significant risks, and specialist opinion should be sought.

Suboxone® is the preferred agent for commencement and stabilisation of patients in Tasmania.

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Patients should be trialled on buprenorphine for a minimum of two weeks. If the patient is experiencing clearly observable side-effects from the buprenorphine they may be switched to methadone at any stage. Where there is any doubt about a patient's side effects from buprenorphine, advice from an Addiction Medicine Specialist should be sought.

It is important to ensure that all patients entering opioid pharmacotherapy are thoroughly assessed prior to commencement of treatment. Ongoing review will ensure that the appropriate treatment is provided, remembering that clinical safety considerations will guide treatment decision making. The following section describes how to conduct a thorough assessment prior entry into pharmacotherapy.

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