

Safe Treatment Induction

In this section you will...

- Gain knowledge on how to safely induct a patient to opioid treatment;
- Be provided with an overview of the process for patient reviews; and
- Develop an understanding of dosing procedures.

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7 Safe Treatment Induction

7.1 Induction to Opioid Treatment

Patients need to begin opioid treatment in a well supervised setting to ensure frequent monitoring. In Tasmania, this will usually be either in the ADS pharmacotherapy clinic or another community setting; it may be also be in a hospital ward or in a general practitioner's rooms. Induction into treatment takes a minimum of 2 weeks for methadone and 1-2 weeks for buprenorphine.

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The chief objectives during induction are to:

- retain the patient in treatment by minimising the discomfort of withdrawal; and
- ensure the patient's and community's safety.

Induction into opioid pharmacotherapy treatment involves two processes, both of which decrease the patient's need to use unsanctioned opioids:

- Stabilisation – abolishing fluctuations between intoxication and withdrawal by titrating the dose against the needs of the patient; and
- Tolerance – reducing the response to additional unsanctioned opioids.

Induction into opioid pharmacotherapy, particularly on methadone, can be fatal. Strategies for improving safety include:

- maintaining good communication and rapport with the patient throughout all phases of treatment;
- developing a collaborative treatment plan that is documented in the patient file;
- practicing cautious initial dosing;
- when clinically indicated, observing patients for intoxication or withdrawal 3-4 hours after their commencement dose;
- the treating team reviewing the patient daily for the first 3-4 days of dosing;
- repeated daily observation of patients is available for at least 2 weeks;
- providing a thorough explanation of intoxicating effects of opioid pharmacotherapy;
- providing a thorough explanation of withdrawal effects;
- reminding patients of the risks of taking other contraindicated drugs, prescribed or illicit, during treatment; and

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- commencing a patient on the program on a Monday, and no later than Wednesday, to allow maximum time to review the patient and ensure clinical safety during stabilisation.

The Tasmanian Opioid Pharmacotherapy Policy and Clinical Practice Standards recommends commencing a new patient on a Monday, and no later than Wednesday.

The initial dose prescribed (either methadone or buprenorphine) will be contingent on the patient's tolerance to opioids. Information from the assessment will provide an estimation of the patient's tolerance. This information includes:

- frequency of use;
- quantity of use;
- time since last use;
- route of administration;
- severity of withdrawal syndrome;
- urine drug screen results;
- findings on medical examination including clinical observation; and
- other corroborative information and history.

If there is doubt about the degree of tolerance, a review of the patient when withdrawal symptoms are being experienced may help to resolve uncertainty about a safe starting dose.

Other factors that will influence the decision about first dose include:

- dosing location;
- availability of staff to observe the patient before and after dosing;
- the concurrent use of benzodiazepines or other psychoactive substances;
- signs of intoxication with substances other than opioids; and
- the risk of overdose, particularly from substances other than opioids.

The patient should be seen immediately before administering the first dose. If the patient is intoxicated, particularly with alcohol and benzodiazepines, the first dose will be delayed. If not intoxicated, the patient can go directly to the pharmacy for dosing.

As discussed in Section 3, patients will usually only be eligible for the program if there is evidence of opioid dependence with neuroadaptation, unless they have a long history of opioid dependence and are at high risk of relapse following a period of abstinence. Consequently, most patients will be experiencing withdrawal prior to induction into the program.

7.1.1 Induction agent of choice

Please refer to Section 3, which outlines the rationale for having buprenorphine as an induction agent of choice, and Suboxone® as the preferred preparation of buprenorphine.

7.2 Induction to methadone pharmacotherapy

Since most patients will already be withdrawing from opioid use before treatment commences, inadequate dosing on methadone may fail to relieve patients' withdrawal symptoms. This increases the likelihood that they will seek to 'top up' their prescribed dose with other opioids. This can have fatal consequences.

Conversely, dosing too high can cause toxicity, sedation, and death. These risks are more immediate than the risk of dosing too low. Furthermore, a low dose can be increased if the patient continues to experience significant withdrawal symptoms. Therefore, the TOPP supports a 'start low and go slow' dosing induction approach to methadone.

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Induction into methadone pharmacotherapy takes a minimum of 2 weeks.

This means starting patients on the lowest dose suitable for their needs within the range specified in this document (see 7.2.2). If a dose is too low, it can be slowly titrated up to achieve stabilisation.

Due to the pharmacological properties of methadone and the time it takes to reach a steady state (see 7.2.1.1), induction into methadone pharmacotherapy takes a minimum of two weeks.

7.2.1 Access to 7 day dosing

Patients are not eligible for methadone takeaway doses during the induction phase, and hence, will need to access supervised dosing at a 7 day dosing pharmacy during this phase. Detailed guidelines for takeaway doses are available in Section 7.

Patients will need access to a 7 day dosing pharmacy during methadone induction.

7.2.2 Determining starting dose

A thorough assessment will provide an insight into the extent of the patient's opioid use history and dependence. If there are difficulties determining a commencement dose,

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particularly when over the counter analgesia is being used (e.g. codeine), then the advice of an Addiction Medicine Specialist should be sought.

7.2.3 Minimum starting dose

Deaths during induction onto methadone have been associated with doses between 25-100 mg per day, with most deaths occurring between 40-60 mg (Drummer et al., 1992 and Caplehorn, 1998). Indeed, 20% of deaths associated with methadone occur during induction.

Therefore the initial dose, particularly for new patients or patients with compromised liver function, should be between 5-20 mg. In fact, a dose of 20 mg for a 70 kg patient is generally safe even in opioid naïve individuals.

7.2.4 Maximum starting dose

A starting dose of 25mg is suitable for patients who:

- show evidence of significant opioid dependence;
- demonstrate signs of moderate to severe opioid withdrawal;
- are using large amounts of heroin and/or other opioid medication; and
- if using heroin, have been using heroin at least twice a day in the last two weeks.

The maximum commencement dose of methadone is 25 mg on the first day of methadone treatment.

7.2.5 Test Dose

Local experience indicates that for some patients a test dose may be appropriate. This allows time for observation of the patient's reaction to the drug prior to giving them the full initial dose.

7.2.6 Supplementary doses

Sometimes patients will continue to experience withdrawal symptoms on the first day after the administration of an initial dose. Since peak serum methadone levels are not attained until three to four hours after oral administration, such persons may be considered for a supplementary dose after that period of time, following careful clinical assessment by the prescribing doctor.

If the patient is experiencing persistent and observable withdrawal signs four hours after the first dose, **a supplementary dose of 5mg** (10 mg in exceptional circumstances) can be considered. A combined dose may be given on the following day. However, the initial dose plus the supplementary dose must not exceed 25 mg on the first day of methadone treatment.

If a supplementary dose is provided, the maximum dose of 25 mg of methadone on the first day of treatment still applies.

7.2.7 Methadone effects

Methadone takes several days of dosing to achieve its full clinical effect. It is particularly important to clearly explain to patients that induction into maintenance treatment takes time, and that they will experience increasing effects from treatment over the first few days even if the dose is not increased. Furthermore, slow onset of action and long half-life mean that the toxic effects of methadone can become life threatening long after ingestion: hence, the minimum 2 week induction period.

7.2.8 Short Opioid Use History

For patients with an opioid use history of less than 6 months in 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.

7.2.9 Complicated Presentation

For patients requiring a high commencement dose, but whose presentation is complicated by significantly high levels of alcohol dependence or polysubstance use, seek advice from an Addiction Medicine Specialist.

7.2.10 Comparing strengths of different opioids

Comparative strengths of opioids listed in pharmacology textbooks are approximations only, and, since consumption of the prescribed opioids are often not supervised, it is not possible to be sure that the patient is consuming all of the quantity reported. Ayonrinde & Bridge (2000) report that in the chronic dosing situation, oral methadone can be up to twenty times as potent as oral morphine on a mg for mg basis. For these reasons, estimating an equivalent starting dose of methadone from these comparative tables should not be attempted.

7.2.11 Reaching a steady state

For most patients, methadone does not reach a steady state until three to four days of daily dosing. For a small percentage of patients, this can be up to 10 days (Drummer et al., 1992). Thus, patients should be seen daily by the treating team for at least the first four days to stabilise them on an adequate dose of methadone. Careful assessment and monitoring each day is necessary as the dose is titrated against the patient's clinical state. The following series of figures shows the pattern of methadone levels in plasma after one and three days of daily dosing, and once a steady state is achieved.

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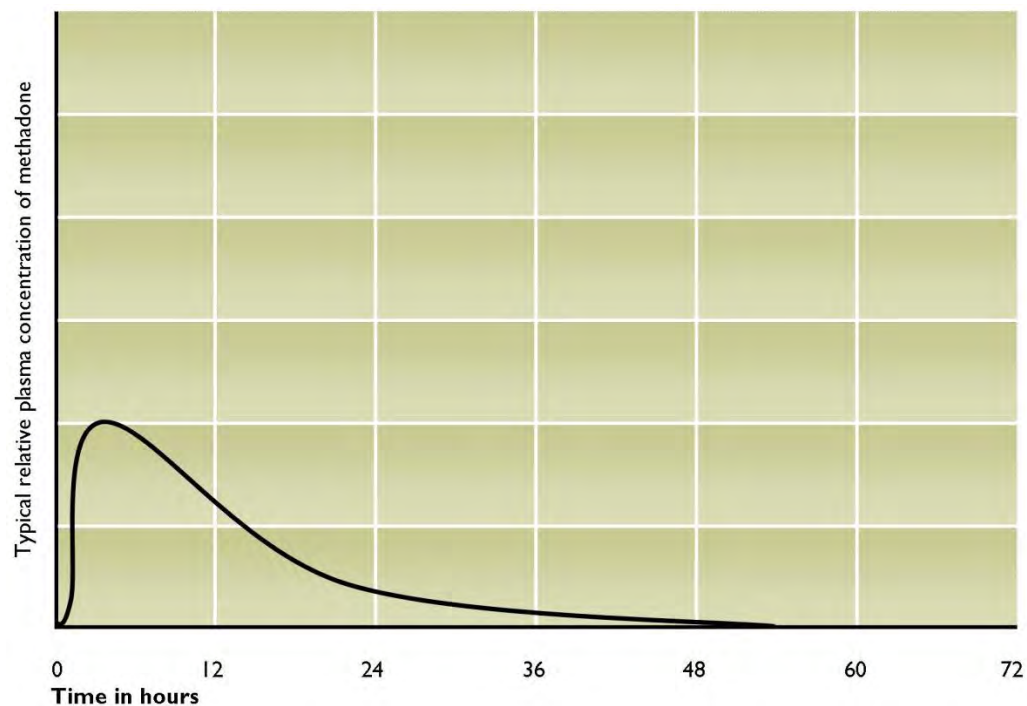


Figure 7.1: Plasma concentration after a single dose of oral methadone

Note: Reproduced from *The Methadone Briefing*, 1996. Retrieved September 14, 2011, from http://www.exchangesupplies.org/drug_information/briefings/the_methadone_briefing/methadone_briefing/section4.html#chemi

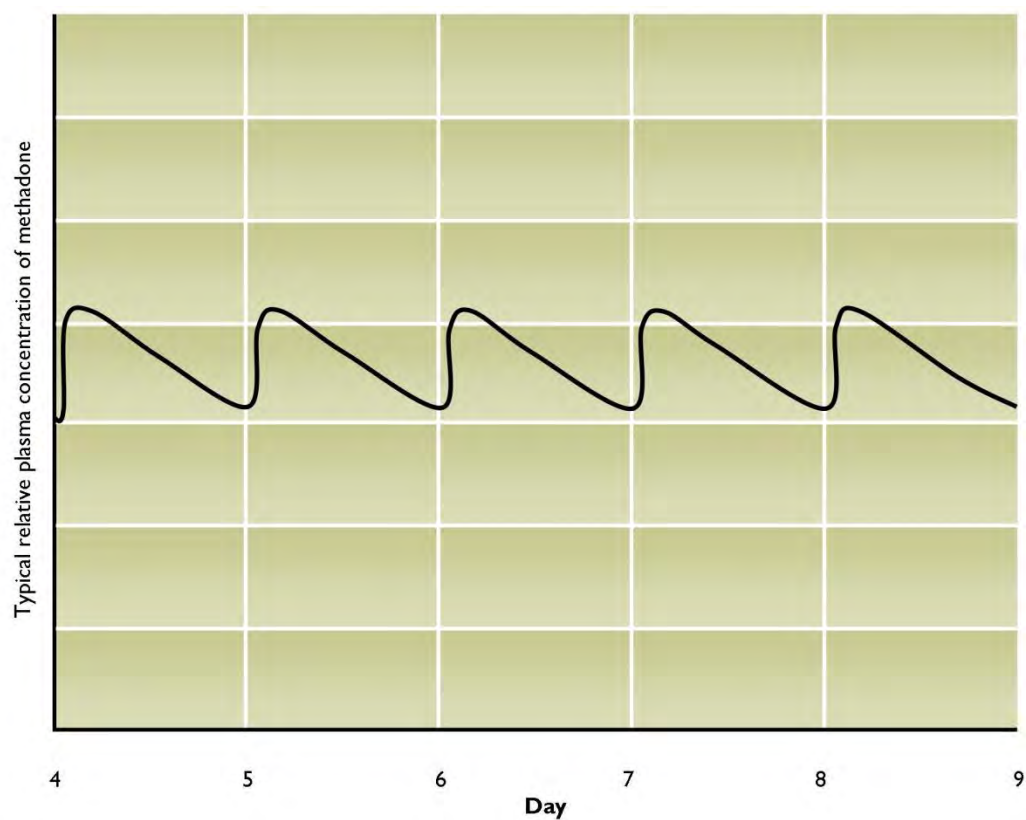


Figure 7.2: Plasma concentration after three daily doses on oral methadone

Note: Reproduced from "Guidance for the use of methadone for the treatment of opioid dependence in primary care.(1st ed.)." By Ford et al, 2005, RCGP, p.7. Substance Misuse Unit, SMMGP, RCGP Sex, Drugs and HIV Task Group and The Alliance: England.

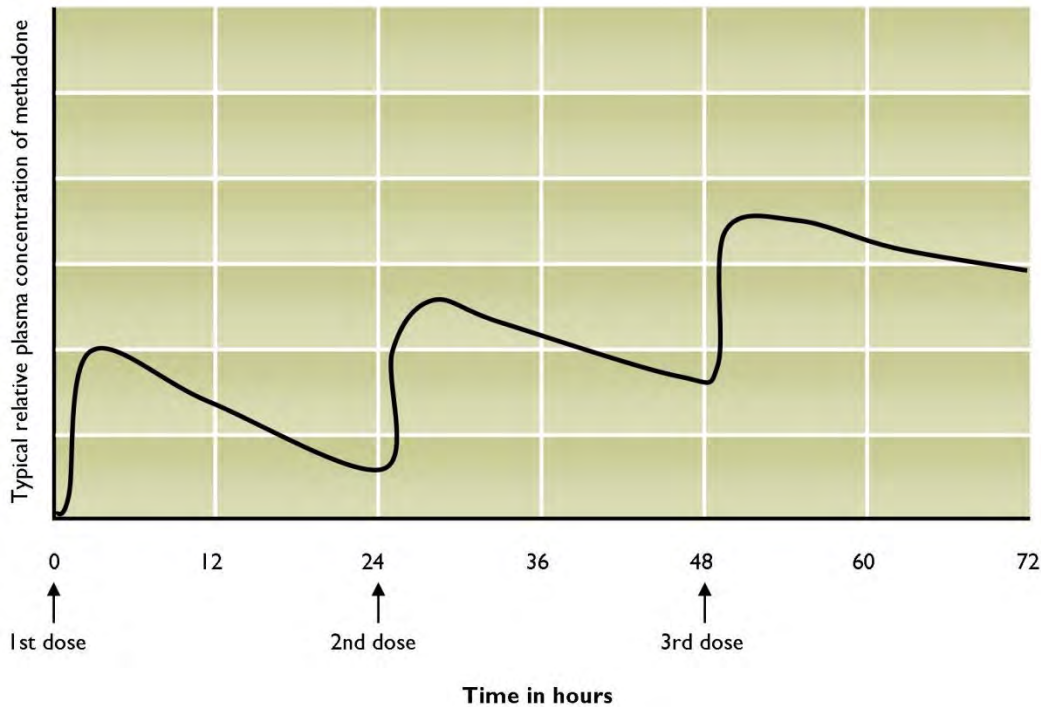


Figure 7.3: Plasma concentration once steady state achieved on oral methadone

Note: Reproduced from "Guidance for the use of methadone for the treatment of opioid dependence in primary care.(1st ed.)." By Ford et al, 2005, RCGP, p.7. Substance Misuse Unit, SMMGP, RCGP Sex, Drugs and HIV Task Group and The Alliance: England.

Steady state does not automatically imply clinical stability of the patient.

7.2.12 Dose increases during induction

Following a dose increase, serum levels can take up to five days (or more) to reach a steady state. Hence, rapid dose increases can exceed the patient's level of tolerance and increase the risk of over-sedation and have toxic or fatal consequences. The following limits apply to dose increases during induction.

Week One:

- Increase the dose by **5-10 mg** every 3 days, subject to assessment;
- Do not increase the dose by more than **20 mg** in the first 7 day period; and
- The maximum dose after the first week is **40 mg**.

Week Two:

- Increase the dose by a **maximum of 10 mg** during the second week; and
- The maximum dose after the second week is **50 mg**.

Subsequent Weeks:

- The maximum dose increase in any subsequent week is **10 mg**.

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If clinical evidence indicates a need for more rapid dose increases during induction, the Tasmanian Opioid Pharmacotherapy Policy and Clinical Practice Standards recommends seeking advice from an Addiction Medicine Specialist, ADS.

7.2.13 Dose decreases during induction

Decrease the dose if there are features of opioid intoxication three to four hours after dosing or if the patient experiences intolerable side effects. A reduction of 5-10 mg or to the previous day's dose may be sufficient. Continue monitoring the patient: clinical judgment will determine if the dose should be decreased further.

7.3 Induction to buprenorphine pharmacotherapy

Buprenorphine differs from methadone in that it displaces other opioids from opioid receptors but has less intrinsic opioid activity, thus precipitating withdrawal symptoms if given while other opioids are still active. Hence, buprenorphine treatment should not be commenced until the patient is in mild to moderate withdrawal. A Clinical Opioid Withdrawal Scale (COWS) score of at least eight (representing the mid-point of the COWS scale) or Subjective Opiate Withdrawal Scale (SOWS) score between 16–25 is a good indicator of the patient's readiness to receive their first dose. (Both scales are included in Appendices X & xx). If no opioid withdrawal signs are present, the patient may be asked to return later in the day or the next day so that withdrawal signs are present before the first dose is given.

As a further guide to avoiding precipitated withdrawal, buprenorphine should not be administered until at least:

- 6-12 hours after the last dose of short acting opioid agent (e.g. heroin or injectable morphine);
- 24 hours after the last dose of slow release morphine or oxycodone; or
- 24-36 hours after the last dose of methadone.

There is considerably less risk of death during induction to buprenorphine treatment in comparison to methadone induction, however, caution is still essential, particularly if the patient may be using other drugs with a sedative effect (e.g., alcohol or benzodiazepines). Nonetheless, contrary to methadone, it is usually safe to achieve rapid induction onto an effective maintenance dose of buprenorphine. Therefore, induction into buprenorphine pharmacotherapy takes a minimum of one week, but can often take up to 2 weeks.

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7.3.1 Access to 7 day dosing

Patients are not eligible for takeaway buprenorphine doses during the induction phase. The preference is for patients to present daily for supervised dosing during buprenorphine induction. However, for patients living in rural and remote areas or with

no access to a 7 day dosing pharmacy, a double dose on the first Saturday is permitted, with the approval of an ADS Addiction Medicine Specialist. See Section 8 for a more detailed explanation of double dosing for buprenorphine.

Patients with no access to a 7 day dosing pharmacy may be double dosed from the first Saturday of buprenorphine induction – with the approval of an Alcohol and Drug Services Addiction Medicine Specialist.

7.3.2 Starting dose

Minimum starting dose

A minimum starting dose of **2-4 mg** per day is suitable if:

- there are only mild signs and symptoms of opioid withdrawal;
- the patient has a low degree of neuroadaptation to opioids;
- there are concerns about concurrent use of alcohol, sedatives (e.g. benzodiazepines) or other illicit opioids;
- there is uncertainty about the timing of recent opioid use; or
- there is a concurrent medical condition, particularly compromised liver functioning.

Maximum starting dose

A starting dose of **4-8 mg** per day is well tolerated by most patients and will lead to rapid stabilisation on an effective maintenance dose and increased retention in treatment. The maximum commencement dose of buprenorphine is 8mg on the first day of treatment.

An initial starting dose of **6-8 mg** per day is suitable if:

- there are considerable signs and symptoms of opioid withdrawal; and
- the patient has a high degree of neuroadaptation to opioids.

The maximum commencement dose of buprenorphine is 8 mg on the first day of treatment.

7.3.3 Test Dose

Local experience indicates that for some patients a test dose may be appropriate. This allows time for observation of the patient's reaction to the drug prior to giving them the full initial dose. This is particularly useful if there are concerns about the patient's potential to experience precipitated withdrawal or other clinical safety concerns.

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7.3.4 Supplementary dose

The patient should be reviewed approximately four hours after the first dose. If the patient is feeling worse, this may be a sign of precipitated withdrawal and no further doses should be given. If the patient is feeling better but is still in withdrawal, a supplementary dose of **2-6 mg can be given**.

However, the initial dose plus the supplementary dose must not exceed 8 mg on the first day of buprenorphine treatment.

If a supplementary dose is provided, the maximum dose of 8 mg of buprenorphine on the first day of treatment still applies.

7.3.5 Dose increases during induction

Rapid, higher dose induction with buprenorphine is both safe and effective, and is generally recommended to increase therapeutic effect and retention in treatment. The target dose is between **12-16 mg** by the end of the first week. Induction into buprenorphine treatment is usually complete by the end of the first week, but can take up to 2 weeks, particularly if the patient requires a higher dose.

After the commencement dose, assess features of intoxication or withdrawal and the patient's perception of dose adequacy. If intoxication is not observed and the dose is not adequate, then the dose may be increased by **2-4 mg** per day up to a maximum of:

- **16 mg** by the end of the first week; and
- **24 mg** by the end of the second week.

7.3.6 Dose reductions during induction

Decrease the dose if there are intolerable side effects or features of intoxication four hours after administration. A reduction to the previous day's dose may be sufficient. Continue monitoring the patient: clinical judgment will determine if the dose should be decreased further.

7.3.7 Managing precipitated withdrawal

The precipitated withdrawal sometimes experienced in buprenorphine induction is reportedly not as severe as withdrawal from opioids such as methadone and heroin. However, patients should be provided with information and advice about how to manage precipitated withdrawal if it occurs.

Nevertheless, if the patient is experiencing highly unpleasant precipitated withdrawal, a single dose of 50 mcg of clonidine may be provided. Due to the risk of cardiac problems and abuse potential of clonidine, the dose must be provided under supervision. A script must not be given to the patient.

To manage precipitated withdrawal – a single dose of clonidine 50 mcg may be administered under supervision.

Patients should be advised that, because of buprenorphine's competitive affinity for opioid receptors, continuing to use other opioids once they have started to take buprenorphine is likely to make stabilisation difficult and is unlikely to reduce their withdrawal symptoms Lintzeris et al., 2006.

7.3.8 Missed doses during indication

Regular dosing during stabilisation is essential for reaching steady state. Due to the time it takes to reach steady state for both methadone and buprenorphine, missed doses have a significant impact on stabilisation. Therefore, if doses are missed during stabilisation, the patient and their dose should be re-assessed. Patients may need to be recommenced on the initial starting dose.

7.3.9 Prescriptions of Buprenorphine and Methadone

Both methadone and buprenorphine are Schedule 8 drugs. Therefore prescriptions cannot be generated using only electronic software. The following information must be handwritten:

- the name of the drug;
- the strength of the drug;
- dispensing instructions; and
- nominated days for take away doses and double dosing arrangements (relevant for maintenance treatment).

Prescriptions for methadone and buprenorphine should never be given directly to patients.

7.4 Alternative Treatment Options

Although most patients in Tasmania will be able to access either methadone or buprenorphine induction and treatment, there will be some exceptional cases in which the patient:

- has a genuine clinical contraindication to both buprenorphine preparations; and
- cannot access a 7 day dosing pharmacy for the methadone induction period.

In this circumstance, prescribers are encouraged to consult with an ADS Addiction Medicine Specialist about an appropriate management plan. The advantages of an inpatient admission, the increased risk of overdose post admission, and the risks of not receiving pharmacological treatment should all be discussed.

One option for such patients is to consider referral to the ADS withdrawal unit. Some patients report that the benefits from inpatient management for withdrawal from

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unsanctioned opioid use can motivate ongoing commitment to opioid pharmacotherapy or other forms of treatment. However, there is a well documented increased risk of overdose and death if a patient returns to previous levels of unsanctioned drug use following their inpatient treatment (Strang et al., 2003).

Therefore, patients will only be considered for opioid withdrawal in this context as a pathway to longer term treatment options that include ongoing care: for example, residential rehabilitation treatment for addiction or a multidisciplinary pain treatment service for pain sufferers.

7.5 Patient Reviews

Medical reviews are required for the prescription of opioid pharmacotherapy. In the public system, specially trained nurses conduct the majority of observations and non-medical reviews, in consultation with the prescribing doctor. In the private system, however, the prescribing doctor will usually be solely responsible for patient reviews. Please note that only medical practitioners can conduct medical examinations (see Section 5 on assessment).

For the first four days treatment, daily reviews by the treating team are required to:

- titrate the patient's optimal doses of methadone or buprenorphine;
- develop a comprehensive assessment of the treatment plan;
- communicate with the pharmacist about missed doses or other indicators of poor treatment compliance; and
- discuss future treatment plans.

As treatment progresses, the treating team should review the patient two to three times a week until stabilised to:

- establish adequacy of dose;
- enquire about withdrawal symptoms or side-effects; and
- monitor unsanctioned drug use and review the treatment plan to ensure clinical safety.

Once stabilised on a therapeutic dose, the treating team should review the patient weekly for a further four to six weeks to:

- monitor progress; and
- monitor effectiveness of the treatment plan.

Once stabilisation is complete and maintenance has commenced, patient reviews can be tapered to fortnightly for a further 6-8 weeks. After this period, a medical review is required at three monthly intervals. Reviews can be conducted more frequently at the request of any member of the treating team which includes the patient, case manager (within ADS), allied health professional, pharmacist or doctor. Any changes in medical management must be authorised by the prescribing doctor.

Within ADS, case management reviews should be conducted at least 6 weekly.

Once stabilisation is complete, patient reviews can occur fortnightly for 6-8 weeks.

After this period, medical reviews are required at 3 monthly intervals.

7.6 Dosing Location

In accordance with the Tasmanian Shared Care Model (Section 3.10), ADS will be responsible for inducing many of the patients commencing opioid pharmacotherapy in Tasmania. During the induction phase, dosing for most of these patients will occur in a pharmacy linked to the ADS pharmacotherapy program in the patient's area.

Patients who present well and without Code of Conduct Violations to ADS services may be referred to, and be dosed at, an alternative community pharmacy following the induction phase.

Doctors and pharmacists in the private setting inducing low risk patients to the program are encouraged to maintain regular communication with each other to determine the patient's ongoing suitability for the community dosing arrangements.

7.7 Methadone and Buprenorphine Dosing Procedure

Patients must satisfy the pharmacist's requirements that the dose is being taken appropriately and that doses are not being diverted. Furthermore, the patient should always be assessed for signs of intoxication prior to dosing. Patients who present intoxicated should never be dosed. A list of symptoms of withdrawal, intoxication and overdose is included in Section 5.

Patients who present intoxicated should never be dosed.

Prior to attending the pharmacy, patients should be advised of the following dosing procedures:

- only the patient can pick up their dose;
- the patient must enter the pharmacy alone;
- no bags or containers are allowed in the dosing area;
- the patient's hands and mouth must be visible to the pharmacist at all times;
- doses must be consumed in direct view of the pharmacist without turning of the head (excluding takeaway doses);
- dose must be consumed directly from the cup or spoon and placed under the tongue in the case of buprenorphine;

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- for buprenorphine, the patient must remain in full view of the pharmacist until the crushed tablets are dissolved under tongue;
- the empty cup or spoon must be shown to the pharmacist before discarding it;
- the patient must speak to the pharmacist, open their mouth, and have a drink of water after dosing if asked to do so; and
- the patient must leave the pharmacy area and clinic vicinity as soon as they have dosed.

If the pharmacist is not satisfied that the dosing procedure has been met by the patient, the patient may be placed under stricter supervision requirements for a period of time, be limited as to where they can pick up their dose, or be deregistered from the program if diversion is reported.

More detailed guidelines for pharmacists dispensing within the program are available in Section 16.

7.8 Moving to maintenance

If the patient is successfully inducted into the opioid pharmacotherapy program, they can begin the maintenance phase, which is outlined in detail in the following section.